# NITRATION OF SIMPLE AROMATICS OVER ZEOLITE CATALYSTS

THIS THESIS IS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

By

**MANSOUR DAHISH S. AJARIM**

SCHOOL OF CHEMISTRY
CARDIFF UNIVERSITY
UNITED KINDOM
2010

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

# DECLARATION

This work has not previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

Signed … Mansour Ajarim … (candidate) Date..24/05/2010

## STATEMENT 1

This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD

Signed… Mansour Ajarim (candidate).Date….24/05/2010….

## STATEMENT 2

This thesis is the result of my own independent work/investigation, except where otherwise stated.

Other sources are acknowledged by explicit references.

Signed… Mansour Ajarim ………. (candidate) Date ..24/05/2010…..

## STATEMENT 3

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed…… Mansour Ajarim ….(candidate) Date ….24/05/2010.

*This thesis is sincerely dedicated To*
*My loving Parents*
*(Dr. Dahish Ajarim and Mrs. Khadejah Alomari)*

*And To My wife*
*(Fatemah Alzahrani)*

# ACKNOWLEDGEMENT

First of all, I thank Allah for giving me the strength and the ability to complete this study.

I would like to expresse my thanks and gratitude to my advisor, Professor Keith Smith, for accepting me as PhD student in his research group.Professor Smith alwayes helpful and suportive.

Special thanks also go out to professor Gamal El-Hiti, for teaching me and the support he gave me in the laboratory.

Indeed, I have many people to thank, and I apologize in advance if I have forgotten anyone. First, and foremost, I must thank my best friends; Dr Mohammad Alotaibi, Dr Amany Hegazy, Mohammad Baashen and Ali Masmaly for thier encouragment, support and help. Also, I would like to thank all of my friends and colleagues within the group (Ahmad, Alaa, Ali, Asim and Mohammad) for their collaboration and support.

Special thanks go to all my dearest brothers, sisters and family, for their support and encouragement and for putting colours in my life, may Allah bless them all.

The great and deep gratitude to my loving parents for endowing me with the right tips to the successful life in this world and the hereafter. Also, my wife for her constant love, kind help, moral supports and encouragement throughout my graduate career, which has imbued everything in my life with value. Lastly and not least, thanks go to my children, Khalid, Reem, Mohammad and Ryan for their inspiring me in their own ways to complete my thesis.

# SUMMARY

The aim of this study was to develop new nitration systems using zeolite catalysts for the nitration of a highly activated compound, phenol, and for highly deactivated aromatics. It was hoped that such systems would produce high yields of the nitro products and in high *para*-selectivity.

## Chapter One

Chapter one describes the important role of Green Chemistry in the chemical industry. For example, modern synthetic methods should ideally be safe, be atom efficient, generate minimal waste, not involve solvent, have minimal energy requirement, be based on renewable resources, and be environmentally benign. Advances have been made by the use of solid catalysts such as zeolites and employing green solvents such as water, supercritical carbon dioxide and ionic liquids.

## Chapter Two

Chapter Two describes a literature survey for the use of zeolite catalysts in nitration reactions of various aromatic compounds. Zeolite catalysts offer approaches to *para*-nitro aromatics, with the advantage of easy separation of the catalyst from the reaction mixture by filtration. Zeolites can be recovered and reused several times to give almost the same yields and selectivities as those obtained when fresh zeolite is used, with the avoidance of toxic waste generated by traditional Lewis acids.

## Chapter Three

Chapter Three describes the nitration of phenol over several types of zeolites using *iso*-propyl nitrate as the nitrating reagent. Zeolite Hβ with a Si/Al ratio of 12.5 was the most active of the catalysts tried and also gave the highest proportion of *para*-nitrophenol, but the *para*/*ortho* ratio was still only around 1:1. Mono nitrophenols are formed in high yields when reactions are carried out over two days in refluxing dichloroethane as a solvent. A somewhat higher yield of mononitration products and a slightly better *para*/*ortho* ratio could be achieved with a larger quantity of HZSM-5 under otherwise similar conditions. The reactions also produced small quantities of *iso*-propoxybenzene as the main by-product.

## Chapter Four

Chapter Four describes the nitration of deactivated aromatics using a nitric acid/acid anhydride/zeolite system. Various types of zeolites were used including proton-exchanged and passivated Hβ. For example, nitration of benzonitrile over Hβ produces a quantitative yield of nitrobenzonitriles comprising only 3- and 4-nitrobenzonitriles, with no 2-nitrobenzonitrile produced in most cases under the conditions tried. Trifluoroacetic and chloroacetic anhydrides were found to be the most active of the anhydrides tried. Also, zeolite Hβ with a Si/Al ratio of 12.5 was the most active of the catalysts tried and also gave high *para*-selectivity. The highest yield of 4-nitrobenzonitrile (33%), with a *para*/*meta* ratio of *ca.* 0.50, was obtained using passivated Hβ. Furthermore, heating easily regenerates the zeolite, which can be reused up to six times to give results similar to those obtained with a fresh sample of the catalyst.

The process was found to be general for the nitration of monosubstituted deactivated aromatic compounds and gave significantly increased proportions of *para*-substituted isomers compared with the results obtained from the traditional mixed acid method.

# Table of contents

## CHAPTER THREE 74

## Catalytic mononitration of phenol using *iso*-propyl nitrate over zeolite catalysts 74

# CHAPTER ONE

# GREEN CHEMISTRY AND HETEROGENEOUS CATALYSIS

# CHAPTER ONE

# GREEN CHEMISTRY AND HETEROGENEOUS CATALYSIS

## 1.1. Introduction in green chemistry

It is widely recognised that there is a growing need for more environmentally friendly processes in the chemical industry. It is also important to produce fine chemicals cleanly and efficiently with the minimum damage to the environment. Obviously, the production of chemicals should be profitable, but recently there are increasing costs associated with the treatment of chemical waste. Therefore, it is very important that the chemical processes are designed to minimize the waste produced. In the case of pharmaceuticals this is especially important as early registration of synthetic routes militates against later adoption of superior 'green' synthetic approaches.

This trend towards what has become known as 'green chemistry' or 'sustainable technology' is really important. Green chemistry is a shift from traditional concepts of process efficiency that generally concentrate on the yields of chemicals to be produced to processes having economic values that support elimination of waste at source and avoidance of use of toxic materials.[1-11] Green chemistry could be defined as the chemistry that utilizes renewable raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the production of chemicals.[12]

## 1.2. Principles of green chemistry

Anastas and Warner have pointed out the guiding principles for the design of environmentally benign chemicals and the processes that can produce such chemicals. The concept they introduced comprises 12 principles of green chemistry, as follows.[1,2]

1. ***Waste prevention instead of remediation***; it is better to prevent waste rather than to treat or clean up waste after it has been generated.
2. ***Atom efficiency***; synthetic methods should be designed to maximize the incorporation of all materials (reactants and reagents) used in the process into the final product.
3. ***Less hazardous and less toxic chemical syntheses***; wherever possible and practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to living organisms and the environment.
4. ***Safer products by design***; chemical products should be designed to maximise their desired function while minimizing their toxicity.
5. ***Safer solvents and auxiliaries***; the use of auxiliary substances, such as solvents and separation agents, should be avoided wherever possible.
6. ***Energy efficiency by design***; energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at room temperature and atmospheric pressure.
7. ***Preferable use of renewable feedstocks***; a raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. ***Shorter syntheses and reduce derivatization***; unnecessary derivatization, such as use of blocking groups, protection/deprotection, temporary modification of physical and chemical processes, should be minimized or

avoided if possible, because such steps require additional reagents and can generate waste.

9. ***Catalysis***; selective catalytic reagents should be used rather than stoichiometric reagents.
10. ***Design products for degradation***; chemical products should be designed so that at the end of their function they break down into non-toxic degradation products and do not persist in the environment.
11. ***Analytical methodologies for pollution prevention***; analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. ***Inherently safer processes***; materials used in a chemical process should be chosen to minimize the potential for chemical accidents such as releases, explosions and fires.

Green chemistry addresses the environmental impact of both chemicals and the processes by which they are produced. Green chemistry eliminates waste at source, *i.e.* it is primary pollution prevention rather than waste curing. It is fair to say that sustainability of a chemical process is an important goal to achieve and green chemistry is the way forward to achieve it.

## 1.3. E-Factor

E-Factor is a very useful measure of the potential environmental acceptability of chemical processes and has been put forward by Sheldon.[13-20] E-Factor is defined as the mass ratio of waste to desirable product resulting from a particular manufacturing process. E-Factor for a particular product can be easily calculated from the number of tons of raw materials purchased and the number of tons of product sold. Water is generally not included in the E factor. For example, when considering an aqueous waste stream only the inorganic salts and organic compounds contained in the water are counted.

The magnitude of the waste production in chemicals manufacture is readily apparent from a consideration of typical E-factors in various chemical industry segments. A higher E-factor means more waste and as a result greater negative environmental impact. The ideal E-factor is zero. In the oil industry, E-factors are very low. However, the E-factor increases dramatically on going from bulk chemicals to pharmaceuticals. This might be due to multi-step syntheses being involved in the production of pharmaceuticals, use of excess reagents and use of large quantities of solvents. Table 1.1 represents the typical annual production volumes of various chemicals and their E-factors.

**Table 1.1: The E-factors for various chemical industries**

| Chemical Industry | Product tonnage | E-Factor |
|---|---|---|
| **Oil refining** | $10^6$-$10^8$ | 0.1 |
| **Bulk chemicals** | $10^4$-$10^6$ | 1—5 |
| **Fine chemicals** | $10^2$-$10^4$ | 5—50 |
| **Pharmaceuticals** | 10-$10^3$ | 25—100 |

### 1.4. Atom efficiency or atom economy

The concept of atom efficiency or atom economy was introduced by Trost.[21,22] It is another useful tool for the rapid evaluation of the amount of waste that would be created by alternative synthetic routes to a specific product. It is calculated by dividing the molecular weight of the desired product by the sum total of the molecular weights of all substances formed in the stoichiometric equation for the reaction involved.

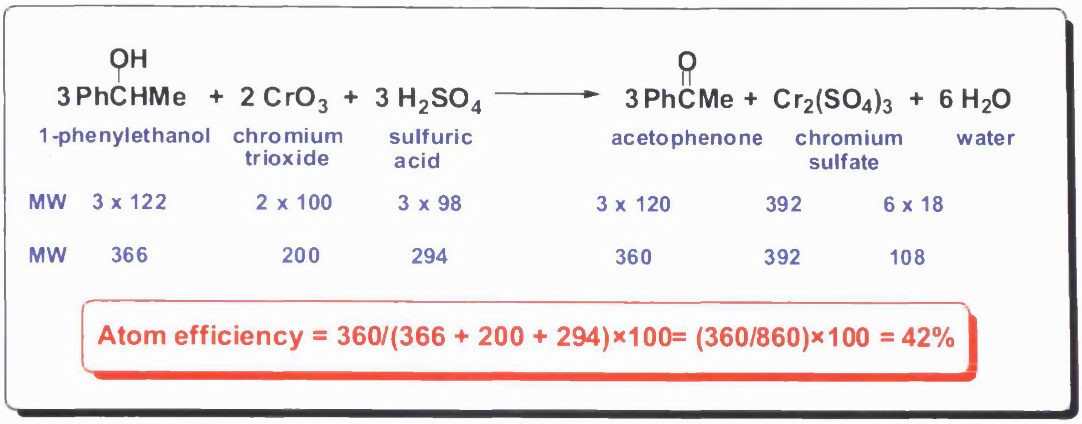


Figure 1.1: Stoichiometric oxidation of 1-phenylethanol with chromium trioxide

For example, Figure 1.1 shows a traditional method for the oxidation of 1-phenylethanol into acetophenone using chromium trioxide in the presence of sulfuric acid. This reaction in principle gives 1.07 kg of chromium sulfate waste for every 1 kg of acetophenone produced. When all reactants are taken in to account, the atom efficiency for the reaction is calculated to be 42%.

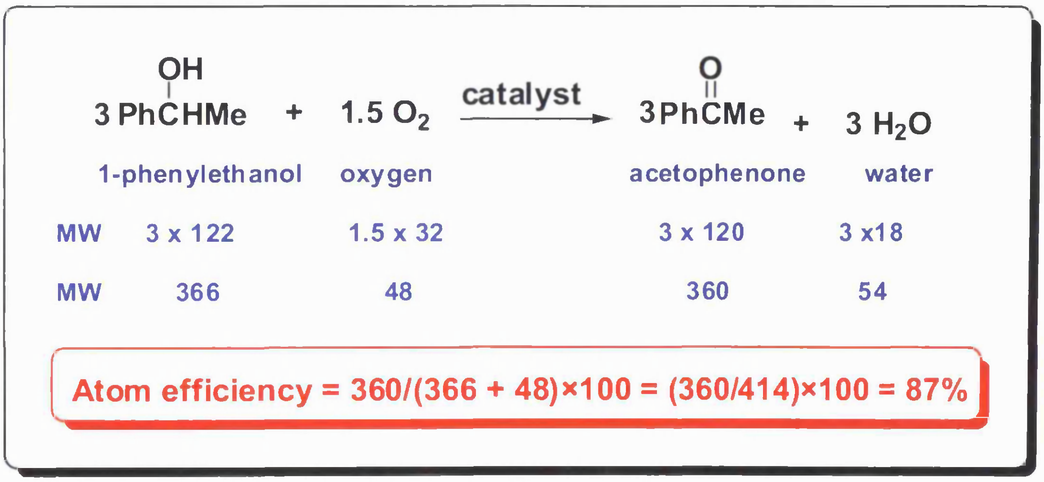


Figure 1.2: Catalytic oxidation of 1-phenylethanol with oxygen

Figure 1.2 shows the catalytic oxidation of 1-phenylethanol directly with oxygen to produce acetophenone. In such a reaction, the only by-product would be water. Clearly, the catalyst has the potential to eliminate most of the waste. The atom efficiency for such a reaction is calculated to be 87%.

There is an inverse relationship between the theoretical E-factor and the atom efficiency. The E-factor is higher if the yield is lower than 100%, while the atom efficiency is obviously lower.

The concepts of E-factors and atom efficiency could be illustrated further by considering the manufacture of phloroglucinol (benzene-1,3,5-triol) in industry.[23]

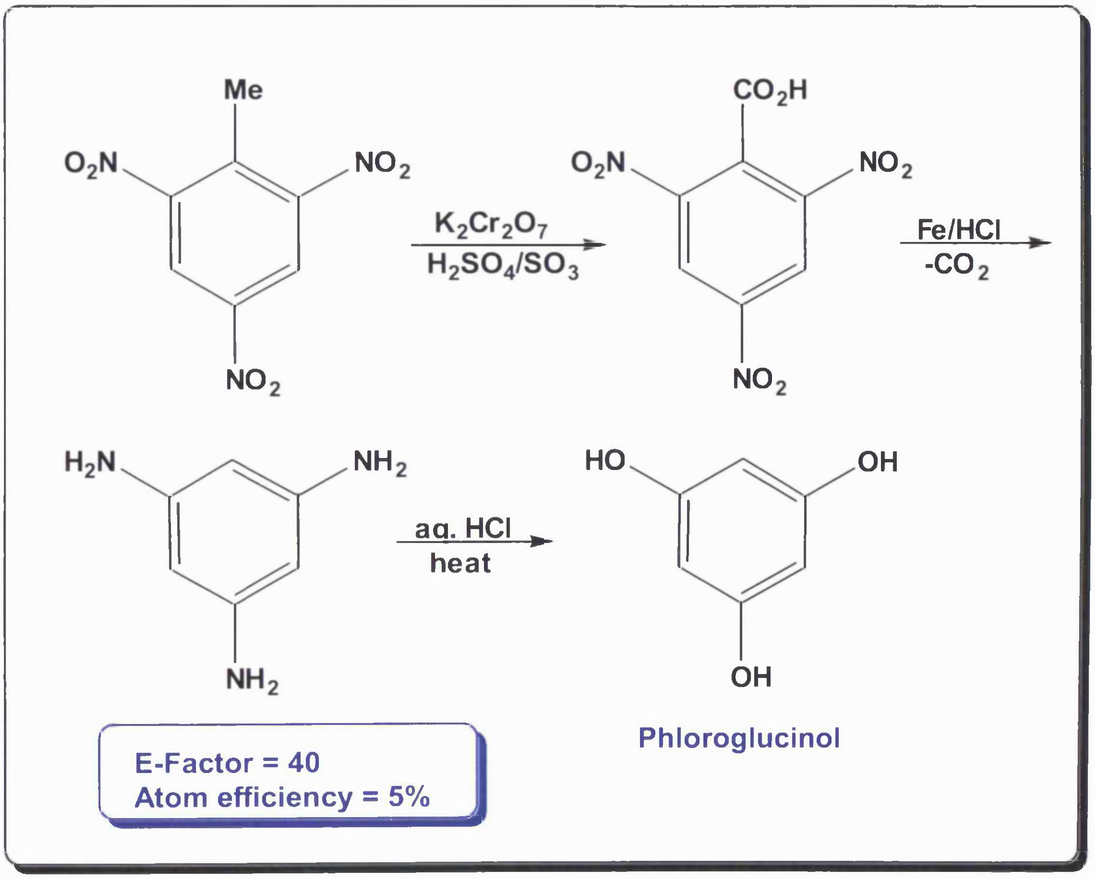


**Figure 1.3: Traditional synthesis of phloroglucinol from TNT**

Figure 1.3 represents the traditional method for the production of phloroglucinol starting from 2,4,6-trinitrotoluene (TNT), which is a perfect example of nineteenth century organic chemistry. The atom efficiency of such a process is around 5% and it has an E-factor of around 40. The process generates 40 kg of solid waste, containing $Cr_2(SO_4)_3$, $NH_4Cl$, $FeCl_2$ and $KHSO_4$, per kg of phloroglucinol.

## 1.5. The environmental quotient (EQ)

The concepts of E-factors and atom efficiency take into account only the mass of waste generated. However, what is important is the environmental impact of this waste as well as its amount. Therefore, the nature of the waste should also be taken into consideration. For example, the environmental impact for the production of one kg of sodium chloride is not the same as for one kg of a chromium salt. In order to take account of these factors the concept of the environmental quotient (EQ) was introduced by Sheldon.[20] The value of EQ for a specific chemical arises when the E-factor (E) is multiplied by an arbitrarily assigned unfriendliness quotient (Q). The value of Q should depend on the toxicity and ease of recyclability of the material generated as waste. For example, a Q value of zero could be assigned for sodium chloride and say 100-1000 to a chromium salt (a heavy metal salt). Also, hydrogen bromide could be given a lower Q value than hydrogen chloride because it is easier to recycle, *via* oxidation to bromine.

It should be noted that Q for a particular substance depends on its volume and the location of the production facilities. For example, it is believed that the generation of 100–1000 tons per annum of sodium chloride is unlikely to cause a waste problem, and could be given a Q value of zero.[10] However, it should be noted that large quantities of sodium chloride as a waste could causes some problems due to the fact that it enhances corrosion of steel and so can cause damage to pipes/machinery etc. On the other hand; the generation of 10,000 tons per annum might cause a disposal problem and could be given a Q value greater than zero. However, when very large quantities of sodium chloride are generated the Q value could decrease again as recycling becomes more viable.

## 1.6. The role of the solvents

Organic reactions often require the use of large quantities of organic solvents.[1,2] However, some solvents are harmful to the environment and humans. Moreover, the use of solvent adds to the cost of a chemical process. Therefore, it is necessary to develop chemical processes that allow chemical reactions to be carried out in the absence of solvent or to find replacements for the harmful and expensive organic solvents. Also, it would be particularly useful if the new solvents could somehow improve the regioselectivity towards production of the desirable products.

Some progress has been made in this area using microwave ovens to allow chemical reactions to be carried out without solvent with the advantages of relatively short reaction time.[24,25] However, not all chemical reactions can be conducted under such conditions. As a result, solvents still need to be used as a medium in which reactions take place. Therefore, more work and development are needed in order to find replacements of common organic solvents by alternative ones. These alternative solvents should be safe, non-toxic, inexpensive and readily available. The following sections provide examples of the progress that has been made in this area.

### 1.6.1. Ionic liquids

Ionic liquids are organic salts with low melting points. In recent years ionic liquids have been used as substitutes for traditional organic solvents in some chemical reactions. Such liquids have convenient physical properties. They are non-volatile, non-flammable, have large liquid ranges, have a high thermal stability, are relatively inexpensive to prepare and have favourable solvation behaviour, which make them useful as green solvents.[26] The most common ionic liquids are those that contain pyridinium and imidazolium residues (Figure 1.4).

Such liquids have been explored as solvents in a number of reactions. Also, ionic liquids could act as catalysts in some chemical reactions. The reaction rates were generally enhanced when reactions were carried out in ionic liquids compared to the corresponding ones conducted in traditional solvents. Moreover, high yields and better selectivities have often been achieved. The ionic liquids can often easily be separated from reaction mixtures by direct distillation of products and can be reused.[27]

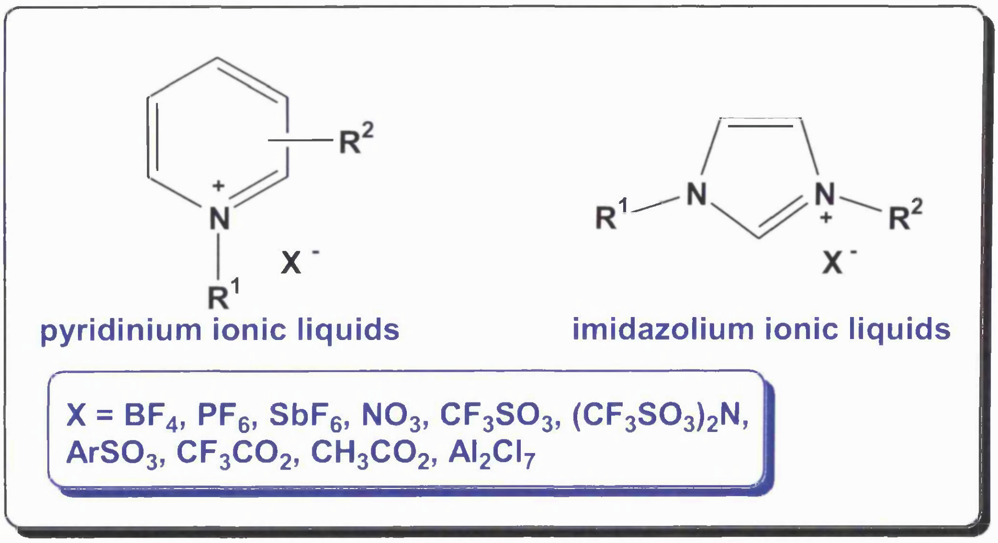


**Figure 1.4: The most common pyridinium and imidazolium ionic liquids**

### 1.6.2. Water

Water is considered to be an ideal solvent for the replacement of organic solvents. Water is safe, non-toxic, neutral, cheap, non-flammable, easy to handle, environmentally friendly, less-volatile than most common organic solvents and readily available. The use of water as a solvent in organic reactions is therefore a big challenge for researchers.[28]

Heterogeneous chemical reactions in water, between water soluble and water insoluble reactants, are often slow. However, the reaction rate in such reactions could be enhanced by the addition of a reagent that can help reactants to transfer from one phase to the other.[29] The process is called phase transfer catalysis if the reaction takes place in the organic layer, and inverse phase transfer catalysis when it occurs in the aqueous layer. The use of phase transfer catalysis is very attractive when any of the following features are important.[30]

1. Elimination of organic solvents.
2. Replacement of flammable, dangerous, and expensive reactants (*e.g.* NaH, $Bu^tOK$, $NaNH_2$) with inexpensive and water soluble ones (*e.g.* $K_2CO_3$, KOH, NaOH).
3. High reactivity and selectivity of the active species.
4. High purity and yield of products.
5. Simplicity and low cost of running the process.
6. Enhancing the reaction rates, lowering the reaction temperature and minimization of waste.

Also, organic solvents could be avoided by the use of aqueous surfactants that aggregate to form micelles. Such a process is called micellar phase transfer catalysis and has been used successfully in some chemical reactions.[31,32]

### 1.6.3. Supercritical fluids

Supercritical carbon dioxide ($ScCO_2$) is widely used as a solvent medium for a wide range of chemical reactions.[33-36] Supercritical carbon dioxide has many advantages such as it is non-reactive, non-flammable, non-polar, inexpensive, easily available, easy to remove from the reaction mixture and easily recyclable. Supercritical carbon dioxide as a solvent may also enhance reaction rates or improvement selectivity in some chemical reactions. However, supercritical carbon dioxide needs high pressures to be produced and contributes to the greenhouse effect and global warming. Also, many compounds do not have good solubility in $scCO_2$ due to its low polarity.

## 1.7. The role of catalysis

The waste generated in the manufacture of organic compounds in industry consists primarily of inorganic salts. This is a direct consequence of the use of large quantities of inorganic reagents in organic synthesis. In particular, fine chemicals and pharmaceuticals manufacture often involves use of stoichiometric reagents. The most common examples are stoichiometric reductions with metals (*e.g.* Na, Mg, Zn or Fe) and metal hydride reagents (*e.g.* $LiAlH_4$ or $NaBH_4$) and oxidations with permanganate, manganese dioxide and chromium(VI) reagents. Also, a wide range of reactions such as sulfonations, nitrations, halogenations, diazotizations and

Friedel-Crafts acylations require the use of stoichiometric amounts of mineral acids (HF, $H_2SO_4$, $H_3PO_4$) or Lewis acids ($BF_3$, $AlCl_3$, $ZnCl_2$). These waste materials may need isolation and special treatment, which can be expensive, environmentally unfriendly and time consuming.[37,38] In order to improve traditional methods of aromatic electrophilic substitution reactions, for example, organic chemists have developed the use of inorganic solid heterogeneous catalysts.[39] Carrying out organic reactions using such inorganic solid catalysts may reduce the environmental difficulties associated with the use of traditional catalysts.

Friedel-Crafts acylation is highly involved in the production of fine chemicals in industrial scale. Friedel-Crafts acylations generally require more than one equivalent of Lewis acid. This is due to the strong complexation of the Lewis acid by the carbonyl group of the acylation product. Zeolite Hβ has been used as a catalyst for the acetylation of anisole using acetic anhydride as the reagent to produce 4-methoxyacetophenone.[40,41] The classical and heterogeneous catalytic Friedel-Crafts acylations of anisole are shown in Figure 1.5.

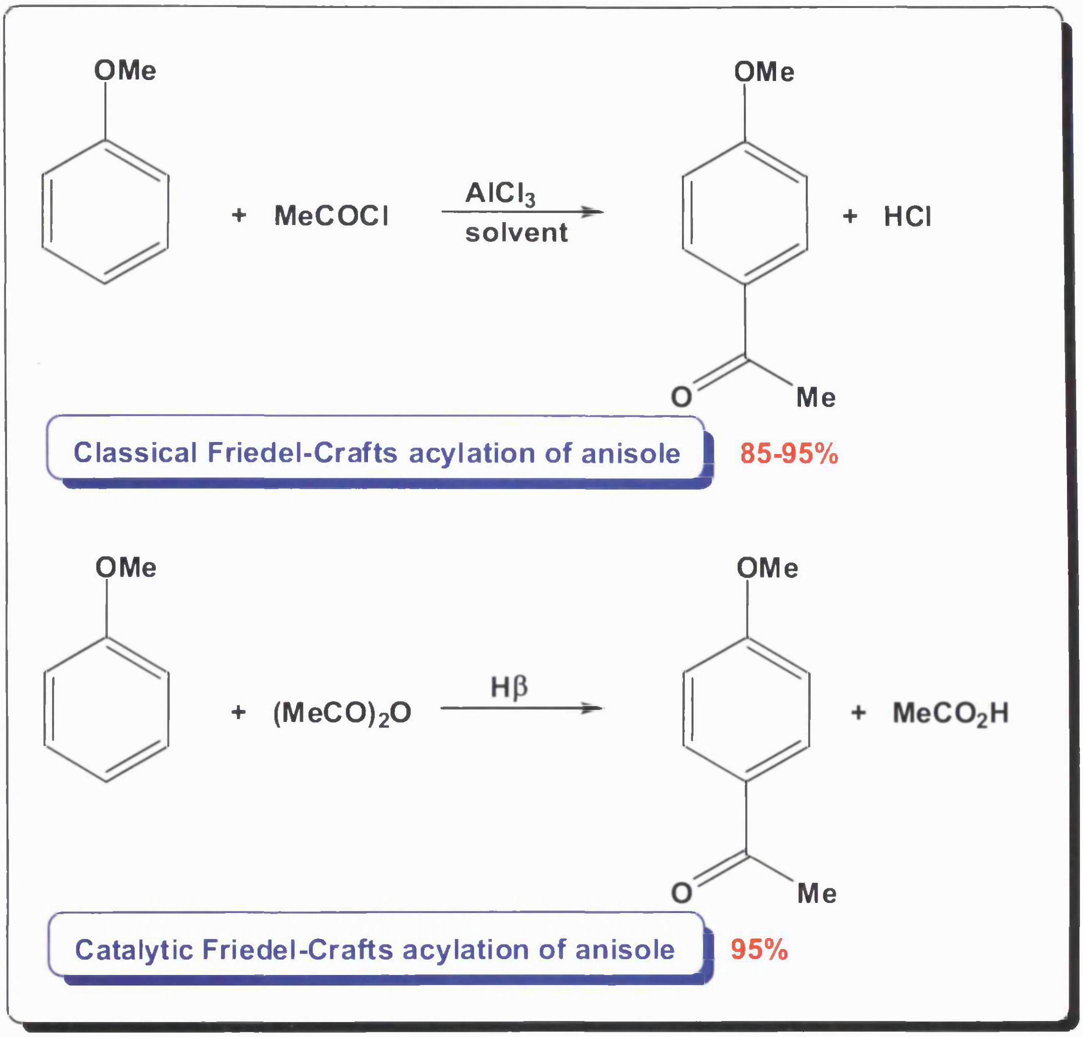


**Figure 1.5: Classical and catalytic Friedel-Crafts acylations of anisole**

The traditional process involves use of acetyl chloride as the acylating reagent in the presence of $AlCl_3$ (1.1 mole equivalents) as an activator in a chlorinated hydrocarbon solvent. Such a process produces 4.5 kg of aqueous waste, containing $AlCl_3$, HCl, solvent residues and acetic acid, per kg of product. On the other hand, the process involving use of zeolite as a catalyst involves use of acetic anhydride as the acylating reagent, thereby avoiding production of HCl in both the acylation reaction and in the synthesis of acetyl chloride. Such catalytic reaction generate 0.035 kg of aqueous waste. These figures indicate that the amount of aqueous waste is more than 100 times less compared to the traditional process. Also, such waste consisted of 99% water, 0.8% acetic acid and less than 0.2% other organics. Moreover, the process requires no solvent and the yield and purity of the product obtained were higher than the ones produced using the traditional method. Table 1.2 shows a comparison between the traditional and catalytic Friedel-Crafts acylations of anisole.

**Table 1.2: Traditional and catalytic Friedel-Crafts acylations of anisole**

| Traditional process (Homogeneous) | Catalytic process (Heterogeneous) |
|---|---|
| $AlCl_3$ ( 1.1 equiv. and non-recyclable) | Hβ (catalytic and regenerable) |
| Chlorinated hydrocarbon | No solvent |
| Hydrolysis work-up | No water necessary |
| Phase separation | No phase separation |
| 85-95% yield | 95% yield, higher purity |
| 4.5 kg of aq. waste per kg of product | 0.035 kg of aq. waste per kg of product |
| Generation of HCl | No HCl produced |

## 1.8. Heterogeneous catalysis

Chemists have developed the use of heterogeneous catalysts instead of traditional reagents in order to overcome many of the limitations associated with the use as activators of large quantities of mineral or Lewis acids, which lead to corrosion problems and formation of large quantities of waste.[39] Heterogeneous catalysis involves the use of a catalyst in a different phase from the reactants while homogeneous catalysis involves the use of a catalyst in the same phase as the reactants.[39]

Heterogeneous solid catalysts can have many advantages such as shape selectivity, reusability, high stability, large internal and external surface area, ability to produce products cleanly and high levels of activity. As a result they have been used in a wide range of organic reactions.[42-44] Some solid catalysts have been found to increase, in certain cases, the selectivity and yield of specific reaction products. Alumina, silica, clays, synclysts and zeolites are inorganic solid catalysts often used in organic synthetic reactions and in particular electrophilic aromatic substitution reactions. The coming sections will focus on the structures and properties of various types of zeolite catalysts.

### 1.8.1. Zeolites

Zeolites belong to a class of synthetic or natural aluminosilicates. The name "zeolite" is derived from the two Greek words "boiling stone" (ζειν/zeio = to boil, and λιθος/lithos = stone). The term was first used by the Swedish mineralogist A. F. Cronsted in 1756.[45] Water in the pores and channels of zeolites converts to steam when zeolites are heated, which gives rise to the name. In 1840, Damour observed that the crystals of zeolites could be reversibly dehydrated with no apparent change in their transparency or morphology.[46] Friedel observed that various solvents such as chloroform, alcohol and benzene were occluded by dehydrated zeolite, which was an indication that the structures of dehydrated zeolites contain open spongy frameworks.[47] The zeolites could be classified according to their polyhedral structures.[48]

Anionic aluminosilicate frameworks (Al-O-Si) form the basis of the crystal lattices of zeolites. Zeolites are crystalline, highly ordered, microporous aluminosilicates with intracrystalline channels and cages of molecular dimensions.

The pores contain cations and water, which equilibrate with the external environment of the zeolites through hydration, dehydration (when zeolites release water by heating) and cation-exchange. If a molecule has a diameter smaller than a zeolite pore aperture then it can access the interior of zeolite crystals, which is known as intercalation.

Zeolites are known for their adsorption properties. There is a high demand for use of FAU-type zeolites in oil refineries. Huge quantities of zeolites are used as catalysts to produce gasoline from crude oil.[49] Zeolites are used for the exchange of hard cations (*e.g.* calcium and magnesium) by softer ones (*e.g.* sodium or potassium) in water. Maximum non-framework cation density increases the extent to which the sieves are able to hold on to polar adsorbates.[49]

### 1.8.2. Structures of zeolites[50,51]

Many naturally occurring and synthetic zeolites are known. The elementary building units of zeolites are $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$ tetrahedra that are linked together through oxygen bridges. The tetrahedra share corners to form ordered three-dimensional macrostructures. The framework structures may contain linked cages, cavities or channels, which are of the right size to allow small molecules to enter (Figure 1.6).

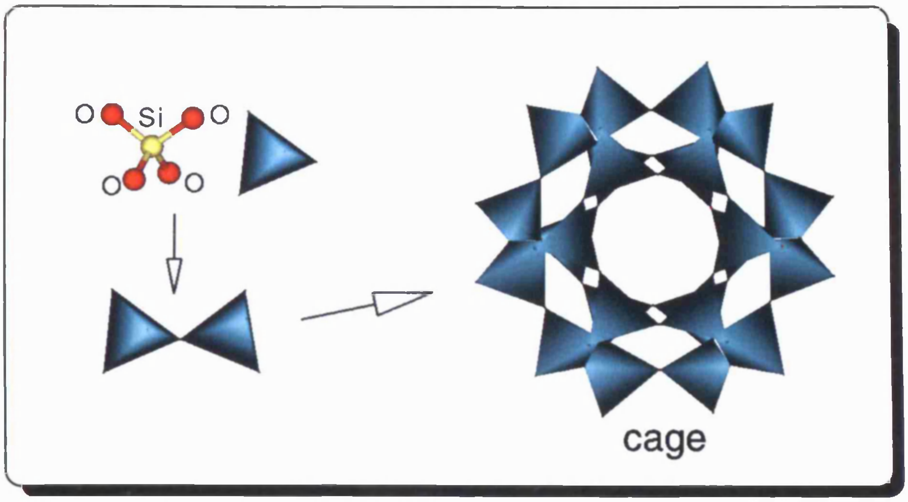


**Figure 1.6: The framework structure of zeolite reproduced by permission from reference 52**

The zeolite framework structure is usually represented by joining the tetrahedral centres with straight lines and ignoring the oxygen atoms between the centres. Each tetrahedron is called a primary unit and is used to build up the structure of the zeolite. Secondary building units (SBUs) are formed when the primary tetrahedral units are linked to each other by tetrahedral atom-oxygen-tetrahedral atom bonds. SBUs can be single rings, double rings or complex ring structures (Figure 1.7).

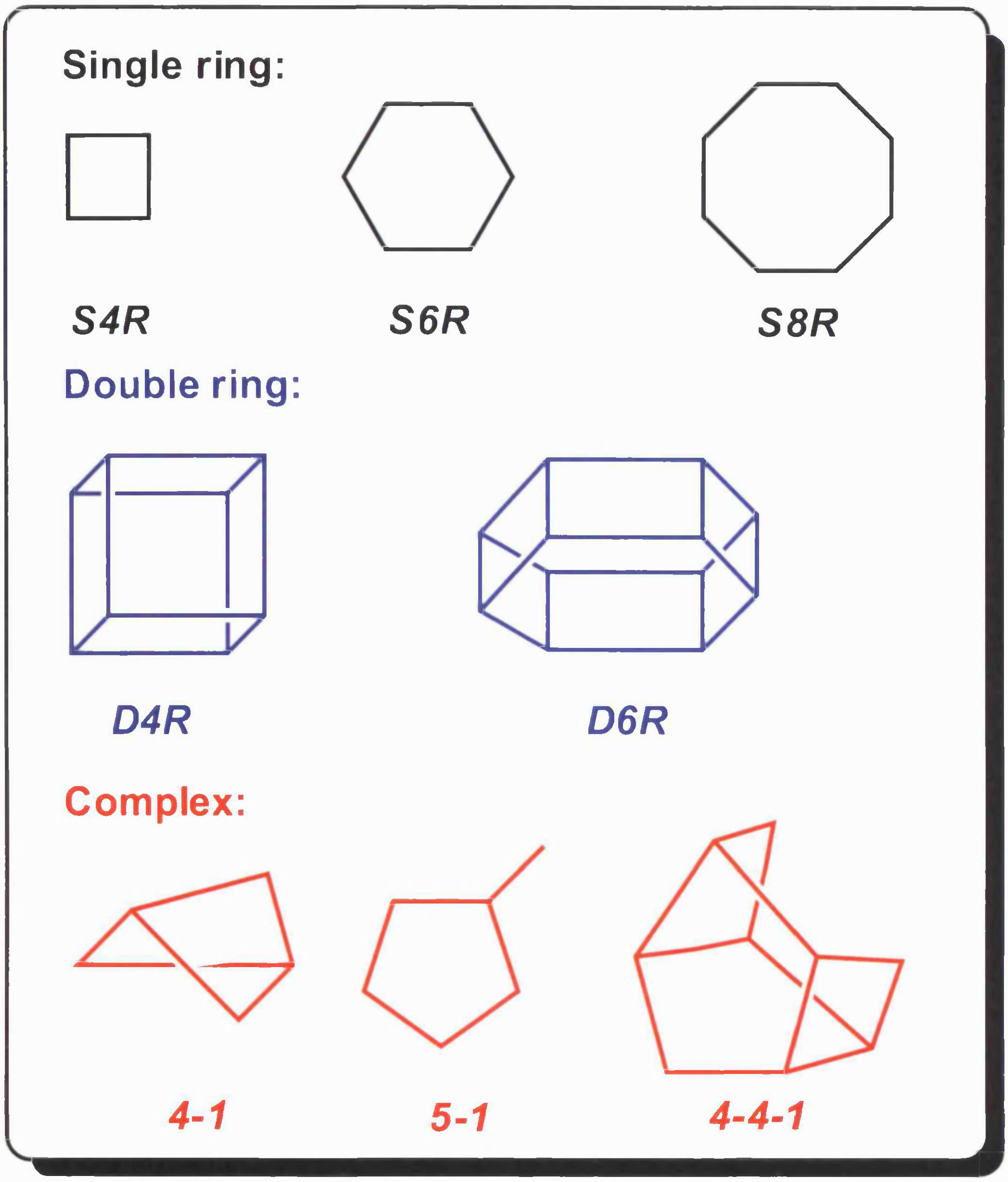


**Figure 1.7: Structures of secondary building units (SBUs)**

When the secondary building units link to each other, they form polyhedral cages and channels. Different SBUs can form different types of polyhedral cages with different shapes. Simple polyhedral cages such as hexahedron and octahedron cage structures are considered as double four-ring SBUs (*D4R*) and double six-ring SBUs (*D6R*), respectively. However, the polyhedral cages can become more complicated frameworks when more tetrahedra are connected to each other (Figure 1.8).

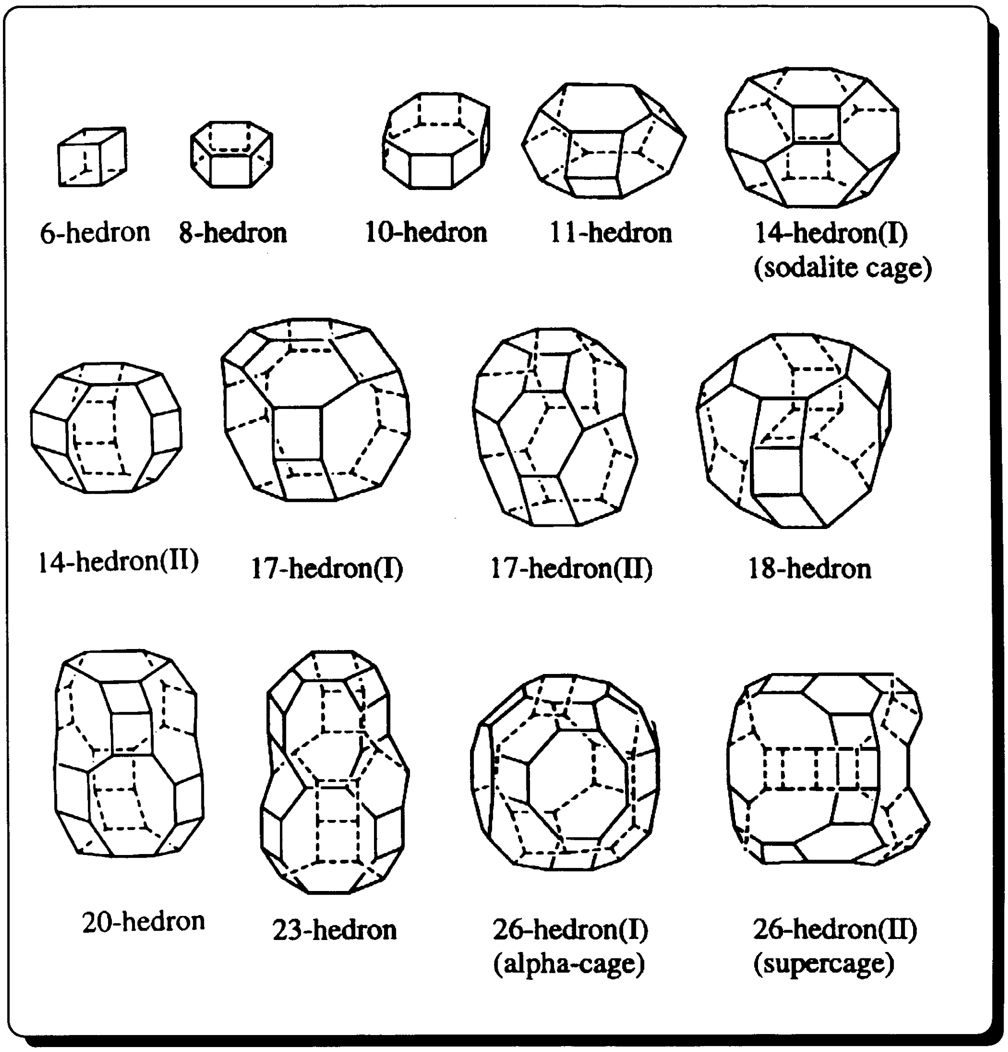


**Figure 1.8: Structures of zeolite polyhedral cages reproduced by permission from reference 51**

The full zeolite structures are formed when the polyhedra are connected to each other, sharing faces and channels, therefore forming crystalline three-dimensional (3D) frameworks containing pores.

Although zeolites have high surface areas (500-700 $m^2/g$), most of this area is internal. This is a very interesting and unusual property of such materials that allows chemical reactions to take place within their pores and therefore provides selectivity.

### 1.8.3. Types of zeolites

The diameter of the pore entrance in a zeolite plays an important role in the ability of a zeolite to contribute to a chemical reaction. For example, the substrate needs to have a smaller molecular diameter than the pore diameter of the zeolite being used in the reaction if it is to enter the pores of the zeolite and access the interior of the zeolite crystal. Zeolites are classified according to their pore sizes as small, medium and large pore zeolites.

#### 1.8.3.1. Small pore zeolites[51-58]

Zeolite A, a small pore zeolite (Figure 1.9), has an approximate empirical formula of $Na_{12}[Al_{12}Si_{12}O_{48}].27\ H_2O$. Zeolite A has an 8-T ring aperture with channel diameters of 4.1 Å.[49,59] Zeolite A is usually used for drying solvents in which only small molecules such as $H_2O$ and *n*-alkanes can pass through its pores. It has cages which are face linked through cubes or 6-hedra and the void space produces further pore systems of 26-hedrons (I) face-shared through 8-T rings, and these then link to each other to create a series of α-cages (Figure 1.9).[52]

The nature of the associated cation has a great influence on the available space within the pores of zeolite A. There are three common cations associated with this type of zeolite: potassium, sodium and calcium. Zeolite $K^+A$ is referred to as 3A molecular sieve, having a pore diameter of around 3 Å. Zeolites $Na^+A$ and $Ca^{2+}A$ are known as 4A and 5A molecular sieves, respectively, according to their channel diameters.

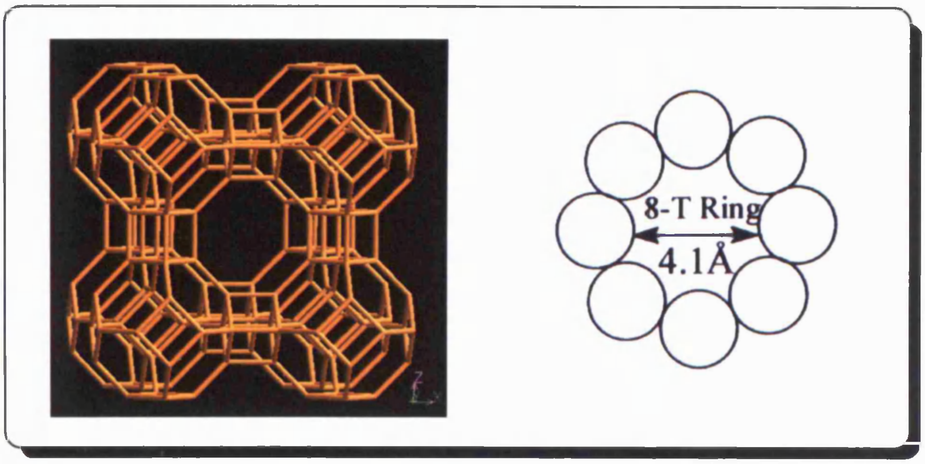


**Figure 1.9: Structure of zeolite A and illustration of an 8-T Ring reproduced by permission from reference 52**

### 1.8.3.2. Medium pore zeolites[57,60]

Zeolite ZSM-5 (Zeolite Socony Mobil-number 5) is an example of a medium pore zeolite. Zeolite ZSM-5 is also known as a MFI zeolite). Its empirical formula is $Na_n[Si_{26-n}Al_nO_{192}].16\ H_2O$, where $n \leq 8$.[51,52] Zeolite ZSM-5 has 10-T ring apertures leading to oval pores of 5.5 x 5.6 Å as shown in Figure 1.10.

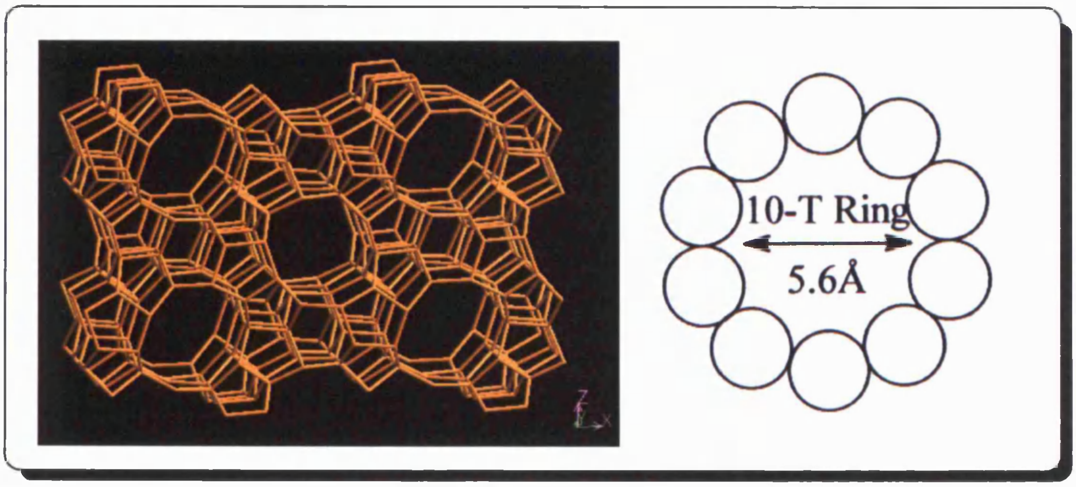


**Figure 1.10: Structure of zeolite ZSM-5 and illustration of 10-T Ring reproduced by permission from reference 52**

The three dimensional structure of zeolite ZSM-5 clearly indicates that the zeolite crystal contains two types of channels, straight channels (5.3 x 5.6 Å) and sinusoidal channels (5.1 x 5.5 Å). The sinusoidal channels are located in planes normal to the axes of the straight channels. This is represented by a set of straight, parallel pores (5.1 x 5.6 Å) intersected by a set of zigzag pores (Figure 1.11).

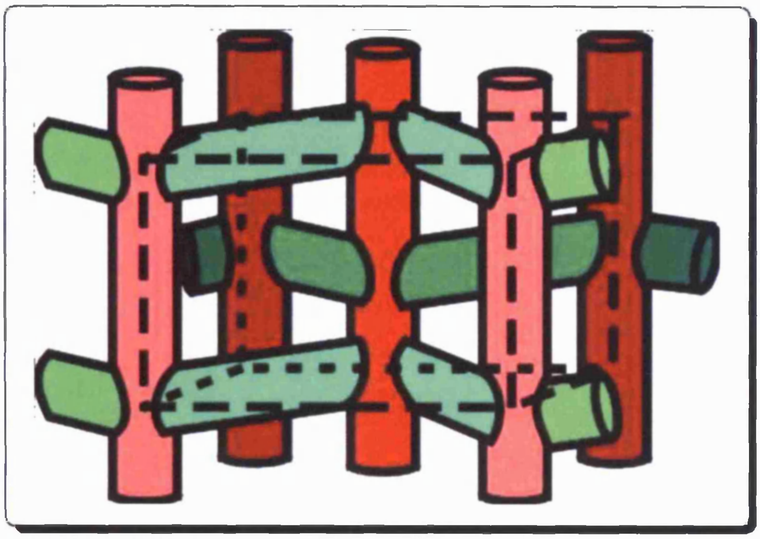


**Figure 1.11: Schematic representation of the intracrystalline pore structure of zeolite ZSM-5 reproduced by permission from reference 52**

### 1.8.3.3. Large pore zeolites

#### 1.8.3.3.1 Zeolites X and Y

Zeolites X and Y are known as synthetic faujasite (FAU). The spherical internal cavity generated when 8 sodalite cages are joined is called the α-cage (or supercage) and is about 13 Å in diameter (Figure 1.12). Zeolites X and Y have sodalite cages, as in zeolite A. However, in contrast to zeolite A, they are formed when only half of the octahedral faces are joined together to form hexagonal prisms. Entry into the spherical α-cage can occur through four identical openings that are 7-8 Å wide. Such relatively large pores allow relatively large molecules to enter the internal channels of zeolites X and Y.[52]

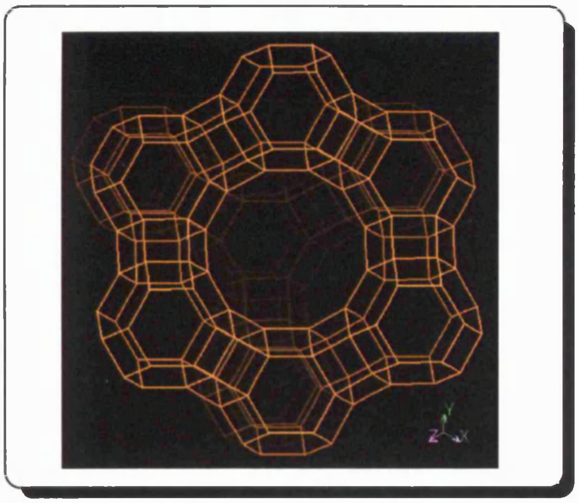


**Figure 1.12: Faujasite structure of zeolites X and Y reproduced by permission from reference 52**

The main difference between zeolites X and Y is the silicon to aluminium (Si/Al) ratio. Zeolite X contains low silicon content with a Si/Al ratio in the range of 1.0-1.5, whereas the Si/Al ration in zeolite Y is always above1.5. Zeolite X contains a higher number of acidic sites than that of zeolite Y as a result of its high aluminium content, but the acid strength of an individual site is lower in zeolite X.

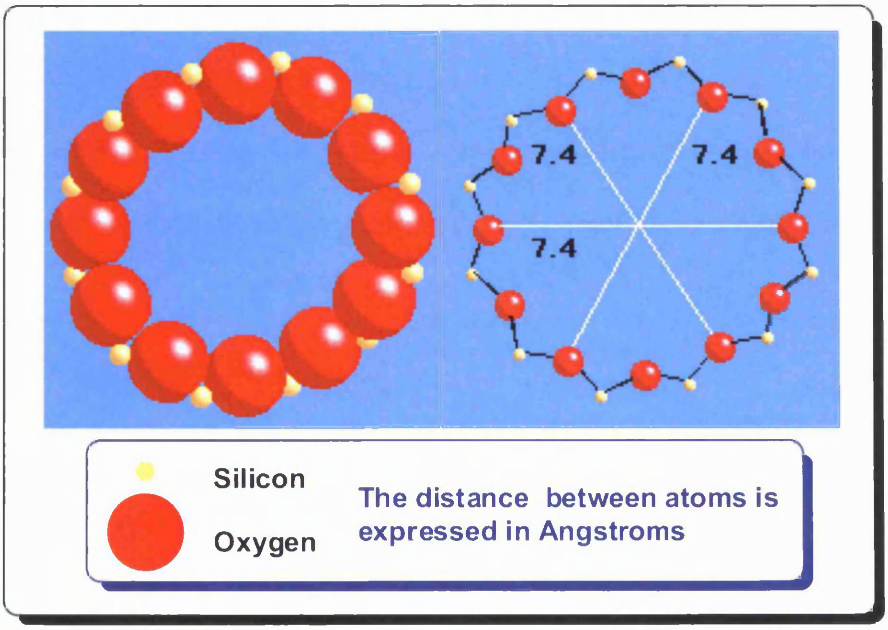


**Figure 1.13: 12-T Ring aperture in zeolites X and Y reproduced with modification by permission from reference 52**

Zeolites X and Y have 12-T ring apertures and the same three-dimensional pore structures (Figure 1.13). Both zeolites can be exchanged with various cations.[52]

### 1.8.3.3.2 Mordenite

The mordenite structure is formed from 5-1 SBUs linked by chains to form channels with 8-T rings and 12-T rings (Figure 1.14.).[52]

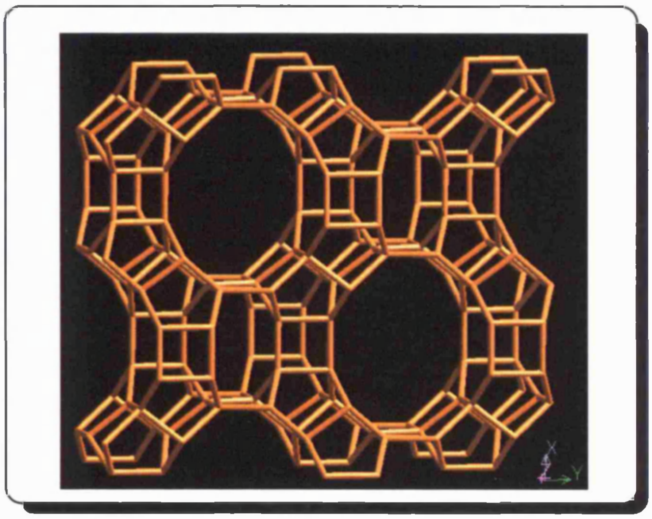


**Figure 1.14: Structure of mordenite reproduced by permission from reference 52**

Mordenite has a high content of silica. In contrast to zeolites X and Y, mordenite contains a one-dimensional system of channels. Mordenite has two interconnected channels, although one is too small to accommodate organic molecules.

### 1.8.3.3.3 Zeolite Beta (β)

Zeolite β was discovered by R. L. Wadlinger in 1967.[61] Zeolite β has a large pore size and complex structure. Zeolite β has a three dimensional pore network with straight channels having 12-T rings. There are two pore diameters of 7.0 x 6.4Å and 5.5 x 5.5Å. The pores are present in a 2:1 ratio. The straight 12-T ring channels go in a and b directions. The third 12-T ring channel, which is tortuous, runs in the c direction (Figure 1.15).

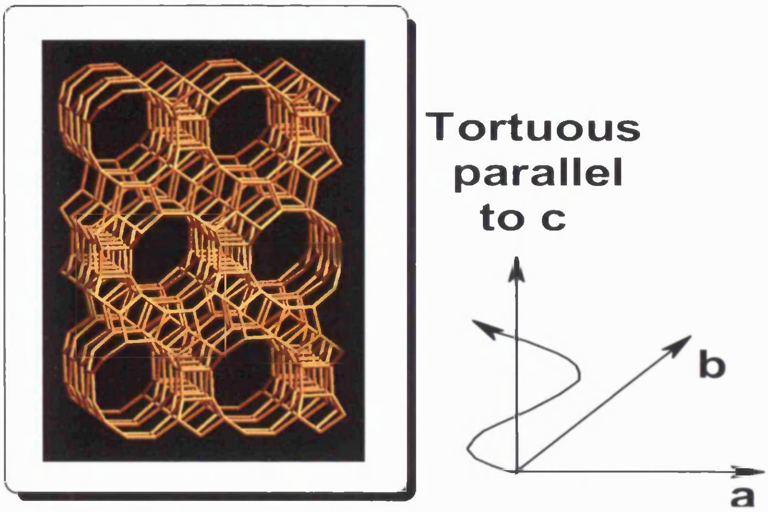
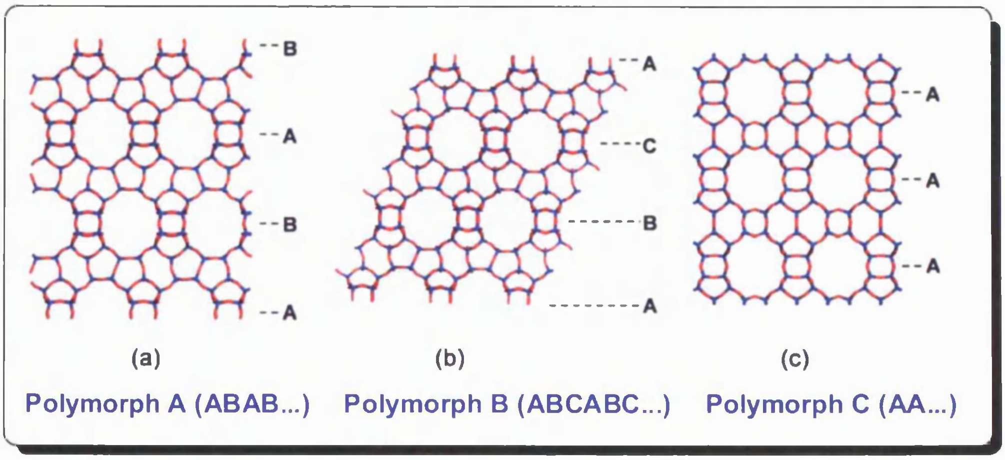


**Figure 1.15: Structure of zeolite β reproduced by permission from reference 52**

Zeolite β has acid site distribution with a high Si/Al ratio of about 13. It is made up of three polymorphic structures, polymorph A (Figure 1.16a), polymorph B (Figure 1.16b) and polymorph C (Figure 1.16c), that differ in the way that the cages are stacked with respect to each other.[62] Polymorph C contains only one repeating unit (*i.e.* AAAA...) and is present in very small amounts because it is unstable. Polymorphs A has two repeating units (ABAB...) and B has three (ABCABC...) (Figure 1.16).



(a) Polymorph A (ABAB...)

(b) Polymorph B (ABCABC...)

(c) Polymorph C (AA...)

**Figure 1.16: Framework structures of polymorph A, polymorph B and polymorph C of zeolite β reproduced by permission from reference 62**

## 1.9. Zeolite composition

Zeolites that have the same pore structure can vary in their Si/Al ratio. For example, the Si/Al ratio in zeolite ZSM-5 is high (10-100) compared to the typical range of most zeolites. However, the lowest Si/Al ratio that can be achieved in aluminosilicate zeolites is 1 according to *Löwenstein*'s Rule.[63] This rule indicates that it is impossible to link $[AlO_4]^-$ tetrahedra directly to each other.[63] The Si/Al ratios in FAU zeolites determine whether they are called zeolite X (low Si/Al ratio, 1.0-1.5) or zeolite Y (Si/Al ratio above 1.5).

### 1.9.1. Cation exchange

The structure of zeolites can be modified *via* cation exchange, which gives rise to a diverse range of physical and chemical properties, allowing zeolites to be adapted for numerous applications. The properties of individual zeolites depend not only upon their framework structure and composition, but also on the non-framework cations they contain.

Substitution of Al for Si in any silicate structure generates an anionic site within the inorganic framework. Therefore, charge neutralization has to take place by either protonation or by interaction with a metal cation or a hydronium ion. The size of zeolite apertures has an important effect on the cation exchange process and must be sufficient for the cation to enter the pores. For example, cations that occupy sites accessible through 8-T rings or larger are usually hydrated, while those occupying sites only accessible through 6-T or smaller apertures are generally unsolvated. Solvated cations are mobile and able to undergo rapid solvent-mediated migration at room temperature while migration of unsolvated cations between anionic framework sites is often slow.

The cation exchange of zeolites is a reversible process (Equation 1.1). The degree of cation exchange depends largely on the zeolite type and the number of cations in solution. Therefore, in order to achieve complete cation exchange, several treatments with fresh solutions of the cation are required.

$$\boxed{M_x\text{ - Zeolite(s)} + M_y^+\text{(aq)} \rightleftharpoons M_y\text{ - Zeolite(s)} + M_x^+\text{(aq)}}$$

**Equation 1.1: Cation exchange in zeolite**

### 1.9.2. Acidity of zeolites

Zeolites are widely used in chemical reactions as solid acidic catalysts. Active Brønsted sites in zeolites can be increased by converting the sodium form to its protonated form. Typically, treatment of $Na^+$-zeolite with an aqueous ammonium salt (Equation 1.2) is used to give the corresponding $NH_4^+$-zeolite, which loses $NH_3$ on heating to produce the corresponding $H^+$-zeolite (Equation 1.3).[57,64]

$$\boxed{Na^+\text{ - Zeolite(s)} + NH_4^+\text{(aq)} \xrightarrow[\text{exchange}]{\text{Cation}} NH_4^+\text{ -Zeolite(s)} + Na^+\text{(aq)}}$$

**Equation 1.2: Generation of $NH_4^+$-zeolite *via* cation exchange**

$$\boxed{NH_4^+\text{ -Zeolite(s)} \xrightarrow{>450\text{ °C}} H^+\text{ -Zeolite(s)} + NH_3\text{(g)}}$$

**Equation 1.3: Generation of $H^+$-zeolite *via* loss of ammonia on heating**

The protons are attached to oxygen atoms of the aluminosilicate network to neutralize the negative charge of the framework and generate Brønsted acid sites (Figure 1.17).

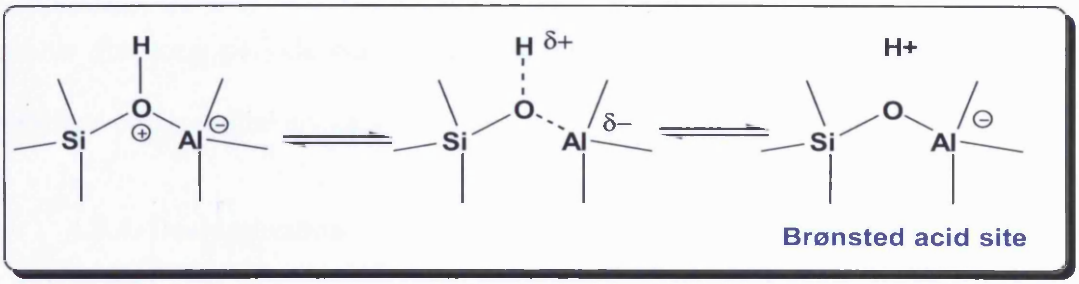


Figure 1.17: Brønsted acid sites in a zeolite structure

### 1.9.3. Calcination of zeolites

Heating a zeolite at high temperature (more than 400 °C) in air for several hours is known as calcination. Calcination can remove any water or organics, possibly obtained from the synthesis of the zeolites. The Brønsted acid sites in zeolites are converted into Lewis acid centres as a result of dehydration that takes place at high temperature.

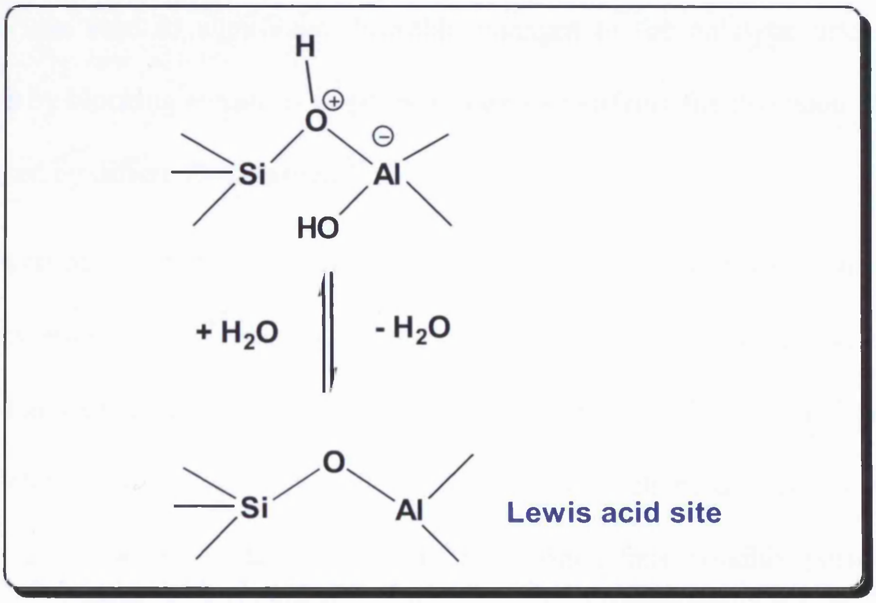


Figure 1.18: Lewis acid sites in a zeolite structure

Elimination of water takes place by removing a proton and a hydroxyl group attached to a nearby atom. As a result of water removal, aluminium centres become Lewis acid sites and act as electron-pair acceptors (Figure 1.18).

Zeolites can absorb water again at room temperature. However, calcining the zeolite for long periods can bring about permanent changes to the framework structure of the zeolite crystals.

### 1.9.4. Dealumination

The process of removing aluminium from a zeolite framework is known as dealumination. This process increases the acid strength of individual sites and the hydrothermal stability of the zeolite structure by increasing the Si/Al ratio. However, the capacity of the zeolites for cation-exchange is decreased.[57]

### 1.9.5. Passivation

Reactions at the external surface of zeolites take place in a non-shape-selective manner. Passivation of zeolites involves deactivation of the catalytic sites on the external surface, for example by the deposition of Si on that surface. Such processes can lead to significant desirable changes to the catalytic and sorption properties by blocking entrances to pores and thus modifying the diffusion resistance experienced by different molecules.[65]

Passivation of external surface sites can be achieved by a number of techniques using bulky molecules. The most common reagents are methylquinoline, ethylenediaminetetraacetate (EDTA) and silane compounds (*e.g.* tetraethoxysilane, trimethylchlorosilane and tetramethoxysilane). The bulkiness ensures that the molecule does not enter into the pores of the zeolite, thus possibly poisoning the internal sites of the zeolite.

### 1.9.6. Shape selectivity

The selectivity of zeolites depends largely on the size and shape of the pore networks. For example, reactants or regents with larger sizes than the pore dimensions will not pass through the pore network easily. On the other hand, smaller size molecules will pass through the pores. This selectivity property can be useful for separating specific isomers selectively from a reaction mixture.[66] Also, this property provides one way in which zeolites can help in directing reactions towards a desired product.[67] The shape selectivity observed for zeolite catalysis has been classified into three different types (Figure 1.19).

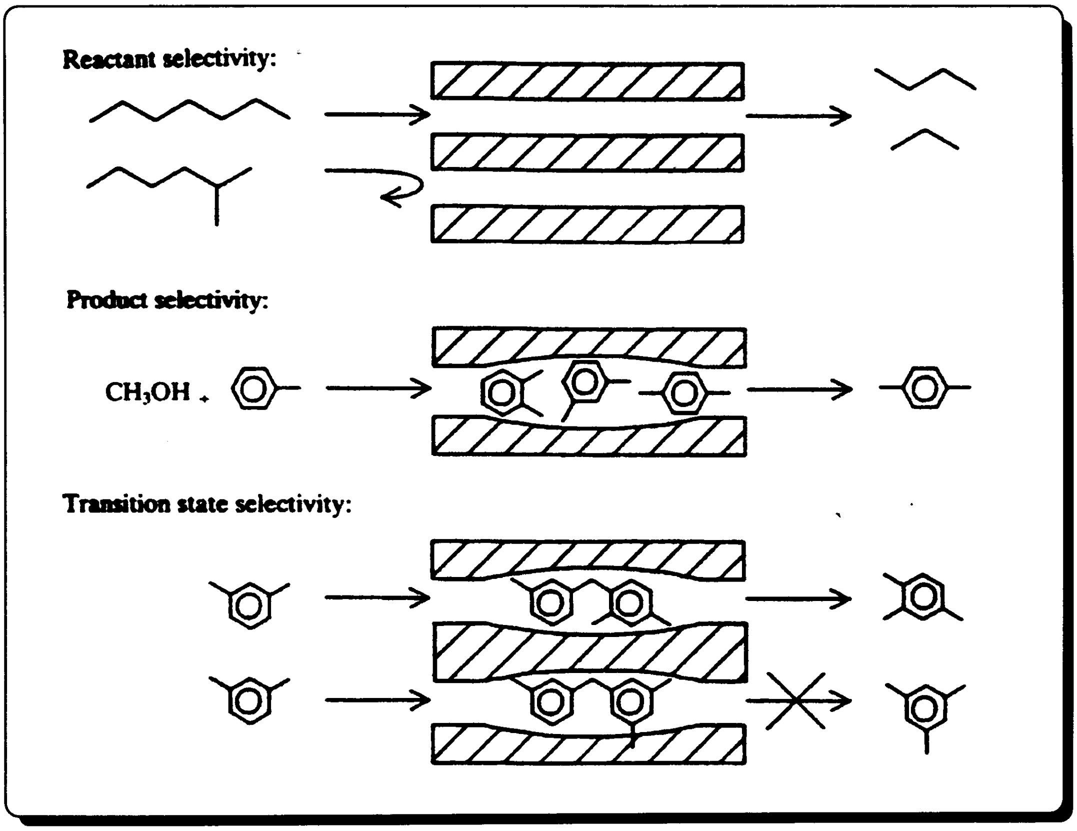


**Figure 1.19: Examples of selectivity in zeolite pores reproduced by permission from reference 51**

1. ***Reactant shape selectivity***. Only reagents with the appropriate dimensions can enter the zeolite pores and react.
2. ***Product selectivity or molecular trafficking***. Only products with the appropriate dimensions will diffuse out of the pores.
3. ***Transition state shape selectivity or restricted transition state selectivity***. The dimension and shape of the transition state within the pores of the zeolite will affect the formation of specific products within the pores.

## 1.10. Conclusion

Modern methods for the production of chemicals should ideally be safe, be atom efficient, generate minimal waste, not involve solvent, have minimal energy requirement, be based on renewable resources, and be environmentally benign. Green chemistry has an important role to play in the chemical industry, to provide greater efficiency. Ideally chemical reactions should proceed with quantitative yield, have low costs and generate no waste. This is a great intellectual challenge, which will drive green chemistry forward. Any improvements will impact greatly on sustainable development and protection of the environment. As a result, the quality of life will be improved for the benefit of human welfare in general. Advances have been made in all of these areas by the use of solid catalysts such as zeolites and employing green solvents such as water, supercritical carbon dioxide and ionic liquids.

## 1.11. References

1. *Green Chemistry: Theory and Practice*, ed. P. Anastas and J. C. Warner, Oxford University Press, Oxford, 1998.
2. *Green Chemical Syntheses and Processes*, ed. P. T. Anastas, L. G. Heine and T. C. Williamson American Chemical Society, Washington DC, 2000.
3. *Green Chemistry: Frontiers in Chemical Synthesis and Processes*, ed. P. T. Anastas and T. C. Williamson, Oxford University Press, Oxford, 1998.
4. P. T. Anastas and M. M. Kirchhoff, *Acc. Chem. Res.*, 2002, **35**, 686.
5. *Benign by Design: Alternative Synthetic Design for Pollution Prevention*, ed. P.T. Anastas and C. A. Farris, ACS Symp. Ser. 577, American Chemical Society, Washington DC, 1994.
6. J. H. Clark and D. J. Macquarrie, *Handbook of Green Chemistry and Technology*, Blackwell, Abingdon, 2002.
7. A. S. Matlack, *Introduction to Green Chemistry*, Marcel Dekker, New York, 2001.
8. M. Lancaster, *Green Chemistry: An Introductory Text*, Royal Society of Chemistry, Cambridge, 2002.
9. *The Chemistry of Waste Minimization*, ed. J. H. Clark, Blackie, London, 1995.
10. *Green Chemistry and Catalysis*, ed. R. A. Sheldon, I. Arends, and U. Hanefeld, Wiley-VCH, Weinheim, Germany, 2007.
11. K. Smith, D. A. Evans and G. A. El-Hiti, *Role of Modern Chemistry in Sustainable Arable Agricultural Products "Sustainable Agriculture I"*, ed. C. Pollock, J. Pretty, I. Crute, C. Leaver and H. Dalton, *Phil. Trans. R. Soc. B*, 2008, **363**, 623.

12. R. A. Sheldon, *C. R. Acad. Sci. Paris, IIc, Chimie/Chemistry*, 2000, **3**, 541.
13. R. A. Sheldon, *Chem. Ind. (London)*, 1992, 903.
14. R. A. Sheldon, *Industrial Environmental Chemistry*, ed. D. T. Sawyer and A. E. Martell, Plenum, New York, 1992, pp. 99-119.
15. R. A. Sheldon, *Precision Process Technology*, ed. M. P. C. Weijnen and A. A. H. Drinkenburg, Kluwer, Dordrecht, 1993, pp. 125-138.
16. R. A. Sheldon, *Chemtech*, March 1994, 38.
17. R. A. Sheldon, *J. Mol. Catal. A: Chem.*, 1996, **107**, 75.
18. R. A. Sheldon, *Chem. Ind. (London)*, 1997, 12.
19. R. A. Sheldon, *J. Chem. Technol. Biotechnol.*, 1997, **68**, 381.
20. R. A. Sheldon, *Pure Appl. Chem.*, 2000, **72**, 1233.
21. B. M. Trost, *Science*, 1991, **254**, 1471.
22. B. M. Trost, *Angew. Chem. Int. Ed.,* **1995**, *34*, 259.
23. T. Iwata, H. Miki and Y. Fujita, *Ullmann's Encyclopedia of Industrial Chemistry*, VCH, Weinheim, 1991, Vol. **A19**, pp. 347.
24. R. S. Varma, *Organic Synthesis using Microwaves and Supported Reagents* in *Microwaves in Organic Synthesis,* ed. A. Loupy, Weinheim: Wiley-VCH, 2002, Chapter 6, pp. 181-218.
25. A. de la Hoz, A. Diaz-Ortiz and A. Moreno, *Chem. Soc. Rev.*, 2005, 164.
26. *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities; Transformations and Processes*, ed. R. D. Rogers and K. R. Seddon, Washington D.C.: American Chemical Society, 2005, Vol. **902**.
27. K. R. Seddon, *J. Chem. Technol. Biotechnol.*, 1997, **68**, 351.
28. U. M. Lindstrom, *Chem. Rev.*, 2002, **102**, 2751.

29. Y. Goldberg, *Phase Transfer Catalysis: Selected Problems and Applications.* Yverdon: Gordon and Breach Science Publishers, 1989.
30. M. Makosza, *Pure Appl. Chem.*, 2000, **72**, 1399.
31. K. G. Kammermeyer and A. G. Volkov, *Interfacial Catalysis*, ed. A. G. Volkov, New York: Marcel Dekker, 2002.
32. W. M. Nelson, *Green Solvents for Chemistry. Perspective and Practice.* New York: Oxford University Press, 2003.
33. P. G. Jessop and W. Leitner, *Chemical Synthesis using Supercritical Fluids*, Weinheim: Wiley, VCH, 1999.
34. O. Kajimoto, *Chem. Rev.*, 1999, **99**, 355.
35. J. R. Hyde, B. Walsh, J. Singh and M. Poliakoff, *Green Chem.*, 2005, **7**, 357.
36. J. W. Wang, A. N. Khlobystov, W. X. Wang, S. M. Howdle and M. Poliakoff, *Chem. Commun.*, 2006, 1670.
37. G. A. Olah, R. Malhotra and S. C. Narang, *Nitration Methods and Mechanisms*, VCH, New York, 1989.
38. R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990.
39. J. H. Clark, A. J. Butterworth, S. J. Tavener and A. J. Teasdale, *J. Chem. Tech. Biotechnol.*, 1997, **68**, 367.
40. S. Ratton, *Chem. Today*, 1997, **3–4**, 33.
41. M. Spagnol, L. Gilbert and D. Alby, in *The Roots of Organic Development*, ed. J. R. Desmurs and S. Ratton, Ind. Chem. Lib., Elsevier, Amsterdam, 1996, Vol. **8**, pp. 29–38.
42. J. H. Clark, *Catalysis of Organic Reactions using Supported Inorganic Reagents*, VCH, New York, 1994.

43. J. H. Clark, K. Martin, A. J. Teasdale and S. J. Barlow, *J. Chem. Soc., Chem. Commun.*, 1995, 2037.
44. M. A. Martin-Luengo and M. Yates, *J. Mat. Sci.*, 1995, **30**, 4483.
45. N. N. Greenwood and A. Earnshaw, *Chemistry of the Elements*, Pergamon Press, Hong Kong, 1984.
46. A. Damour, *Ann. Mines*, 1840, **17**, 191.
47. G. Friedel, *Bull Soc. Chim. Fr.*, 1896, **19**, 94.
48. J. M. Thomas, *Angew. Chem. Int. Ed. Engl.*, 1988, **29**, 1673.
49. H. V. Bekkum, *Introduction to Zeolite Science and Practice*, Elsevier, Amsterdam, 2001.
50. S. Singh and S. Dev, *Tetrahedron*, 1993, **49**, 10959.
51. K. Smith, *Solid Supports and Catalysts in Organic Synthesis*, Ellis Horwood, Chichester, 1992, pp. 25-37.
52. C. Baerlocher, W. M. Meier and D. H. Olson, *Atlas of Zeolite Framework types*, 5th Ed., Elsevier, Amsterdam, 2001.
53. D. W. Breck and T. B. Reed, *J. Am. Chem. Soc.*, 1956, **78**, 5972.
54. W. Hölderich, M. Hesse and F. Naumann, *J. Am. Chem. Soc.*, 1956, **78**, 5963.
55. F. Schwochow and L. Puppe, *Angew. Chem. Int. Ed. Engl.*, 1975, **14**, 620.
56. R. Seff, *Acc. Chem. Res.*, 1976, **9**, 121.
57. J. V. Smith, *Chem. Rev.*, 1988, **88**, 149.
58. L. Bronssard and D. P. Shoemarker, *J. Am. Chem. Soc.*, 1960, **82**, 1041.
59. M. M. J. Treacy and J. B. Higgins, *Collection of simulated XRD Powder Patterns for Zeolite*, Elsevier, Amsterdam, 2001.
60. M. Katoh, T. Yamazaki and S. Ozawa, *Bull. Chem. Soc. Jpn*, 1994, **67**, 1246.
61. R. L. Wadlinger, G. T. Kerr and E. J. Rosinski, *US Pat.*, 1967, 330869.

62. A. Corma, M. Moliner, Á. Cantín, M. J. Díaz-Cabañas, J. L. Jordá, D. Zhang, J. Sun, K. Jansson, S. Hovmöller, and X. Zou, *Chem. Mater.*, 2008, **20**, 3218.

63. W. Löwenstein, *Amer. Minertral.*, 1954, **95**, 343.

64. A. Corma, *Chem. Rev.*, 1995, **95**, 559.

65. C. T. O'Connor, K. P. Möller and H. Manstein, *Kona*, 2007, **25**, 230.

66. K. Smith, P. He and A. Taylor, *Green Chem.*, 1999, **1**, 35.

67. K. Smith, Z. Zhenhua and P. K. G. Hodgson, *J. Mol. Catal. A*, 1998, **134**, 121.

# CHAPTER TWO

# REGIOSELECTIVE NITRATION REACTIONS OF SIMPLE AROMATICS OVER ZEOLITE CATALYSTS

# CHAPTER TWO

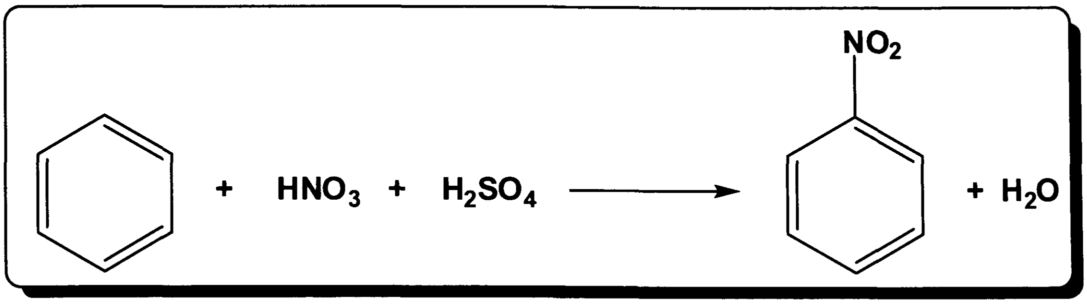
# Regioselective nitration reactions of simple aromatics over zeolite Catalysts

## 2.1. Introduction

Many valuable materials are synthesised on a large scale where electrophilic aromatic substitution reactions are involved. Such substituted aromatics are very useful as synthetic intermediates for the production of various materials with various applications. Indeed, electrophilic aromatic substitution, in particular nitration reactions, have been well reviewed.[1-5]

Generally, nitro compounds are produced as a result of reaction between an aromatic compounds and nitrating reagents. Nitration can occur on the aromatic ring (on carbon), oxygen or nitrogen atom to give the corresponding nitro compounds, nitrates and nitroamines, respectively.[4]

Benzene was discovered by Faraday in 1825 and he attempted its nitration.[2] In 1834 Mitscherlich successfully nitrated benzene with fuming nitric acid. In 1847 a mixture of nitric acid and sulfuric acid (known as mixed acids) was used by Mansfield for the nitration of aromatic compounds on an industrial scale (Scheme 2.1). Sulfuric acid acts as a catalyst to assist the production of nitrating species (nitronium ion; $NO_2^+$) and also to remove the water produced during the course of the reaction.[6]

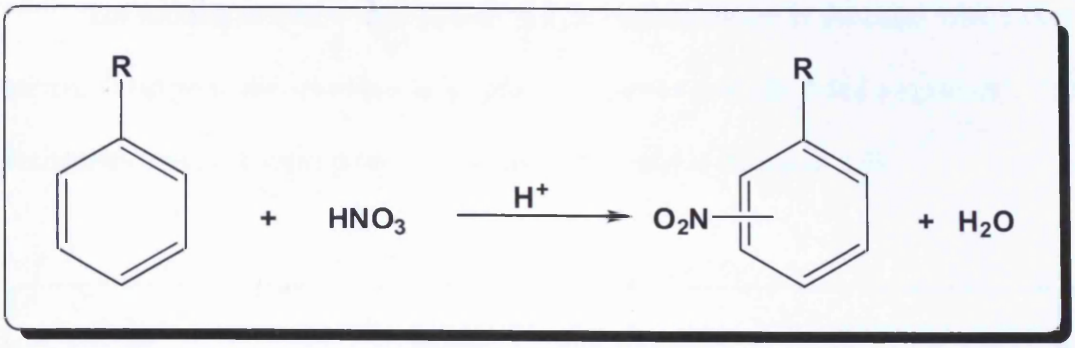


**Scheme 2.1: Nitration of benzene with a mixture of $HNO_3$ and $H_2SO_4$ (mixed acids)**

Recently, nitration of aromatic compounds became one of the most widely studied chemical reactions for various reasons. **Firstly**, nitration reactions of aromatic compounds are easily accomplished to give the corresponding nitro derivatives and generally in high yields. **Secondly**, they are easy to carry out under various reaction conditions. **Thirdly**, the reactions can be stopped efficiently and cleanly at the mononitration stage as a result of the powerful deactivating nature of the nitro group. **Fourthly**, the reactions produce various nitro isomers that have high melting and boiling points and therefore pure isomers can be obtained relatively easily, *via* fractional distillation for example. **Fifthly**, the nitration products can be used as precursors for the production of various useful derivatives, some of which have industrial importance.[7,8]

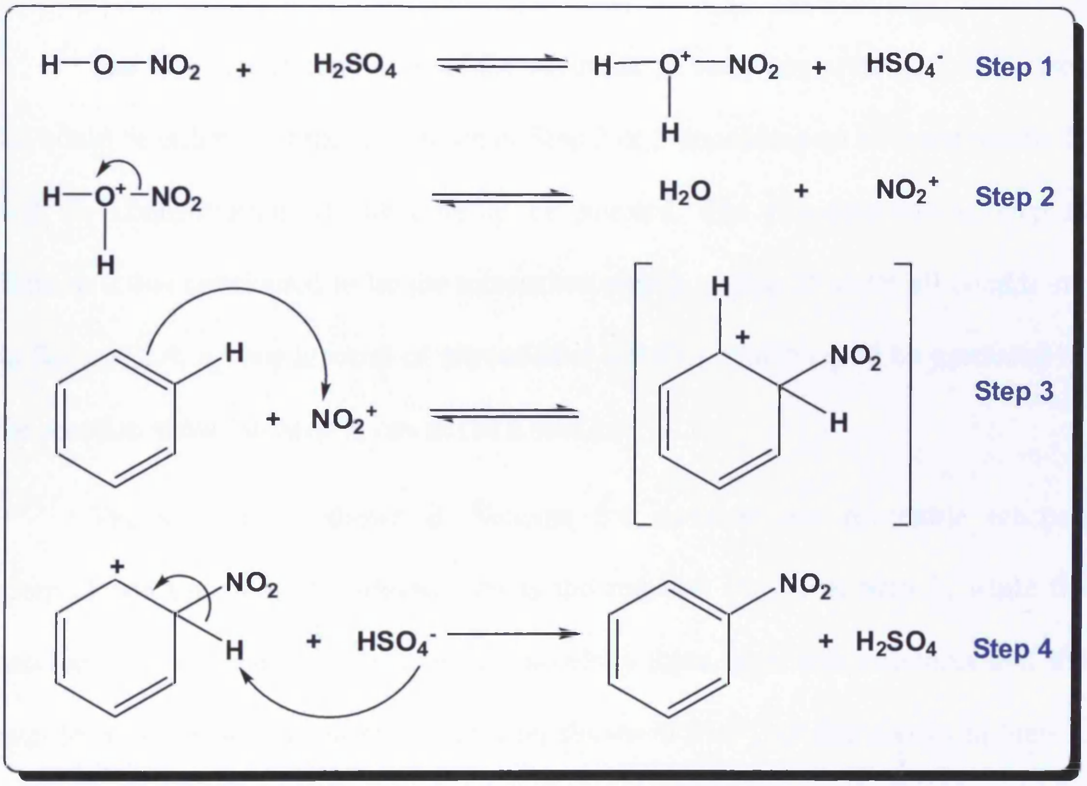
## 2.2. Mechanism of nitration reactions of aromatic compounds

The mechanism of nitration of aromatic compounds, using nitric acid in acid medium, was studied by Ingold *et al.*[9-11] (Scheme 2.2). The nitronium ion ($NO_2^+$) is formed easily from nitric acid under acidic conditions.[12,13] The $NO_2^+$ species is believed to be the active species involved in such nitration reactions.



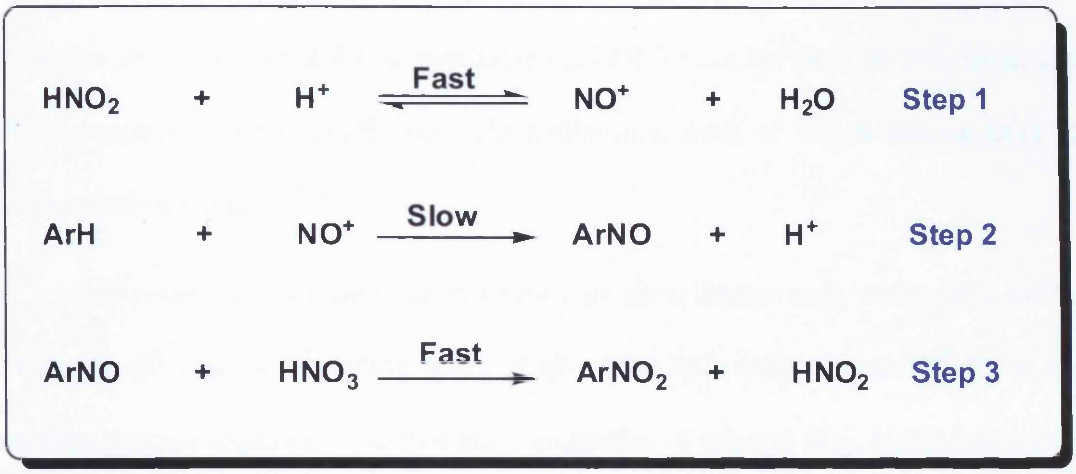
**Scheme 2.2: Nitration of aromatic compounds using nitric acid in acidic medium**

The mechanism of nitration was found to be dependent on the substrate's reactivity and the reaction conditions.[14-16] Two main mechanisms are known, shown in Schemes 2.3 and 2.4. The first mechanism takes place through the nitronium ion and is very common for many aromatic compounds (Scheme 2.3).



**Scheme 2.3: Nitration of aromatic compounds via nitronium ion ($NO^{2+}$)**

The second mechanism (Scheme 2.4) is only common in the cases where very reactive substrates are involved (*e.g.* phenol, amines and alkylated aromatics). The mechanism involves some form of nitrous acid catalysis (Scheme 2.4).



$$HNO_2 + H^+ \underset{}{\overset{\text{Fast}}{\rightleftharpoons}} NO^+ + H_2O \quad \text{Step 1}$$

$$ArH + NO^+ \xrightarrow{\text{Slow}} ArNO + H^+ \quad \text{Step 2}$$

$$ArNO + HNO_3 \xrightarrow{\text{Fast}} ArNO_2 + HNO_2 \quad \text{Step 3}$$

**Scheme 2.4: Nitration of activated aromatic compounds *via* nitrosonium ion ($NO^+$)**

The rate-determining step of the sequence of reactions presented in Scheme 2.3 could be either the reaction shown in Step 2 or 3 depending on both the reactivity and the concentration of substrate to be nitrated. The rate-determining step in Scheme 2.4 is considered to be the nitrosation step (*i.e.* Step 2) under all conditions. In Scheme 2.4, a trace amount of nitrous acid ($HNO_2$), which could be produced by the reaction shown in Step 3, can act as a catalyst.

The mechanism shown in Scheme 2.4 involves one reversible reaction (Step 1) and the rate-determining step is the reaction shown in Step 2, while the mechanism represented in Scheme 2.3 involves three reversible reactions and the rate-determining step is either the reaction shown in Step 2 or that shown in Step 3. Moreover, Scheme 2.3 involves nitric acid as the only source of nitro groups whereas in Scheme 2.4 both nitric acid and nitrous acid could be the source for nitro groups.

## 2.3. Traditional nitration of aromatic compounds

Nitro aromatic compounds are very important as intermediate products. They can be used in the production of many industrial materials with various applications, such as pharmaceuticals, dyes, polymers, perfumes, explosives, pesticides and fertilizers. For example, 2,4-dinitrotoluene (2,4-DNT) can be used for the production of toluene diisocyanate (TDI) and toluenediamine, both of which can be used to produce polyurethanes.[17-19]

However, the commercial syntheses of nitro compounds commonly suffer serious disadvantages, including some or all of the following defects.[20-30] **First**, the nitration process requires the use of large quantities of mineral (*e.g.* $H_2SO_4$) or Lewis acids, which are corrosive and often difficult to recycle, as activators. **Second**, the reaction work-up involves aqueous washing stages that might lead to the generation of large quantities of corrosive and toxic waste by-products which are environmentally unfriendly, difficult to recycle and expensive to treat. **Third**, the desired products are often obtained in low yields. **Fourth**, the nitration reaction often produces mixtures of regioisomers with low selectivity.

Sulfuric acid acts as the catalyst in such nitration reaction, while, nitric acid is the source of the nitro group (*i.e.* the source for the nitrating species; $NO_2^+$). Sulfuric acid encourages formation of the nitronium ion by providing an acidic medium (Equation 2.1). The absence of sulfuric acid leads to a decrease in reaction rate and the reaction becomes slower and therefore low yields of nitro products may be obtained. Also, sulfuric acid deactivates the water produced probably *via* protonation. This will further encourage formation of the nitronium ion (Equations 2.2 and 2.3). Therefore, in principle any other catalyst that could fulfil these roles could be used instead of sulfuric acid (the catalyst in this case) in such nitration reactions.

$$H^+ + HNO_3 \rightleftharpoons H_2O + NO_2^+$$

**Equation 2.1: Formation of nitronium ion ($NO_2^+$)**

$$H_2SO_4 + H_2O \rightleftharpoons H_3O^+ + HSO_4^-$$

**Equation 2.2: Absorption of water by $H_2SO_4$**

$$HSO_4^- + H_2O \rightleftharpoons H_3O^+ + SO_4^{2-}$$

**Equation 2.3: Absorption (protonation) of water by $HSO_4^-$**

Many efforts are therefore being made to develop environmentally friendly and cleaner processes, especially for the regioselective production of *para*-nitro products. The ability to control the selectivity of the nitration process is fundamental to achieving success in the area. Therefore, it is necessary to gain control through the use of external reagents. It is well recognised that acidic solid catalysts such as zeolites can play an important role in the development of cleaner organic synthesis through their abilities to act as recyclable heterogeneous catalysts, support reagents, entrain by-products, avoid aqueous work-ups and enhance product selectivities.[31-42] The presence of zeolite catalysts in liquid phase reactions can provide sites capable of enhancing the reaction rate. Also, by having these sites located within the rigid pores of the inorganic matrix they also impose additional constraints on the reacting partners, favouring the production of one regioisomer, usually the most linear one (*e.g.* the *para*-isomer), over other possible ones (*e.g.* *ortho*-).

Zeolites can provide acidic sites that are as acidic as concentrated sulfuric acid in some cases (high Si/Al ratios). However, large amounts of zeolite would be required for the role of a zeolite to be equivalent to that of sulfuric acid as a catalyst.[31,32] For example, 2 Kg of zeolite is required for the nitration of 92 g of toluene to produce mono-nitrotoluenes quantitatively in absence of sulfuric acid.[32] Not only would such a high quantity of solid be inconvenient and highly expensive but also the substrate and reagent would be completely absorbed into the pores to leave a dry material. Therefore, for zeolites to be useful in nitration reactions they cannot take on the role of water-remover and their role as proton donor must be catalytic. Also, zeolite would need to catalyse the reaction, so it should be capable of protonating to produce nitronium ion, and the by-product should be less prone to quenching the nitration reaction than the water produced in the case of nitric acid.

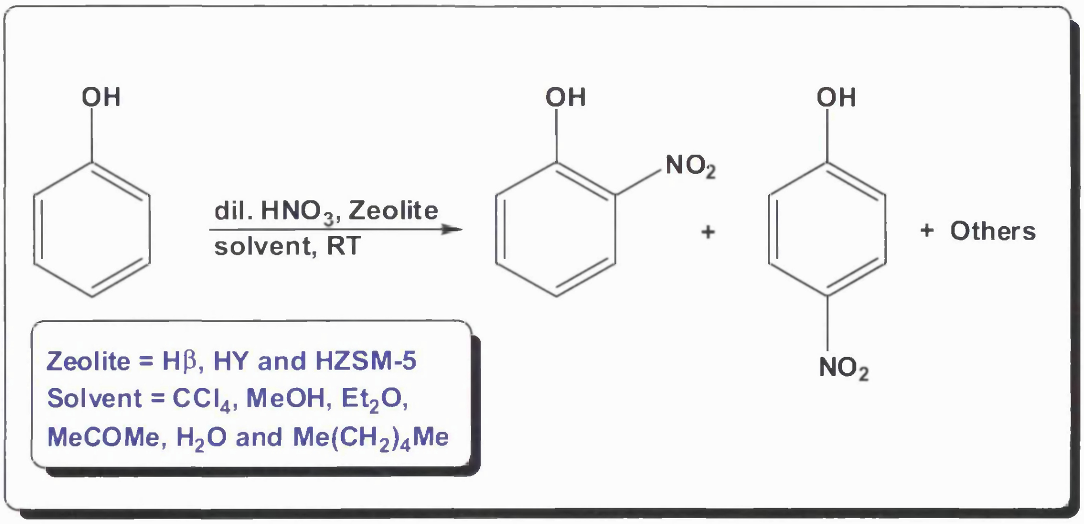
Smith's group have investigated the nitration reactions of simple aromatic compounds over catalytic amounts of various zeolite catalysts under mild conditions and have achieved high yields and high *para*-selectivities in many cases.[31,32]

## 2.4. Selective nitration of activated aromatic compounds

The nitrations of activated aromatic compounds (*e.g.* phenol) are important organic reactions as the nitro products are extensively used as intermediates for the manufacture of drugs and pharmaceuticals. Phenol can be nitrated traditionally using a mixture of nitric and sulfuric acids to produce nitrophenols. It was found that the *ortho/para* ratio decreases from around 2.1 to around 0.9 as the concentration of sulfuric acid increases.[43] Such a nitration reaction suffers several serious disadvantages. **First**, the *para/ortho* ratio obtained is always low and the *ortho*-isomer is often predominant. **Second**, it is difficult to stop the reaction at the mono-nitration stage and the formation of dinitro products is facile. **Third**, formation of oxidised products is common. **Fourth**, there is a possibility of formation of unspecified resinous tarry materials resulting from over-oxidation of the starting material. Therefore, major efforts have been made to develop a greener processes for the nitration of phenol.

Several nitration systems that involve use of solid catalysts have been developed for the nitration of phenol to produce the corresponding nitrophenols. Nitric acid and acetyl nitrate are the most popular nitrating reagents used in nitration of phenol. Various solids have been used as catalysts in such nitration reactions. The most common solids used include silica gel,[44] metal salt modified clays,[45] mixed metal oxides[46] and a variety of strongly acidic solids such as heteropolyacids,[47,48] sulfated MCM-41,[49] silica impregnated with sulfuric acid[50] or a hydrogen sulfate salt,[51] sulfated titania[52,53] and sulfated mixed metal oxides.[54] It was found that with highly acidic solids *ortho*-nitrophenol generally predominates to a much greater extent than with a mixture of sulfuric and nitric acids, regardless of the structure of the solid. A report by Milczak *et al.* claims high *para* selectivity in nitration of phenol over metal oxides[47] but such observations are difficult to interpret. Also, a *para/ortho* ratio of 49/31 was obtained from nitration of phenol using nitric acid (60%) and $Bi(NO_3)_3$ over KSF.[55] However, a low *para/ortho* ratio was obtained when a metal-modified KSF was used as a catalyst with $HNO_3$ as the reagent.[56,57]

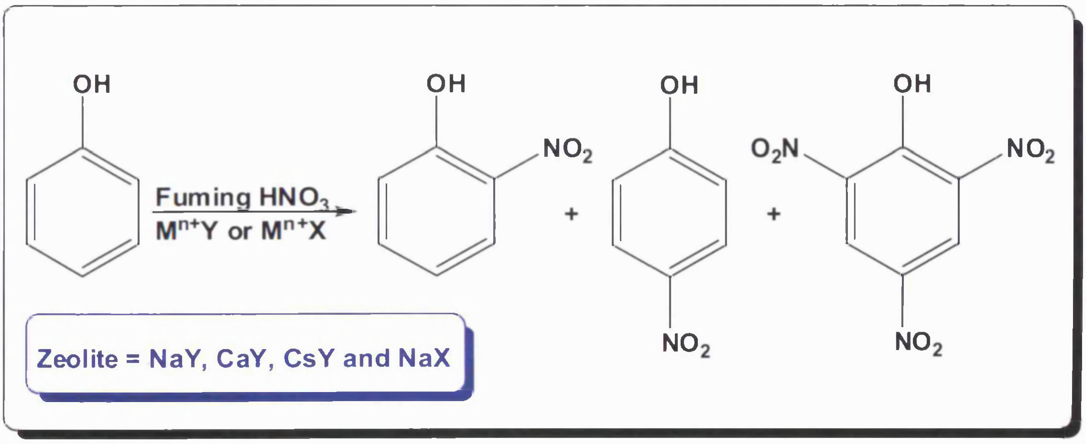
Zeolite β[58] and a series of non-acidic or weakly acidic ion-exchanged zeolites[59] have been used as catalysts in the nitration reactions of phenol. Again, with the highly acidic zeolites *ortho*-nitrophenol was the major product. Even zeolite Hβ gives a very high proportion of the *ortho*-isomer, despite the fact that zeolites are normally associated with increased *para*-selectivity in electrophilic substitution reactions of aromatic compounds. For example, phenol was nitrated using dilute nitric acid at room temperature in a solvent over various types of zeolites to produce a mixture of nitrophenols in which the *ortho*-isomer was predominant (Scheme 2.5).[58]



**Scheme 2.5: Nitration of phenol using dil. $HNO_3$ in different solvents over various types of zeolite catalysts at room temperature**

Zeolite Hβ was found to be the most active catalyst among the zeolites tried. Also, the *ortho/para* ratios were found to be dependent on the solvent used. The *ortho/para* proportion was highest (87/10) when $CCl_4$ was employed as the solvent and lowest (49/48) when diethyl ether was the solvent.[58] A significant of quantity of benzoquinone (3-60% yield) was also obtained as a side-product due to oxidation of phenol. This by-product was the major product (60%) when methanol was the solvent and minor (3%) when diethyl ether or $CCl_4$ was the solvent.

Phenol was also nitrated using fuming nitric acid over various cation-exchanged faujasite zeolites (Scheme 2.6) in hexane as a solvent.[59] At lower loading level of phenol (3.6 molecules per supercage), nitration of phenol over CsY as a catalyst led to predominant formation of 4-nitrophenol (*para/ortho* ratio = *ca.* 4.7) in which conversion was 75%. Also, under such conditions 2,4,6-trinitrophenol was produced in 6% yield. However, at higher loading level of phenol (39 molecules per supercage), the *ortho*-product was the major one, with an *ortho/para* ratio of 58/32. Also, 2,4,6-trinitrophenol was produced in 8% yield along with an unidentified product in *ca.* 2% yield. Similar results were produced when NaY and NaX were used as catalysts.[59]



**Scheme 2.6: Nitration of phenol using fuming $HNO_3$ over various cation-exchanged faujasite zeolites**

A remarkable *ortho*-selectivity, in which 2-nitrophenol was produced exclusively, was obtained when nitration of phenol using fuming nitric over NaY zeolite was performed in the solid state. However, the conversion was always low (12-23%). The conversion was increased when the quantity of nitric acid was increased but the *ortho*-selectivity was reduced significantly. For example, increasing the quantity of nitric acid by 30-50% provided higher yields of nitrophenols (40-59%) but the reaction became less selective towards the *ortho*-isomer (*ortho*/*para* ratio = 4.1-2.8). However, the *ortho*-isomer was still the major product under all conditions, along with significant quantities of 2,4,6-trinitrophenol (11-54%) and an unspecified product (3-12%).[59]

## 2.5. Selective nitration of moderately activated aromatic compounds

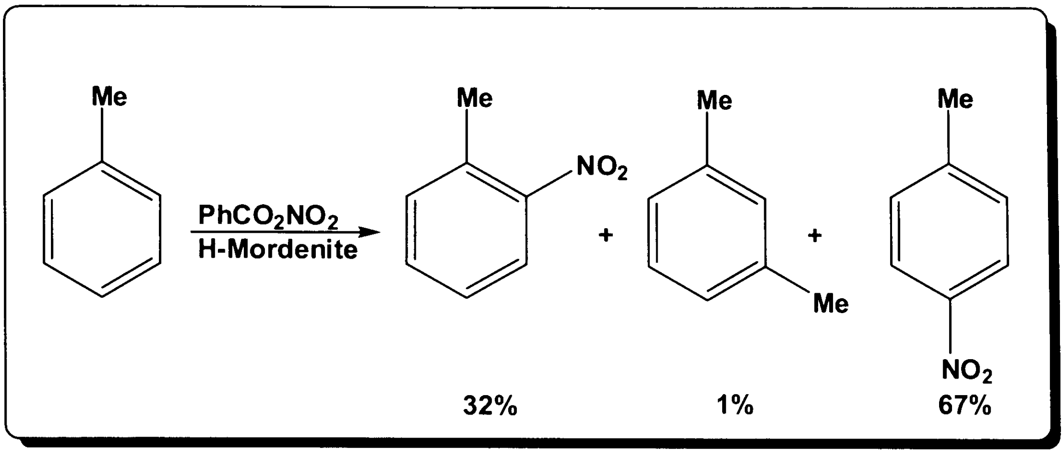
Regioselective nitration of toluene and other simple aromatics of moderate activity over zeolite catalysts has been the subject of various reports.[31,32] The selectivities in such reactions were found to depend on the nature of both the catalyst and the nitrating agent.

Smith's group have nitrated toluene with benzoyl nitrate over a zeolite catalyst.[60] Benzoyl nitrate can produce nitronium ion in acidic medium (*i.e.* over zeolite) and benzoic acid was formed as a by-product (Equation 2.4).

$$\boxed{PhCO_2NO_2 \quad + \quad H^+ \quad \rightleftharpoons \quad PhCO_2H \quad + \quad NO_2^+}$$

**Equation 2.4: Generation of $NO_2^+$ from benzoyl nitrate in acid medium**

Nitration of toluene using benzoyl nitrate took place over various types of zeolites in different solvents.[60] The use of solvent tends to increase the mobility of the reaction mixture and diffusion of the materials through the zeolite pores. The yield obtained was relatively high with high *para*-selectivity compared to the traditional method. H-Mordenite was found to be the most effective catalyst among zeolites tried. For example, nitration of toluene with benzoyl nitrate over H-mordenite gave mononitrated toluenes in quantitative yield and the *ortho/meta/para* proportion was 32/1/67 (Scheme 2.7).



**Scheme 2.7: Nitration of toluene using benzoyl nitrate over H-mordenite**

When the reaction described in Scheme 2.7 was carried out over surface-deactivated ZSM-11 in hexane as a solvent, the reaction was more *para*-selective, giving a high proportion of 4-nitrotoluene (98%), but in only low yields.[61-63] The low yield obtained makes the process unattractive for commercial scale application. Moreover, benzoyl nitrate could be relatively expensive to produce compared to other nitrating reagents.

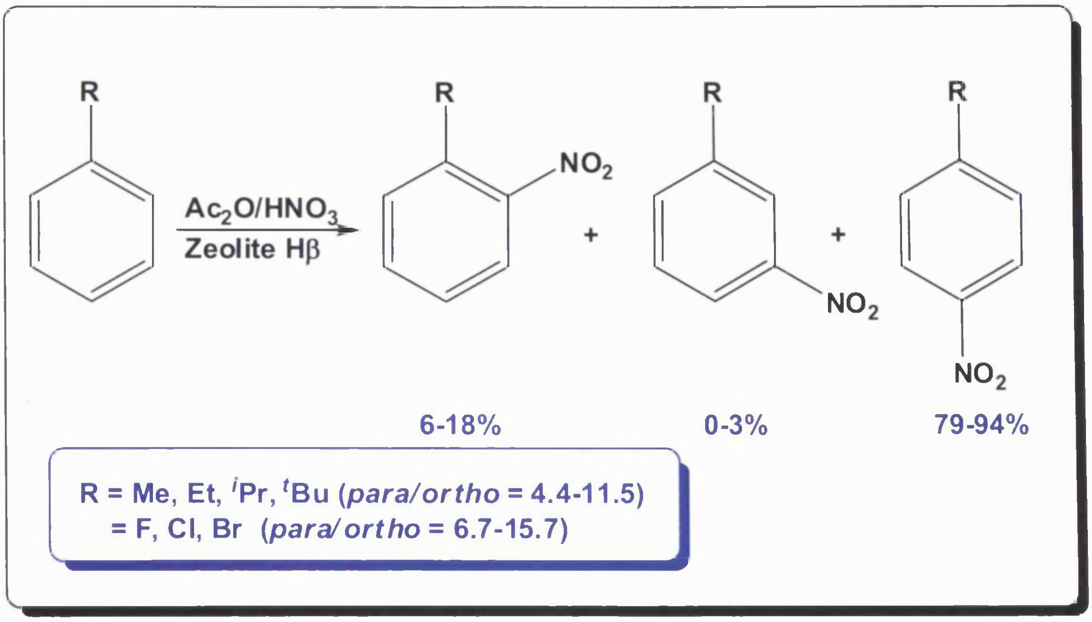
Toluene was nitrated successfully using alkyl nitrates over various types of zeolites. It was found that when HZSM-5 zeolite with a high silica content (Si/Al = 1000) was used as the catalyst and the reaction was highly diluted, mononitrated toluenes were produced in 54% yield with a *para/ortho* ratio in the region of 19. Unfortunately, such a nitration reaction of toluene seems not attractive for large-scale application and suffers several disadvantages. **First**, the reaction requires a very large quantity of the zeolite.[64] **Second**, HZSM-5 with high Si/Al ratio (*e.g.* Si/Al = 1000) is not widely available. **Third**, use of more widely available HZSM-5 zeolite with Si/Al = 30 was found to be less selective.[64]

Smith's research group has investigated regioselective nitration reactions of toluene using acyl nitrates over zeolites under various conditions.[65] The goal from such a detailed study was to find a nitration process that would give high yields of nitro products with high *para*-selectivities. Also, use of inexpensive reagents and avoiding the need for large quantities of solvents were desirable. Acetyl nitrate is inexpensive to produce and seemed to offer a useful possibility. It can be generated *in situ* by mixing acetic anhydride and nitric acid (Equation 2.5).

$$Ac_2O + HNO_3 \rightleftharpoons AcONO_2 + AcOH$$

**Equation 2.5: Generation of acetyl nitrate ($AcONO_2$) from reaction of nitric acid and acetic anhydride**

Indeed, nitrations of simple mono-substituted aromatic compounds such as alkylbenzenes and halobenzenes using a nitric acid/acetic anhydride/zeolite Hβ system were successful to produce the corresponding nitro compounds in 92-99% yields with high *para*-selectivities (Scheme 2.8).[65] The reaction conditions were mild (room temperature), the reaction time was short (10-30 min) and no solvent was employed in the process.



**Scheme 2.8: Nitration of alkylbenzenes and halobenzenes using a $HNO_3/Ac_2O/H\beta$ system at room temperature**

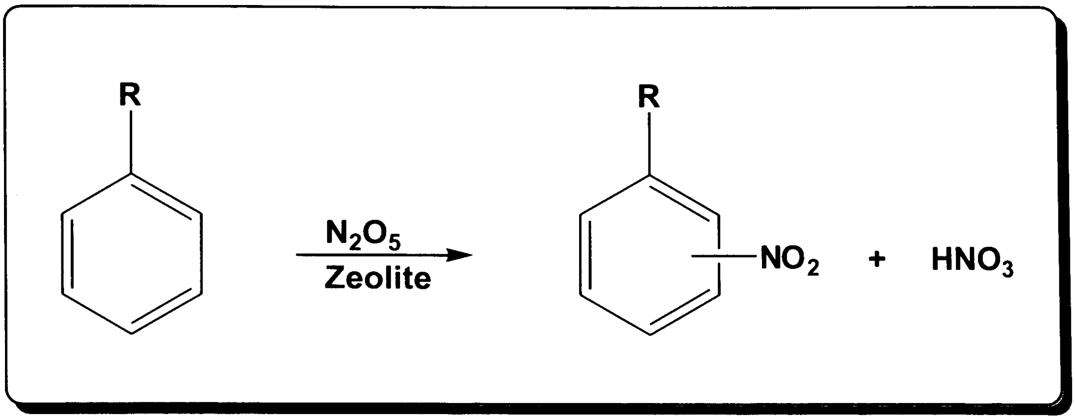
Zeolite Hβ was found to be the most effective catalyst among the ones tried and provided the highest *para*-selectivity. For example, nitration of toluene gave a quantitative yield of mononitrotoluenes, of which 79% was 4-nitrotoluene; fluorobenzene gave a quantitative yield of mononitro compounds, of which 94% was 4-fluoronitrobenzene; and *tert*-butylbenzene gave a 92% yield of mononitro products, of which 90% was the 4-nitro isomer and 8% was the 2-nitro isomer.[65] These results simply represent the highest *para*-selectivities yet achieved in nitration reactions for such mono-substituted benzenes in which nitro products were produced quatitatively.[65]

It was found that the order of addition of the materials had a significant effect on the *para*-selectivity of the reaction. The best order involved premixing nitric acid with the zeolite, followed by the addition of acetic anhydride and then the aromatic compound was added lastly. This is consistent with the formation of acetyl nitrate predominantly within the pores of the zeolite, where reaction with the substrate then takes place.

This process has many advantages. **First**, aromatic compounds can be nitrated not only quantitatively but also selectively towards the *para*-isomers. Also, no dinitro compounds were formed in any significant amount. **Second**, the reagents used (acetic anhydride and nitric acid) are accessible reagents and inexpensive. Also, no solvent was used, which makes the process attractive for large scale applications. **Third**, the conditions employed were mild; nitration took place at room temperature and the reaction took place within half an hour. **Fourth**, the process was general and could be applied to a range of substrates of moderate activity, which are the ones that often give low *para*-selectivity in traditional nitrations. **Fifth**, the zeolite could be recycled many times and still produce results similar to those obtained with a fresh sample. Moreover, the only by-product was acetic acid, which could be separated from the nitration products by distillation.

Nitration of substituted aromatics was also been attempted using nitric acid over a catalytic amount of zeolite while the water produced as a by-product was removed by azeotropic distillation as the reaction proceeded.[66-68] However, although the process successfully involved use of a modest quantity of zeolite, higher temperatures and longer reaction times were needed. Also, the yields and selectivities obtained were lower than those obtained with a nitric acid/acetic anhydride/zeolite system.

Mono-substituted aromatics can also be readily nitrated more *para*-selectively with dinitrogen pentoxide over a zeolite catalyst (Scheme 2.9).[69] However; the process involves formation of one mole of $HNO_3$ per mole of product, which could deactivate the zeolite. Moreover, the reagent cannot be easily produced and needs special equipment.

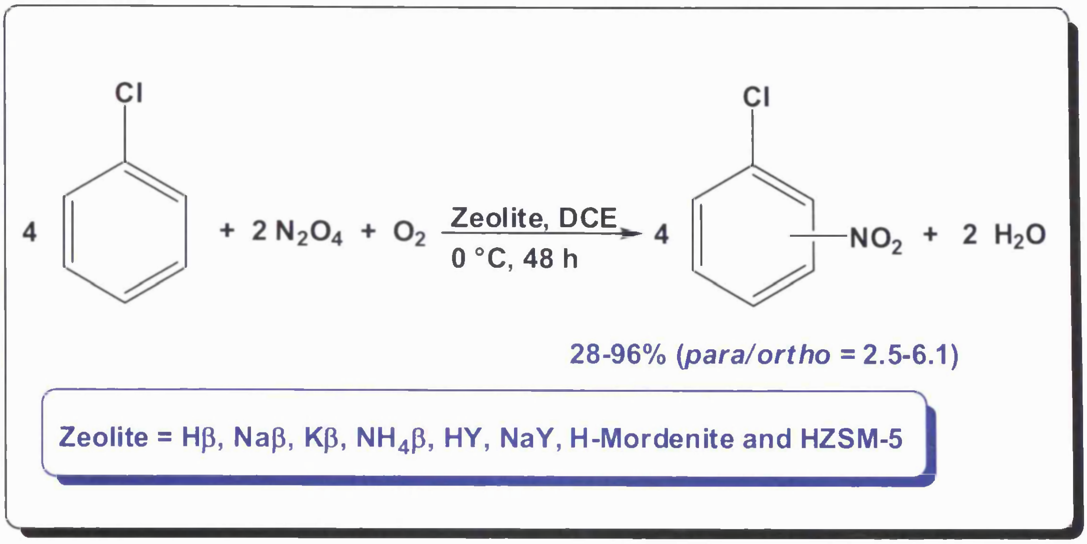


**Scheme 2.9: Nitration of simple mono-substituted aromatics using $N_2O_5$ over zeolite**

Vapour phase nitration with nitrogen dioxide at high temperatures over zeolites was also reported, but generally no high yield or *para*-selectivity was obtained.[70-73] However, nitration of chlorobenzene using nitrogen dioxide in the presence of oxygen over zeolite Hβ at a high temperature (150 °C) gave chloronitrobenzenes in low yield (38%) and the *ortho*/*meta*/*para* product distribution was 3/1/96.[74]

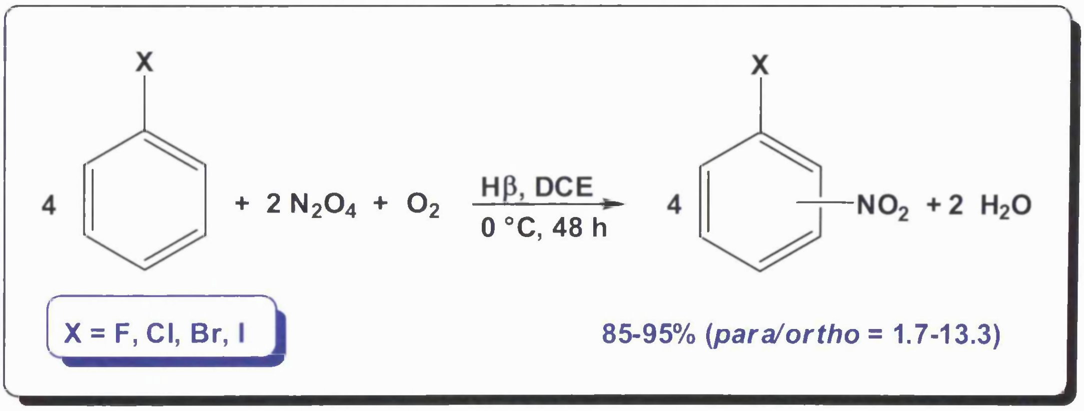
Smith's group reported the regioselective nitration of chlorobenzene using dinitrogen tetroxide over zeolite catalysts.[75,76] Nitration of chlorobenzene with excess liquid $N_2O_4$ in the presence of oxygen over various types of zeolites in dichloroethane at 0 °C for 48 h was successful in producing the corresponding nitro products in high yields with a high *para*-selectivity (Scheme 2.10).[75,76]

Zeolites Hβ and Naβ produced chloronitrobenzenes in 90 and 96% yields, respectively, in which the proportion of the *para*-isomer was 85% in both cases. Zeolite Y also gave a high yield of chloronitrobenzenes (91%) with a lower *para*-selectivity (81%). Other zeolites such as H-mordenite and HZSM-5 gave low yields (28-42%) and low *para*-selectivities (*para/ortho* ratio = *ca.* 2.7).[75,76]



**Scheme 2.10: Nitration of chlorobenzene using $N_2O_4$ in dichloroethane over various zeolite catalysts at 0 °C for 48 h**

The $N_2O_4/O_2$/Hβ system was applied successfully for the nitration of a range of halobenzenes to produced the corresponding nitro compounds in excellent yields (*ca.* 95%) with moderate *para*-selectivities (Scheme 2.11).[75,76]

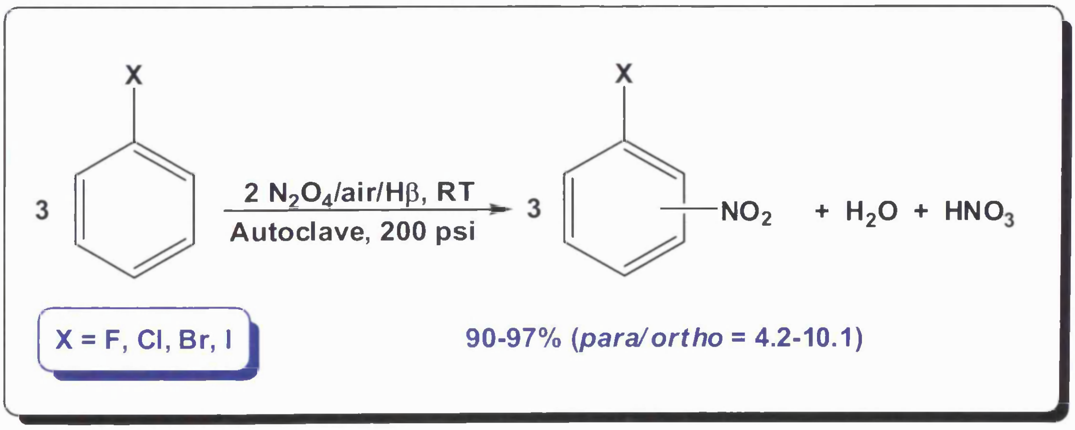


**Scheme 2.11: Nitration of halobenzenes over $N_2O_4/O_2$/zeolite Hβ system in dichloroethane at 0 °C for 48 h**

The process represented in Scheme 2.11 provided a clean synthetic route for the production of halogenonitrobenzenes. However, the process was not highly selective towards the *para*-products and involved use of a large excess of dinitrogen tetroxide. Moreover, the process required use of a halogenated solvent, cooling and a reaction time of 48 h.

Better *para*-selectivities but at low conversion were achieved by the Suzuki group using the substrate as its own solvent in the liquid phase.[77] The group of Smith has overcome some of the disadvantages associated with the process represented in Scheme 2.11 by carrying out the nitration reaction in an autoclave without the use of a solvent.

Nitration of halobenzenes with a stoichiometric quantity of dinitrogen tetroxide in the presence of air in an autoclave (200 psi) at room temperature for 14-16 hours successfully produced the corresponding nitro product in excellent yields (90-97%) with reasonable *para*-selectivities (Scheme 2.12).[76,78]



**Scheme 2.12: Nitration of halobenzenes over $N_2O_4$/air/zeolite Hβ system in autoclave at room temperature for 14-16 h**

Unfortunately, the stoichiometry was not as indicated in Schemes 2.10 and 2.11, but instead resulted in the production of one mole of nitric acid along with one mole of water for each 3 moles of product (Scheme 2.12). The production of nitric acid as by-product can deactivate the zeolite.

Nitration of toluene using a $N_2O_4/O_2$/zeolite system in the gas-phase was also reported by Prins.[79] The molar ratios of oxygen to toluene were varied for each experiment, while the toluene to $N_2O_4$ ratios were varied from 1:1 to 1:10.[79] Under the conditions tried no dinitrotoluenes were formed. It was found that the yields of nitrotoluenes and the *para*-selectivity were enhanced as the concentration of the nitrating reagent increased. However, as a result of the use of an excess of nitrating reagent oxidation products (*e.g.* benzaldehyde) were produced. Also, the concentration of oxygen affected the yield and the *para*-selectivity. Low concentration of oxygen resulted in low yields of nitrotoluenes with an increases in the *para*-selectivity, while high concentrations of oxygen resulted in the formation of oxidation products in significant quantities. However, the selectivity towards 4-nitrotoluene in these reactions was not exceptional.

## 2.6. Selective nitration of deactivated substrates

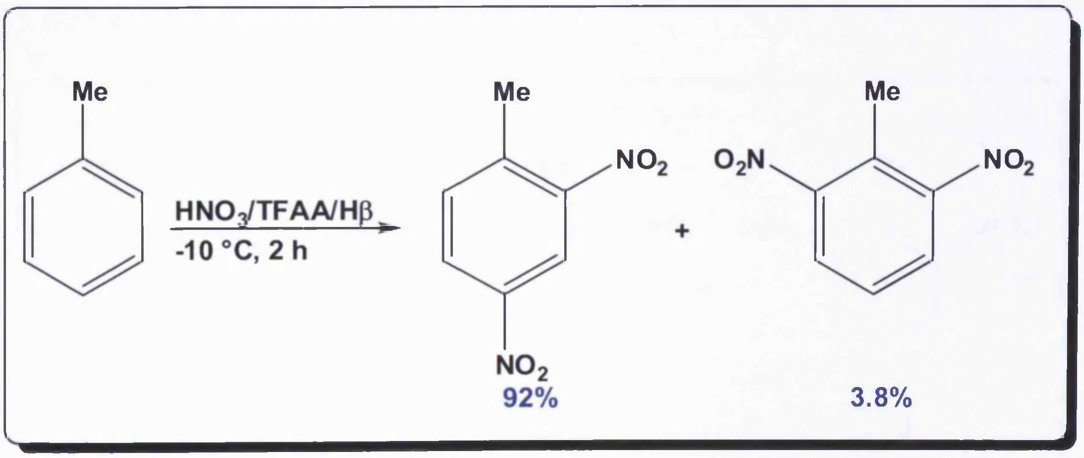
The traditional method for nitration of deactivated aromatic compounds involves the use of aggressive nitric acid-oleum mixtures. For example, nitration of benzonitrile gave nitrobenzonitriles in which the *ortho*/*meta*/*para* ratio was 17/81/2.[4]

Several catalytic systems were developed for the nitration of deactivated aromatics. These include $N_2O_5$ in the presence of $Fe(acac)_3$,[80] urea nitrate and nitrourea,[81] vanadium(V) oxytrinitrate,[82] and nitric acid in the presence of

MCM-41-supported metal bis[(perfluoroalkyl)sulfonyl]imidese.[83] Unfortunately, such reagents still gave mainly the *meta*-isomers as the major products along with significant quantities of the *ortho*-isomers. Also, under such conditions the *para*-selectivity was very low.

Traditional dinitration of toluene takes place with mixed acids to produce dinitrotoluenes in which 2,4-/2,6-dinitritoluene ratio is only 4/1. There have been several attempts to improve the single-step dinitration process of toluene by the use of solid catalysts.[67-69] The nitration system having nitric acid, acid anhydride and solid catalyst has been used successfully for the regioselective dinitration of toluene in a single step. For example, the 2,4-:2,6-dinitritoluene ratio can be improved to 9:1 (in 85% yield) when nitration is carried out over claycop, using nitric acid and acetic anhydride.[45] However, the process requires a large excess of nitric acid and the use of halogenated solvent (*e.g.* carbon tetrachloride). The 2,4-/2,6- ratio was improved to 14 when the reaction was carried out with nitric acid over a zeolite β catalyst.[84]

The group of Smith have investigated the dinitration of toluene using $HNO_3$ and trifluoroacetic anhydride (TFAA) over zeolite in a single step (Scheme 2.13).[85]

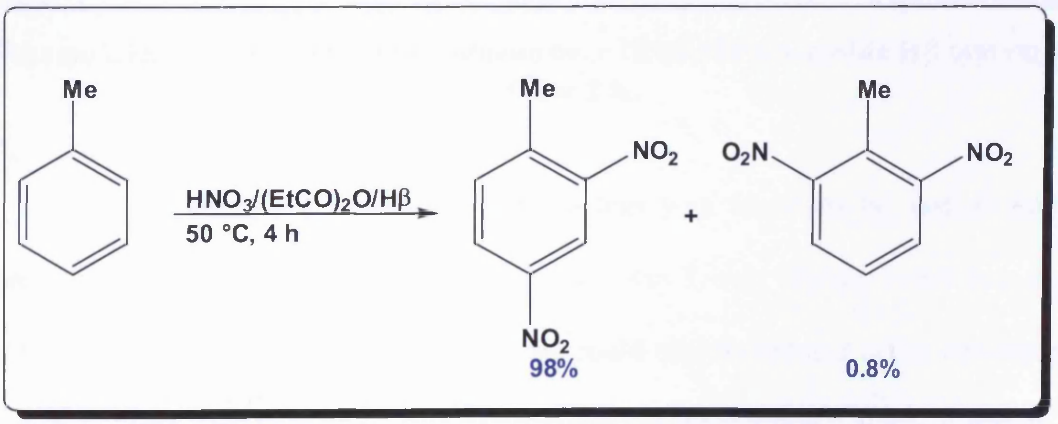


**Scheme 2.13: Double nitration of toluene over a $HNO_3$/TFAA/zeolite Hβ system at -10 °C for 2 h**

Zeolite Hβ was found to be the most effective and selective among the zeolites tried towards the production of 2,4-dinitrotoluene (Scheme 2.13). For example, an almost quantitative yield (98%) of dinitrotoluenes was obtained in which the yield of 2,4-dinitrotoluene was 92% and the 2,4-:2,6-dinitotoluene ratio was 24 when the nitration reaction of toluene was carried out over $HNO_3$/TFAA/Hβ at -10 °C for 2 h (Scheme 2.13).[85]

Even greater selectivity (70:1; in 96% yield) was obtained when the reaction was conducted in two stages, with trifluoroacetic anhydride added only in the second stage.[85] However, it is recognised that trifluoroacetic anhydride's volatility, toxicity and cost may render it unattractive for commercial processes.

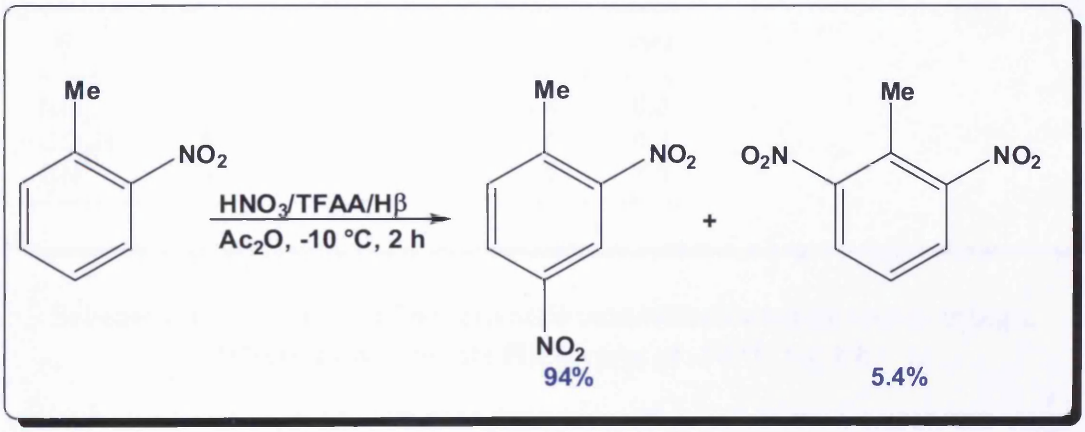
Smith has improved the process represented in Scheme 2.13 and overcome the problems associated with such a process by the use of a less toxic, less volatile and cheaper acid anhydride.[86] Indeed, double nitration of toluene using a nitration system comprising nitric acid, propanoic anhydride and zeolite Hβ gave 2,4-dinitrotoluene in 98% yield with a 2,4-:2,6-dinitotouene ratio of over 120.[86] The reaction conditions were mild (reaction temperature 50 °C) and the reaction time was 4 h (Scheme 2.14).



**Scheme 2.14: Double nitration of toluene over $HNO_3/(EtCO)_2O$/zeolite Hβ system at 50 °C for 4 h**

Pure 2,4-dinitrotoluene (2,4-DNT) was isolated from the reaction mixture in 94% yield by simply filtering the zeolite, concentrating the mother liquor, and recrystallization from diethyl ether.

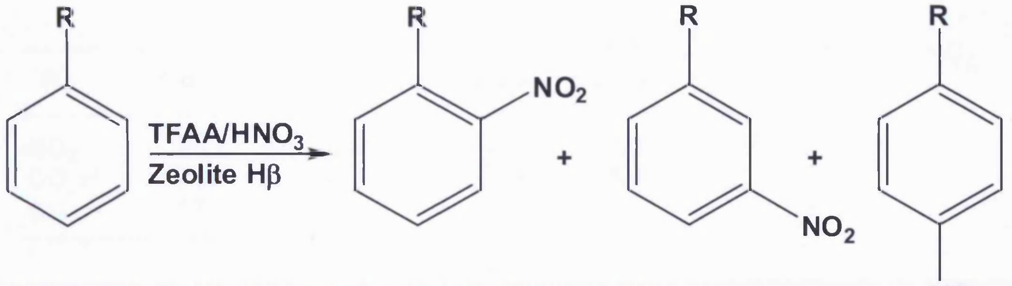
Nitration of 2-nitrotoluene using a mixture of $HNO_3$ and TFAA at -10 °C for 2 h without zeolite has also been reported by Smith.[85] Under such conditions dinitrotoluenes were produced in only 16% yield and the 2,4-:2,6-dinitrotoluene ratio was 2. Both the yield and *para*-selectivity were significantly enhanced when zeolite Hβ was employed as a catalyst.[85] For example nitration of 2-nitrotoluene using the $HNO_3$/TFAA/Hβ system in the presence of acetic anhydride as a diluent gave a quantitative yield of dinitrotoluenes in which 2,4-:2,6-dinitrotoluene ratio was 17 (Scheme 2.15).[85]



**Scheme 2.15: Nitration of 2-nitrotoluene over $HNO_3$/TFAA/zeolite Hβ system at -10 °C for 2 h**

In the absence of a diluent the reaction was found to be fast at room temperature and the 2,4-:2,6-dinitrotoluene ratio was 3, only slightly better than that in the absence of zeolite (2). 4-Nitrotoluene could also be nitrated under conditions similar to those used in the case of 2-nitrotoluene but the reaction was much slower.

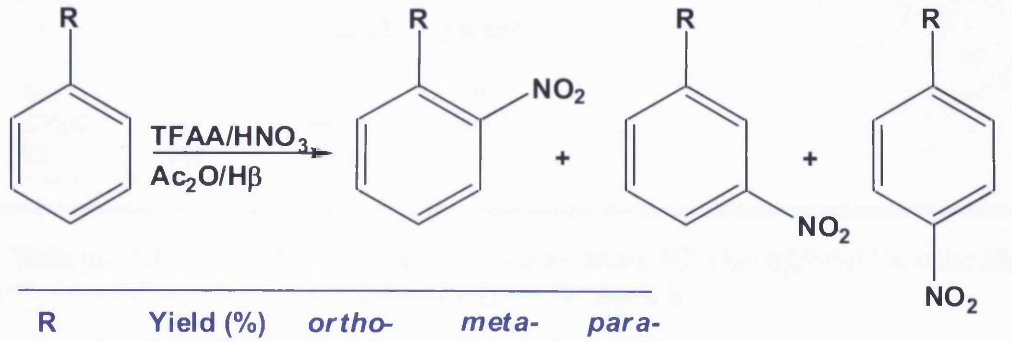
Nitration of a series of deactivated monosubstituted benzenes, that contain *meta*-directing deactivating groups, using a $HNO_3$/TFAA/Hβ system (Scheme 2.16) at -10 °C for 2 h was also reported by Smith.[85] Reasonable yields (54-86%) of nitro products were obtained in which *meta*-nitro products were still vastly predominant in all cases.[85] The proportions of the *ortho*- and *para*-isomers were higher than the corresponding ones produced from the traditional nitration of these substrates using mixed acids.



| R | Yield (%) | *ortho-* | *meta-* | *para-* |
|---|---|---|---|---|
| $NO_2$ | 72 | 3.6 | 63.4 | 5.0 |
| $CO_2H$ | 86 | 1.7 | 83.4 | 0.9 |
| CN | 54 | 7.0 | 40.0 | 7.0 |

**Scheme 2.16: Nitration of deactivated monosubstituted benzenes using a $HNO_3$/TFAA/zeolite Hβ system at -10 °C for 2 h**

Nitration of the same series of deactivated monosubstituted benzenes using the $HNO_3$/TFAA/$Ac_2O$/Hβ system was also investigated (Scheme 2.17).[85] This system provided lower yields but was a little more selective towards the *para*-isomers. For example, nitrobenzonitriles were produced in only 17% yield, the yield of the *para*-isomer being 3.2%. The increases in the *para*-selectivity could be as a result of shape-selectivity imposed on the transition state. In the case of benzoic acid, nitrobenzoic acids were produced in 74% yield, with the yield of *para*-isomer being 7.4%. There was also a significant quantity of the *ortho*-isomer, possibly resulting from rearrangement of benzoyl nitrate formed *in situ*. However, the *meta*-isomers were still predominant in all cases.[85]

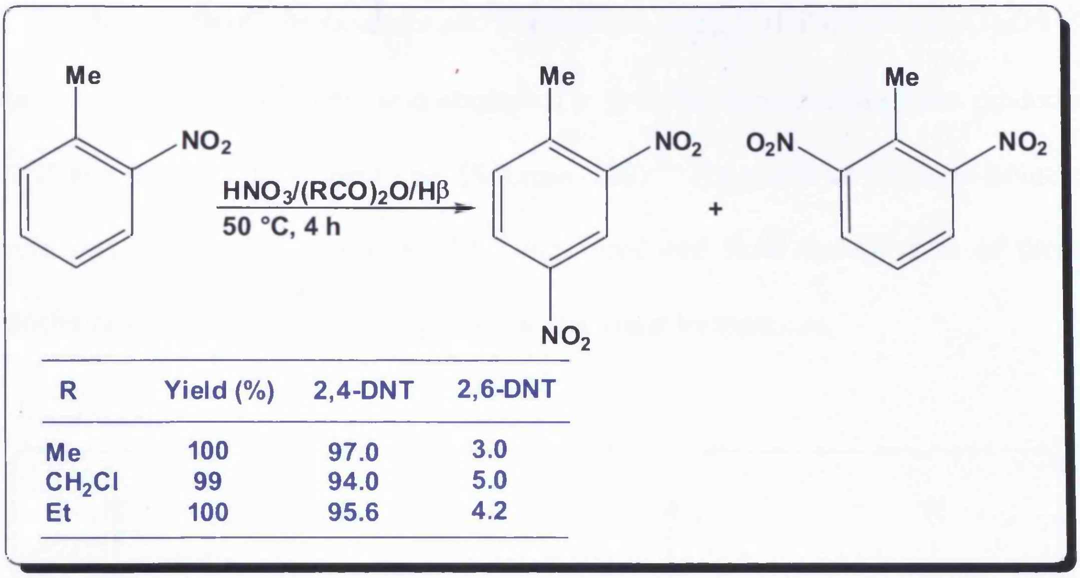


| R | Yield (%) | *ortho-* | *meta-* | *para-* |
|---|---|---|---|---|
| $NO_2$ | 25 | 0.5 | 22.7 | 1.8 |
| $CO_2H$ | 74 | 8.1 | 58.5 | 7.4 |
| CN | 17 | 1.7 | 12.1 | 3.2 |

**Scheme 2.17: Nitration of deactivated monosubstituted benzenes using a $HNO_3$/TFAA/$Ac_2O$/zeolite Hβ system at -10 °C for 2 h**

Smith has also developed a system for the *para*-selective nitration of 2- and 4-nitrotoluenes by varying the acid anhydride in the previous system.[86] For example nitration of 2-nitrotoluene over $HNO_3$/$Ac_2O$/Hβ system at 50 °C for 4 h gave a quantitative yield of dinitrotoluenes in which the yield of 2,4-dinitrotoluene was 97% (Scheme 2.18).[86]

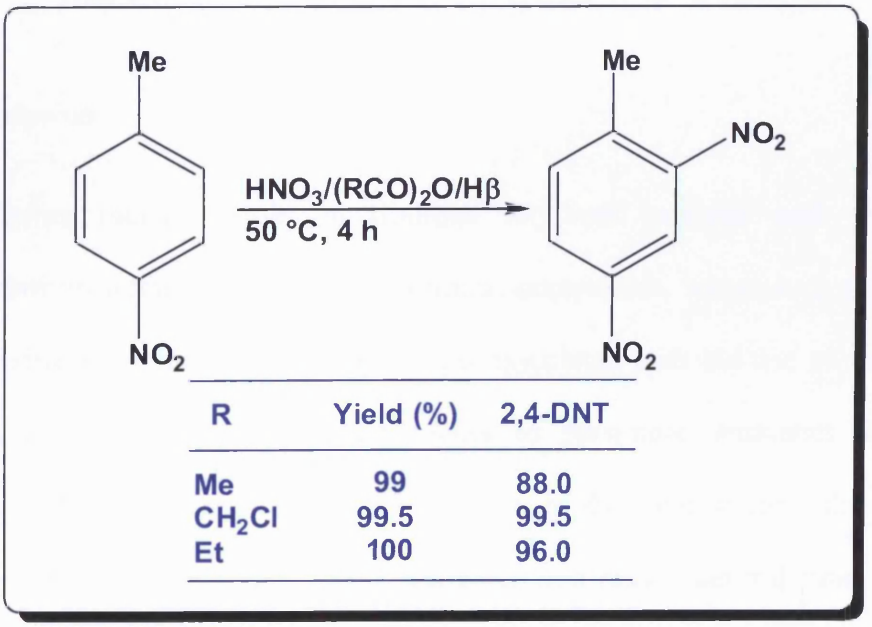
It was found that the reaction involving use of acetic anhydride provided higher *para*-selectivity than those reactions employing propanoic and chloroacetic anhydrides (Scheme 2.18).[86]



| R | Yield (%) | 2,4-DNT | 2,6-DNT |
|---|---|---|---|
| Me | 100 | 97.0 | 3.0 |
| $CH_2Cl$ | 99 | 94.0 | 5.0 |
| Et | 100 | 95.6 | 4.2 |

**Scheme 2.18: Nitration of 2-nitrotoluene using $HNO_3/(RCO)_2O$/zeolite Hβ systems at 50 °C for 4 h**

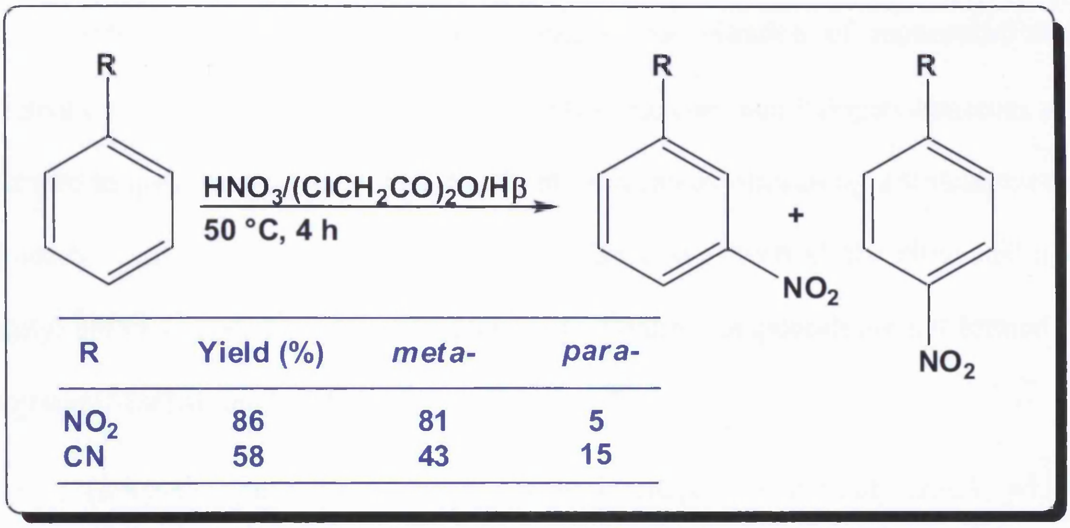
Also, nitration of 4-nitrotoluene over various $HNO_3/(RCO)_2O$/zeolite Hβ systems were attempted (Scheme 2.19).[86] The use of chloroacetic anhydride in such nitration reactions provided exclusively 2,4-dinitrotoluene in quantitative yield (Scheme 2.19).



| R | Yield (%) | 2,4-DNT |
|---|---|---|
| Me | 99 | 88.0 |
| $CH_2Cl$ | 99.5 | 99.5 |
| Et | 100 | 96.0 |

**Scheme 2.19: Nitration of 4-nitrotoluene using $HNO_3/(RCO)_2O$/zeolite Hβ systems at 50 °C for 4 h**

Nitrations of nitrobenzene and benzonitrile using a $HNO_3/(ClCH_2CO)_2O/H\beta$ system at 50 °C for 4 h were also attempted to give the corresponding nitro products in 86 and 58% yields, respectively (Scheme 2.20).[86] The yields of the *para*-isomers were higher than their corresponding ones produced from the nitration of these substrates over a $HNO_3/TFAA/H\beta$ system at a lower temperature.



| R | Yield (%) | *meta-* | *para-* |
|---|---|---|---|
| $NO_2$ | 86 | 81 | 5 |
| CN | 58 | 43 | 15 |

**Scheme 2.20: Nitration of nitrobenzene and benzonitrile using a $HNO_3/(ClCH_2CO)_2O$/zeolite Hβ system at 50 °C for 4 h**

## 2.7. Conclusion

Zeolite catalysts offer possibilities for both catalysis and selectivity enhancement in nitration reactions of aromatic compounds, where such effects are much needed to overcome various problems associated with the use of traditional methods. Zeolite catalysts offer approaches to *para*-nitro aromatics as major products, with the advantage of easy separation of the catalyst from the reaction mixture by filtration. Zeolites can be recovered and reused several times to give almost the same yields and selectivities as those obtained when fresh zeolite is used, with the avoidance of toxic waste generated by traditional Lewis acids.

Phenol has been nitrated successfully using nitric acid over various types of zeolites. With highly acidic solids *ortho*-nitrophenol generally predominates to a much greater extent than with a mixture of sulfuric and nitric acids, regardless of the structure of the solid. Even zeolite Hβ gave a very high proportion of the *ortho*-product, despite the fact that zeolites are normally associated with increased *para*-selectivities in aromatic substitution reactions.

$HNO_3/Ac_2O/H\beta$ is an effective system for nitration of monosubstituted aromatic substrates of moderate activity. Alkylbenzenes and halogenobenzenes are nitrated in quantitative yields with excellent *para* selectivities using a stoichiometric quantity of nitric acid and enough acetic anhydride to convert all the nitric acid into acetyl nitrate and all the water into acetic acid. Dinitro compounds are not formed in any significant amounts.

However, when the nitration system is adapted to include TFAA, which enhances the reactivity considerably, the nitration of deactivated aromatics occurs readily. Optimisation of the process has enabled the most selective double nitration of toluene yet attained, giving 2,4-dinitrotoluene in high yield. It is recognised that trifluoroacetic anhydride's volatility, toxicity and cost may render it unattractive for larger scale commercial processes, but recovery of TFAA should be easy. The process has been improved by the use of less toxic, less volatile and cheaper acid anhydrides such propanoic anhydride. The system has been used successfully for the production of 2,4-dinitrotoluene selectively in 98% yield from double nitration of toluene using a $HNO_3/(EtCO)_2O/H\beta$ system.

In an alternative approach to mononitration of simple aromatics, dinitrogen tetroxide has been used over Hβ. This provides selectivity for *para*-substitution that is higher than in the traditional approach, though there is still need for further improvement of the system.

When $HNO_3/(ClCH_2CO)_2O/H\beta$ was used for the nitration of 2-nitrotoluene, 2,4-dinitrotoluene was produced in a 94% yield along with a 5% yield of 2,6-dinitrotoluene. This system produced 99.5% yield of 2,4-dinitrotoluene when it was applied to nitration of 4-nitrotoluene under identical conditions.

Nitration of 2-nitrotoluene using a $HNO_3/Ac_2O/H\beta$system gave 2,4-dinitrotoluene in 97% yield along with a 3% yield of 2,6-dinitrotoluene. This result indicated that acetic anhydride was somewhat more selective than propionic and chloroacetic anhydrides in nitration of 2-nitrotoluene. On the other hand, nitration of 4-nitrotoluene under identical conditions to those used for nitration of 2-nitrotoluene produced exclusively of 2,4-dinitrotoluene in quantitative yield when chloroacetic anhydride was used. This result indicated that chloroacetic anhydride was more selective than acetic and propionic anhydrides in nitration reaction of 4-nitrotoluene.

## 2.8. References

1. P. B. delaMare and J. H. Ridd, *Aromatic Substitution, Nitration and Halogenation*, Butterworths, London, 1959.
2. K. Schofield, *Aromatic Nitration*, Cambridge University press, Cambridge, 1980.
3. C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Bell, London, 1969.

4. G. A. Olah, R. Malhotra and S. C. Narang, *Nitration Methods and Mechanisms*, VCH, New York, 1989.
5. R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990.
6. E. R. Ward, *Chem. Br.*, 1979, **15**, 297.
7. S. H. Almeer, *Synthesis and Analysis of Nitro Compounds under Zeolite Catalysis*, Ph.D., University of Wales Swansea, 2001.
8. A. J. Musson, *Solids as Catalysts for Regioselective Nitration Reactions*, Ph.D., University of Wales Swansea, 1997.
9. C. K. Ingold, D. J. Millen and H. G. Poole, *J. Chem. Soc.*, 1950, 2576.
10. R. J. Gillespie, C. K. Ingold, E. G. Hughes and E. R. A. Peeling, *J. Chem. Soc.*, 1950, 2504.
11. E. D. Hughes, C. K. Ingold and T. I. Reed, *J. Chem. Soc.*, 1950, 2400.
12. N. C. Marziano, A. Tomasin, C. Tortato and J. M. Zaldivar, *J. Chem. Soc. Perkin Trans. 2*, 1998, 1973.
13. N. C. Marziano, A. Tomasin and M. Sampoli, *J. Chem. Soc. Perkin Trans. 2*, 1995, 1995.
14. L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, 1963, **1**, 35.
15. G. A. Olah, *Acc. Chem. Res.*, 1971, **4**, 240.
16. J. H. Ridd, *Acc. Chem. Res.*, 1971, **4**, 248.
17. *Ullmanns's Encyclopedia of Industrial Chemistry*, VCH, Weinheim, 1991.
18. R. B. Seymour and G. B. Kauffman, *J. Chem. Ed.*, 1992 **69**, 909.
19. D. Randall and S. Lee, *The Polyurethanes Book*, Wiley, New York, 2002.
20. *RSC Clean Technology Monographs*, ed. J. H. Clark, Cambridge, 2000.
21. J. H. Clark, *Green Chem.* 1999, **1**, 1.

22. *Green Chemistry: Challenging Perspectives*, ed. P. Tundo and P. T. Anastas, Oxford Science: Oxford, 2000.
23. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press: Oxford, 1998.
24. M. Spagnol, L. Gilbert, and D. Allby, In *The Roots of Organic Development*, ed. J.-R. Desmurs and S. Rattoy, Elsevier: Amsterdam, 1996, pp. 29.
25. *Chemistry of Waste Minimisation*, ed. J. H. Clark, Chapman and Hall: London, 1995.
26. K. Suzuki, H. Kitagawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1993, *66*, 3729.
27. T. Mukaiyama, T. Ohno, T. Nishimura, S. Suda and S. Kobayashi, *Chem. Lett.*, 1991, 1059.
28. R. M. Roberts and A. A. Khalaf, *Friedel-Crafts Alkylation*, Marcel Dekker: New York, 1984.
29. G. A. Olah, *Friedel-Crafts Chemistry*, Wiley-Interscience: New York, 1973.
30. S. H. Sharman, *J. Am. Chem. Soc.*, 1962, **84**, 2945.
31. K. Smith and G. A. El-Hiti, *Curr. Org. Synth.*, 2004, **1**, 253.
32. K. Smith and G. A. El-Hiti, *Curr. Org. Chem.*, 2006, **10**, 1603.
33. J. H. Clark, *Acc. Chem. Res.*, 2002, **35**, 791.
34. *Principles and Practice of Heterogeneous Catalysis*, ed. J. M. Thomas, and W. J. Thomas, VCH: Weinheim, 1997.
35. *Catalysis of Organic Reactions using Supported Inorganic Reagents*, ed. J. H. Clark, VCH: New York, 1994.
36. J. H. Clark, S. R. Cullen, S. J. Barlow and T. W. Bastock, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1117.

37. L. Delaude, P. Laszlo and K. Smith, *Acc. Chem. Res.*, 1993, **26**, 607.

38. K. Smith, In *New Aspects of Organic Synthesis II*, ed. Z. Yoshida and Y. Ohshiro, Kadonsha: Tokyo and VCH Weinheim, 1992, pp. 43.

39. M. Batters, In *Solid Supports and Catalysts in Organic Synthesis*, ed. K. Smith, Ellis Horwood: Chichester, 1992, pp. 130-170.

40. K. Smith, In *Catalysis of Organic Reactions*, ed. M. G. Scaros and M. L. Prunier, Marcel Dekker: New York, 1991, pp. 91.

41. H. Heany, *The Bimolecular Aromatic Friedel-Crafts Reactions In Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press: Oxford, 1991, Vol. **2**, Chapter 3.2, pp. 733-752.

42. *Introduction to Zeolite Science and Practice*, ed. H. van Bekkum, E. M. Flanigan and J. C. Jansen, *Stud. Surf. Sci. Catal.*, 1991, vol. **58**.

43. R. G. Coombes, J. G. Golding and P. Hadjigeorgiou, *J. Chem. Soc.*, *Perkin Trans. 2*, 1979, 1451.

44. J. A. R. Rodrigues, A. P. de Oliveira Filho, P. J. S. Moran and R. Custódio, *Tetrahedron*, 1999, **55**, 6733.

45. B. Gigante, A. O. Prazeres, M. J. Marcelo-Curto, A. Cornélis and P. Laszlo, *J. Org. Chem.*, 1995, **60**, 3445 and references cited therein.

46. T. Milczak, J. Jacniacki, J. Zawadzki, M. Malesa and W. Skupiński, *Synth. Commun.*, 2001, **31**, 173.

47. M. M. Heravi, T. Benmorad, K. Bakhtiari, F. F. Bamoharram and H. H. Oskooie, *J. Mol. Catal. A: Chem.*, 2007, **264**, 318.

48. S. Mallick and K. M. Parida, *Catal. Commun*, 2007, **8**, 1487.

49. K. M. Parida and D. Rath, *J. Mol. Catal. A: Chem.*, 2006, **258**, 381.

50. J. M. Riego, Z. Sedin, J.-M. Zaldlvar, N. C. Marzianot and C. Tortato, *Tetrahedron Lett.*, 1996, **37**, 513.
51. M. A. Zolfigol, E. Ghaemi and E. Madrakian, *Molecules*, 2001, **6**, 614.
52. K. R. Sunajadevi and S. Sugunan, *Catal. Commun.*, 2005, **6**, 611.
53. K. R. Sunajadevi and S. Sugunan *Mater. Lett.*, 2006, **60**, 3813.
54. A. S. Khder and A. I. Ahmed, *Appl. Catal., A*, 2009, **354**, 1530;
55. M. Shi and S.-C. Cui, *Adv. Synth. Catal.*, 2003, **345**, 1197.
56. W.-P. Yin and M. Shi, *Tetrahedron*, 2005, **61**, 10861.
57. M. Shi, S.C. Cui and W.-P. Yin, *Eur. J. Org. Chem.*, 2005, 2379.
58. S. P. Dagade, V. S. Kadam and M. K. Dongare, *Catal. Commun.*, 2002, **3**, 67.
59. T. Esakkidurai and K. Pitchumani, *J. Mol. Catal. A: Chem.*, 2002, **185**, 305.
60. K. Smith, *Bull. Soc. Chim. Fr.*, 1989, 272.
61. S. M. Nagy, E. A. Zubkov, and V. G. Shubin, *Bull. Acad. Sci. USSR, Chem. Ser.*, 1989, 1780 (pp. 1933 in the Russian original).
62. S. M. Nagy, K. A. Yarovoy, M. M. Shakirov, V. G. Shubin, L. A. Vostrikova, and K. G. Ione, *J. Mol. Catal.*, 1991, **64**, L31.
63. S. M. Nagy, K. A. Yarovoy, V. G. Shubin, and L. A. Vostrikova, *Phys. Org. Chem.*, 1994, **7**, 385.
64. T. J. Kwok, K. Jayasuriya, R. Damavarapu and B. W. Brodman, *J. Org. Chem.*, 1994, **59**, 4939.
65. K. Smith, A. Musson and G. A. DeBoos, *J. Org. Chem.*, 1998, **63**, 8448.
66. X. Peng, N. Fukui, M. Mizuta and H. Suzuki, *Org. Biomol. Chem.*, 2003, **1**, 2326.
67. A. Kogelbauer, D. Vassena, R. Prins, and J. N. Armor, *Catal. Today*, 2000, **55**, 151.

68. D. Vassena, A. Kogelbauer and R. Prins, *Catal. Today*, 2000, **60**, 275.

69. R. P. Claridge, N. L. Lancaster, R. W. Miller, R. B. Moodie and J. P. B. Sandall, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1815.

70. I. Schumacher, *Eur. Pat.*, 0,053,031, 1981.

71. A. Germain, T. Akouz and F. Figueras, *J. Catal.*, 1994, **147**, 163.

72. A. Germain, T. Akouz and F. Figueras, *Appl. Catal. A: Gen.*, 1996, **136**, 57.

73. X. Peng and H. Suzuki, H. *Org. Lett.*, 2001, **3**, 3431.

74. N. F. Salakhutdinov, K. G. Ione, E. A. Kobzar and L. V. Malysheva, *Zh. Org. Khim.*, 1993, **29**, 546.

75. K. Smith, S. Almeer and S. J. Black, *Chem. Commun.*, 2000, 1571.

76. K. Smith, S. Almeer, S. J. Black and C. Peters, *J. Mater. Chem.*, 2002, **12**, 3285.

77. X. Peng, H. Suzuki and C. Lu, *Tetrahedron Lett.*, 2001, **42**, 4357.

78. K. Smith, S. Almeer and C. Peters, *Chem. Commun.*, 2001, 2748.

79. M. G. Kuba, R. Prins and G. D. Pirngruber, *Appl. Catal. A: Gen.*, 2007, **333**, 78.

80. R. R. Bak and A. J. Smallridge, *Tetrahedron Lett.*, 2001, **42**, 6767.

81. J. Almog, A. Klein, A. Sokol, Y. Sasson, D. Sonenfeld and T. Tamiri, *Tetrahedron Lett.*, 2006, **47**, 8651.

82. M. F. A. Dove, B. Manz, J. Montgomery, G. Pattenden and S. A.Wood, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1589.

83. Y. Yuan, J. Nie, Z. Zhang and S. Wang, *Appl. Catal. A: Gen.*, 2005, **295**, 170.

84. D. Vassena, A. Kogelbauer, R. Prins and J. Armor, *Abstracts from EuropaCat-IV*, Rimini, 1999, p. 222.

85. K. Smith, T. Gibbins, R. W. Millar and R. P. Claridge, *J. Chem. Soc. Perkin Trans. 1*, 2000, 2753.

86. M. H. H. Alotaibi, *Selective Dinitration of Toluene over Zeolites*, Ph.D Thesis, Cardiff University, Cardiff, UK, 2008.

# CHAPTER THREE

# CATALYTIC MONONITRATION OF PHENOL USING *iso*-PROPYL NITRATE OVER ZEOLITE CATALYSTS

# CHAPTER THREE

# Catalytic Mononitration of Phenol using *iso*-Propyl Nitrate over Zeolite Catalysts

## 3.1. Introduction

The synthesis of valuable industrial, pharmaceutical, agrochemical and fine chemicals frequently involves electrophilic aromatic substitution reactions. Indeed, substituted aromatic compounds represent useful intermediates in many synthetic processes. For example, aromatic nitro compounds are versatile chemical feed stocks for a wide range of industrial products, such as pharmaceuticals, agrochemicals, dyestuffs and explosives, and aromatic nitration is one of the most important and widely studied chemical reactions.[1,2]

The traditional method of phenol nitration involves the use of a mixture of nitric and sulfuric acids to produce nitrophenols in which the *ortho*/*para* ratio decreases from around 2.1 to around 0.9 as the concentration of sulfuric acid increases.[3] However, the poor selectivity and other disadvantages of this process have stimulated efforts to develop cleaner and more environmentally benign processes. Another problem associated with the nitration of phenol is the facile formation of dinitrophenols, oxidised products and unspecified resinous tarry materials resulting from over-oxidation of phenol.

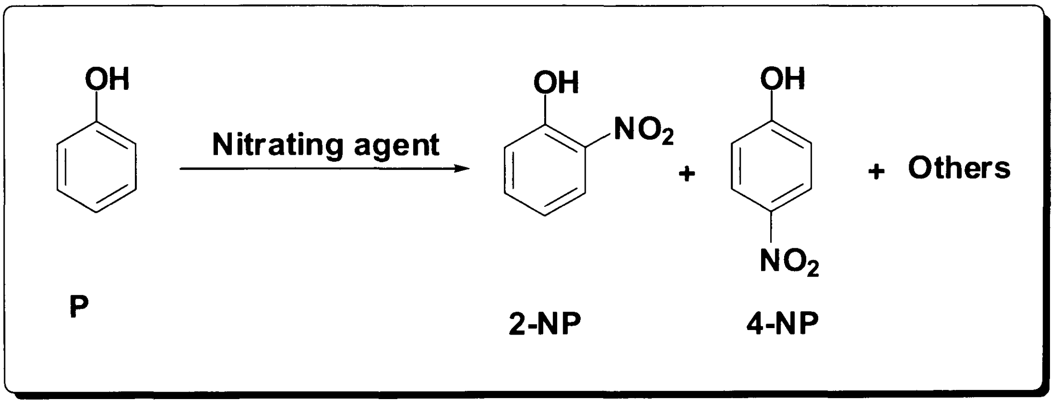
It is well recognised that zeolites and other solid catalysts can play an important role in the development of greener organic syntheses through their abilities to act as recyclable heterogeneous catalysts, support reagents, entrain by-products, avoid aqueous work-ups and enhance product selectivities.[4-11] For example,

K. Smith's group have shown that zeolites or other solids can have advantages in alkylation,[12] acylation,[13,14] methanesulfonylation,[15] bromination,[16] chlorination,[17] and nitration[18-22] of aromatic compounds.

Several solid catalytic systems have been developed for the nitration of phenol to nitrophenols. The most popular reagents have been nitric acid and acetyl nitrate and solids used include silica gel,[23] metal salt modified clays,[24] mixed metal oxides,[25] a variety of strongly acidic solids (*e.g.* heteropolyacids,[26] sulfated MCM-41,[27] silica impregnated with sulfuric acid[28] or a hydrogen sulfate salt,[29] sulfated titania,[30] sulfated mixed metal oxides[31] and zeolite Hβ[32]), and a series of non-acidic or weakly acidic ion-exchanged zeolites.[33] The selectivities observed are interesting. With the highly acidic solids *ortho*-nitrophenol generally predominates to a much greater extent than with a mixture of sulfuric and nitric acids, regardless of the structure of the solid. Even zeolite Hβ gives a very high proportion of the *ortho*-product, despite the fact that zeolites are normally associated with increased *para*- selectivities in aromatic substitution reactions. By contrast, different degrees of *para*-selectivity have been reported with some of the less acidic solids. However, such observations are difficult to interpret since nitric acid is capable of nitrating phenol (albeit in a rather messy fashion) without catalysis by added agents and because the mechanism of nitration is complicated,[1,2,34] potentially involving some or all of the following: direct nitration of the ring; addition to Wheland intermediates; elimination of nitrous acid from such adducts; nitrosation by any nitrous acid produced; phenyl nitrate as an intermediate; cyclohexadienone intermediates; rearrangement reactions; and oxidation. In several of the reactions involving solid catalysts reported above, the problem of formation of oxidation product during nitration of phenol appears to be less significant.

In continuation of K. Smith's research group interest in aromatic nitration reactions over solid catalysts,[18-22] we decided to investigate the nitration reaction of phenol under various conditions. Some of the results reported in this chapter have already been published.[35]

The first task was to choose the nitrating reagent since phenol undergoes ready nitration with a range of nitrating reagents (Scheme 3.1). Indeed, nitration of phenol with dilute nitric acid produces nitrophenols in moderate yield (*ca.* 61%), with an *ortho*/*para* ratio of around 36/25.[36] Use of concentrated nitric acid leads to a mixture of nitration and oxidation products and indeed oxidation of phenol is always difficult to control.



**Scheme 3.1: Nitration of phenol to nitrophenols**

### 3.2. Nitration of phenol with $HNO_3$ loaded over zeolites

It was reported that nitric acid loaded over silica can be used as a selective nitrating system for phenol to produce 4-nitrophenol in high selectivity.[25] Therefore, it was of interest to investigate if the nitration of phenol with concentrated nitric acid loaded over zeolite would take place selectively towards the *para*-isomer. Two types of zeolites were chosen, namely Hβ (a large pore zeolite) and HZSM-5 (a medium pore zeolite). Nitric acid (100%; 14 ml) was slowly added to zeolite

HZSM-5 (Si/Al = 30, 6.0 g) or Hβ (Si/Al = 12.5, 6.0 g), which were calcined at 550 °C for 24 h before use. 1,2-Dichloroethane (10 ml) was added and the mixture was stirred for 5 minutes. The mixture was left for 3 days at room temperature, during which the solvent completely evaporated leaving nitric acid adsorbed on zeolite.

We attempted the nitration reaction of phenol (3.3 mmol) with nitric acid loaded zeolite HZSM-5 (Si/Al = 30; 1 g) in dichloroethane (25 ml) at room temperature for 30 min. Zeolite HZSM-5 was then removed from the reaction mixture by filtration and washed with acetone and the washings were combined with the filtrate from the reaction mixture. The reaction mixture was analysed by quantitative GC using tetradecane as a standard.

Nitrophenols were formed in a yield of 84%, with a *para/ortho* ratio *ca.* 1, along with 2,4-dinitrophenol (8%) and 2,6-dinitrophenol (8%). The results clearly indicated that such a nitration system is quite reactive, producing dinitrophenols even at room temperature. It is also noted that all of the phenol had been consumed. However, we decided to investigate the reaction further, by varying the reaction time up to 96 h, in order to see the effect of reaction time on both yield and selectivity. Each reaction was carried out under identical conditions except for the reaction time. The results obtained are recorded in Table 3.1.

As can be seen from Table 3.1, the reaction time has an effect on both yields and selectivity. The yield of 2,4-dinitrophenol was increased from only 8% to 41% when the reaction time was increased from 0.5 to 4 h. However, the yield of 2,6-DNP was almost the same (*ca.* 8%), so that the ratio 2,4-DNP/2,6-DNP became *ca.* 5. Increasing the reaction time further to 96 h gave a quantitative yield of DNP and the reaction was even more selective towards 2,4-DNP (2,4-DNP/2,6-DNP = 7.4). The results also indicated that the mass balance in all reactions was high (96-100%).

**Table 3.1: Nitration of phenol with nitric acid loaded over zeolite HZSM-5 (Si/Al = 30)[a]**

| Time (h) | Yield (%) | | | | Conversion[b] | Mass Balance (%)[c] |
|---|---|---|---|---|---|---|
| | 2-NP | 4-NP | 2,4-DNP | 2,6-DNP | | |
| **0.5** | 44 | 40 | 8 | 8 | 100 | 99 |
| **2** | 44 | 14 | 35 | 7 | 100 | 100 |
| **4** | 34 | 14 | 41 | 7 | 100 | 96 |
| **96** | 4 | — | 81 | 11 | 100 | 97 |

[a] A mixture of phenol (0.32 g; 3.3 mmol) and zeolite HZSM-5/$HNO_3$ (Si/Al = 30; 1.0 g) in 1,2-dichloroethane (25.0 ml) was stirred at room temperature for the stated reaction time.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum percentage of phenol, 2-NP, 4-NP, 2,4-DNP and 2,6-DNP, calculated by quantitative GC.

Clearly, the process has potential to produce DNP quantitatively in reasonable selectivity but is not attractive for mononitration of phenol. We also decided to use zeolite Hβ loaded with $HNO_3$ under conditions similar to those used with HZSM-5 to see what effect the type of zeolite could have on the nitration process in terms of selectivity and yields of products. The results obtained are recorded in Table 3.2.

Again, the results recorded in Table 3.2 indicated that the yield of dinitrophenols was increased over time. Also, the 2,4-DNP/2,6-DNP ratio improved over the reaction time. Indeed, the results were quite similar to the ones produced using HZSM-5 loaded with $HNO_3$. It seems likely therefore that zeolite type has little effect on the nitration process and that the main effect was due to the presence of nitric acid itself.

**Table 3.2: Nitration of phenol with nitric acid loaded over zeolite Hβ (Si/Al = 12.5)**[a]

| Time (h) | Yield (%) | | | | Conversion[b] | Mass Balance (%)[c] |
|---|---|---|---|---|---|---|
| | 2-NP | 4-NP | 2,4-DNP | 2,6-DNP | | |
| **0.5** | 45 | 47 | 5 | — | 100 | 97 |
| **2** | 36 | 21 | 35 | 6 | 100 | 98 |
| **4** | 26 | 15 | 51 | 6 | 100 | 98 |
| **96** | 4 | — | 81 | 11 | 100 | 97 |

[a] A mixture of phenol (0.32 g; 3.3 mmol) and zeolite Hβ/$HNO_3$ (Si/Al = 25; 1.0 g) in 1,2-dichloroethane (25.0 ml) was stirred at room temperature for the stated reaction time.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum percentage of phenol, 2-NP, 4-NP, 2,4-DNP and 2,6-DNP as calculated by quantitative GC.

The results also indicated that the 2,4-/2,6-DNP ratios were changed over reaction time (*ca.* from 6 after 2 h to 7.4 after 96 h). Such changes could be due to the isomerisation of 2,6-DNP to 2,4-DNP. However, this possibility is not likely. The more likely possibility is that the DNPs were formed due to further nitration of NPs. The 2,4-isomer would be the almost exclusive product formed due to nitration of 4-NP. It was clear that the percentage of 4-NP decreased over time (47% after 30 minutes and 21% after 2 h) while the percentage of 2,4-DNP significantly increased (5% after 30 minutes and 35% after 2 h). This reflects the fact that nitration of 4-NP is much faster than that of 2-NP. However, after a relatively longer reaction time (4 h) the rates of nitration of both 2-NP and 4-NP become competitive. During this period the selectivity for formation of 2,4-DNP reduces slightly, since the reaction of the 2-NP produces a lower ratio of 2,4- to 2,6-DNP.

Our attention was next turned to use of acetyl nitrate as the nitrating reagent in the presence of zeolites HZSM-5 (Si/Al = 30) and Hβ (Si/Al = 12.5) as solid acidic catalysts.

## 3.3. Nitration of phenol with acetyl nitrate over zeolite catalysts

Acetic anhydride ($Ac_2O$) is cheaper, less toxic and more volatile than other anhydrides. Therefore, we chose initially to investigate the direct nitration of phenol using $HNO_3$, acetic anhydride and a zeolite catalyst. Acetyl nitrate could be generated quantitatively *in situ* from the reaction between acetic anhydride and nitric acid (Equation 3.1).

$$(CH_3CO)_2O + HNO_3 \rightleftharpoons CH_3CO(O)NO_2 + CH_3CO_2H$$

**Equation 3.1: Generation of acetyl nitrate *in situ* from reaction of acetic anhydride and nitric acid**

Dinitrogen pentoxide is believed to be produced *in situ* if the reaction mixture contains excess nitric acid (Equation 3.2).[34]

$$(CH_3CO)_2O + 2\,HNO_3 \rightleftharpoons N_2O_5 + 2\,CH_3CO_2H$$

**Equation 3.2: Generation of $N_2O_5$ from reaction of acetic anhydride with excess nitric acid**

Also, the presence of water in the nitric acid or in the system could hydrolyse the acetic anhydride to produce acetic acid (Equation 3.3).

$$(CH_3CO)_2O \quad + \quad 2\,H_2O \quad \rightleftharpoons \quad 2\,CH_3CO_2H$$

**Equation 3.3: Hydrolysis of acetic anhydride by water**

Nitration of phenol with acetyl nitrate over a zeolite catalyst is expected to be a fast reaction. Unfortunately, the reaction is also very exothermic, and may need careful observation and/or cooling. Therefore, the first task in the present contest was to establish suitable conditions for the nitration of phenol using the $HNO_3/Ac_2O$/zeolite system.

It was important to be sure that the acetic anhydride was highly pure; therefore, its distillation was carried out. The scale of nitration of phenol was based on the use of 9.5 mmol of phenol. Theoretically, 19 mmol of nitric acid (100%) and at least 19 mmol of acetic anhydride are required to convert phenol (19 mmol) into dinitrophenols quantitatively. However, production of acetyl nitrate from dilute nitric acid requires the use of an excess of acetic anhydride to react with the water present in the system. This leads to the production of acetic acid, which may deactivate the zeolite. It is therefore beneficial to use highly concentrated nitric acid (100%) for the production of acetyl nitrate. In the first instance we decided to use a large excess of both acetic anhydride and nitric acid in order to ensure quantitative production of dinitrophenols.

Initially, we attempted dinitration of phenol (9.5 mmol) with nitric acid (30 mmol) and acetic anhydride (30 mmol) over zeolite HZSM-5 (2 g) in 1,2-dichloroethane (50 ml) at room temperature for various reaction times. The results are recorded in Table 3.3.

These results clearly indicated that acetyl nitrate is a very reactive nitrating reagent for the double nitration of phenol. The yield of 2,4-DNP was 68% along with 5% of 2,6-DNP with no mono-nitrated phenols after only 30 minutes. Increasing the time further did not improve the yield of 2,4-DNP and under such conditions, 2,4,6-TNP (7%) was obtained. It is also clear that the mass balance was low (67-80%) under the conditions tried.

**Table 3.3: Dinitration of phenol with acetyl nitrate over zeolite HZSM-5 (Si/Al = 30)[a]**

| **Time (min)** | **Yield (%)** | | | | | **Conversion[b]** | **Mass Balance (%)[c]** |
|---|---|---|---|---|---|---|---|
| | **2-NP** | **4-NP** | **2,4-DNP** | **2,6-DNP** | **2,4,6-TNP** | | |
| **5** | 18 | — | 46 | 3 | — | 100 | 67 |
| **15** | 7 | — | 60 | 5 | — | 100 | 72 |
| **30** | — | — | 68 | 5 | — | 100 | 73 |
| **120** | — | — | 68 | 5 | 7 | 100 | 80 |

[a] A mixture of phenol (0.90 g; 9.5 mmol), nitric acid (30 mmol; 1.25 ml), acetic anhydride (30 mmol; *ca* 3.0 ml) and zeolite HZSM-5 (Si/Al = 30; 2.0 g) in 1,2-dichloroethane (50 ml) was stirred at room temperature for the stated reaction time.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum percentage of phenol, 2-NP, 4-NP, 2,4-DNP, 2,6-DNP and 2,4,6-TNP as calculated by quantitative GC.

We also investigated similar nitration reactions of phenol with nitric acid and acetic anhydride over zeolite Hβ in 1,2-dichloroethane at room temperature for 0.5 and 2 h. The results obtained are recorded in Table 3.4.

Similar results were obtained with zeolite Hβ. However the yields and mass balances were lower than the ones obtained when HZSM-5 was employed as the catalyst. The low mass balances could be due to formation of other products that did not show in GC, such as oxidation and/or acetylation products, since excess nitric acid (3 mole equivalents) was used. Indeed, the total weight of materials in the crude reaction product mixtures represented *ca.* 98% of the mass expected in each case, indicating that there was little if any physical loss of materials during the course of the reactions.

**Table 3.4: Dinitration of phenol with acetyl nitrate over zeolite Hβ (Si/Al = 12.5)[a]**

| **Time (min)** | **Yield (%)** | | | | **Conversion[b]** | **Mass Balance (%)[c]** |
|---|---|---|---|---|---|---|
| | **2-NP** | **4-NP** | **2,4-DNP** | **2,6-DNP** | | |
| **5** | **25** | — | 45 | — | 100 | 70 |
| **15** | **17** | — | 45 | 4 | 100 | 66 |
| **30** | **5** | — | 48 | 3 | 100 | 56 |

[a] A mixture of phenol (0.90 g; 9.5 mmol), nitric acid (30 mmol; 1.25 ml), acetic anhydride (30 mmol; *ca.* 3.0 ml) and zeolite Hβ (Si/Al = 12.5; 2.0 g) in 1,2-dichloroethane (50 ml) was stirred at room temperature for the stated reaction time.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum percentage of phenol, 2-NP, 4-NP, 2,4-DNP and 2,6-DNP as calculated by quantitative GC.

### 3.4. Mononitration of phenol with acetyl nitrate over zeolite catalysts

It was of interest to study the mononitration of phenol using acetyl nitrate over zeolite catalysts to see the selectivity of such reactions at the mono-nitration stage. Therefore, nitration of phenol (9.5 mmol) using $HNO_3$ (*ca.* 13 mmol) and acetic anhydride (10 mmol) over zeolite HZSM-5 and Hβ in DCM (50 ml) were attempted at room temperature for various reaction times. The results obtained are recorded in Tables 3.5 and 3.6, respectively.

**Table 3.5: Mononitration of phenol with acetyl nitrate over zeolite HZSM-5 (Si/Al = 30)[a]**

| Time (min) | Yield (%) | | | | Conversion[b] | Mass Balance (%)[c] |
|---|---|---|---|---|---|---|
| | P | 2-NP | 4-NP | 2,4-DNP | | |
| **5** | 2 | 49 | 31 | 20 | 98 | 102 |
| **15** | 2 | 43 | 31 | 22 | 98 | 98 |
| **30** | 2 | 42 | 19 | 35 | 100 | 98 |

[a] A mixture of phenol (0.90 g; 9.5 mmol), nitric acid (13 mmol; *ca.* 0.56 ml), acetic anhydride (10 mmol; 1.0 ml) and zeolite Hβ (Si/Al = 12.5; 2.0 g) in 1,2-dichloromethane (50 ml) was stirred at room temperature for the stated reaction time.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum of P, 2-NP, 4-NP and 2,4-DNP% as calculated by quantitative GC.

**Table 3.6: Mononitration of phenol with acetyl nitrate over zeolite Hβ (Si/Al = 12.5)[a]**

| Time (min) | Yield (%) | | | | Conversion[b] | Mass Balance (%)[c] |
|---|---|---|---|---|---|---|
| | P | 2-NP | 4-NP | 2,4-DNP | | |
| **5** | 2 | 49 | 49 | — | 98 | 100 |
| **15** | 1 | 50 | 50 | — | 99 | 101 |
| **30** | 1 | 45 | 21 | 31 | 99 | 98 |

[a] A mixture of phenol (0.90 g; 9.5 mmol), nitric acid (13 mmol; *ca.* 0.56 ml), acetic anhydride (10 mmol; 1.0 ml) and zeolite Hβ (Si/Al = 12.5; 2.0 g) in 1,2-dichloromethane (50 ml) was stirred at room temperature for the stated reaction time.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum of phenol, 2-NP, 4-NP and 2,4-DNP% as calculated by quantitative GC.

It is clear that nitration of phenol took place quantitatively and the mass balance in phenol derivatives was almost 100%. When HZSM-5 was used the reaction was selective towards 2-NP and 2,4-DNP. 2-Nitrophenol was produced in the range of 42-49% yields, while the yields of 4-nitrophenol produced were 19-31% under the conditions tried. Also, 2,4-dinitrophenol was produced in significant quantities even after 5 minutes reaction and there was no indication for the formation of 2,6-dinitrophenol. Increasing reaction time to 30 minutes led to the production of products in yields similar to those obtained when HZSM-5 was used as the catalyst for 30 min. Clearly, nitration of phenol over HZSM-5 is a bit faster at the beginning of the reaction comparing with ones carried out over Hβ. The reason for this observation is not yet clear. Clearly, reaction was fast and it was difficult to control the selectivity and/or proportions of products. It seems likely that both zeolites Hβ and HZSM-5 gave 2-NP and 4-NP in roughly equal proportions especially at the start of the reaction. However, the use of an excess of $HNO_3$ could lead to the production of 2,4-DNP as a result of nitration of NPs. The differences between the yields of 2,4-DNP in the two cases are probably due to how much $HNO_3$ was used since it was difficult to measure the quantity of $HNO_3$ each time with high accuracy.

## 3.5. Effect of different quantities of zeolites Hβ (Si/Al = 12.5) on nitration of phenol using acetyl nitrate

In order to test the effect of quantity of zeolite Hβ on the selectivity of nitration of phenol, we attempted various reactions in which quantities of zeolite Hβ (Si/Al = 12.5) were varied from 1 to 3 g for 9.5 mmol of phenol. It was hoped that the *para*/*ortho* ratio could be increased by increasing the quantity of Hβ as a result of increasing the number of active sites. The results obtained are recorded in Table 3.7.

**Table 3.7: Nitration of phenol with acetyl nitrate over various quantities of zeolite Hβ (Si/Al = 12.5)[a]**

| Hβ, g | Yield (%) | | | Conversion[b] | Mass Balance[c] (%) | *p/o* ratio |
|---|---|---|---|---|---|---|
| | phenol | 2-NP | 4-NP | | | |
| **1** | 1 | 48 | 48 | 99 | 99 | 1 |
| **2** | 1 | 50 | 50 | 99 | 101 | 1 |
| **3** | 4 | 47 | 47 | 96 | 98 | 1 |

[a] A mixture of phenol (0.90 g; 9.5 mmol), nitric acid (10 mmol; *ca.* 0.5 ml), acetic anhydride (10 mmol; 1.0 ml) and zeolite Hβ (Si/Al = 12.5) in 1,2-dichloromethane (50 ml) was stirred at room temperature for 5 minutes.

[b] Percentage of residual phenol was calculated by quantitative GC.

[c] Sum of P, 2-NP, 4-NP, 2,4-DNP and 2,6-DNP% as calculated by quantitative GC.

The results indicated that the quantity of zeolite has no effect in the nitration reaction of phenol, which was not expected at all. To understand the reasons for these unexpected results we attempted nitration of phenol with acetyl nitrate in the absence of zeolite. It was found that the result obtained was identical with the one obtained from the reactions involving use of Hβ. This again proved that acetyl nitrate is a very reactive nitrating reagent for the nitration of phenol and that no catalyst is required. The results also proved that the catalyst does not improve either the yield or the selectivity under the conditions tried. In the light of these results it was reasonable not to investigate such reactions over zeolite HZSM-5.

In general, the results obtained with acetyl nitrate are not very informative for several reasons. ***Firstly***, this nitrating reagent reacts with phenol in the absence of zeolite catalyst more or less in the same way as it does with catalyst. ***Secondly***, the amount of catalyst does not make a difference in terms of product yield or *para/ortho* selectivity. ***Thirdly***, the amount of nitric acid was difficult to measure accurately in every reaction. Therefore, we turned our attention to investigate nitration of phenol in the presence of a zeolite catalyst under conditions that would provide more meaningful results.

The task at this point was to use a less active nitrating reagent that would not react with the phenol in the absence of a catalyst, so that the influence of the catalyst might be more critical. First, we chose *iso*-propyl nitrate as the reagent, which is commercially available and cheap, over Hβ zeolite as a catalyst. We are not aware of any previous studies using this reagent for nitration of phenol.

### 3.6. Nitration of phenol using *iso*-propyl nitrate over zeolite catalysts

Nitration of aromatic compounds can be carried out with alkyl nitrates (*i.e.* alkyl esters of nitric acid) catalysed by both Lewis and Brønsted acids.[8] Generation of the $NO_2^+$ ion only occurs in the presence of an acid as shown in Equation 3.4.

$$\mathrm{RONO_2} \;+\; \overset{\oplus}{\mathrm{H}} \;\longrightarrow\; \overset{\oplus}{\mathrm{NO_2}} \;+\; \mathrm{ROH}$$

**Equation. 3.4: Generation of the $NO_2^+$ ion from alkyl nitrates in acidic medium**

Initially, we investigated the nitration reaction of phenol (9.5 mmol) in dichloroethane (DCE) in the absence of any zeolite catalyst for 48 h under reflux conditions. The reaction mixture was worked-up and analysed by GC using tetradecane as internal standard. The GC result clearly indicated that no reaction took place under such conditions. Even use of a longer reaction time failed to produce any nitration products. It was therefore believed that *iso*-propyl nitrate was not a strong enough nitrating reagent for this reaction in the absence of a catalyst. Therefore, we decided to repeat the reaction again under similar conditions except for addition of zeolite Hβ (Si/Al = 12.5; 2 g) as a catalyst to see what effect the catalyst could have on the reaction.

The reaction mixture was allowed to cool to room temperature and the catalyst was collected by filtration and then washed several times with analytical grade acetone until the filtrate became colourless. The filtrate was collected and made up to 100 ml in a volumetric flask and tetradecane was added as the internal standard. The reaction mixture was quantified by quantitative GC.

The GC results showed that both 2- and 4-nitrophenols were formed in equal proportions (*ca.* 30% each). The GC trace also showed the formation of another product in about 2% yield (Table 3.8). Under the conditions tried no phenol remained. Also, it was clear that the mass balance was low, with only 62% of material accounted for. The task at this point was to identify and characterise the side product obtained.

**Table 3.8: Nitration of phenol with *iso*-propyl nitrate**[a]

| **Catalyst** | **Yield (%)** | | | | **Conversion**[b] | **Mass Balance (%)** | ***p/o* ratio** |
|---|---|---|---|---|---|---|---|
| | **P** | **2-NP** | **4-NP** | **unidentified product** | | | |
| **No catalyst** | 56 | — | — | — | 44 | 56 | — |
| **Hβ** | — | 30 | 30 | *ca.* 2 | 100 | 62 | 1 |

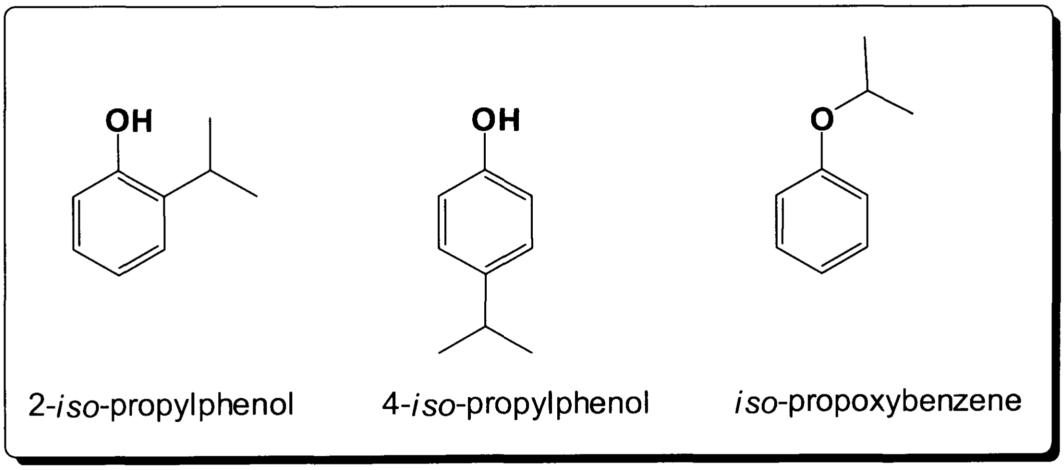
[a] A mixture of phenol (0.90 g; 9.5 mmol) and *iso*-propyl nitrate (2.0 g, 19.0 mmol) dichloroethane (50 ml) in the presence or absence of Hβ (Si/Al = 12.5; 2.0 g) was heated under reflux for 48 hours.

[b] Sum of phenol, 2-NP, 4-NP and the unknown product % calculated by quantitative GC.

## 3.7. Characterization of the by-product

As discussed above, nitration of phenol with *iso*-propyl nitrate gave nitrophenols in 60% yield. A by-product was formed that was clear in the GC trace. In order to identify the by-product a sample of product mixture was therefore subjected to GC-MS. The mass spectra confirmed the presence of 2-nitrophenol and 4-nitrophenol in addition to the by-product.

The by-product showed a molecular ion at *m/z* = 136 and a base peak at *m/z* = 94. The fragmentation pattern suggested loss of propene ($C_3H_6$) which is an indication for the presence of an *iso*-propyl group. The by-product was therefore believed to be 2-*iso*-propylphenol, 4-*iso*-propylphenol or *iso*-propoxybenzene (Figure 3.1). Indeed, it has been reported that alkylation of aromatic compounds can take place, to produce alkyated products, along with nitration products, when phenols are nitrated with secondary or tertiary alkyl nitrates.[36]



2-*iso*-propylphenol 4-*iso*-propylphenol *iso*-propoxybenzene

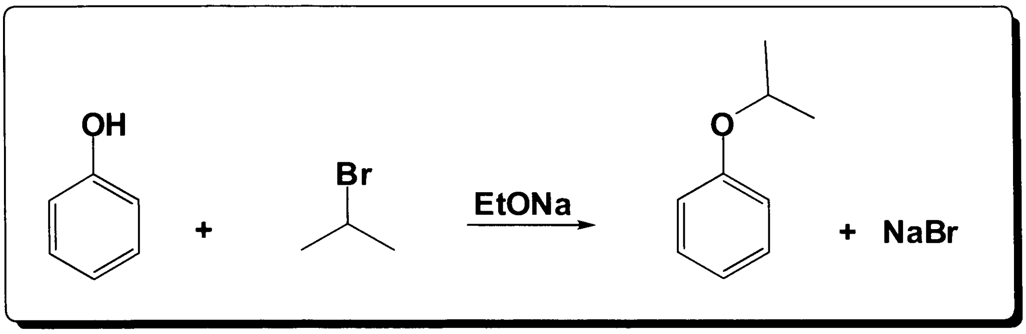
**Figure 3.1: Structures of 2-*iso*-propylphenol, 4-*iso*-propylphenol and *iso*-propoxybenzene**

The possible formation of 2-*iso*-propylphenol or 4-*iso*-propylphenol was first considered. However, the fragmentation patterns of both *iso*-propylphenols, as reported in *The Eight Peak Index of Mass Spectra*,[37] did not match the pattern observed from the GC-mass spectrum of the by-product. Also, when standard solutions of pure 2-*iso*-propylphenol and 4-*iso*-propylphenol were injected into the GC, the retention times for such compounds were different than that for the by-product. This observation ruled out the possible formation of either of the *iso*-propylphenols as the by-product formed during nitration of phenol using *iso*-propyl nitrate over zeolite Hβ.

The other possibility was that *iso*-propoxybenzene (*iso*-propyl phenyl ether) might be the by-product. This compound was not listed in *The Eight Peak Index of Mass Spectra*; however, similar compounds such as *n*-propyl phenyl ether showed very similar fragmentation patterns to that obtained from the GC-mass spectrum for the by-product. In order to establish the by-product's structure, a pure sample was needed, so that it could be injected into the GC to compare its GC retention time with the one produced in the mixture containing the by-product. Unfortunately, *iso*-propoxybenzene was not commercially available. Therefore, we decided to prepare it in order to obtain a pure sample.

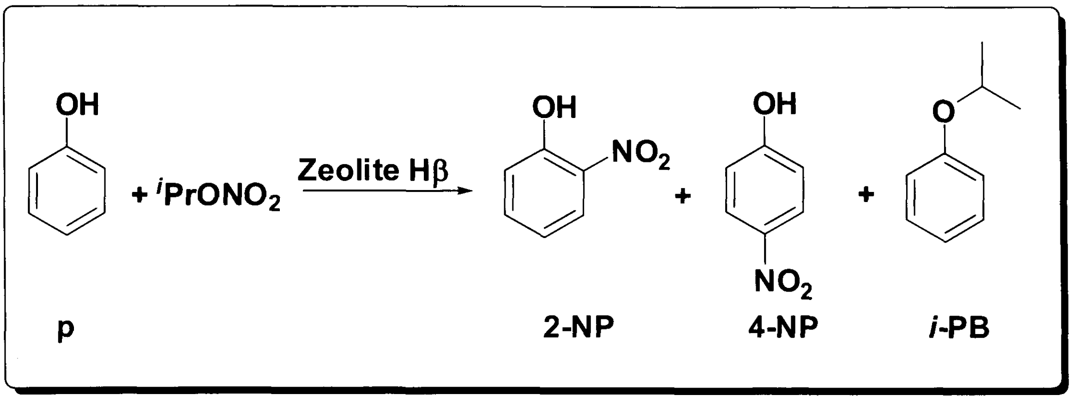
### 3.8. Preparation of *iso*-propoxybenzene from reaction of phenol and *iso*-propyl bromide

*iso*-Propoxybenzene is a liquid at room temperature; it has a melting point of -33.5 °C and a boiling point of 176 °C at atmospheric pressure, 62 °C at 12 Torr.[38] There are several reports in the literature on the preparation and characterisation of *iso*-propoxybenzene.[38-44] There are also reports that describe its mass spectrum[45,46] and its rearrangement into both 2- and 4-*iso*-propylphenols.[47] We chose a method involving the reaction of phenol with 2-bromopropane in the presence of sodium ethoxide, obtained *in situ* from the reaction of sodium with ethanol, under reflux conditions for 6 h (Scheme 3.2).[39]



**Scheme 3.2: Preparation of *iso*-propoxybenzene from reaction of phenol and 2-bromopropane in the presence of sodium ethoxide under reflux conditions**

Following work-up, the TLC showed the formation of a new product, *iso*-propoxybenzene, which was purified by simple distillation. The product was obtained in modest yield and its purity was checked by both GC analysis and $^1$H NMR spectroscopy. Both GC and $^1$H NMR spectrum of *iso*-propoxybenzene indicated that it was highly pure. The GC trace confirmed that the retention time of this compound was exactly the same as for the by-product obtained during nitration of phenol using *iso*-propyl nitrate and the nitration reaction can therefore now be written as shown in Scheme 3.3.



**Scheme 3.3: Nitration of phenol using *iso*-propyl nitrate over Hβ zeolite**

The by-product having been characterised, the yield could be confirmed by quantitative GC, which showed that it was obtained in 2% yield, confirming the mass balance as 62%. Our attention was therefore turned next to investigation of the reasons for the low mass balance obtained from nitration of phenol using *iso*-propyl nitrate over zeolite Hβ.

## 3.9. Possibilities for the low mass balance in nitration of phenol using *iso*-propyl nitrate

As discussed earlier, the total amount of material identified accounted for only 62% of the substrate used. This result clearly indicated that around 38% of the material was not accounted for. There are at least three possible explanations for the low mass balance obtained.

***Firstly***, there might be formation of other side products, *e.g.* oxidation products, which did not show up in the GC trace. However, this possibility was unlikely since the total weight of the product obtained after removal of the solvent correspond very closely to the amount calculated from the GC trace.

***Secondly***, since the weight of material accounted for was low, it was possible that some products were trapped within the pores of zeolite. This possibility could be tested by destruction of the zeolite. Therefore, hydrofluoric acid (HF) was added to the zeolite recovered from a nitration reaction of phenol and the mixture was stirred for 15 minutes. Sodium hydroxide solution (1 M) was added to the mixture and the solid was removed by filtration. The filtrate was extracted with diethyl ether and the organic layer was dried over anhydrous $MgSO_4$ and then was analysed by GC. The GC results revealed no peaks, suggesting that there were no materials trapped within the pores of zeolite, which therefore makes this possibility unlikely as the explanation for the low mass balance.

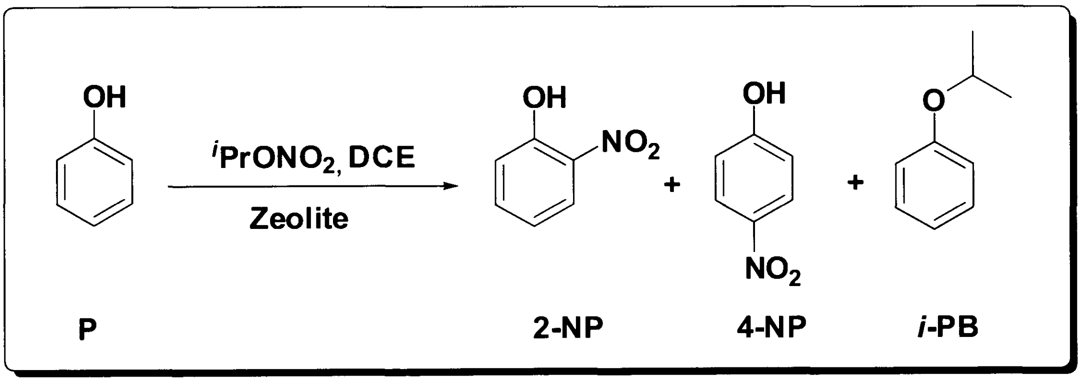
***Thirdly***, some materials might be lost from the reaction mixture by evaporation during the reaction since the reaction time was long (48 h). In order to test this possibility we decided to investigate a large scale nitration reaction of phenol. In principle, the percentage of materials lost and/or any error in calculation should be minimised compared to those in the small scale nitration reaction used previously. Therefore, nitration of phenol (66.5 mmol) using *iso*-propyl nitrate (133 mmol) in DCE over zeolite Hβ (14 g) under reflux conditions for 48 h was attempted. Following work-up, the reaction mixture was analysed by GC using tetradecane as the internal standard. The GC results showed that 2-NP and 4-NP were formed in equal proportions (15% each) along with phenol (29%) and *iso*-propoxybenzene (2%). Again, the mass balance was low (61%). The results were somewhat similar to those obtained from small scale nitration reaction but the reaction was slower. Since the results are not conclusive, we decided to investigate the possible evaporation of materials further in an attempt to find reasons for the low mass balance.

Several experiments were conducted in which 9.5 mmol of P, 2-NP, 4-NP, 2,4-DNP and 2,6-DNP were heated under reflux conditions for up to 72 h separately and as a mixture in DCE in the presence of Hβ (Si/Al = 12.5; 2 g). The GC results suggested that some materials were lost from the reaction mixtures by evaporation during the reaction time. Indeed, this was confirmed by carrying out the nitration reaction of phenol (9.5 mmol) in an autoclave (from which evaporation was impossible) under otherwise identical conditions. This gave nitrophenols in almost quantitative yield (94%), with equal proportions of 2-NP and 4-NP (2-NP/4-NP = 1), along with 4% of *iso*-propxybenzene. The individual evaporation tests showed that the main component to be lost was phenol and that any small losses of products did not affect the proportions significantly. Therefore, for subsequent studies it was reasonable to use normal reflux apparatus, which is easy and more convenient to use, while recognising that the total observed yields of components would inevitably be less than 100%, but in the expectation that the proportions of components would be meaningful and the losses of products through evaporation during reaction would be of negligible proportions.

In order to determine the best reaction conditions, several factors were looked at. The type and quantity of zeolite catalysts (with different Si/Al ratios), the temperature, the reaction time, different solvents, the number of equivalents of *iso*-propyl nitrate used, as well as different alkyl nitrates, were investigated to optimise the reaction conditions. The effects of these parameters are discussed in following sections.

## 3.10. Effect of different types of zeolites in nitration of phenol

In order to test the effect of the nature of the zeolite catalyst in the nitration of phenol, a number of different acidic zeolites were screened for efficiency in the reaction under similar reaction conditions except for the nature of catalyst. A range of different zeolites (Hβ, HY, H-mordenite and H-ZSM-5) was chosen for this study. Also, various silicon to aluminium ratios for each zeolite were chosen, to see the effect of acid strength and number of active sites on their reactivity. Therefore, nitration of phenol (9.5 mmol) with *iso*-propyl nitrate (19 mmol) over various types of zeolites in DCE under reflux conditions for 48 h was attempted (Scheme 3.4). The results obtained after work up and GC analysis are shown in Table 3.9 and also are represented in Figure 3.2.



**Scheme 3.4: Nitration of phenol using *iso*-propyl nitrate over zeolite catalyst**

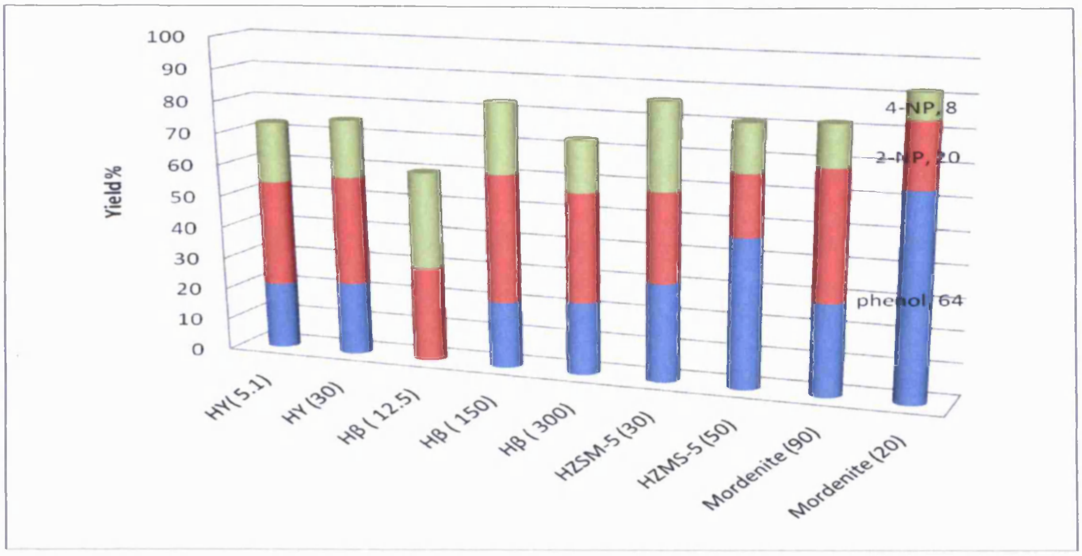


**Figure 3.2: Nitration of phenol with *iso*-propyl nitrate using various zeolites**

**Table 3.9: Nitration of phenol with *iso*-propyl nitrate using various zeolites[a]**

| Zeolite (Si/Al) | Yield (%) | | | | Conversion[b] | Mass Balance (%) | *p/o* ratio |
|---|---|---|---|---|---|---|---|
| | P | 2-NP | 4-NP | *i*-PB | | | |
| **No catalyst** | 56 | — | — | — | 44 | 56 | — |
| **Hβ (12.5)** | 0 | 30 | 30 | 2 | 100 | 62 | 1.00 |
| **Hβ (150)** | 21 | 40 | 22 | 5 | 79 | 88 | 0.55 |
| **Hβ (300)** | 23 | 34 | 16 | 4 | 77 | 77 | 0.47 |
| **HY(5.1)** | 21 | 33 | 19 | 3 | 79 | 76 | 0.58 |
| **HY (30)** | 23 | 34 | 18 | 5 | 77 | 80 | 0.53 |
| **H-mordenite (20)** | 64 | 20 | 8 | 1 | 36 | 93 | 0.40 |
| **H-mordenite (90)** | 29 | 40 | 13 | 1 | 71 | 83 | 0.33 |
| **HZSM-5 (30)** | 31 | 28 | 27 | — | 69 | 86 | 0.96 |
| **HZMS-5 (50)** | 47 | 19 | 15 | — | 53 | 81 | 0.79 |

[a] A mixture of zeolite (2.0 g), phenol (0.90 g, 9.5 mmol) and *iso*-propyl nitrate (2.0 g, 19.0 mmol) in DCE (50 ml) was refluxed for 48 h.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] Sum percentage of P, 2-NP, 4-NP and *i*-PB, as calculated by quantitative GC.

According to Table 3.9, when the reaction was carried out in the absence of any catalyst, no reaction occurred. However, all types of zeolites tried catalysed the reaction. The reaction was complete (*i.e.*, no phenol remaining) only when the large pore zeolite Hβ (Si/Al = 12.5) was used as the catalyst. Other Hβ catalysts with higher Si/Al ratio (150 or 300) gave nitrophenols in comparable or lower yields (50-62%) and with a lower 4-NP/2-NP ratio (*ca.* 0.55 and 0.47, respectively), along with unreacted phenol (21–23%), suggesting that sites that are more highly acidic (as present in the samples with higher Si/Al ratios) favour *ortho-* product formation, but that the availability of fewer numbers of acidic sites causes some slowing down of the reaction. Within each of the zeolite types the trend to lower 4-NP/2-NP ratios as the Si/Al ratio increased was observed. Zeolite HY, however, behaved in a manner comparable to samples of Hβ with higher Si/Al ratios, while H-Mordenite, a large pore zeolite with a more restrictive channel structure, gave an even higher predominance of 2-nitrophenol over 4-nitrophenol (4-NP/2-NP ratio 0.33 for the sample with Si/Al ratio = 90), but at somewhat lower conversions. Mordenite, although having relatively large entry ports to the channels, contains a one-dimensional channel system, which both restricts diffusion within the channel and provides no very large cavities in which several species can interact. The low conversion may suggest that the reaction took place to a less significant extent within the pores of the zeolite. It was probably catalysed less selectively by acidic sites on the external surface of the zeolite. Similarly, HZSM-5, a medium pore zeolite having narrower pore openings than the other zeolites, also gave rather low conversions and low yields of nitrophenols (34–55%). However, HZSM-5 resulted in higher 4-NP/2-NP ratios (around 0.96–0.79) than Mordenite and was comparable in selectivity with Hβ.

As a result of these findings, zeolite Hβ (Si/Al = 12.5) and HZSM-5 (Si/Al = 30), which were found to produce the highest yields of 4-NP, were selected for further studies. We first attempted the nitration reactions of phenol over zeolite Hβ as the catalysts using various reaction conditions in an attempt to improve the process.

### 3.11. Effect of other alkyl nitrates on nitration of phenol over zeolite Hβ

It was of interest to study the effect of other alkyl nitrates on both reactivity and selectivity of nitration of phenol. Commercially available alkyl nitrates such as *n*-propyl nitrate and *iso*-butyl nitrate (Figure 3.3) were chosen and were used as the nitrating reagents over zeolite Hβ (2 g) to nitrate phenol (9.5 mmol) under reflux conditions for 48 h in DCE (Scheme 3.5). The results obtained are recorded in Table 3.10.

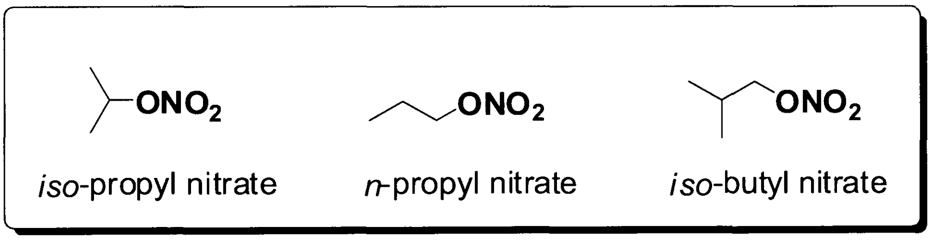
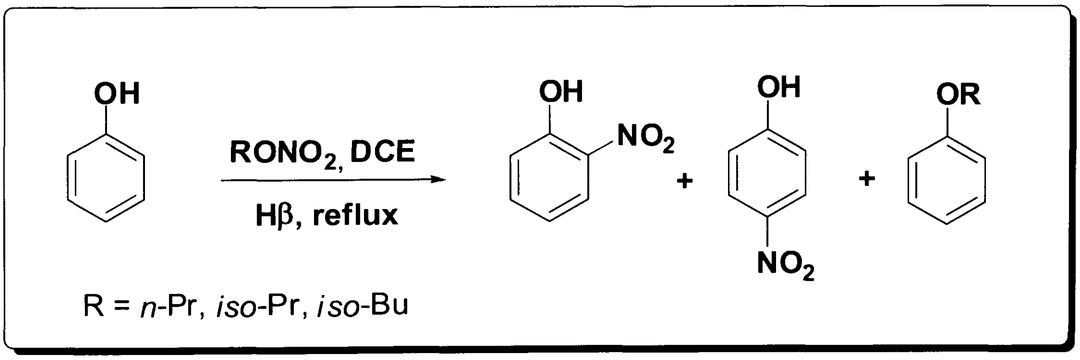


**Figure 3.3: Structures of various alkyl nitrates**



**Scheme 3.5: Nitration of phenol using alkyl nitrate over Hβ catalyst**

The results recorded in Table 3.10 indicated that all three alkyl nitrates tried were reactive and were able to nitrate phenol under the conditions tried. However *iso*-propyl nitrate was the most reactive one and gave the highest yields of nitrophenols (60%), comparing with *n*-propyl nitrate (40%) and *iso*-butyl nitrate (44%) under identical reaction conditions. This may suggest that the protonated secondary-alkyl nitrate is either present in higher concentration or breaks down more readily than the primary-alkyl equivalents. However, increasing reaction time to 96 hours and changing the solvent to the lower boiling DCM resulted in an increase in the yield of nitrophenols when *iso*-butyl nitrate was used as the nitrating reagent.

**Table 3.10: Nitration of phenol with alkyl nitrates using zeolite Hβ (Si/Al = 12.5)**[a]

| Nitrating agent | Yield (%)[b] | | | Conversion | Mass Balance (%) | *p/o* ratio |
|---|---|---|---|---|---|---|
| | P | 2-NP | 4-NP | | | |
| ***iso*-propyl nitrate** | — | 30 | 30 | 100 | 60 | 1.0 |
| ***n*-propyl nitrate** | 10 | 20 | 20 | 90 | 50 | 1.0 |
| ***iso*-butyl nitrate** | 16 | 19 | 25 | 84 | 64[c,d] | 1.3 |
| ***iso*-butyl nitrate**[e] | 1 | 23 | 25 | 99 | 53[c,d] | 1.1 |
| ***iso*-butyl nitrate**[f] | — | 31 | 35 | 100 | 66 | 1.1 |

[a] A mixture of Hβ (Si/Al = 12.5; 2.0 g), phenol (0.90 g, 9.5 mmol) and the appropriate alkyl nitrate (19 mmol) in DCE (50 ml) was refluxed for 48 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] *iso*-Butoxybenzene was formed in these reactions in a yield of *ca.* 2%.
[d] Includes 2% of 2,4-dinitrophenol also identified in the product mixture.
[e] Reaction carried out for 96 h.
[f] Reaction was carried out for 96 h but in DCM.

The selectivity towards 4-NP was higher with *iso*-butyl nitrate than with the other two nitrates, possibly because the *iso*-butyl nitrate occupies greater space within the pores, thus compressing the transition state somewhat. However, since the major issue at this point was to try to increase the yields of nitration products, it was reasonable to choose *iso*-propyl nitrate as the nitrating in further studies since this was both the most reactive and the cheapest among the alkyl nitrates tried.

## 3.12. Effect of solvent type in nitration of phenol over zeolite Hβ

In order to test the effect of the solvent in the reaction depicted in Scheme 3.3, several reactions were carried out over zeolite Hβ (Si/Al = 12.5) under identical conditions except for the nature of the solvent and the reflux temperature at which the reaction was therefore conducted. Various solvents with different boiling points such as dichloromethane (DCM), acetone, chloroform, acetonitrile, 1,2-dichloroethane (DCE) and tetrachloroethylene have been chosen and were used as solvents in nitration reactions of phenol (9.5 mmol). The results obtained after work-up and quantitative GC analysis are recorded in Table 3.11 and also represented in Figure 3.4.

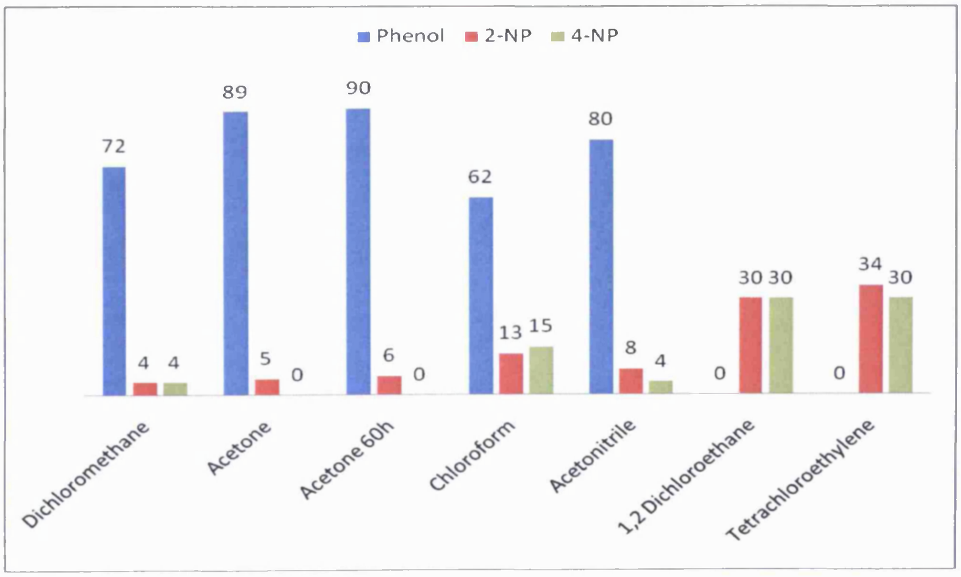


**Figure 3.4: Effect of solvent in nitration of phenol using zeolite Hβ**

The results suggested that within the group of chlorinated hydrocarbon solvents reflux temperature was the major factor influencing the reaction. The yields of nitrophenols were highest when the reaction was carried out in the higher boiling solvents DCE or tetrachloroethylene and lowest in low-boiling dichloromethane, but the 2-NP/4-NP ratio remained approximately constant at around *ca.* 1 for all such solvents. By contrast, at comparable temperatures, reactions in the polar solvents were much slower, leading to lower yields, and much more selective towards the *ortho*-isomer. For example, the results indicated that the conversion was very low in acetone (10%) and low in acetonitrile (20%). Clearly, acetone and acetonitrile are not good solvents for the nitration reaction, possibly because they compete with the alkyl nitrate for protonation at the acid sites of the zeolite.

**Table 3.11: Nitration of phenol with *iso*-propyl nitrate using various solvents according to Scheme 3.2 for 48 h**[a]

| Solvent | B.P of solvent °C | Yield (%) | | | | Conversion[b] | Mass Balance[c] (%) |
|---|---|---|---|---|---|---|---|
| | | P | 2-NP | 4-NP | *i*-PB | | |
| **Dichloromethane** | **40** | 72 | 4 | 4 | 2 | 28 | 82 |
| **Acetone** | **56** | 89 | 5 | — | 1 | 11 | 95 |
| **Acetone**[d] | **56** | 90 | 6 | — | 1 | 10 | 97 |
| **Chloroform** | **60** | 62 | 13 | 15 | 2 | 38 | 92 |
| **Acetonitrile** | **82** | 80 | 8 | 4 | — | 20 | 92 |
| **1,2-Dichloroethane** | **83** | — | 30 | 30 | 2 | 100 | 62 |
| **Tetrachloroethylene** | **121** | — | 34 | 30 | — | 100 | 64 |

[a] A mixture of Hβ (Si/Al = 12.5; 2.0 g), phenol (0.90 g, 9.5 mmol) and *iso*-propyl nitrate (2.0 g, 19.0 mmol) in solvent (50 ml) was refluxed for 48 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] Sum percentage of P, 2-NP, 4-NP and *i*-PB, as calculated by quantitative GC.
[d] Reaction carried out under reflux for 72 h.

## 3.13. Effect of reaction temperature in nitration of phenol over zeolite Hβ

In order to separate the effects of solvent nature from those of temperature for reactions in chlorinated hydrocarbon solvents, reactions in several such solvents (DCM, DCE and tetrachloroethylene) were conducted at a range of temperatures, controlled by the temperature of the heating bath in which the reaction vessel was placed. The results obtained after work-up followed by quantitative GC analysis using tetradecane as internal standard are recorded in Table 3.12. Also, the results obtained with DCE and tetrachloroethylene as solvents are represented in Figures 3.5-3.8.

The product profiles obtained at any given bath temperature were similar for all three solvents, indicating that reaction temperature was a more important variable than the rather small differences in the properties of the different chlorinated hydrocarbon solvents. Interestingly, reactions conducted at lower temperatures generally showed greater selectivity towards the *ortho*-isomer than ones conducted at elevated temperatures. For example, only 2-NP (up to 2% at room temperature or 4% at 45 °C) and no 4-NP was produced at the lower temperatures, regardless of the type of solvent used. The reasons for the high *ortho*-selectively are not clear, but presumably the reaction was very slow at such temperatures and only a low proportion of the molecules were capable of achieving the necessary activation energy to produce 4-NP. The yields of nitrophenols increased further when the reaction temperature was increased to 65 °C but the reactions became less selective towards the *ortho*- isomer. The yields of nitrophenols were quite high (60-66%) when reactions were carried out under reflux conditions in DCE or tetrachloroethylene as solvents and the *ortho/para* ratios were *ca.* 1. As a result of these findings, DCE and tetrachloroethylene were the best solvents. However, for subsequent experiments it was appropriate to use refluxing DCE as the solvent of choice because it is cheaper and has a lower boiling point than tetrachloroethylene.

**Table 3.12: Nitration of phenol in various solvents at different temperatures**[a]

| Solvent | Heating bath Temperature (°C) | Yields (%)[b] | | | |
|---|---|---|---|---|---|
| | | P | 2-NP | 4-NP | *i*-PB |
| **Dichloromethane** | 20 | 97 | — | — | — |
| **1,2-Dichloroethane** | 20 | 97 | — | — | — |
| **Tetrachloroethylene** | 20 | 81 | 2 | — | — |
| **1,2-Dichloroethane** | 45 | 68 | 4 | — | 3 |
| **Tetrachloroethylene** | 45 | 77 | 3 | 3 | — |
| **Dichloromethane** | 65[c] | 52 | 10 | 5 | — |
| **1,2-Dichloroethane** | 65 | 52 | 10 | 5 | 3 |
| **Tetrachloroethylene** | 65 | 64 | 7 | 4 | 3 |
| **1,2-Dichloroethane** | 80 | 34 | 16 | 14 | 2 |
| **1,2-Dichloroethane** | 95[c] | — | 30 | 30 | 2 |
| **Tetrachloroethylene** | 95 | — | 34 | 32 | 3 |
| **Tetrachloroethylene** | 130[c] | — | 34 | 30 | — |

[a] A mixture of Hβ (Si/Al = 12.5; 2.0 g), phenol (0.90 g, 9.5 mmol) and *iso*-propyl nitrate (2.0 g, 19.0 mmol) in solvent (50 ml) was stirred for 48 h at the stated temperature.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] Bath temperature above reflux temperature of solvent, but reaction temperature would be lower than the recorded bath temperature and not higher than the reflux temperature.

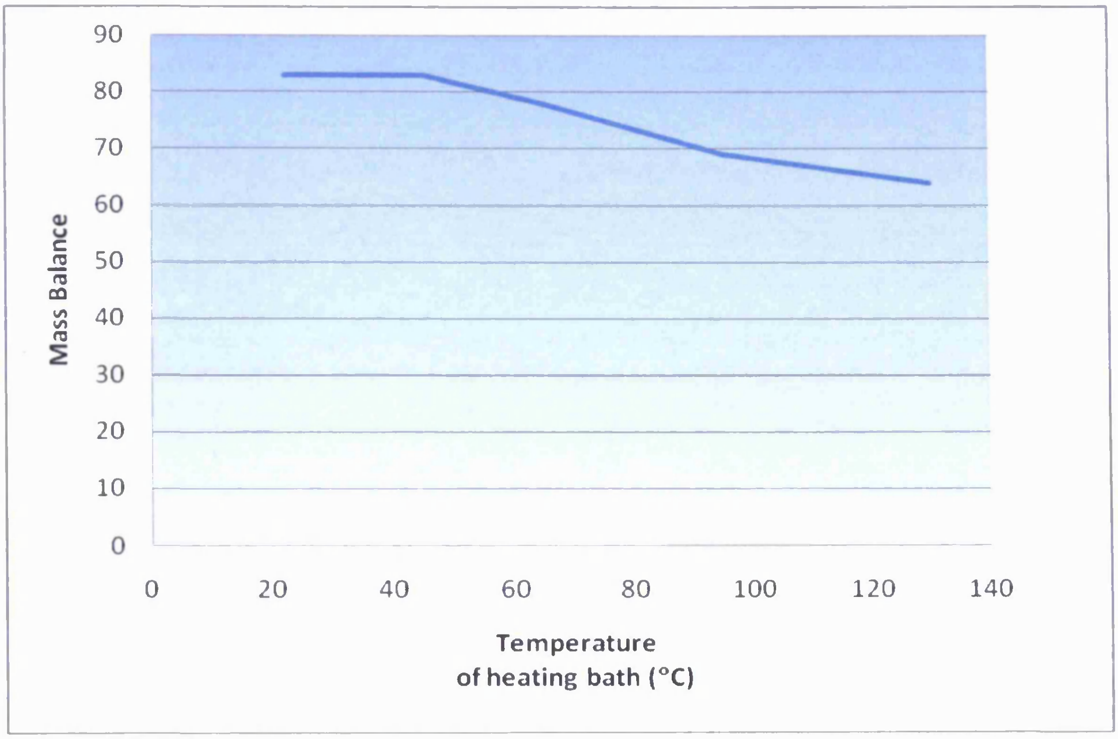


**Figure 3.5: Effect of temperature on mass balance in nitration of phenol in dichloroethane as a solvent over Hβ**

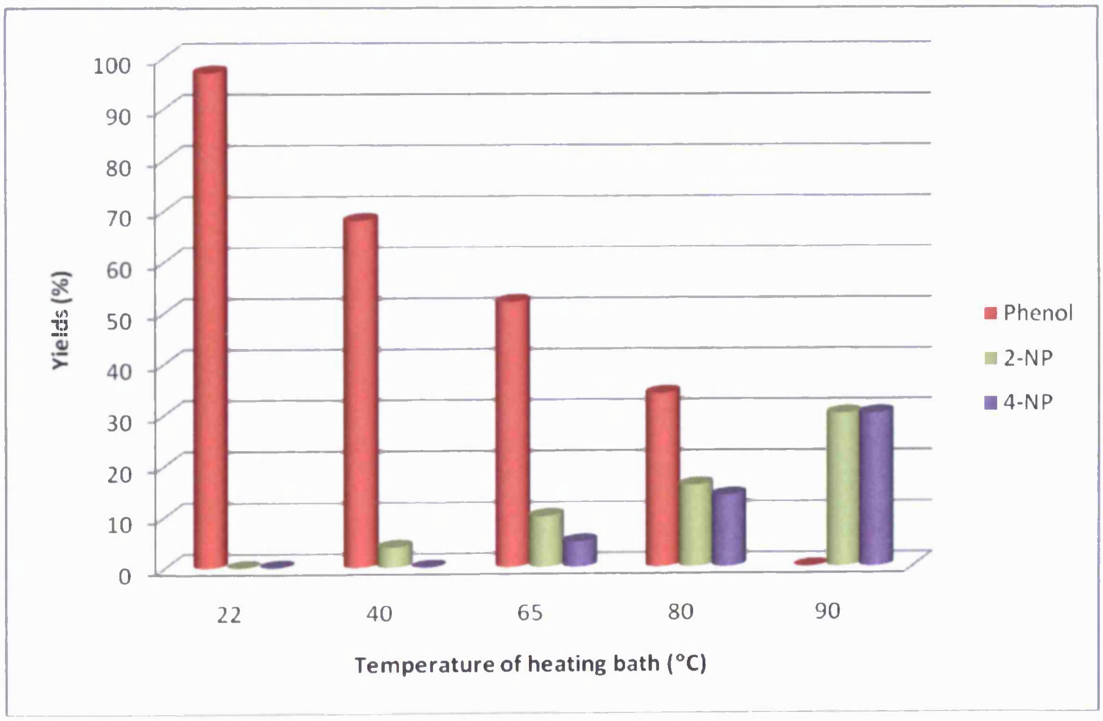


**Figure 3.6: Effect of temperature on yields of nitrophenol in nitration of phenol in dichloroethane as a solvent over Hβ**

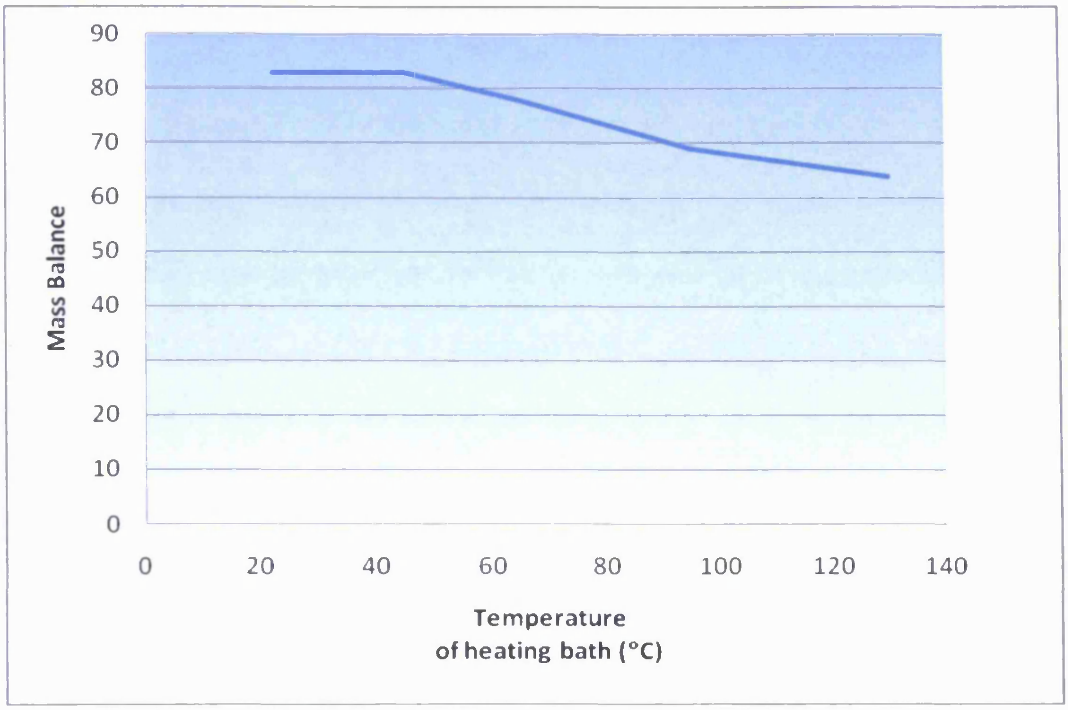


**Figure 3.7: Effect of temperature on mass balance in nitration of phenol in tetrachloroethylene as a solvent over Hβ**

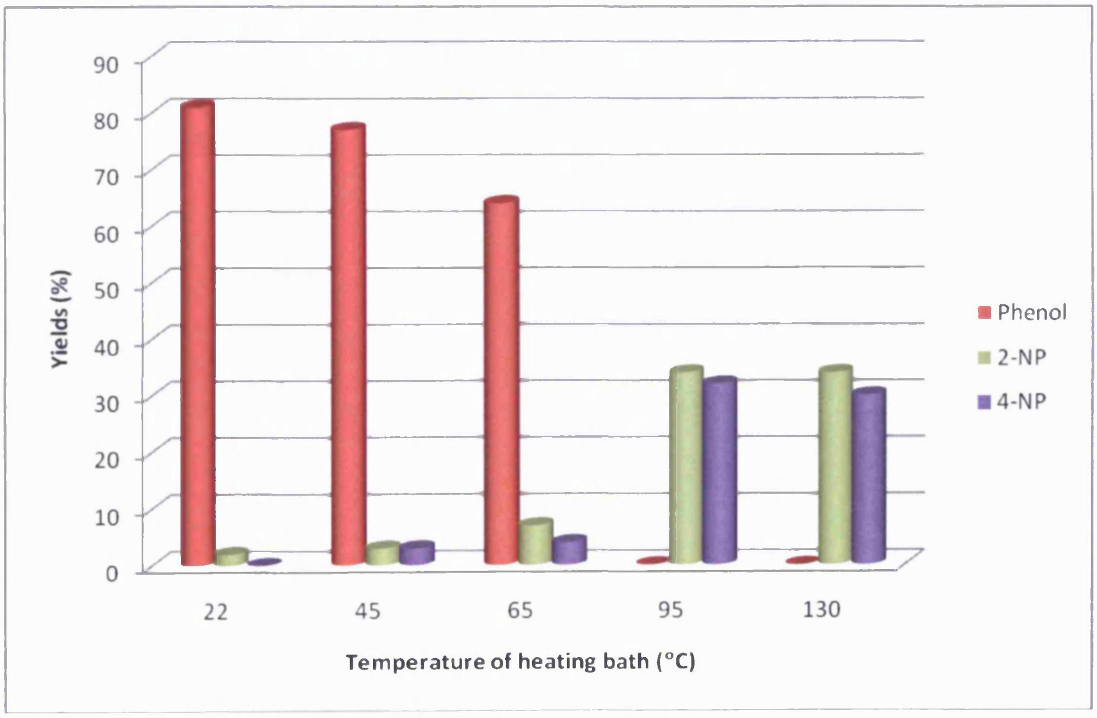


**Figure 3.8: Effect of temperature on yield of nitrophenol in nitration of phenol in tetrachloroethylene as a solvent over Hβ**

## 3.14. Effect of reaction time on nitration reaction of phenol using zeolite Hβ

It is very important to know the optimum reaction time which will allow the production of a high yield of the desirable product in high selectivity. Also, another purpose of this investigation was to test the progression of the nitration reaction. Also, in order to check whether the standard period of 48 hours used in reactions thus far was actually required for reactions in refluxing DCE, a series of nitration reactions of phenol (9.5 mmol) with *iso*-propyl nitrate (19 mmol) was conducted in DCE over zeolite Hβ (Si/Al = 12.5; 2 g) over various reaction times, while the other conditions remained the same. The results obtained, after work-up and quantitative GC analysis, are recorded in Table 3.13.

**Table 3.13: Nitration of phenol in refluxing DCE for various reaction times[a]**

| Reaction Time (h) | Yields (%)[b] | | | |
|---|---|---|---|---|
| | P | 2-NP | 4-NP | *i*-PB |
| **6** | 42 | 19 | 15 | 2 |
| **12** | 31 | 20 | 19 | 3 |
| **24** | 14 | 24 | 24 | 3 |
| **36** | 10 | 25 | 25 | 3 |
| **48** | — | 30 | 30 | 2 |

[a] A mixture of Hβ (Si/Al = 12.5; 2 g), phenol (0.90 g, 9.5 mmol) and *iso*-propyl nitrate (2.00 g, 19.0 mmol) in DCE (50 ml) was refluxed for the appropriate reaction time.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

The results shown in Table 3.13 indicated that there was a trend which shows that increasing the reaction time resulted in an increased yield of nitrophenols and a slight increase in the selectivity for 4-NP. The yield of 2-NP was 19% with a 2-:4-NP ratio of 1.27 when the reaction time was 6 hours, increasing to 24% with a ratio of 1 when the reaction time was 24 h. Increasing the reaction time further from 24 h to 36 h resulted in a very small increase in the yield of 2-NP (1%) and the 2-:4-NP ratio remained at 1. This shows that the majority of the reaction took place within 24 h and that the reaction was significantly slower thereafter. However, more detailed consideration of the results revealed several interesting points.

The amount of *iso*-propoxybenzene remained almost constant over the period of the study (2-3%). Clearly, *iso*-propoxybenzene was produced rapidly, along with 2-NP and 4-NP, during the first 6 hours of the reaction, but it did not increase further at all over longer reaction periods.

Also, the *ortho*/*para* ratio fell slightly from 1.27 after 6 h to 1 after 24-48 h, indicating that 2-NP was produced more rapidly than 4-NP at the start of the reaction but that 4-NP was produced more rapidly than 2-NP in the later stages. It is possible that over longer reaction times (more than 24 h) some dealumination of the zeolite took place, leading both to a lower reaction rate and a greater tendency for 4-NP production. Whatever the precise reasons, it seems that there is a small benefit to be gained from running the reaction for a longer period.

As a conclusion, the results showed that a reaction period of 48 hours was needed for the reaction to go to completion. The reactions conducted for shorter periods appeared to give slightly greater selectivity for the *ortho-* isomer than ones conducted over longer periods.

## 3.15. Effect of concentration on nitration of phenol over zeolite Hβ

We next investigated the effect of concentration on the reaction by conducting nitration reactions of phenol in different amounts of DCE. It was expected that dilution of the reaction mixture might increase selectively towards the *para*-isomer but at the expense of reaction rate. A series of experiments was conducted in which the amount of DCE was varied from 20 to 100 ml for a reaction involving a fixed quantity of phenol (9.5 mmol) over zeolite Hβ (2 g) under reflux conditions for 48 h. Each reaction was carried under identical conditions except that the quantity of solvent was different. The results obtained from such reactions, after their work up and quantitative GC analysis, are recorded in Table 3.14.

**Table 3.14: Nitration of phenol using *iso*-propyl nitrate in DCE at various concentrations[a]**

| **1,2-Dichloroethane (ml)** | **Yields (%)[b]** | | | | **Mass balance (%)[c]** |
|---|---|---|---|---|---|
| | **P** | **2-NP** | **4-NP** | ***i*-PB** | |
| **20** | — | 28 | 24 | 1 | 53 |
| **30** | — | 30 | 25 | 4 | 59 |
| **40** | — | 26 | 25 | 4 | 55 |
| **50** | — | 30 | 30 | 2 | 62 |
| **60** | — | 30 | 31 | 2 | 63 |
| **70** | 13 | 27 | 20 | 4 | 64 |
| **80** | 12 | 27 | 20 | 4 | 63 |
| **100** | 15 | 31 | 27 | 1 | 74 |

[a] A mixture of Hβ (Si/Al = 12.5; 2.0 g), phenol (0.90 g, 9.5 mmol) and *iso*-propyl nitrate (2.0 g, 19.0 mmol) in the stated quantity of DCE was refluxed for 48 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] Sum of yields of identified products as calculated by quantitative GC.

The results in Table 3.14 showed that reaction was complete (no phenol remaining) in up to 60 ml of DCE but was not yet complete after 48 hours in more dilute conditions (70-100 ml). However, the yields of nitrophenols were somewhat constant. Mass balances generally improved with increased dilution, consistent with lower losses by evaporation of phenol from more dilute solutions. Subject to experimental error limits, it appeared that the proportion of the *para*-isomer went through a maximum in the middle of the range of concentrations tried, although the differences were not large. Since both the yields of nitration products and the *ortho*/*para* selectivity were at a maximum when the quantity of solvent was around 50-60 ml, it was considered reasonable to use 50 ml of DCE in subsequent nitration reactions of 9.5 mmol of phenol.

## 3.16. Effect of quantity of zeolite Hβ (Si/Al = 12.5) on nitration reaction of phenol using zeolite Hβ

In an attempt to increase the yield of nitrophenols and/or improve the selectivity of nitration of phenol, a series of experiments was conducted in which the quantity of zeolite Hβ was varied for a reaction involving a fixed quantity of phenol (9.5 mmol). It was expected that increasing the quantity of zeolite would directly affect the reactivity and selectivity due to an increase in the pore volume and the number of active sites in the zeolite sample. The amount of Hβ was varied from 0.5 to 3 g and experiments were carried out under identical conditions for 48 h under reflux conditions in DCE. The results obtained are recorded in Table 3.15.

**Table 3.15: Nitration of phenol with *iso*-propyl nitrate using various amounts of zeolite Hβ (Si/Al = 12.5)[a]**

| **Hβ (12.5) (g)** | **Yield (%)** | | | | **Conversion[b]** | **Mass Balance[c] (%)** | ***p/o* ratio** |
|---|---|---|---|---|---|---|---|
| | **P** | **2-NP** | **4-NP** | ***i*-PB** | | | |
| **0.5** | 43 | 17 | 12 | 3 | 57 | 75 | 0.8 |
| **1** | 22 | 23 | 23 | 3 | 78 | 71 | 1 |
| **2** | — | 30 | 30 | 2 | 100 | 62 | 1 |
| **3** | — | 32 | 30 | 2 | 100 | 64 | 0.94 |

[a] A mixture of Hβ (Si/Al = 12.5), phenol (0.90 g, 9.5 mmol) and *iso*-propyl nitrate (2.0 g, 19.0 mmol) in DCE (50 ml) was refluxed for 48 h.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] Sum of phenol, 2-NP, 4-NP and *iso*-propoxybenzene% calculated by quantitative GC.

The trend on increasing the quantity of zeolite was an increase in the yield of products. For example, the yield of nitro-products was increased from 29% to 60% when the quantity of zeolite Hβ was increased from 0.5 g to 2 g.

It is clear that the quantity of Hβ zeolite used affected the rate of reaction. However, increasing the quantity of the catalyst over 2 g did not substantially affect the selectivity of the reaction. This may have been because the reaction mixture was less mobile and stirring the mixture became difficult. The 4-NP/2-NP ratio was almost constant (*ca.* 1). As a conclusion, the results in Table 3.15 indicated that use of Hβ in more than 2 g quantity gave no benefit in terms of yield of nitro-products or selectivity. Therefore, 2 g of Hβ is suitable for nitration of 9.5 mmol of phenol.

## 3.17. Effect of quantity of *iso*-propyl nitrate in nitration of phenol over zeolite Hβ

Further studies were conducted in which the quantity of *iso*-propyl nitrate was varied in order to see what effect the reagent concentration could have on both yield and selectivity in nitration of phenol. A series of experiments was conducted under similar conditions except that the quantity of *iso*-propyl nitrate was varied from 9.5 to 38 mmol for nitration of phenol (9.5 mmol). The results obtained are recorded in Table 3.16.

The results in Table 3.16 revealed that the yields of nitrophenols were low (45-51%) when *iso*-propyl nitrate was used in quantities less than 19 mmol for 9.5 mmol of phenol. Using more than 19 mmol of *iso*-propyl nitrate gave higher yields of nitrophenols (59-69%), however, the reaction became more selective towards the *ortho-* isomer.

**Table 3.16: Nitration of phenol with various amounts of *iso*-propyl nitrate over zeolite Hβ (Si/Al = 12.5)[a]**

| *iso*-propyl nitrate (mmol) | Yield (%) | | | | Conversion[b] | Mass Balance (%)[c] | *p/o* ratio |
|---|---|---|---|---|---|---|---|
| | P | 2-NP | 4-NP | *i*-PB | | | |
| **9.5** | 15 | 22 | 13 | 2 | 85 | 52 | 0.59 |
| **14.0** | 11 | 27 | 24 | 1 | 89 | 62 | 0.89 |
| **19.0** | — | 30 | 30 | 2 | 100 | 62 | 1.00 |
| **28.5** | — | 39 | 30 | 4 | 100 | 73 | 0.77 |
| **38.0** | — | 37 | 22 | 3 | 100 | 71[d] | 0.59 |

[a] A mixture of Hβ (Si/Al = 12.5; 2.0 g), phenol (0.90 g, 9.5 mmol) and various quantities of *iso*-propyl nitrate in DCE (50 ml) was refluxed for 48 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] Sum of yields of identified products as calculated by quantitative GC.
[d] Includes 9% of 2,4-dinitrophenol also identified in the product mixture.

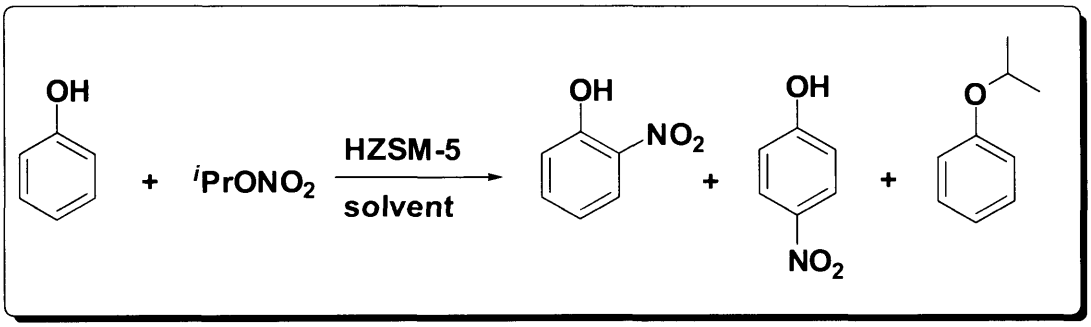
Clearly, the reaction rate increased as more reagent was used, resulting in a trend to higher product yields. Recorded mass balances were also higher, presumably because a greater proportion of the phenol was converted into products rather than being lost through evaporation. The effect on product proportions was interesting in that the proportion of 2-NP was significantly higher than that of 4-NP at both high and low concentrations of *iso*-propyl nitrate, but the two were formed in comparable amounts when 19 mmol of the reagent was used. At the high reagent concentrations this could be due to selective conversion of 4-NP into 2,4-dinitrophenol, which was detected in the mixture from the highest concentration reaction. At the lower concentrations it may be that a greater proportion of the reaction occurs at the external surface of the zeolite rather than in the pores, and 2-NP is the major product from such unselective nitration.

It did not appear likely that any further improvements in yield or selectivity would be achieved with zeolite Hβ as the catalyst and our attention was next turned to investigation of the nitration of phenol with *iso*-propyl nitrate over HZSM-5 under reaction conditions similar to those used in the case of zeolite Hβ.

### 3.18. Effect of reaction time on nitration of phenol over zeolite HZSM-5

We have shown previously that nitration of phenol was successfully achieved using *iso*-propyl nitrate as the nitrating reagent over zeolite Hβ in DCE as a solvent for 48 h under reflux conditions. Under such conditions nitrophenols were produced in reasonable yields and the *para/ortho* ratio was *ca.* 1. Also, we have shown that HZSM-5 (Si/Al = 30) could be used as an effective catalyst in nitration of phenol (Table 3.9).

It was of interest to investigate further the nitration of phenol using *iso*-propyl nitrate over HZSM-5 (Si/Al = 30) in order to try to find conditions under which nitrophenols could be produced quantitatively and selectivity. Therefore, a series of experiments was conducted in which phenol (9.5 mmol) in DCE (50 ml) was allowed to react with *iso*-propyl nitrate (19 mmol) for various reaction times over zeolite HZSM-5 (Si/Al = 30; 2 g) under reflux conditions (Scheme 3.6). Each reaction was conducted under identical condition expect for the reaction time, which was varied from 24 to 96 h. Each reaction was worked-up and the reaction mixtures were quantified by the use of quantitative GC using tetradecane as the internal standard. The results obtained are recorded in Table 3.17.



**Scheme 3.6: Nitration of phenol using *iso*-propyl nitrate over zeolite HZSM-5 in solvent under reflux conditions**

The results recorded in 3.17 showed that increasing the reaction time increased the yield of nitrophenols. Cleary, reaction time was an important factor in the nitration of phenol over HZSM-5. For example, the yield of nitrophenols was increased from 35% when the reaction time was 24 hours to 57% when the reaction time was increased to 48 hours. By increasing the reaction time further to 72 hours, the yield of nitrophenols was increased further to 62% along with 7% of 2,4-DNP. Increasing the reaction time over 72 h led to the production of 2,4-DNP in significant quantities (10-16%), primarily at the expense of 4-NP, which shows that 4-nitrophenol is nitrated more readily than 2-nitrophenol under these conditions.

**Table 3.17: Nitration of phenol with *iso*-propyl nitrate over zeolite HZSM-5 (Si/Al = 30) in DCE**[a]

| Time (h) | Yield (%) | | | | | Conversion[b] | Mass Balance (%)[c] |
|---|---|---|---|---|---|---|---|
| | P | 2-NP | 4-NP | 2,4-DNP | *i*-PB | | |
| **24** | 56 | 20 | 15 | — | — | 44 | 91 |
| **48** | 31 | 29 | 28 | — | 1 | 69 | 89 |
| **72** | 17 | 32 | 30 | 7 | 1 | 83 | 86 |
| **84** | 4 | 37 | 25 | 10 | 1 | 96 | 77 |
| **96** | — | 35 | 22 | 16 | — | 100 | 73 |

[a] A mixture of phenol (0.90 g; 9.5 mmol), *iso*-propyl nitrate (2.0 g, 19.0 mmol) and HZSM-5 (Si/Al = 30; 2.0 g) in DCE (50 ml) was heated under reflux for the stated reaction time.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum of P, 2-NP, 4-NP, 2,4-DNP and *i*-PB% as calculated by quantitative GC.

Although the yields of nitration products increased with reaction time, the mass balances decreased, consistent with the loss of phenol by evaporation during the prolonged reactions. However, mass balances were generally higher at any given time than the corresponding ones for cases where Hβ was used as the catalyst, even though the yields of nitration products were somewhat lower with HZSM-5 as the catalyst. This is consistent with the zeolite having narrower pores (HZSM-5) being more effective at retaining the phenol within its pores, thereby limiting its availability for evaporation, but also having insufficient space within its pores for reaction to take place therein, so that the reaction is actually slower than with zeolite Hβ.

Overall, zeolite HZSM-5, a medium pore zeolite, was found to deliver a higher yield of nitrophenols than zeolite Hβ, but required a longer time to do so and production of 2,4-DNP as a by-product became a problem over such reaction times. Furthermore, the use of zeolite HZSM-5 (Si/Al = 30) for a longer reaction time did not improve the selectivity of the reaction towards 4-NP and 48 h was therefore reasonable to use as a reaction time.

## 3.19. Effect of type of solvent in reaction of phenol over zeolite HZSM-5 (Si/Al = 30)

In an attempt to increase the yield of nitrophenols further, the nitration of phenol was carried out over zeolite HZSM-5 in various solvents. The solvents, namely diethyl ether ($Et_2O$), dichloromethane (DCM), 1,2-dichloroethane (DCE) and tetrachloroethylene (TCE), differed in their boiling points (diethyl ether, 35 °C; dichloromethane, 40 °C; 1,2-dichloroethane, 83 °C ; tetrachloroethylene, 121 °C), which would be significant since reactions were carried out under reflux conditions [for 48 h in the presence of zeolite HZSM-5 (2 g)]. The results obtained from this series of reactions after work up followed by quantitative GC are recorded in Table 3.18.

The results indicated that the solvents tried except diethyl ether can accommodate the reaction. It seems that diethyl ether is not a good solvent for nitration of phenol under the conditions tried. The general trend on increasing the boiling point of solvent was an increase in *ortho*-nitrophenol. When TCE was used as the solvent, 2,4-DNP was produced in 6% yield and was increased to 29% when the reaction time was 72 h.

**Table 3.18: Nitration of phenol with *iso*-propyl nitrate in different solvents over zeolite HZSM-5 (Si/Al = 30)[a]**

| Solvent | B.P of solvent °C | Yield (%) | | | | | Conversion[b] | Mass Balance (%)[c] |
|---|---|---|---|---|---|---|---|---|
| | | P | 2-NP | 4-NP | 2,4-DNP | *i*-PB | | |
| **$Et_2O$** | 35 | 60 | — | — | — | — | 40 | 60 |
| **DCM[d]** | 40 | 44 | 3 | 2 | — | — | 56 | 49 |
| **DCE** | 83 | 31 | 29 | 28 | — | 1 | 69 | 89 |
| **TCE** | 121 | — | 38 | 30 | 6 | 1 | 100 | 75 |
| **TCE[d]** | 121 | — | 24 | 9 | 29 | — | 100 | 62 |

[a] A mixture of phenol (0.90 g; 9.5 mmol), *iso*-propyl nitrate (2.0 g, 19.0 mmol) and HZSM-5 (Si/Al = 30) in the appropriate solvent (50 ml) was heated under reflux for 48 h.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum of P, 2-NP, 4-NP, 2,4-DNP and *i*-PB% as calculated by quantitative GC.
[d] Reaction for 72 h.

It seems likely that either DCE or TCE could be used successfully as a solvent and would provide similar yields and selectivity. However, in terms of high boiling point and high cost, TCE is not recommended as a solvent and DCE was used in further investigations. Similar observations were noticed when zeolite Hβ was used as the catalyst under similar reaction conditions. Also, it can be seen that when reaction was carried out in the higher boiling point solvent (TCE) the reaction was complete and no phenol remained.

## 3.20. Effect of type of alkyl nitrate on nitration of phenol over zeolite HZSM-5 (Si/Al = 30)

In order to investigate the effect of the nature of the alkyl nitrate on nitration of phenol we decided to use *n*-butyl and *iso*-butyl nitrates under conditions very similar to those used with *iso*-propyl nitrate, for various times. The time was varied from 48 to 96 h and reactions were carried out under identical conditions except that the reaction time and type of nitrate were different. The results obtained, after work up and quantitative GC analysis of reactions mixtures, are recorded in Table 3.19.

**Table 3.19: Nitration of phenol with various alkyl nitrates over zeolite HZSM-5 (Si/Al = 30)[a]**

| Alkyl nitrate | Time (h) | Yield (%)[b] | | | | Mass Balance (%)[c] |
|---|---|---|---|---|---|---|
| | | P | 2-NP | 4-NP | 2,4-DNP | |
| ***iso*-propyl nitrate** | **48** | 31 | 29 | 28 | — | 86 |
| ***n*-butyl nitrate** | **48** | 72 | 6 | — | — | 78 |
| ***iso*-butyl nitrate** | **48** | 80 | 5 | — | — | 85 |
| ***iso*-butyl nitrate[d]** | **96** | 49 | 1 | 1 | — | 51 |
| ***iso*-butyl nitrate[e]** | **96** | 55 | 7 | 7 | 11 | 69 |
| ***iso*-butyl nitrate[f]** | **96** | 4 | 10 | 17 | 33 | 64 |

[a] Reactions were carried out with zeolite HZSM-5 (Si/Al= 30; 2.0 g), phenol (0.90 g; 9.5 mmol) and *iso*-butyl nitrate (2.0 g, 19.0 mmol) in dichloroethane (50 ml) under reflux conditions for the stated reaction time.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum of P, 2-NP, 4-NP, 2,4-DNP and 2,6-DNP% calculated by quantitative GC.
[d] Reaction carried out in dichloromethane (DCM) under reflux conditions.
[e] Reaction carried out in dichloroethane (DCE) under reflux conditions.
[f] Reaction carried out in tetrachloroethylene (TCE) under reflux conditions.

The results showed that only low yields (5-6%) of 2-NP were produced when either *n*-butyl or *iso*-butyl nitrate was used under reflux conditions in DCE for 48 h. Carrying out the reaction with *iso*-butyl nitrate for 96 h led to an increase in the yield of nitrophenols (7% each) but also resulted in production of 11% of 2,4-DNP. Also, we attempted this reaction with two different solvents, DCM and TCE, under reflux conditions for 96 h. For all of the reactions carried out over the longer reaction period the mass balances were lower, consistent with greater loss of phenol through evaporation. The yield of nitrophenols was only 2% when DCM was used as the solvent, indicating that the reaction was very slow at the modest reflux temperature of that solvent. In the highest boiling solvent, TCE, the total yield of nitration products was greatest, but there was a very high proportion of 2,4-DNP (33%). Interestingly, the proportion of 4-NP was significantly higher than that of 2-NP, which is in contrast to the situation when *iso*-propyl nitrate was used as the reagent under otherwise similar conditions (see Table 3.18). It is not clear why, with *iso*-butyl nitrate, the 4-NP should be further nitrated less readily than the 2-NP, when in all other cases the reverse has been observed.

However, it seemed that using *n*-butyl or *iso*-butyl nitrate had no major benefit for the production of high yields of mononitrophenols. Therefore, our attention was next turned to study the effect of quantity of zeolite HZSM-5 (Si/Al = 30) on the reaction using *iso*-propyl nitrate.

### 3.21. Effect of quantity of zeolite HZSM-5 (Si/Al = 30) on nitration of phenol

In order to investigate the effect of the quantity of zeolite on both reactivity and selectivity of nitration of phenol, a series of reactions was conducted in which the quantity of zeolite HZSM-5 was varied from 1 to 4 g for 9.5 mmol of phenol. Reactions were carried out in refluxing DCE for 48 h under identical conditions except that the quantity of the catalyst was different. The results obtained are recorded in Table 3.20.

The results indicated that the quantity of zeolite had an effect on the reaction. The general trend on increasing the quantity of HZSM-5 (Si/Al = 30) from 1 to 3 g was an increase in conversion and yield of nitrophenols. However, increasing the zeolite quantity to 4 g did not increase either the conversion or yield of nitrophenols, presumably because the mobility of the reaction mixture became difficult. Therefore it was concluded that 3 g of zeolite would be a better choice in such nitration reactions.

**Table 3.20: Nitration of phenol with *iso*-propyl nitrate using various quantities of zeolite HZSM-5 (Si/Al = 30)[a]**

| **HZSM-5 (g)** | **Yield (%)** | | | | **Mass Balance (%)[c]** | ***p/o* ratio** |
|---|---|---|---|---|---|---|
| | **P** | **2-NP** | **4-NP** | ***i*-PB** | | |
| **1** | 36 | 25 | 24 | 1 | 85 | 1 |
| **2** | 31 | 29 | 28 | 1 | 89 | 1 |
| **3** | 10 | 36 | 43 | 1 | 89 | 1.2 |
| **4** | 27 | 29 | 32 | — | 88 | 1.1 |

[a] A mixture of phenol (0.90 g; 9.5 mmol), *iso*-propyl nitrate (2.0 g, 19.0 mmol) and HZSM-5 (Si/Al= 30) in DCE (50 ml ) was heated under reflux for 48 h.
[b] Percentage of residual phenol was calculated by quantitative GC.
[c] Sum of P, 2-NP, 4-NP, 2,4 DNP and *i*-PB%, calculated by quantitative GC.

We next conducted a nitration of phenol (9.5 mmol) over zeolite HZSM-5 (Si/Al = 30, 3 g) under reflux in dichloroethane for a prolonged reaction time (84 h). As expected, the conversion of phenol was 100% under such conditions, and the yields of 2-NP, 4-NP and 2,4-DNP were 38, 25 and 24%, respectively, with no *iso*-propoxybenzene detected. This was not as good as the shorter reaction period in terms of yield of mononitration products.

In conclusion, therefore, the highest yield of mononitration products from reaction of phenol (9.5 mmol) with an alkyl nitrate over a zeolite catalyst are with a reaction time of 48 h over zeolite HZSM-5 (Si/Al = 30, 3 g) with *iso*-propyl nitrate

(19 mmol), which gives high yields of mononitrophenols with a *para/ortho* ratio of 1.2. However, clearly the use of zeolites has not resulted in the development of a highly *para*-selective reaction.

### 3.22. Conclusions

Proton forms of several zeolites are able to catalyse the reaction of phenol with *iso*-propyl nitrate, which does not take place in the absence of a catalyst. Zeolite Hβ with a Si/Al ratio of 12.5 was the most active of the catalysts tried and also gave the highest proportion of *para*-nitrophenol, but the *para/ortho* ratio was still only around 1:1. Mono nitrophenols are formed in high yields (almost quantitative if steps are taken to prevent evaporation of phenol from the reaction vessel) when reactions are carried out over two days in refluxing DCE. The slow step is probably formation of an active nitrating species, which then probably reacts rather indiscriminately at the relatively high temperatures employed, leading to the low selectivity observed. A somewhat higher yield of mononitration products and a slightly better *para/ortho* ratio could be achieved with a larger quantity of HZSM-5 under otherwise similar conditions.

The reactions also produced small quantities of *iso*-propoxybenzene as the main by-product. *iso*-Propoxybenzene has been identified by GC-MS of a product mixture and by preparation of an authentic sample of the product.

## 3.23. Experimental Section

### 3.23.1. Materials

Chemicals and solvents were purchased from Aldrich Chemical Company and used without further purification. Commercial zeolites were purchased from Aldrich Chemical Company or Zeolyst International. All zeolite catalysts were freshly calcined at 550 °C for a minimum of 6 h prior to use.

### 3.23.2. Analysis and Characterisation of the Products

Product mixtures from the nitration reactions of phenol (Scheme 3.1) were subjected to gas chromatography on a HEWLETT PACKARD SERIES II 5890 gas chromatograph, fitted with a ZEBRON ZB-5 (5% phenyl polysiloxane) 30 m length column. The GC conditions used for analysis were: 60 °C for 1 minute, ramped to 160 °C at 15 °C/min and held for 3 min. The injection temperature was 250 °C and the detection temperature 300 °C. Tetradecane was used as an internal standard. Phenol and *iso*-propyl nitrate are commercial materials and were used without further purification.

*iso*-Propoxybenzene was characterised by NMR spectroscopy and mass spectrometry. The $^1H$ NMR spectrum of *iso*-propoxybenzene was recorded on a Bruker AV400 spectrometer operating at 400 MHz for $^1H$ measurement. The sample was run in $CDCl_3$ and tetramethylsilane (TMS) was used as the internal standard. Chemical shifts $\delta$ are reported in parts per million (ppm) relative to TMS. The $^1H$ multiplicities are reported d (doublet), dd (double doublet), t (triplet) and sep (septet).

The Electron-Impact Mass Spectrum (EI-MS) of *iso*-propoxybenzene was recorded on a VG 12-250 low resolution quadrupole instrument. The high resolution mass spectrum (accurate mass measurement) of *iso*-propoxybenzene was performed on a ZAB-E high resolution double-focusing instrument.

The Gas Chromatography Mass Spectrum (GCMS) analysis of the products mixture was recorded on a Fisons GC8000 gas chromatograph fitted with a 95% dimethylpolysiloxane 5% phenol (30 m, 0.32 mm ID, film thickness 1μm) capillary column, directly interfaced with a Fisons Masslab MD800 low-resolution GCMS instrument using the electron impact (EI) technique. Mass charge ratios are given in Daltons followed by their percentage relative abundance.

### 3.23.3. GC Analytical procedure

All available expected isomeric products [purchased from Aldrich Chemical Company (99% purity), or obtained following purification following traditional nitration reactions] were injected into the GC individually to record the retention time for each product (see Table 3.21).

**Table 3.21:** Retention time for each standard

| Expected products | Retention time (min) |
|---|---|
| Phenol (P) | 1.33 |
| 2-Nitrophenol (2-NP) | 2.75 |
| 4-Nitrophenol (4-NP) | 6.06 |
| 2,4-Dinitrophenol (2,4-DNP) | 6.01 |
| 2,6-Dinitrophenol (2,6-DNP) | 6.33 |
| Tetradecane (TD) | 4.15 |
| *iso*-Propoxybenzene (*i*-PB) | 1.96 |

Tetradecane was used as a standard in all reactions because it did not overlap with any of the expected products or the starting materials and also it had clear integration. A known weight of each potential component was mixed with a known weight of tetradecane. The mixture was dissolved in analytical grade acetone in a volumetric flask (100 ml). A small quantity (0.5 µl) from each mixture was injected into the GC for a few times and the response factor (RF) for each component was calculated using Equation 3.5. The average response factor (RF) was then calculated for each component.

$$\text{R.F. of compound} = \frac{\text{mass of compound}}{\text{mass of tetradecane}} \cdot \frac{\text{peak area of tetradecane}}{\text{peak area of compound}}$$

**Equation 3.5: Calculation of response factor (RF)**

The response factors (RF) were then used to quantify each reaction mixture and the weight of each product was calculated, using Equation 3.6.

$$\text{mass of compound} = \text{R.F. compound} \cdot \text{mass of tetradecane} \, \frac{\text{peak area of compound}}{\text{peak area of tetradecane}}$$

**Equation 3.6: Calculation of mass of reaction components**

The number of mmol of each component was then calculated from its weight and these figures were used to calculate yields and ratios of products.

### 3.23.4. Calculation of the yield

Equation 3.7 was used to calculate the yield of different product from each reaction mixture.

$$\text{Yield of product (x)} = \frac{\text{no. of mmol of product (x)}}{\text{no. of mmol of starting material}} \text{ X } 100$$

**Equation 3.7: Calculation of yield of products**

### 3.23.5. Calculation of Ratios

Equation 3.8 was used to calculate the ratio between isomers.

$$\text{Ratio of X:Y} = \frac{\text{Yield of X}}{\text{Yield of Y}}$$

**Equation 3.8: Calculation of isomers ratios**

### 3.23.6. Calculation of Mass balance

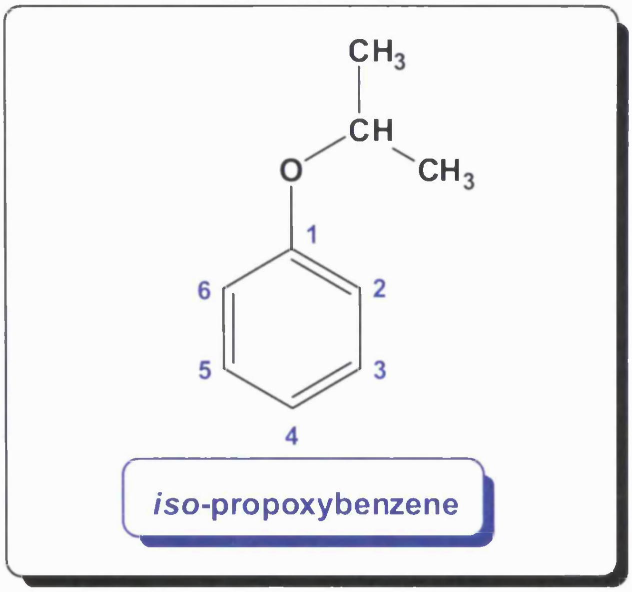
In this thesis the term mass balance is used to mean the sum of the yields (%) of nitro products together with the remaining starting material (if there is any). The mass balance in most cases was low (*ca.* 65%), suggesting that there were losses of material during the long reaction times at reflux temperatures.

### 3.23.7. Typical experimental procedure for the nitration of phenol in the presence of an acidic zeolite catalyst

Quantities are recorded in the footnotes to the appropriate tables or text. All reactions were carried out in a 250 ml round bottomed flask equipped with a water condenser and a magnetic stirrer. In a typical experiment, a mixture of zeolite Hβ (Si/Al = 12.5; 2.0 g), *iso*-propyl nitrate (2.0 g, 19.0 mmol) and phenol (0.90 g, 9.5 mmol) in 1,2-dichloroethane (DCE, 50 ml) was heated under reflux for the appropriate reaction time. At the end of the reaction period, the bulk sample was filtered and the catalyst was washed with DCE (3 x 30 ml). The solution was concentrated under reduced pressure and then made up to 50 ml with DCE in the presence of tetradecane (0.10 g) as an internal standard. The mixture was analysed by gas chromatography and the yields of all identified components were calculated.

### 3.23.8. Preparation of the *iso*-propoxybenzene

A mixture of finely cut sodium (1.15 g, 50 mmol) and absolute ethanol (30 ml) was stirred until the sodium dissolved. Phenol (4.70 g; 50 mmol) was added to the sodium ethoxide produced in situ, followed by the addition of 2-bromopropane (6.70 g; 55 mmol). The mixture was brought to reflux and stirred under reflux for 6 hours. Ethanol and excess of 2-bromopropane were removed by distillation using a steam bath. To the residue obtained after distillation diethyl ether (30 ml) and water (30 ml) were added. The layers were separated and the organic layer was washed with aqueous sodium hydroxide (15%; 2 x 30 ml) to remove any unreacted phenol. The organic layer was washed with water (2 x 30 ml), dried over anhydrous $MgSO_4$, filtered and then purified by distillation. Pure *iso*-propoxybenzene was obtained in 40% yield (2.76 g) as a colourless liquid. The structure of *iso*-propoxybenzene was confirmed by various analytical techniques involving $^1H$ NMR and mass spectrometry and the data were consistent with published results.[37-46] Also, the material obtained was pure as checked by GC.



$^1$H NMR ($CDCl_3$): $\delta$=7.17 (apparent t, $J$ = 7.5 Hz, 2 H, H-3/H-5), 6.82 (t, $J$ = 7.5 Hz, 1 H, H-4), 6.80 (d, $J$ = 7.5 Hz, 2 H, H-2/H-6), 4.45 (septet, $J$ = 6.0 Hz, 1 H, CH), 1.24 (d, $J$ = 6.0 Hz, 6 H, 2 $CH_3$).

EI-MS: $m/z$ (%): 136 ($M^+$, 100) and 94 [$(M - C_3H_6)^+$, 100].

HRMS: $m/z$ calc. for $C_9H_{12}O$ ($M^+$), 136.0883; found, 136.0884.

### 3.23.9. Breakdown of zeolites with HF

Hydrofluoric acid (100 ml, 35%) was added to recovered zeolite (7.0 g) in a 1000 ml beaker, the mixture was stirred for 2-3 minutes to dissolve the zeolite, and then aqueous sodium hydroxide (1 M; 300 ml) was added and the mixture was diluted with water (300 ml) (to avoid damaging the Buchner funnel) and then filtered. The filtrate was extracted with diethyl ether (6 × 80 ml) and the extract was washed with water (3 × 90 ml). The solid was washed with acetone (3 x 30 ml) and the combined organic extracts were dried over magnesium sulfate ($MgSO_4$). The material was filtered, and the filtrate was evaporated under reduced pressure. The residue obtained was then injected into the GC.

## 3.24. References

1. K. Schofield, *Aromatic Nitration*, Cambridge University press, Cambridge, 1980.
2. G. A. Olah, R. Malhotra and S. C. Narang, *Nitration Methods and Mechanisms*, VCH, New York, 1989.
3. R. G. Coombes, J. G. Golding and P. Hadjigeorgiou, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1451.
4. J. H. Clark, *Acc. Chem. Res.*, 2002, **35**, 791.
5. *Catalysis of Organic Reactions using Supported Inorganic Reagents*, ed. J. H. Clark VCH, New York, 1994.
6. L. Delaude, P. Laszlo and K. Smith, *Acc. Chem. Res.*, 1993, **26**, 607.
7. K. Smith, In: *New Aspects of Organic Synthesis II*, eds. Z. Yoshida and Y. Ohshiro Kadonsha, Tokyo and VCH, Weinheim, 1992, 43.
8. M. Butters, In *Solid Supports and Catalysts in Organic Synthesis*, ed. K. Smith, Ellis Horwood, Chichester, 1992, 130.
9. K. Smith, In *Catalysis of Organic Reactions*, ed. M. G. Scaros and M. L. Prunier, Marcel Dekker, New York, 1991, 91.
10. K. Smith and G. A. El-Hiti, *Curr. Org. Synth.*, 2004, **1**, 253.
11. K. Smith and G. A. El-Hiti, *Curr. Org. Chem.*, 2006, **10**, 1603.
12. K. Smith, S. D. Roberts and G. A. El-Hiti, *Org. Biomol. Chem.*, 2003, **1**, 1552.

13. K. Smith, G. A. El-Hiti, A. J. Jayne and M. Butters, *Org. Biomol. Chem.*, 2003, **1**, 1560.
14. K. Smith, G. A. El-Hiti, A. J. Jayne and M. Butters, *Org. Biomol. Chem.*, 2003, **1**, 2321.
15. K. Smith, G. M. Ewart, G. A. El-Hiti and K. R. Randles, *Org. Biomol. Chem.*, 2004, **2**, 3150.
16. K. Smith, G. A. El-Hiti, M. E. W. Hammond, D. Bahzad, Z. Li and C. Siquet, *J. Chem. Soc. Perkin Trans. 1*, 2000, 2745.
17. K. Smith, M. Butters, W. E. Paget, D. Goubet, E. Fromentin and B. Nay, *Green Chem.*, 1999, **1**, 83.
18. K. Smith, A. Musson and G. A. DeBoos, *J. Org. Chem.*, 1998, **63**, 8448.
19. K. Smith, T. Gibbins, R. W. Millar and R. P. Claridge, *J. Chem. Soc. Perkin Trans. 1*, 2000, 2753.
20. K. Smith, S. Almeer and S. J. Black, *Chem. Commun.*, 2000, 1571.
21. K. Smith, S. Almeer, and C. Peters, *Chem. Commun.*, 2001, 2748.
22. K. Smith, S. Almeer, S. J. Black and C. Peters, *J. Mater. Chem.*, 2002, **12**, 3285.
23. J. A. R. Rodrigues, A. P. de Oliveira Filho, P. J. S. Moran and R. Custódio, *Tetrahedron*, 1999, **55**, 6733.
24. W.-P. Yin and M. Shi, *Tetrahedron*, 2005, **61**, 10861; B. Gigante, A. O. Prazeres, M. J. Marcelo-Curto, A. Cornélis and P. Laszlo, *J. Org. Chem.*, 1995, **60**, 3445; and references cited therein.
25. T. Milczak, J. Jacniacki, J. Zawadzki, M. Malesa and W. Skupiński, *Synth. Commun.*, 2001, **31**, 173.

26. M. M. Heravi, T. Benmorad, K. Bakhtiari, F. F. Bamoharram and H. H. Oskooie, *J. Mol. Catal. A: Chem.*, 2007, **264**, 318; S. Mallick and K. M. Parida, *Catal. Commun*,, 2007, **8**, 1487.

27. K. M. Parida and D. Rath, *J. Mol. Catal. A: Chem.*, 2006, **258**, 381.

28. J. M. Riego, Z. Sedin, J.-M. Zaldlvar, N. C. Marzianot and C. Tortato, *Tetrahedron Lett.*, 1996, **37**, 513.

29. M. A. Zolfigol, E. Ghaemi and E. Madrakian, *Molecules*, 2001, **6**, 614.

30. K. R. Sunajadevi and S. Sugunan, *Catal. Commun.*, 2005, **6**, 611; K. R. Sunajadevi and S. Sugunan *Mater. Lett.*, 2006, **60**, 3813.

31. A. S. Khder and A. I. Ahmed, *Appl. Catal., A*, 2009, **354**, 1530.

32. S. P. Dagade, V. S. Kadam and M. K. Dongare, *Catal. Commun.*, 2002, **3**, 67.

33. T. Esakkidurai and K. Pitchumani, *J. Mol. Catal. A: Chem.*, 2002, **185**, 305.

34. R. Taylor, *Electrophilic Aromatic Substitution*; Wiley, Chichester, 1990, p. 263; D. Vione, S. Belmondo and L. Carnino, *Environ. Chem. Lett.*, 2004, **2**, 135.

35. K. Smith, M. D. Ajarim, G. A. El-Hiti and C. Peters, *Top Catal.*, 2009, **52**, 1696.

36. K. Smith, In: *Solid Supports and Catalysts in Organic Synthesis*, Ellis Horwood Ltd., Chichester, 1992.

37. Eight Peak Index of Mass Spectra, 3rd ed., The Royal Society of Chemistry, Nottingham University, Nottingham, 1983.

38. J. J. Houser, M. C. Chen and S. S. Wang, *J. Org. Chem.*, 1974, **39**, 1387.

39. R. A. Smith, *J. Am. Chem. Soc.*, 1934, **56**, 717.

40. W. T. Olson, H. F. Hipsher, C. M. Buess, I. A. Goodman, I. Hart, J. H. Lamneck and L. C. Gibbons, *J. Am. Chem. Soc*, 1947, **69**, 2451.

41. J. B. Niederl and S. Natelson, *J. Am. Chem. Soc*, 1931, **53**, 1928.

42. B. A. Stoochnoff and N. L. Benoiton, *Tetrahedron Lett.*, 1973, **1**, 21.

43. M. A. Keegstra, T. H. A. Peters and B. Lambert, *Tetrahedron*, 1992, **48**,3633.

44 A. I. Vogel, *J. Chem. Soc.*, 1948, 616.

45. S. K. Chung and K. Sasamoto, *J. Org. Chem.*, 1981, **46**, 4590.

46. D. Harnish and J. L. Holmes, *J. Am. Chem. Soc*, 1991, **113**, 9729.

47. T. B. Dorris, F. J. Sowa and J. A. Nieuwland, *J. Am. Chem. Soc*, 1938, **60**, 656.

# CHAPTER FOUR

# SELECTIVE NITRATION OF DEACTIVATED MONO-SUBSTITUTED BENZENES

# CHAPTER FOUR

# Selective nitration of deactivated mono-substituted benzenes

## 4.1. Introduction

As discussed in previous chapters, nitration of aromatic compounds is one of the most important and widely studied chemical reactions[1-5] because nitro aromatic compounds are very important intermediates for the production of industrially important chemicals and are used in the synthesis of polyurethanes, explosives, agrochemicals, pharmaceuticals, fragrances and dyes.[6,7]

The traditional method for nitration of deactivated aromatic compounds involves the use of a mixture of nitric and sulfuric acids in the ratio of 1:2 and gives the corresponding nitro derivatives in high yield, with the *meta*-isomers predominating. Under such conditions, *para*-isomers are produced in low yield.[1] For example, nitration of benzonitrile gave nitrobenzonitriles in which the *ortho*/*meta*/*para* ratio was 17/81/2.[1] We were interested to see if a process could be devised that would give higher yields of *para*-isomers.

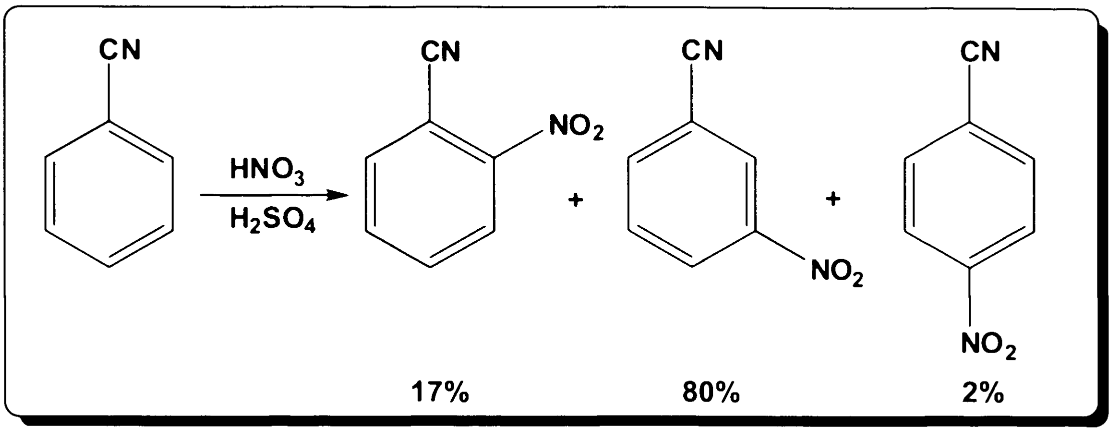
The poor selectivity and other disadvantages of the traditional process have stimulated efforts to improve the mixed acids process, resulting in sulfuric acid being replaced by other acidic reagents such as perchloric acid or $P_2O_5$.[8-10] However, these processes still suffer from serious limitations. For example, the work-up procedure may lead to the generation of large quantities of corrosive waste, which are expensive to dispose of or to recycle. Of course, the selectivity for *para*-isomer remains very low as the reactions still produce mainly *meta*-isomers.

Several catalytic systems have been developed for the nitration of deactivated aromatics. These include nitrogen dioxide at low temperatures in the presence of ozone,[11] $N_2O_5$ in the presence of Fe(acac)$_3$ as a catalyst,[12] urea nitrate and nitrourea,[13] nitroguanidine and ethylene glycol dinitrate in concentrated acid,[14] vanadium(V) oxytrinitrate in dichloromethane at room temperature,[15] $NO_2BF_4$[16] and nitric acid in the presence of MCM-41-supported metal bis[(perfluoroalkyl)sulfonyl]imides in dichloroethane.[17] Unfortunately, such reagents still gave mainly the *meta*-products and the *para*-selectivity was low. Moreover, *ortho*-isomers were often formed in relatively high proportions under the conditions. Also, when benzonitrile was nitrated with urea nitrate, 3-nitrobenzamide was produced in a high yield (78%) due to hydrolysis of the initially obtained, 3-nitrobenzonitrile.[13]

Again, as explained in earlier chapters, it is well recognised that zeolites and other solid catalysts can play an important role in the development of greener organic syntheses through their abilities to act as recyclable heterogeneous catalysts, support reagents, entrain by-products, avoid aqueous work-ups and enhance product selectivities.[18-25] For example, K. Smith's group have shown that zeolites or other solids can have advantages in alkylation,[26] acylation,[27,28] methanesulfonylation,[29] bromination,[30] chlorination[31] and nitration[32-37] of aromatic compounds.

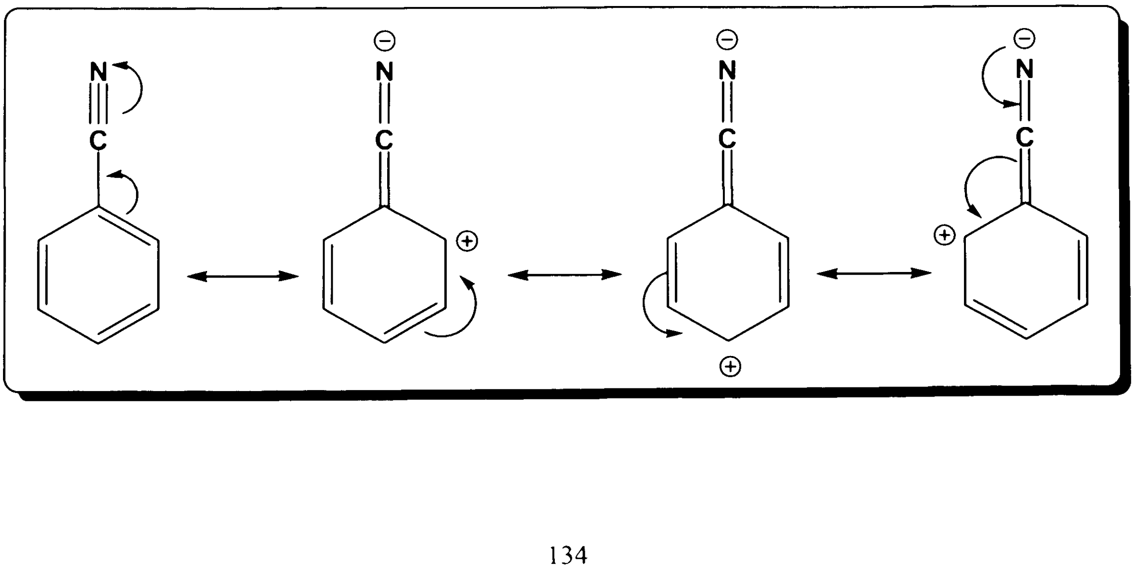
Our aim was to investigate whether nitration of benzonitrile and other deactivated aromatics could take place selectively and catalytically by the use of acidic solid catalysts such as zeolites. Before doing so, we attempted nitration of benzonitrile using the traditional procedure in order to see if the reported results could be achieved and also this result could be used as a baseline for comparison with the ones to be produced over solid catalysts. The work represented in this chapter has been published.[38]

Nitration of benzonitrile with a mixture of $HNO_3$ and $H_2SO_4$ at 0 °C for 10 minutes in a solvent free process gave a mixture of nitrobenzonitriles in quantitative yields in which the *meta:ortho:para* ratio was 80:17:2 (Scheme 4.1). This result is identical with the one reported under similar conditions.[1]



**Scheme 4.1: Nitration of benzonitrile using mixed acids**

The *meta*-isomer is expected to be the major product from nitration of benzonitrile due to the electron withdrawing effect of the cyano group (CN), which tends to decrease the electron density on the ring especially at the 2- and 4-positions (Scheme 4.2). The results also indicated that a significant quantity of the *ortho*-product was formed, presumably because the cyano group is linear and provides little steric hindrance to *ortho*-nitration. However, it is not obvious why the amount of *para*-isomer is so much lower than that of the *ortho*-isomer.



**Scheme 4.2: Electron withdrawing effect of cyano group on reactivity of benzonitrile towards electrophilic substitution reactions**

Various attempts have been made previously within the group of Keith Smith to find conditions under which deactivated mono-substituted benzenes could be nitrated effectively and selectively.[37,39] Chloroacetic anhydride $[(ClCH_2CO)_2O)]$ and trifluoroacetic anhydride (TFAA) were found to be the most reactive anhydrides among the acid anhydrides tried.[37,39] For example nitration of deactivated substrates, such as nitrobenzene, benzonitrile and benzoic acid, using a nitric acid, trifluoroacetic anhydride and zeolite Hβ system at low temperature (-10 °C) gave the corresponding nitro products in 17-86% yields in which the proportions of the *para*-isomers were in the range of 1-19%.[37,39] Also, under some of the conditions tried there was no evidence for formation of *ortho*- isomer.

We thought that more work needed to be done in order to improve the yield and selectivity in this reaction. Therefore, we decided to undertake a detailed study of nitration of benzonitrile and other deactivated aromatics over zeolites under various reaction conditions. The reactions involve use of acid anhydrides and nitric acid, which readily produce acyl nitrates quantitatively *in- situ* (Equation 4.1).[1]

$$HNO_3 + (RCO)_2O \rightleftharpoons RCO_2H + RC(O)ONO_2$$

**Equation 4.1: Production of acyl nitrates from reaction of nitric acid with acid anhydrides**

Dinitrogen pentoxide can be produced *in situ* if the reaction mixture contains excess nitric acid (Equation 4.2).[2] Also, under such conditions an additional molecule of the corresponding carboxylic acid is formed.

$$2\,HNO_3 + (RCO)_2O \rightleftharpoons N_2O_5 + 2\,RCO_2H$$

**Equation 4.2: Formation of dinitrogen pentoxide**

Also, the presence of water in the nitric acid could hydrolyse the acid anhydride to produce the corresponding carboxylic acid (Equation 4.3).

$$(RCO)_2O + H_2O \rightleftharpoons 2\,RCO_2H$$

**Equation 4.3: Effect of water on acid anhydride**

The first task in the present contest was to investigate the direct nitration of benzonitrile using the $HNO_3/(RCO)_2O/H\beta$ system.

## 4.2. Nitration of benzonitrile with a $(ClCH_2CO)_2O/HNO_3/H\beta$ system in DCM at room temperature

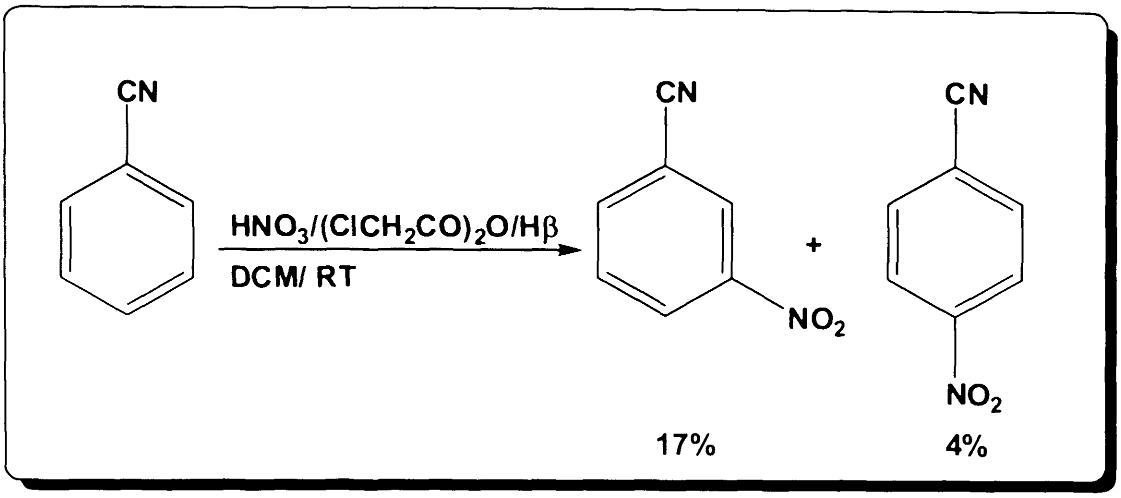
Previous results within our group indicated that $(ClCH_2CO)_2O$ and/or TFAA were the most effective anhydrides among the anhydrides used but yields of nitro products were only moderate and the selectivity towards the *para*-isomer was low in most cases.[37,39] Therefore, we decided to use chloroacetic anhydride first with nitric acid in nitration of benzonitrile. It was expected that chloroacetic anhydride would be less reactive than TFAA as an anhydride but at the same time it was hoped that it would be more selective. Mixing nitric acid and chloroacetic anhydride can readily produce chloroacetyl nitrate quantitatively *in-situ* (Equation 4.4).[1]

$$HNO_3 + (ClCH_2CO)_2O \rightleftharpoons ClCH_2CO_2H + ClCH_2C(O)ONO_2$$

### Equation 4.4: Production of chloroacetyl nitrate *in-situ*

The scale of nitration of benzonitrile was based on the use of 9.5 mmol of benzonitrile. Theoretically, 9.5 mmol of nitric acid (100%) and at least 9.5 mmol of chloroacetic anhydride are required to convert benzonitrile (9.5 mmol) into nitrobenzonitriles quantitatively. However, production of chloroacetyl nitrate from dilute nitric acid requires the use of an excess of chloroacetic anhydride to react with the water present. This leads to the production of chloroacetic acid, which would deactivate the zeolite. It is therefore beneficial to use highly concentrated nitric acid (100%) for the production of chloroacetyl nitrate (Equation 4.4). However, previous results indicated that acyl nitrate should be used in a large excess. The literature showed that zeolite Hβ (Si/Al = 12.5) was one of the most efficient catalysts in the nitration reactions of simple aromatics using various types of nitrating species.[32-37] Therefore, zeolite Hβ (Si/Al = 12.5) was initially chosen as the catalyst.

Initially, benzonitrile (9.5 mmol) was added to stirred mixture of chloroacetic anhydride (19 mmol), $HNO_3$ (19 mmol) and zeolite Hβ (Si/Al = 12.5; 2 g) in dichloromethane (DCM, 20 ml) (Scheme 4.3) in a 250 ml round-bottomed flask equipped with a magnetic bar. Also, the flask was equipped with an air condenser to which a calcium chloride tube was attached. The mixture was stirred for 2 h at room temperature before analytical grade acetone (*ca.* 10 ml) was added to the mixture through the condenser. The whole mixture was stirred for 5 min and zeolite Hβ was removed by suction filtration. The zeolite was washed repeatedly with acetone (3 x 15 ml) until the zeolite became white and/or the filtrate became colourless. The washings were combined and transferred to a 100 ml volumetric flask into which tetradecane was added as internal standard. The mixture was then quantitatively analysed by GC.



**Scheme 4.3: Nitration of benzonitrile at room temperature with a $(ClCH_2CO)_2O/HNO_3/H\beta$ system**

It was found that the yield of nitrobenzonitriles was 21% and that the *meta*:*para* ratio was 17:4 (Scheme 4.3). Also, there was no evidence for the formation of 2-nitrobenzonitrile under the conditions tried. The GC analysis also indicated clearly that most of the starting material (*ca.* 80%) was recovered. The low yield of nitrobenzonitriles prompted us to investigate the reaction further in an attempt to find conditions under which the yield and/or selectivity could be improved.

The obvious factor was varying the reaction time in the hope that more time could allow completion of the reaction. It was very important to know the optimum reaction time which would allow the production of a high yield of the desirable product. Also, another purpose of these experiments was to test the progression of the nitration reaction of benzonitrile. Therefore, attention was next turned to investigate how the reaction time affects the yield of 4-nitrobenzonitrile. Nitration of benzonitrile with chloroacetyl nitrate over zeolite Hβ was investigated using various reaction times (5 min to 24 h) under identical conditions to those described in Scheme 4.3. Each reaction was worked up and analysed quantitatively by GC using tetradecane as an internal standard. The results obtained are recorded in Table 4.1 and also represented graphically in Figure 4.1.

**Table 4.1: Effect of the reaction time on nitration of benzonitrile over the $(ClCH_2CO)_2O/HNO_3/H\beta$ system at room temperature according to Scheme 4.3**[a]

| *TIME (h)* | *Yield (%)*[b] | | | *Conversion*[c] | *Mass Balance (%)* |
|---|---|---|---|---|---|
| | **BN** | **4-NBN** | **3-NBN** | | |
| **5 min** | 95 | 0 | 4 | 5 | 99 |
| **0.5** | 80 | 4 | 17 | 20 | 101 |
| **2** | 80 | 4 | 17 | 20 | 101 |
| **3** | 82 | 4 | 16 | 18 | 102 |
| **4** | 80 | 4 | 15 | 20 | 99 |
| **8** | 80 | 5 | 18 | 20 | 103 |
| **24** | 78 | 4 | 17 | 22 | 99 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), chloroacetic anhydride (19 mmol, 3.25 g) and zeolite Hβ ( Si/Al = 12.5; 2 g) in DCM (20 ml) was stirred at room temperature for the appropriate reaction time.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] 100 - BN %.

The results shown in Table 4.1 and Figure 4.1 indicated that there was no further reaction after 30 minutes, with the yield of *para*-isomer always being in the range of only 4-5% along with 15-18% yield of the *meta*-isomer. This shows that 20% of the reaction took place within the first 30 min and the reaction stopped thereafter. It is not realistic that leaving the reaction for an even longer period would cause any further increase in the yield of nitrobenzonitriles (NBNs).

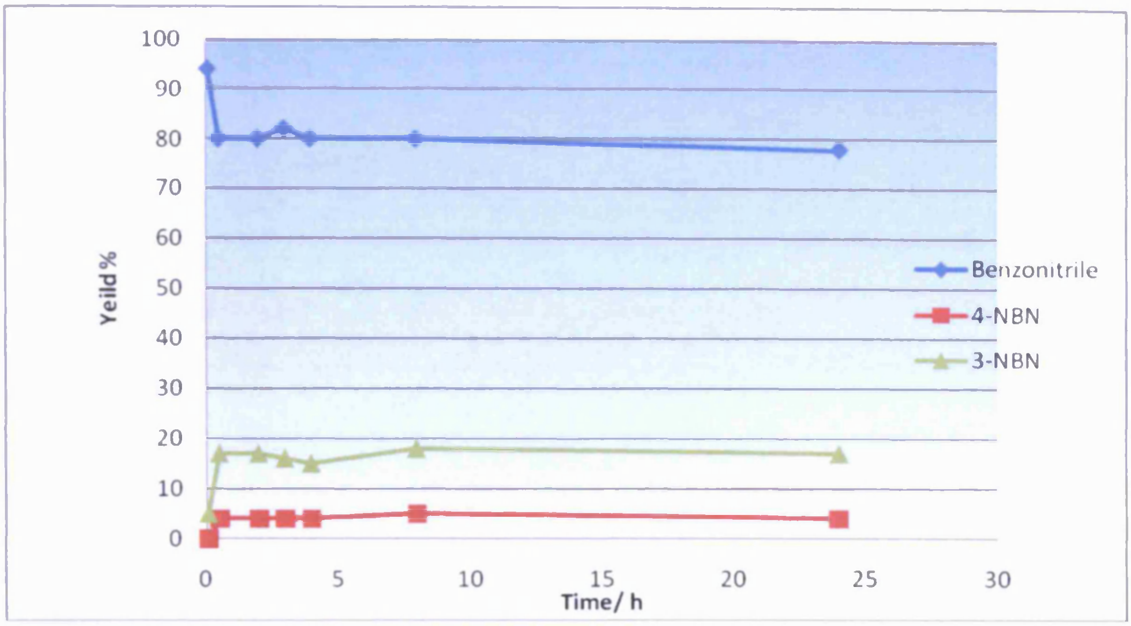


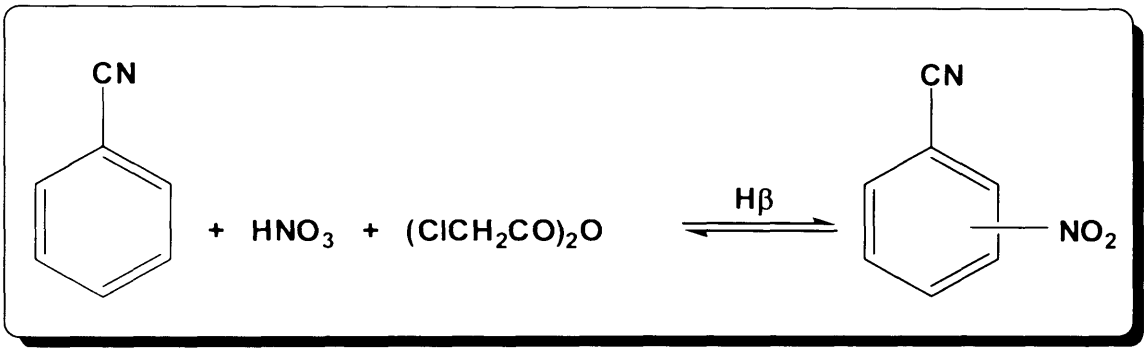
**Figure 4.1: Effect of reaction time on nitration of benzonitrile at room temperature**

It is also clear that the reaction time was not the major factor causing incomplete conversion under such conditions, which was not expected. There are three possible explanations for these results.

**Firstly**, chloroacetyl nitrate may not be very stable over time and might undergo decomposition. In order to test this possibility two experiments were carried out. The first one involved preparation of chloroacetyl nitrate and leaving it to stir for 2 h before benzonitrile was introduced; the mixture was then stirred for a further 2 h at room temperature. Following work-up, the GC result indicated that NBNs were formed in exactly the same proportion as when the reaction was carried out normally (Table 4.1, Entry 3). This suggests that decomposition of the acyl nitrate over time was not the explanation for the low conversion.

The second experiment involved nitration of benzonitrile using chloroacetyl nitrate in the presence of zeolite Hβ for 2 h at room temperature, after which toluene was added. Toluene is more reactive than benzonitrile and it would react faster if chloroacetyl nitrate were still available in the reaction mixture. The GC result indicated the presence of isomeric nitro toluenes, suggesting that there was indeed unreacted nitrating agent available. These two experiments suggested that the low yield of NBNs obtained was not due to decomposition or loss of chloroacetyl nitrate and reduced the likelihood of this possibility as a cause of the problems.

**Secondly**, nitration of BN at room temperature to produce NBNs might be reversible (Scheme 4.4), which would lead to an equilibrium between BN and the product NBNs and once equilibrium had been reached no further increase in product yield would be achieved.



**Scheme 4.4: Equilibrium between BN and NBNs**

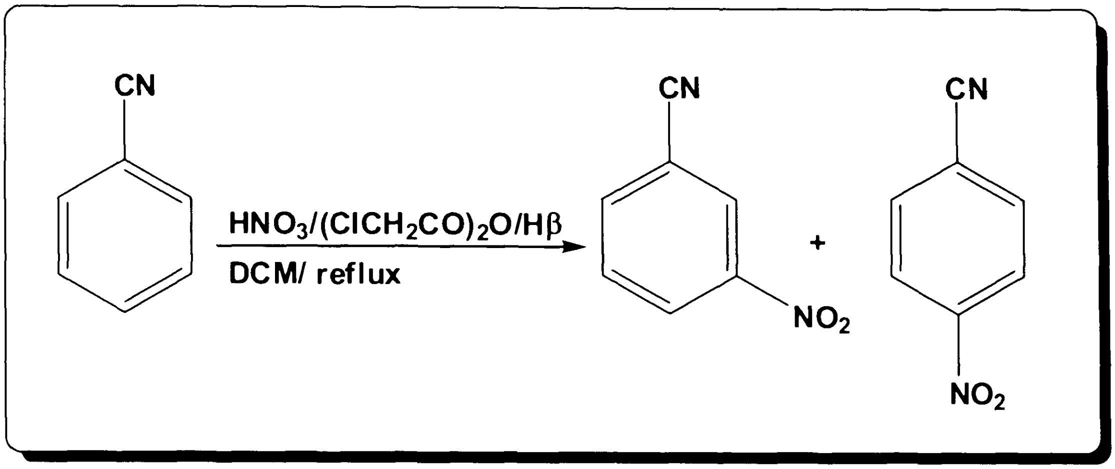
In order to test this possibility we carried out a reaction of a mixture of nitrobenzonitriles with chloroacetic acid and zeolite Hβ. If the reaction in Scheme 4.4 occurs as equilibrium, some BN should be formed. However, when this reaction was carried out there was no evidence for formation of BN, which suggests that the reaction is not reversible under these conditions.

**Thirdly**, the zeolite Hβ might be deactivated after 2 h, possibly by the chloroacetic acid formed in the course of the reaction or by reaction of the anhydride with any water in the nitric acid. Increasing the reaction temperature would have the effect of weakening the binding of the chloroacetic acid to the surface of the zeolite and thereby might allow the zeolite to continue to act as a catalyst even in the presence of the carboxylic acid. Therefore, an experiment was attempted in which the reaction temperature was increased to the reflux temperature of the solvent (dichloromethane).

Nitration of BN (9.5 mmol) using nitric acid (19 mmol) and chloroacetic anhydride (19 mmol) in DCM (20 ml) over Hβ (2 g) was carried out for 2 h under reflux. The GC result clearly indicated that the yield of NBNs was increased to 69% instead of 21% when the reaction was carried out at room temperature. Therefore, a more detailed study of the reaction under reflux conditions was conducted.

## 4.3. Nitration of benzonitrile with a $(ClCH_2CO)_2O/HNO_3/H\beta$ system in DCM under reflux conditions

Nitration of benzonitrile with a $(ClCH_2CO)_2O/HNO_3/H\beta$ system in DCM under reflux conditions (Scheme 4.5) was attempted over various reaction times. The reaction was identical to the one reported in Scheme 4.3, except that the reaction was carried out under reflux conditions. The reaction mixture was worked up as described before (Section 4.2) and analysed by GC. The results obtained are recorded in Table 4.2 and also represented graphically in Figure 4.2.



**Scheme 4.5: Nitration of benzonitrile with a $(ClCH_2CO)_2O/HNO_3/H\beta$ system in DCM under reflux conditions**

**Table 4.2: Effect of reaction time on nitration of benzonitrile over a $(ClCH_2CO)_2O/HNO_3/H\beta$ system under reflux according to Scheme 4.5[a]**

| Time (h) | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **5 min** | 80 | 4 | 16 | 20 | 100 |
| **0.5** | 58 | 7 | 35 | 42 | 100 |
| **2** | 32 | 15 | 54 | 68 | 100 |
| **4** | 25 | 18 | 56 | 75 | 99 |
| **8** | 22 | 17 | 60 | 78 | 99 |
| **24** | 20 | 17 | 63 | 80 | 100 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml) chloroacetic anhydride (19 mmol, 3.25 g) and zeolite Hβ (Si/Al = 12.5; 2 g) in DCM (20 ml) was heated under reflux conditions for the stated reaction time.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] 100 - BN %.

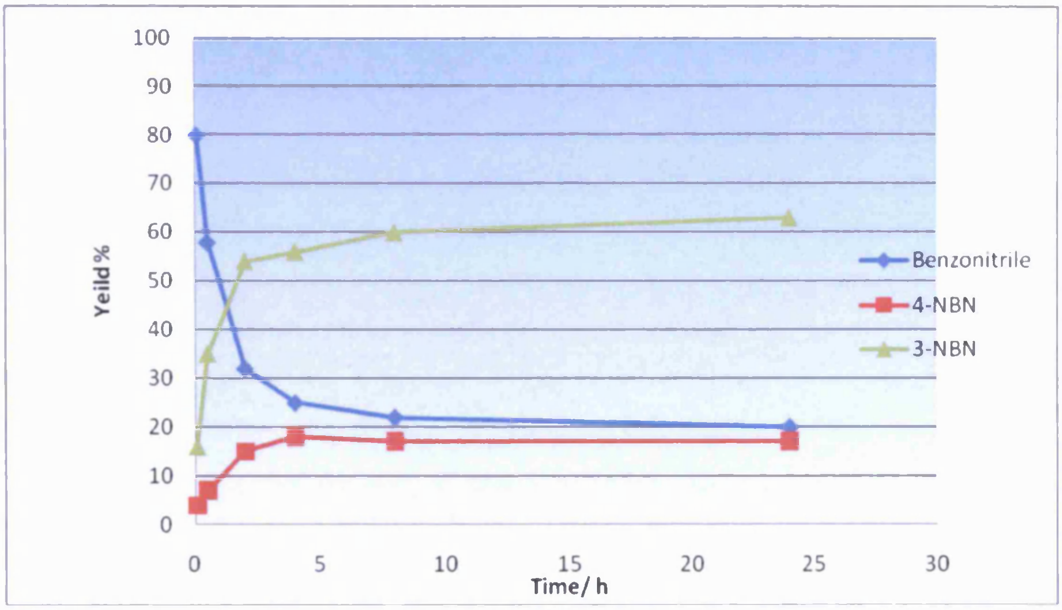


**Figure 4.2: Effect of reaction time on yield of nitrobenzonitriles under reflux conditions**

The results in Table 4.2 indicated a trend in which the selectivity of the reaction remained constant, but the yield of NBNs was increased on increasing the reaction time up to 4 h. For example, the yield of NBNs was increased rapidly from 20% to 42% when the time was increased from 5 to 30 min. The yield was increased further to 69% when the reaction time was 2 hours. However, the yield of NBNs was increased by only 5% on increasing the reaction time from 2 to 4 hours. Also, there was a further increase in the yield of nitrobenzonitriles by 6% on increasing the reaction time from 4 to 24 hours. Clearly the majority of the reaction took place within the first 4 hours. Therefore, 4 hours as a reaction time is more suitable and convenient and was chosen for future experiments.

It appeared that the limiting factor was not that the reaction had been conducted under conditions that were too mild, but that the reaction had stopped for whatever reasons. It was possible that the catalyst was not the best one for the reaction under such conditions. If so, conducting the reaction under reflux conditions in the presence of various types of zeolites might improve the situation. Therefore our attention was next turned to the effect of zeolite type on nitration of benzonitrile.

## 4.4. Nitration of benzonitrile over several types of zeolites in DCM under reflux

Several types of large pore zeolites (Hβ, HY, NaY, Mordenite, and Ferrierite) and a medium pore zeolite (H-ZSM-5) were chosen for this study. Also, various silicon to aluminium ratios for some zeolites were chosen, to see the effect of acid strength and number of active sites on their reactivity as catalysts in nitration of benzonitrile. Identical reactions to that described in Scheme 4.4 were attempted with chloroacetyl nitrate, produced *in-situ* from reaction of chloroacetic anhydride and nitric acid, in dichloromethane as solvent under reflux conditions for 4 h. Each reaction was worked-up and analysed by GC. The results obtained are shown in Table 4.3, and represented graphically in Figure 4.3. In order to illustrate the effect of zeolite on yield, the reaction was also attempted without zeolite (Table 4.3; Entry 1).

In the absence of any catalyst, no reaction occurred. Also, when the reaction was carried out over zeolite H-ZSM-5 (a medium pore zeolite) as catalyst, no nitrobenzonitriles were formed, presumably because the pores are not large enough to accommodate the reaction. These results imply that the reaction probably did not take place to any significant extent within the pores of the H-ZSM-5 zeolite. Also, it seems there was no reaction at the external surface of the zeolite, presumably due to the low number of acidic sites on the surface.

**Table 4.3: Effect of various types of zeolite on nitration of benzonitrile over $(ClCH_2CO)_2O/HNO_3/H\beta$ system under reflux conditions[a]**

| Zeolite (Si/Al) | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **No catalyst** | 100 | 0 | 0 | 0 | 100 |
| **Hβ (12.5)** | 25 | 18 | 56 | 75 | 99 |
| **Hβ (150)** | 42 | 11 | 46 | 58 | 99 |
| **Hβ (300)** | 27 | 12 | 62 | 73 | 101 |
| **HY (12.5)** | 80 | 4 | 14 | 20 | 98 |
| **HY (28)** | 70 | 2 | 27 | 30 | 99 |
| **NaY (12.5)** | 42 | 6 | 52 | 58 | 100 |
| **HZSM-5 (30)** | 100 | 0 | 0 | 0 | 100 |
| **H-Mordenite (20)** | 98 | 0 | 0 | 0 | 98 |
| **Ferrierite** | 102 | 0 | 0 | 0 | 102 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), chloroacetic anhydride (19 mmol, 3.25 g) and zeolite (2 g) in DCM (20 ml) was heated under reflux for 4 hours.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] 100 - BN%.

The results were very similar when ferrierite and mordenite (large pore zeolites) were used as catalysts. Ferrierite and mordenite, although they have relatively large entry ports to the channels, contain a one-dimensional channel system, which restricts diffusion within the channels and inhibits interaction between species. Thus, again the reaction does not take place within the pores of the zeolites or even at the outer surface. By contrast, all samples of large pore zeolites with three-dimensional channels (zeolites β and Y) showed significant conversions of benzonitrile into nitrobenzonitriles.

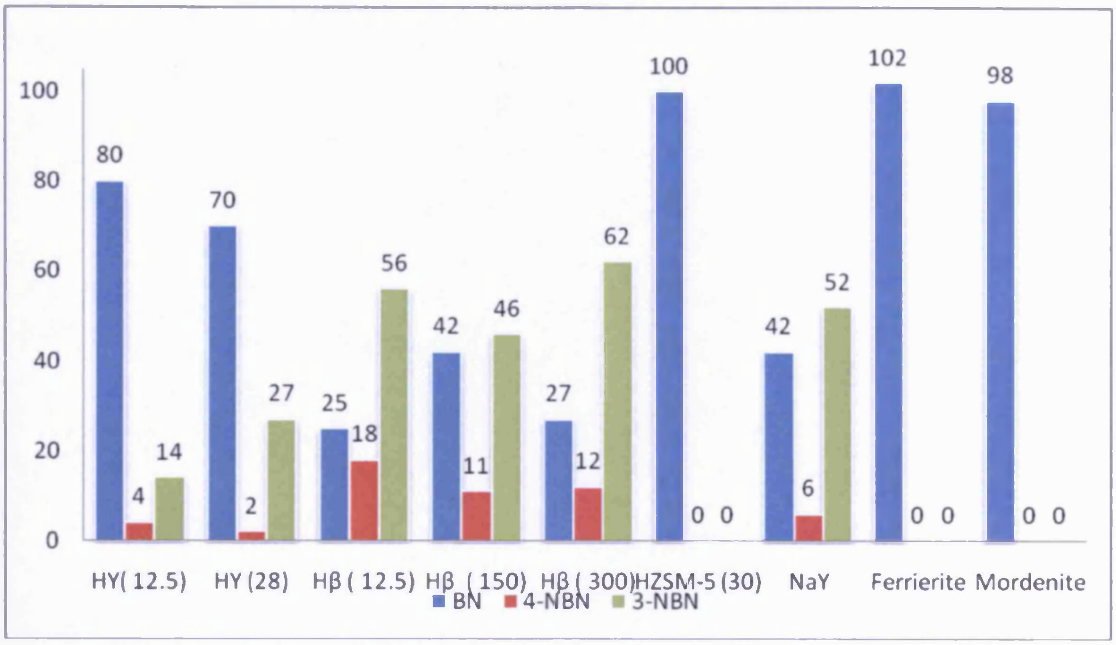


**Figure 4.3: Effect of zeolite type on the yield of nitrobenzonitriles**

The Si/Al ratio of the zeolites used influenced the selectivity of the reactions, with the samples having lower Si/Al ratios giving higher proportions of 4-substituted product than those with higher Si/Al ratios. Thus, when zeolite HY (Si/Al = 12.5) was used as a catalyst the 4-NBN:3-NBN ratio was 4:14 (0.29:1). However, over zeolite HY (Si/Al = 28) the reaction was much less selective, giving a ratio of 2:27 (0.07:1). Similarly, with zeolite Hβ the 4-NBN:3-NBN ratio varied from 18:56 (0.32:1) over Hβ (Si/Al = 12.5) to 12:62 (0.19:1) over Hβ (Si/Al = 300).

Previous studies had indicated that HY was a good catalyst in nitration of mono-substituted benzenes, but that it is not as good as Hβ.[37,39] Both zeolites have large entry ports and three dimensional intersecting channel structures that lead to large cavities capable of accommodating several interacting molecules simultaneously, but the channels in Hβ are more tortuous. It seems that the channels are too open, in the present context, to impose sufficient constriction on the transition state for nitration to cause great selectivity for formation of the *para*-isomer, although with both zeolites having Si/Al ratios of 12.5 the ratio of *para*:*meta* products is around 0.3:1, which is much higher than in traditional nitration reactions, and the *ortho*-product is formed in tiny proportion if at all, unlike in traditional nitration reactions.

The differences in yields obtained with two different samples of HY can be understood in terms of the number and strengths of the acidic sites, which are associated with the Al centres in the lattice. When there is a low Si/Al ratio, there are many acidic sites, but the acid strength of each site is low. It appears that the strength of the acid sites in HY (Si/Al = 12.5) was too low to catalyse nitration of benzonitrile very effectively, leading to a low yield of NBNs. The strength of the sites increases as the Si/Al increases, but the number of sites diminishes. It appears that by a Si/Al ratio of 28 the strength of the acid sites was high enough to catalyse the reaction more effectively, but the smaller number of such sites still limited the extent of reaction. The effect of Si/Al ratio on yield was less clear cut for the samples of zeolite Hβ, but all three samples resulted in significantly higher yields than with the samples of HY. It is therefore clear from Table 4.3 that the best catalyst among all the zeolites tried was zeolite Hβ with a Si/Al ratio of 12.5, the very one that was selected from the beginning of the project. Therefore, it seemed that the best catalyst had already been found.

Zeolite NaY was also tried in the reaction. It gave a higher yield of NBNs (58%) than HY, but the reaction was less selective for the *para*-isomer.

None of the zeolites tried (HY, NaY, mordenite, ferrierite and H-ZSM-5) gave a better conversion than the one originally studied (zeolite Hβ). One possibility for that could be that the zeolites had become deactivated under the reaction conditions. Therefore, in an attempt to force the reaction to completion we decided to use more zeolite Hβ (Si/Al = 12.5) and to study the effect of its quantity on the yield and selectivity of the nitration of benzonitrile.

## 4.5. Nitration of benzonitrile over a $(ClCH_2CO)_2O/HNO_3/H\beta$ system using various quantities of zeolite Hβ (Si/Al = 12.5) under reflux conditions

As reported in Table 4.4 the nitration of benzonitrile, according to Scheme 4.5, using Hβ (Si/Al = 12.5) gave almost 74 % of NBNs. However, the reaction was never complete and always starting material remained. Therefore, it was of interest to study the effect of the amount of catalyst. It was expected that increasing the amount of zeolite would directly affect the rate and selectivity due to an increase in the pore volume and the number of active sites in the zeolites. The amount of Hβ was varied from 0.5 to 3 g and experiments were carried out under identical conditions under reflux conditions in DCM for 4 h. Each reaction was worked up and quantified by GC. The results are recorded in Table 4.4 and represented graphically in Figure 4.4.

The results clearly indicated that the quantity of zeolite plays an important role in the reaction. For example, no nitro products were obtained when no zeolite was used, while the yield of nitrobenzonitriles was 55% when 0.5 g of Hβ was used and was increased to 62% when the amount was 1 g. The yield was increased further to 74% when 2 g of zeolite Hβ was used, but when the quantity of zeolite was increased to 3 g the yield of NBNs decreased to 46%. This was presumably because the reaction mixture was less mobile and stirring the mixture became difficult. The *meta*/*para* ratio was almost constant regardless of the quantity of catalyst used.

Again, it seems that 2 g of Hβ are enough to catalyse the reaction of 9.5 mmol of benzonitrile and such quantity was used in future reactions.

**Table 4.4** **Effect of quantity of Hβ (Si/Al = 12.5) on nitration of benzonitrile over $(ClCH_2CO)_2O/HNO_3/H\beta$ system in DCM under reflux conditions[a]**

| Hβ (12.5) (g) | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **No catalyst** | 100 | 0 | 0 | 0 | 100 |
| **0.5** | 46 | 11 | 44 | 54 | 101 |
| **1** | 37 | 14 | 48 | 63 | 99 |
| **2** | 25 | 18 | 56 | 75 | 99 |
| **3** | 55 | 11 | 35 | 45 | 101 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), chloroacetic anhydride (19 mmol, 3.25 g) and different quantities of zeolite Hβ (Si/Al = 12.5) in DCM (20 ml) was heated under reflux for 4 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] 100 - BN%.

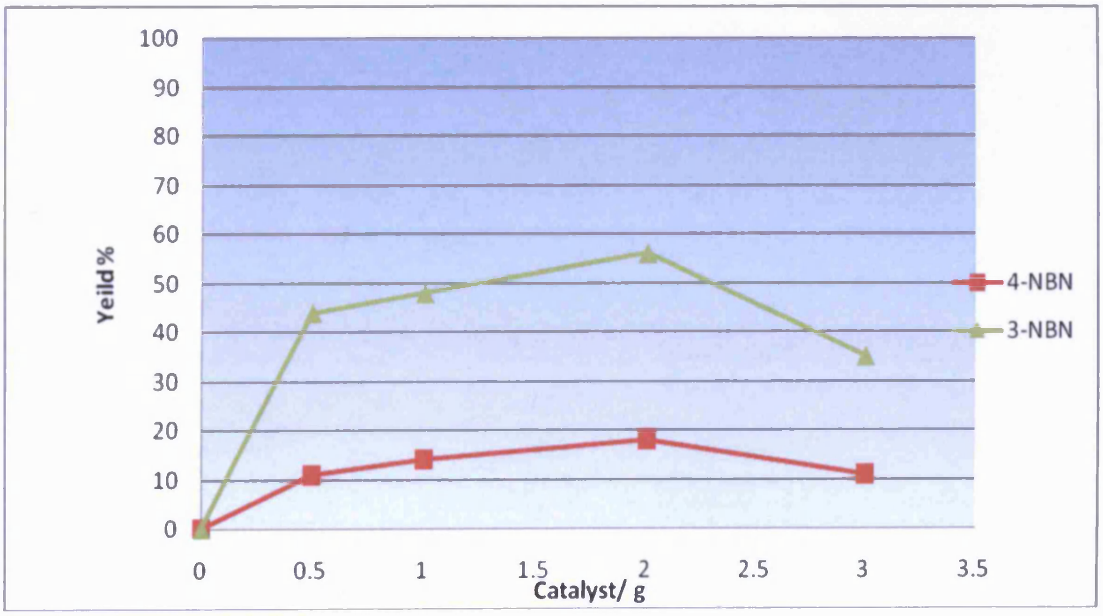


**Figure 4.4: Effect of quantity of Hβ (Si/Al = 12.5) on nitration of benzonitrile under reflux conditions**

## 4.6. Effect of solvent on nitration of benzonitrile over $(ClCH_2CO)_2O/HNO_3/H\beta$ system under reflux conditions

All reactions carried out so far employed dichloromethane (DCM) as a solvent and under the conditions tried the best yield of 4-nitrobenzonitrile and 3-nitrobenzonitrile was 18 and 56%, respectively. It was of interest to see what effect the solvent could have on the reaction. Therefore, several reactions were carried out over zeolite Hβ (Si/Al = 12.5), under identical conditions except for the nature of the solvent and the reflux temperature at which the reaction was therefore conducted.

We chose various solvents with different boiling points (b.p.), namely dichloromethane, (b.p. 40 °C), chloroform, (b.p. 61 °C), 1,2-dichloroethane, (b.p. 83 °C) and acetone (b.p. 56 °C). Each reaction of benzonitrile (9.5 mmol) was carried out using the $(ClCH_2CO)_2O/HNO_3/H\beta$ system in the chosen solvent. The reaction mixtures were worked up and analysed by quantitative GC using tetradecane as internal standard. The results obtained are recorded in Table 4.5.

**Table 4.5: Effect of solvent on nitration of benzonitrile over $(ClCH_2CO)_2O/HNO_3/H\beta$ system under reflux conditions**[a]

| Solvent | Reflux Temp. (°C) | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|---|
| | | BN | 4-NBN | 3-NBN | | |
| **Dichloromethane** | **40** | 25 | 18 | 56 | 75 | 99 |
| **Chloroform** | **61** | 37 | 14 | 48 | 63 | 99 |
| **Dichloroethane** | **83** | 70 | 8 | 24 | 30 | 102 |
| **Acetone** | **56** | 100 | 0 | 0 | 0 | 100 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml) and chloroacetic anhydride (19 mmol, 3.25 g) and zeolite Hβ (Si/Al = 12.5; 2 g) in solvent (20 ml) was heated under reflux for 4 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] 100 - BN %.

As can be seen from Table 4.5, the highest conversion (75 %) was obtained when DCM was used as a solvent and yields of 4-NBN and 3-NBN were 18 and 56%, respectively, as seen previously. For all the chlorinated hydrocarbon solvents used the reaction proceeded and the *para/ortho* ratio was similar for all such solvents. Reflux temperature seemed to be the major factor influencing the yield of the NBNs. The yields 3-NBN and 4-NBN were highest when the reaction was carried out in the lowest boiling solvent (DCM) and lowest in high-boiling dichloroethane (DCE). It seemed likely that the chloroacetyl nitrate intermediate was breaking down or escaping from the reaction mixture at elevated temperatures. In order to test this possibility, mixtures containing solvent (chloroform or DCE), zeolite, nitric acid and chloroacetic anhydride, in the same proportions as used for the reactions represented in Table 4.5, but without benzonitrile, were heated at reflux for 4 hours, after which benzonitrile was added and the mixtures were then refluxed for a further 4 hours. For the case of DCE, no NBNs were formed and 100% of the benzonitrile remained. In the case of chloroform, just 17% of 3-NBN and 6% of 4-NBN were formed and 76% of benzonitrile remained. This clearly supports the view that the active reagent is lost from the mixtures during heating. It seemed that the best solvent was DCM and had already been used in the earlier studies.

By contrast, at comparable temperatures, reaction in the polar solvent acetone produced no product at all and only starting material was recovered. This clearly indicated that acetone is not a good solvent for such reactions. Possible reasons could be that the acetone might not be dry and any water present could destroy the nitrating reagent, or that the solvent completely deactivates the catalyst, or that chloroacetyl nitrate might react with acetone itself. No signal was detected by GC other than the signal for BN, so this last possibility seems unlikely. In any event, it seemed that the best solvent (DCM) had already been used in the earlier studies.

## 4.7. Effect of quantity of chloroacetic anhydride on nitration of benzonitrile

The best yield of 4-nitrobenzonitrile obtained so far was 18%, and the total yield of nitrobenzonitriles was 74%. However, 24% of BN was recovered from the reaction. In an attempt to push the reaction to completion, we decided to use an excess of chloroacetic anhydride. It has been reported that acid anhydride should be used in excess over nitric acid in order to destroy any water that might present in the system or in the nitric acid,[39] but we decided to use an even greater excess of the anhydride.

Therefore, a series of reactions was carried out in which the amount of chloroacetic anhydride was varied from 19 to 30 mmol for 9.5 mmol of benzonitrile. All reactions were carried out with the $HNO_3/(ClCH_2CO)_2O/H\beta$ system in DCM (20 ml) under reflux conditions for 4 h. The results are recorded in Table 4.6.

The results clearly indicated a trend in which conversion increased when the quantity of chloroacetic anhydride was increased. For example, the yield of nitrobenzonitriles was 81% when 20 mmol of chloroacetic anhydride was used, but complete when 25 mmol of chloroacetic anhydride was used. Under the latter conditions the yield of nitrobenzonitriles was quantitative, but the yield of 4-nitrobenzonitrile was still only 18%, indicating that the *para*-selectivity had decreased, presumably because the reaction became faster. Clearly, the reaction could be completed in less than 4 hours with a larger excess of chloroacetic anhydride, but with some reduction in selectivity for the *para*-isomer.

**Table 4.6: Effect of quantity of chloroacetic anhydride on nitration of benzonitrile with a $(ClCH_2CO)_2O/HNO_3/H\beta$ system[a]**

| Chloroacetic anhydride (mmol) | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **19** | 25 | 18 | 56 | 75 | 99 |
| **20** | 19 | 18 | 60 | 81 | 97 |
| **25** | 0 | 18 | 81 | 100 | 99 |
| **30** | 0 | 18 | 80 | 100 | 98 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), chloroacetic anhydride and zeolite Hβ (Si/Al = 12.5, 2 g) in DCM (20 ml) was heated under reflux conditions for 4 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] 100 - BN%.

Our attention was next turned to the use of other anhydrides in the nitration reaction of benzonitrile, in order to study the effect of such anhydrides on the rate and selectivity of the reaction.

## 4.8. Nitration of benzonitrile using various acid anhydride/nitric acid/Hβ systems in DCM under reflux conditions

Various anhydrides with different reactivity were used in order to see what effect the nitrating species could have on the reaction. Acetic, propanoic, chloroacetic, dichloroacetic and trifluoroacetic anhydrides (Figure 4.5) were chosen as anhydrides, which on reactions with nitric acid would produce acetyl, propanoyl, chloroacetyl, dichloroacetyl and trifluoroacetyl nitrates, respectively, *in-situ* (Figure 4.6).

**$(CH_3CO)_2O$**
**acetic anhydride**

**$(CH_3CH_2CO)_2O$**
**propanoic anhydride**

**$(ClCH_2CO)_2O$**
**chloroacetic anhydride**

**$(Cl_2CHCO)_2O$**
**dichloroacetic anhydride**

**$(CF_3CO)_2O$**
**trifluoroacetic anhydride**

**Figure 4.5: Structures of various acid anhydrides**

Nitration reactions of benzonitrile (9.5 mmol) with the acid anhydrides (19 mmol), $HNO_3$ (19 mmol) and Hβ (Si/Al = 12.5; 2 g) in DCM as a solvent under reflux conditions for 4 h were attempted under identical conditions except for the nature of the anhydride. We also attempted reaction with $HNO_3$ alone, without anhydride, for comparison. The results obtained are recorded in Table 4.7.

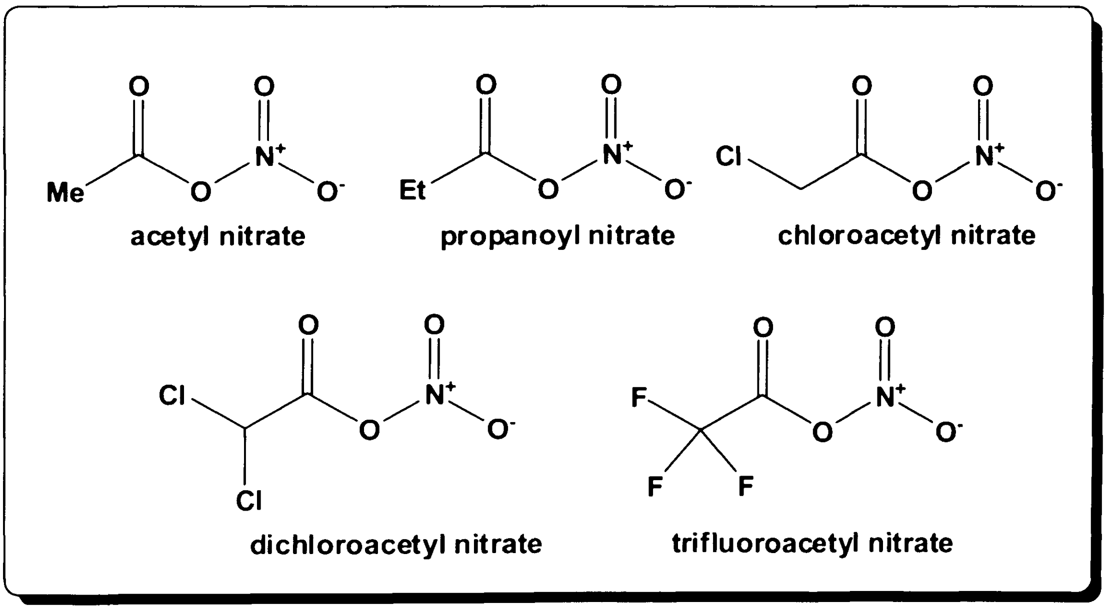


**Figure 4.6: Structures of various acyl nitrates generated *in-situ* from reactions of nitric acid and the corresponding acid anhydrides**

As shown in Table 4.7, there were no NBNs produced when the reaction was carried out with $HNO_3$ alone, acetyl nitrate or propanoyl nitrate. These results confirmed the fact that such nitrating species are not strong enough for such a deactivated substrate. On the other hand, both chloroacetyl nitrate and trifluoroacetyl nitrate accommodated the reaction and produced 74% and 96% yield of nitrobenzonitriles, respectively. The results also indicated that trifluoroacetyl nitrate is more effective than chloroacetyl nitrate. However, the *para/meta* ratio was relatively low (0.28; cf. 0.32 for chloroacetyl nitrate). The results obtained using dichloroacetic anhydride gave a 56% yield of NBNs but the reaction showed unusual selectivity – the *para/meta* ratio was 0.37, but there was also a significant quantity of the *ortho*-isomer.

**Table 4. 7: Effect of various nitrating reagents on nitration of benzonitrile under reflux conditions in DCM**[a]

| **Nitration reagent** | **Yield (%)**[b] | | | **Conversion**[c] | **Mass Balance (%)** |
|---|---|---|---|---|---|
| | **BN** | **4-NBN** | **3-NBN** | | |
| **$HNO_3$** | 97 | 0 | 0 | 0 | 97 |
| **Acetyl nitrate** | 101 | 0 | 0 | 0 | 101 |
| **Propanoyl nitrate** | 72 | 0 | 0 | 0 | 72 |
| **Chloroacetyl nitrate** | 25 | 18 | 56 | 75 | 99 |
| **Dichloroacetyl nitrate** | 35 | 15 | 41 | 65 | 101[d] |
| **Trifluoroacetyl nitrate** | 4 | 21 | 75 | 96 | 100 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), acid anhydride (19 mmol) and zeolite Hβ ( Si/Al = 12.5; 2 g) in DCM (20 ml) was heated under reflux conditions for 4 h.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] 100 - BN %.

[d] 2-Nitrobenzonitrile was produced in 10% yield.

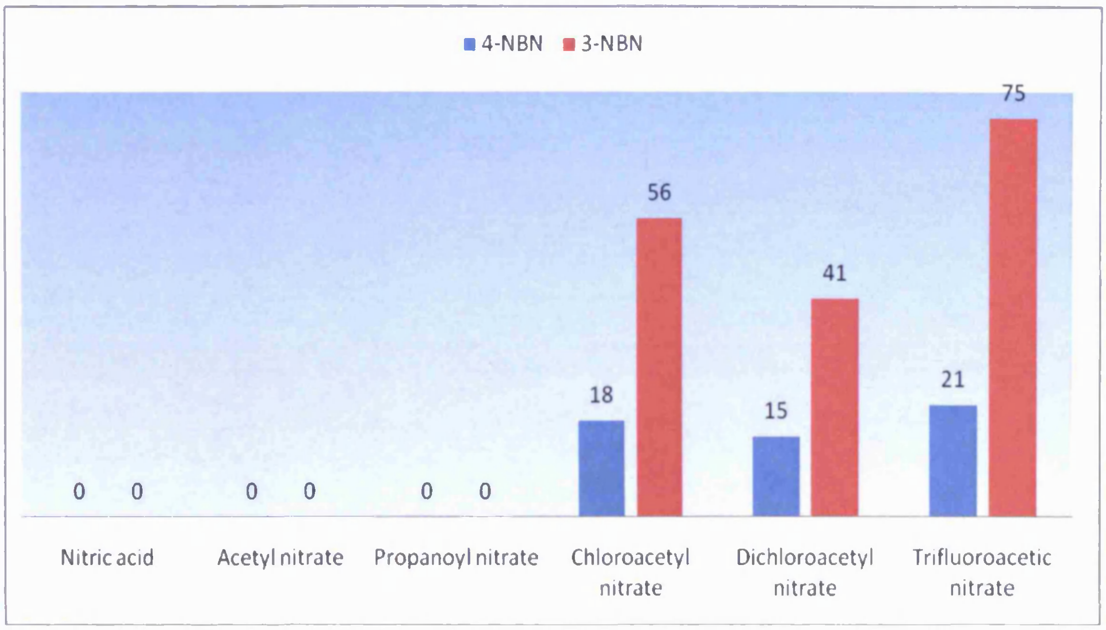


**Figure 4.7: Effect of nitrating reagents on nitration of benzonitrile**

If it is assumed that the yields reflect the reactivity of the systems, then the order of reactivity appears to be trifluoroacetyl nitrate > chloroacetyl nitrate > dichloroacetyl nitrate > acetyl nitrate, propanyl nitrate and $HNO_3$. Trifluoroacetic anhydride is intrinsically more reactive than chloroacetic and dichloroacetic anhydride, so it had been expected to produce a higher yield of NBNs. On the other hand, it seems that dichloroacetic anhydride, which is more sterically hindered than chloroacetic anhydride, may result in restricted access of the nitrating reagent to the zeolite pores. We decided to investigate the reaction further using trifluoroacetic anhydride under various reaction conditions in an attempt to improve the selectivity for 4-nitrobenzonitrile.

## 4.9. Nitration of benzonitrile using a TFAA/$HNO_3$/Hβ system in DCM under reflux conditions

Previous results (Section 4.8; Table 4.7) indicated that trifluoroacetic anhydride (TFAA) is more reactive than all other anhydrides tried in nitration of benzonitrile over zeolite Hβ under the conditions tried. The yield of the *para*-isomer was 21% and the reaction was nearly complete within 4 hours.

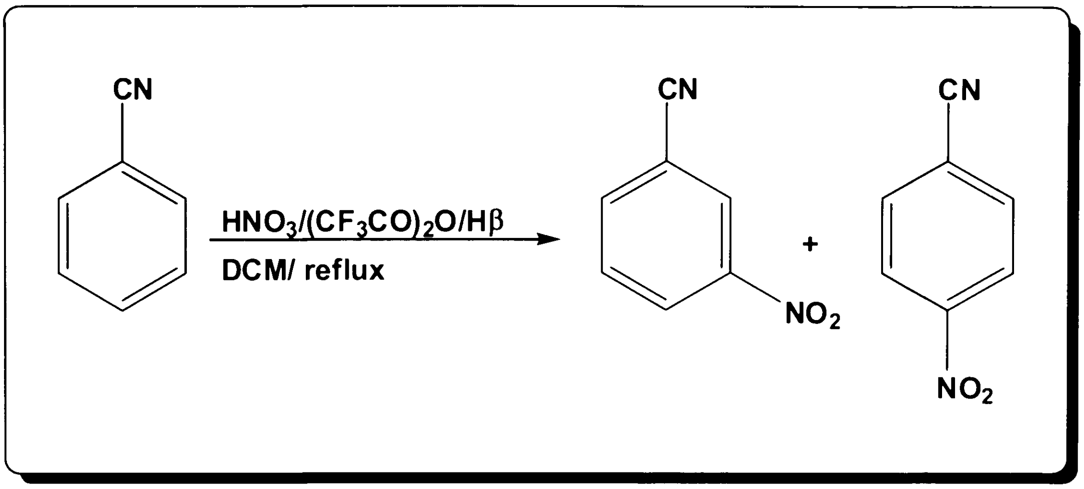
In principle, trifluoroacetic anhydride could produce trifluoroacetyl nitrate quantitatively *in situ* (Equation 4.5).

$$HNO_3 + (CF_3CO)_2O \rightleftharpoons CF_3CO_2H + CF_3C(O)ONO_2$$

**Equation 4.5: Production of trifluoroacetyl nitrate *in situ* from reaction of $HNO_3$ and TFAA**

Trifluoroacetyl nitrate is expected to be much more reactive than chloroacetyl nitrate. Therefore, we decided to carry out the same reaction again but for only 2 hours to see if 4 hours as a reaction period is necessary. It was found that the yield of nitrobenzonitriles was 81%, with the *para*-isomer at 18%. Benzonitrile (19%) was recovered. It seems likely therefore that 4 hours as a reaction period is necessary for the reaction to be complete under these conditions. However, it was believed that the reaction could be complete within 2 hours by using a larger excess of the anhydride.

In an attempt to increase the yield of NBNs, a series of experiments was conducted in which the amount of trifluoroacetic anhydride was varied from 20 to 25 mmol for a reaction involving a fixed quantity of benzonitrile (9.5 mmol) and nitric acid (19 mmol) (Scheme 4.6). The literature shows that acid anhydride should be in excess of the nitric acid.[1]



**Scheme 4.6: Nitration of benzonitrile with a $HNO_3/(CF_3CO)_2O/H\beta$ system**

For the reaction involving use of 20 mmol of TFAA, the GC results showed formation of nitrobenzonitriles in 81% yield, with 4-nitrobenzonitrile at 18%, identical with those obtained with 19 mmol of TFAA.

The GC results for the reaction involving use of 22 mmol of TFAA for 2 h showed formation of 3-nitrobenzonitrile and 4-nitrobezonitrile in 64% and 18% yield, respectively, and the presence of unreacted benzonitrile in the range of 16%. It was clear that the 2 mmol extra of TFAA brought only a very small increase (1%) in the overall yield of nitrobenzonitriles. Increasing the reaction time to 4 h led to an improvement in the yield of benzonitriles (96%), with 21% being 4-nitrobenzonitrile, along with residual benzonitrile (4%), but this was identical with the result for 19 mmol under comparable conditions. Next, we decided to use 25 mmol of TFAA and 4 hours as a reaction time for future experiments to make sure that reactions were complete.

Our attention was next turned to study the effect of quantity of zeolite on the yield and selectivity of the reaction under these conditions.

## 4.10. Effect of quantity of zeolite Hβ on nitration of benzonitrile using a TFAA/$HNO_3$/Hβ system in DCM under reflux conditions

In theory, the rate of production of NBNs should increase when the amount of the zeolite is increased, because the number of pores in which the reaction can occur and the number of active catalytic sites are increased when the amount of zeolite Hβ present in the mixture is increased.

Therefore, a series of experiments was conducted for nitration of benzonitrile (9.5 mmol) using TFAA (25 mmol) and $HNO_3$ (19 mmol) in DCM under reflux conditions for 4 hours over Hβ. The quantity of Hβ was varied from 0.10-4.0 g. Each reaction was carried under identical conditions, worked-up and analysed by GC. The results obtained are recorded in Table 4.8 and represented in Figure 4.8.

**Table 4.8: The effect of quantity of zeolite Hβ (Si/Al = 12.5) on nitration of benzonitrile with a $HNO_3$/TFAA/Hβ system according to Scheme 4.6[a]**

| Hβ (g) | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **No catalyst** | 100 | 0 | 0 | 0 | 100 |
| **0.10** | 4 | 24 | 72 | 96 | 100 |
| **0.25** | 0 | 23 | 77 | 100 | 100 |
| **0.50** | 0 | 23 | 77 | 100 | 100 |
| **2.0** | 0 | 24 | 76 | 100 | 100 |
| **4.0** | 0 | 23 | 77 | 100 | 100 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), TFAA (25 mmol, 3.5 ml) and zeolite Hβ in DCM (20 ml) was heated under reflux conditions for 4 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] 100 - BN%.

The results recorded in Table 4.8 clearly indicated that nitration of benzonitrile (9.5 mmol) under these conditions could be catalysed with as little as 0.10 g of Hβ. The reaction was nearly complete (96%) and the yield of 4-nitrobenzonitrile was 24%, with a *para/meta* ratio of 0.33. Also, only 4% of benzonitrile remained. From the results it was clear that there was no advantage in using the zeolite in more than 0.25 g quantity for the particular conditions chosen, since neither the yield nor the selectivity of the reaction were influenced by the amount of the zeolite beyond that.

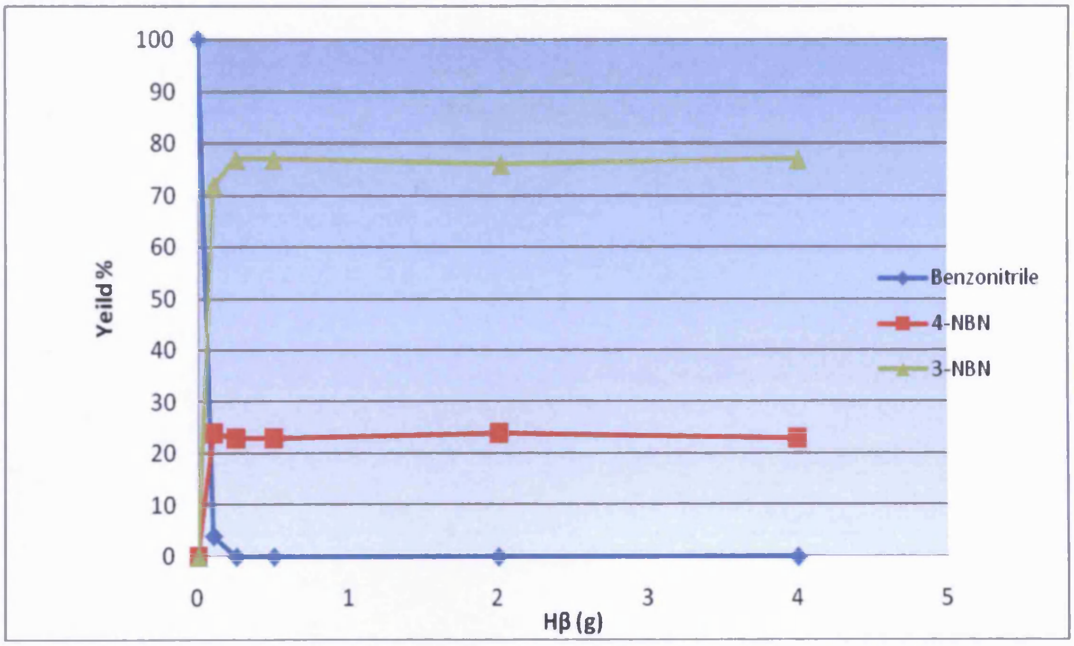


**Figure 4.9: Effect of quantity of zeolite Hβ (Si/Al = 12.5) on nitration of benzonitrile**

Having discovered that the reaction could be carried out successfully with only 0.1 g of catalyst, we decided to investigate the effect of reaction time under such circumstances.

## 4.11. Effect of reaction time on nitration of benzonitrile with a $HNO_3$/TFAA/Hβ system in DCM under reflux conditions

It is very important to know the optimum reaction time which will allow the production of a high yield of the desirable product. Also, another purpose of these experiments was to test the progression of the nitration reaction. Therefore, a series of experiments was conducted using benzonitrile (9.5 mmol), nitric acid (19 mmol), trifluoroacetic anhydride (25 mmol) and Hβ (0.10 g) in DCM (20 ml) under reflux conditions for various reaction times (30 min to 6 hours). The results are recorded in Table 4.9.

**Table 4.9: Effect of reaction time on nitration of benzonitrile with $HNO_3$/TFAA/Hβ according to Scheme 4.6**[a]

| TIME (h) | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **0.5** | 40 | 13 | 46 | 60 | 99 |
| **1** | 35 | 14 | 50 | 75 | 99 |
| **2** | 5 | 23 | 72 | 95 | 100 |
| **4** | 4 | 24 | 72 | 96 | 100 |
| **5** | 3 | 23 | 74 | 97 | 100 |
| **6** | 0 | 24 | 75 | 100 | 99 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), TFAA (25 mmol, 3.5 ml) and zeolite Hβ ( Si/Al= 12.5; 0.1g) in DCM (20 ml) was heated under reflux for the stated reaction time.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] 100 - BN %.

The results shown in Table 4.9 indicated that there was a trend that increasing the reaction time resulted in an increased yield of NBNs. Nitrobenzonitriles were obtained in only 59% yield when the reaction time was only 30 min and 40% of benzonitrile remained. Also, under such conditions the yield of 4-nitrobenzonitrile was only 13%, which improved significantly to 23% along with only 5% of starting material when the reaction time was 2 hours. The majority (95%) of the reaction took place within 2 h and the reaction was significantly slower thereafter. Also, the *meta*/*para* ratio after 2 h was almost constant.

Next we decided to investigate the possibility to reuse the zeolite to find out if we could make this system greener and more attractive.

### 4.12. Efficiency of recycled zeolite in nitration of benzonitrile

In order to make the nitration system used greener and more economical, the possibility of reusing the zeolite was investigated. Zeolites were recovered following extraction of the products and were then reused. An initial reaction of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml) and TFAA (25 mmol, 3.5 ml) in DCM (20 ml) under reflux conditions for 4 h using fresh zeolite Hβ (0.25 g), that had been activated at 550 °C, was carried out. The zeolite was recovered and the products were worked up as usual, involving filtration and washing of the zeolite with acetone.

The used zeolite was moved to the furnace and calcined overnight at 550 °C. Then, a reaction was conducted under identical conditions to those described before, but using the activated recovered zeolite. The whole process was repeated six times using the same batch of catalyst, but the reactions were scaled down due to small physical losses of zeolite during recovery. The results obtained are recorded in Table 4.10.

It can be seen from Table 4.10 that the zeolite could be effectively recycled and could be reused at least six times with no reduction in either the yields of products or the *para*-selectivity. This is of significant benefit in terms of green chemistry and economy.

**Table 4.10: Efficiency of recycled calcined zeolite in nitration of benzonitrile**[a]

| Run | Yield (%)[b] | | | Mass Balance (%) |
|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | |
| **1** | 0 | 24 | 76 | 100 |
| **2** | 0 | 24 | 77 | 101 |
| **3** | 0 | 24 | 78 | 102 |
| **4** | 0 | 23 | 77 | 100 |
| **5** | 0 | 24 | 78 | 100 |
| **6** | 0 | 22 | 79 | 101 |
| **7** | 0 | 22 | 78 | 100 |

[a] Initial reaction carried out using benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), TFAA (25 mmol, 3.5 ml) and Hβ (Si/Al = 12.5, 0.25 g) in DCM (20 ml) was heated under reflux conditions for 4 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

The results obtained so far clearly showed that the maximum yield of 4-nitrobenzonitrile that could be produced was in the range of 24% and it seemed likely that this was the maximum we could achieve using Hβ as a catalyst. However, our hope was to increase the yield of 4-nitrobenzonitrile even further, by using various $M^{n+}\beta$ catalysts. Therefore, our attention was next turned to the preparation and use of various cation-exchanged β zeolites to see what effect the cations could have on the reactivity and selectivity of the reaction. The first task was the preparation of various cation-exchanged β catalysts.

## 4.13. Nitration of benzonitrile with a TFAA/$HNO_3$/$M^{n+}\beta$ system in DCM under reflux conditions

The type of cation impacts on the electric field inside a zeolite's pores, but the pores are also changed. Therefore, the strength of adsorption of molecules in zeolite pores can be dominated by interactions of the adsorbate with the electric field made by the cations, but the acid-base properties of the framework can also play an important role in determining adsorption characteristics. The oxygen atoms attached to the aluminium atoms give the zeolite framework a negative charge that allows the zeolite to trap cations. The exchangeable cation is an acid site and the framework oxygen nearest to the cation provides a basic site. If the aluminium framework content increases the number of basic sites increases. These acid-base properties, along with the size of metal cations plays an important role in cation exchange. We chose various cations, which differ in their valency, electronegativity and size, such as $K^+$, $Zn^{2+}$, $Hg^{2+}$, $Fe^{3+}$, $Al^{3+}$, $Cd^{2+}$, $La^{3+}$, $In^{3+}$ and $Ce^{3+}$, for study.

The selected cations needed to be introduced into the pores of the zeolites to replace the proton. The idea was to abstract the proton from the zeolite and exchange the cation and then use the zeolite to study the effect of such cations on the nitration reaction of deactivated substrates such as benzonitrile. Therefore, several ion-exchanged zeolites were prepared.

The procedure for ion-exchange is straightforward and general (Equation 4.6). Table 4.11 shows the cation salts used to prepare the cation exchanged zeolites $M^{n+}\beta$.

$$\boxed{M_x^{n+}\text{-Zeolite (s)} + M_y^{n+}\text{ (aq)} \rightleftharpoons M_y^{n+}\text{-Zeolite (s)} + M_x^{n+}\text{ (aq)}}$$

**Equation 4.6: Cation exchange of zeolites**

**Table 4.11: Types of $M^{n+}\beta$ zeolites prepared from reaction of their corresponding salts and Hβ according to Equation 4.6[a]**

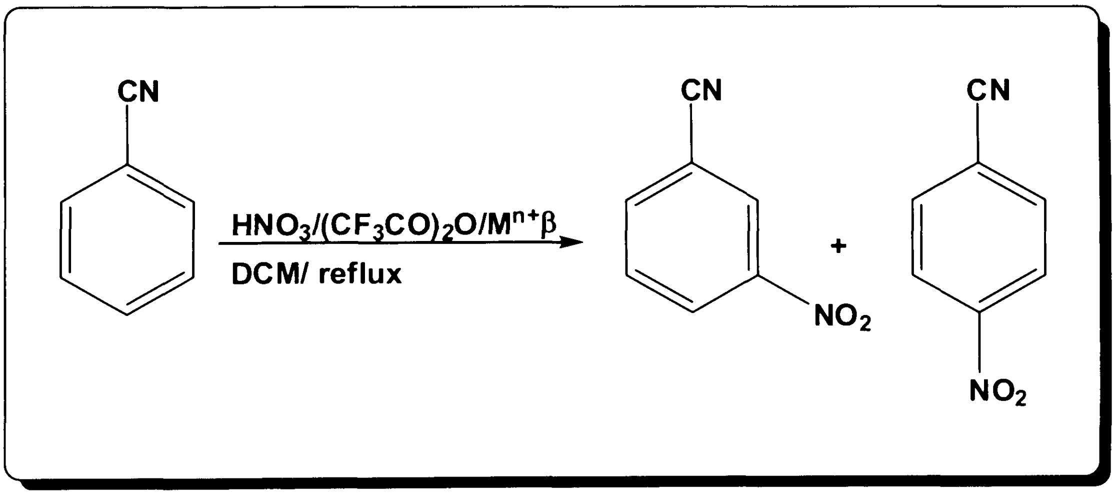
| Zeolites | Metal salt used |
|---|---|
| $K^{+}\beta$ | $CH_3COOK . 4 H_2O$ |
| $Zn^{2+}\beta$ | $Zn(CH_3COO)_2 . 2 H_2O$ |
| $Hg^{2+}\beta$ | $Hg(CH_3COO)_2$ |
| $Fe^{3+}\beta$ | $FeCl_3$ |
| $Al^{3+}\beta$ | $Al(CH_3COO)_3$ |
| $Cd^{2+}\beta$ | $Cd(CH_3COO)_2$ |
| $La^{3+}\beta$ | $La(CH_3COO)_3$ |
| $In^{3+}\beta$ | $InCl_3$ |
| $Ce^{3+}\beta$ | $Ce(CH_3COO)_3$ |

[a] Zeolite Hβ (Si/Al 12.5, 3.0 g) in aqueous metal salt solution (50 ml, 1 M) was heated under reflux conditions for 1 h. The zeolite was filtered, then the process was repeated with fresh metal salt solution.

The procedure involved reaction of zeolite Hβ (3 g) with a metal salt (acetate or chloride) as 50 ml of 1M solution in water, under reflux for 1 h. The zeolite was filtered and washed with distilled water, and then refluxed again with fresh metal salt solution (50 ml; 1M). The zeolite was filtered and any excess metal salt was removed by washing the zeolite thoroughly with clean water. The cation exchanged zeolite was dried in an oven at 110 °C for 30 min, then crushed and calcined overnight at

550 °C. We found that attempts to make a 1 M solution of some metal salts resulted in a saturated solution, so the amount of acetate or chloride salt dissolved in the solutions was changed in accordance to this observation, depending on each different salt. No attempts were made to estimate the degree of cation-exchange in individual cases.

Having prepared various cation-exchanged β zeolites, the next task was to use such zeolites as catalysts in nitration of benzonitrile. The procedure used was identical to that used before when Hβ zeolite was used as the catalyst. Therefore, a series of reactions was attempted in which a mixture $M^{n+}\beta$ (2 g), $HNO_3$ (19 mmol), TFAA (25 mmol) and benzonitrile (9.5 mmol) in DCM (20 ml) was heated under reflux for 4 h (Scheme 4.7). The results obtained are recorded in Table 4.12 and also represented in Figure 4.10.



**Scheme 4.7: Nitration of benzonitrile over $M^{n+}\beta$ under reflux conditions**

**Table 4.12: Nitration of benzonitrile with a $HNO_3$/TFAA/$M^{n+}\beta$ system according to Scheme 4.6[a]**

| Entry | $M^{n+}\beta$ | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|---|
| | | BN | 4-NBN | 3-NBN | | |
| **1** | **Hβ** | 0 | 24 | 76 | 100 | 100 |
| **2** | **$K^+\beta$** | 90 | 0 | 7 | 10 | 97 |
| **3** | **$Zn^{2+}\beta$** | 2 | 17 | 80 | 98 | 99 |
| **4** | **$Cd^{2+}\beta$** | 0 | 22 | 78 | 100 | 100 |
| **5** | **$Hg^{2+}\beta$** | 54 | 11 | 34 | 46 | 99 |
| **6** | **$Al^{3+}\beta$** | 2 | 22 | 77 | 98 | 101 |
| **7** | **$Al^{3+}\beta^d$** | 0 | 22 | 79 | 100 | 101 |
| **8** | **$Fe^{3+}\beta$** | 0 | 24 | 77 | 100 | 101 |
| **9** | **$Fe^{3+}\beta^d$** | 0 | 28 | 73 | 100 | 101 |
| **10** | **$In^{3+}\beta$** | 0 | 15 | 85 | 100 | 100 |
| **11** | **$La^{3+}\beta$** | 0 | 14 | 87 | 100 | 101 |
| **12** | **$Ce^{3+}\beta$** | 0 | 15 | 85 | 100 | 100 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), TFAA (25 mmol, 3.5 ml) and the appropriate zeolite (2 g) in DCM (20 ml) was heated under reflux for 4 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] 100 - BN %.
[d] Catalyst (4 g) was used.

The results recorded in Table 4.12 showed some interesting features. For example, the yield of nitrobenzonitriles was only 7%, with no 4-nitrobenzonitrile formed, when $K^+\beta$ was used as catalyst (Entry 2). In contrast, Hβ gave a quantitative yield of nitrobenzonitriles with 24% of 4-nitrobenzonitrile under identical conditions. Both hydrogen and potassium are in Group 1 and this could mean that the yield decreases down the group as the cation becomes larger. The larger $K^+$ may block entry to the pores of the zeolite, spoiling its potential as a catalyst. The small amount of nitrobenzonitrile produced may have arisen by reaction at the external surface, thereby reducing the tendency to produce *para*-isomer and also limiting the yield because of the relatively small number of available sites. Another significant difference between the two cation-exchanged forms of the zeolite is in their acidity, with the proton form being much more acidic than the potassium form. Whatever the precise explanation, it is interesting to note that the situation contrasts markedly with that of zeolite NaY (Si/Al= 12.5) with chloroacetyl nitrate as the reagent. In that case the sodium-exchanged form gave a significantly higher yield of nitro products than the proton form (HY) (Table 4.3).

For the divalent cation zeolites $Zn^{2+}\beta$, $Cd^{2+}\beta$ and $Hg^{2+}\beta$ the yield of nitrobenzonitriles was high in the case of $Zn^{2+}\beta$ and $Cd^{2+}\beta$ (Table 4.12; Entries 3 and 4) but only moderate with $Hg^{2+}\beta$ (Table 4.12; Entry 5). The high yields could presumably be due to the small divalent cations that allow easier entry to the pore network. The lower yield with $Hg^{2+}\beta$ would be consistent with the larger cation causing greater constriction to access to the pore network. There was also a slight increase in *para-* selectivity going from $Zn^{2+}\beta$ to $Hg^{2+}\beta$ as the cations get larger, but at the expense of overall yield.

All trivalent cations (Table 4.12; Entries 6-12) produced quantitative yields of nitrobenzonitriles, presumably because none of these cations result in significant steric hindrance. 4-Nitrobenzonitrile yield was in the range of 14%-24%. However, the fact that the *para-* selectivity decreased with the larger cations is more difficult to understand. $Fe^{3+}\beta$ and $Al^{3+}\beta$ gave the best *para*-selectivity among this group of zeolites.

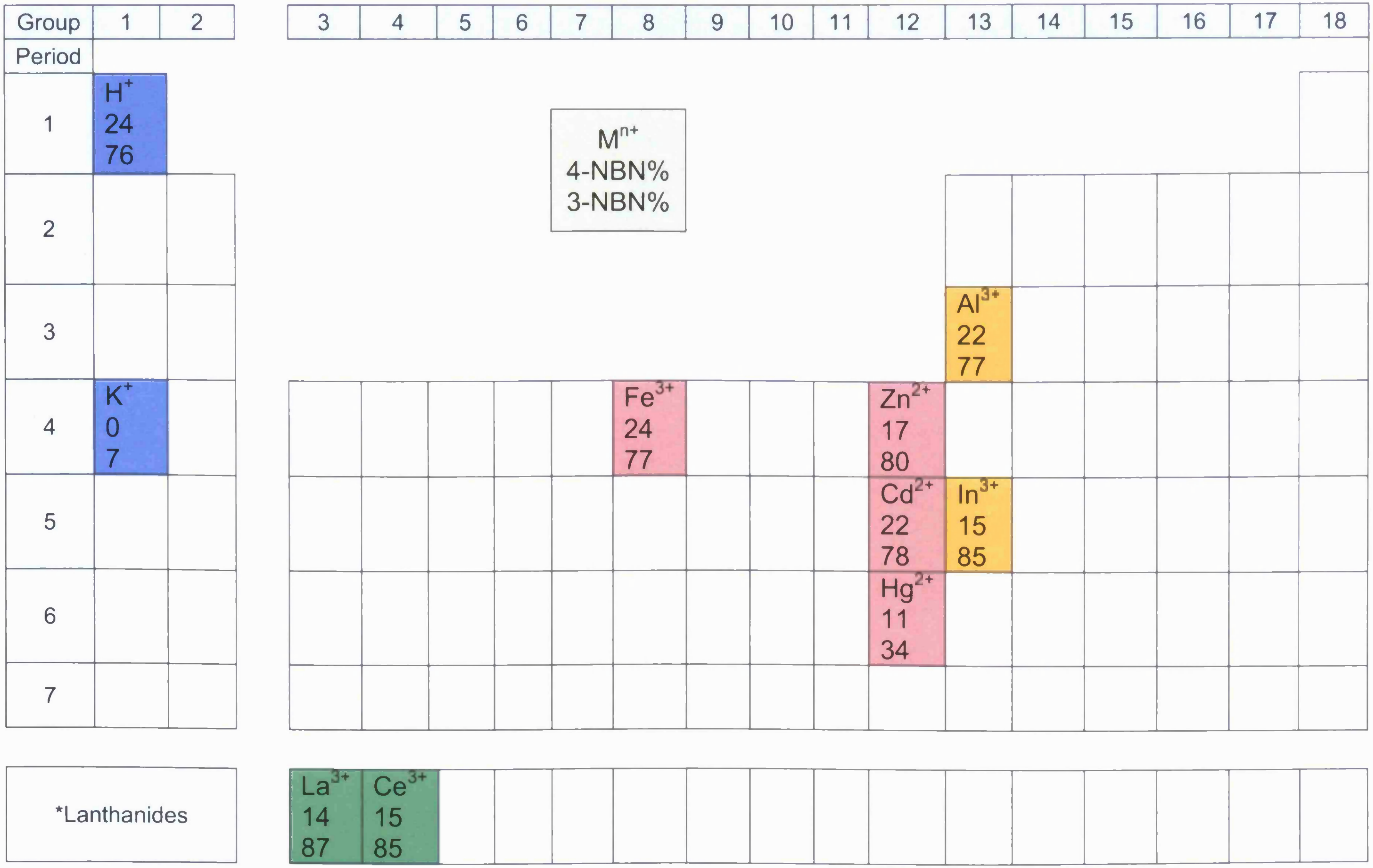


Figure 4.10: Yields of 3-NBN and 4-NBN for reaction of benzonitrile over various cation-exchanged forms of zeolite β.

It should be borne in mind that the cases which provided results out of line may have arisen from poor exchange, impurities or pore blocking. For example, $Fe^{3+}\beta$ and $In^{3+}\beta$ required many water washes before becoming halide-free and the degree of exchange was not established. Given that few of the cation-exchanged zeolites had even matched the *para*-selectivity of Hβ, the benefit to be gained from extending this study to other cations, as had been done within the group for other reactions,[40] could not justify the amount of work involved in such a study.

It was considered that there was a relationship in selectivity between the radius of the cations exchanged (R) and the number of negative charges to be balanced (e). Granted this is a crude relationship, but given that zeolite β has two sites in a cavity then two cations with a combined diameter of 4R will sit on 1/e of these sites and only a certain amount of void space will remain. The values of 4R/e show that figures in the range of 0.04 to 2.0 give good reactivity and high yields, and give *para*-selectivity between 14% and 24% (Table 4.13). On the other hand, higher values of 4R/e gave poorer yields of NBNs. In the case of $Hg^{2+}$, with 4R/e of 2.04, the proportion of *para*-isomer was somewhat higher, but with $K^+$, with 4R/e of 5.52, virtually no *para*-isomer was formed, probably because all the reaction took place at the external surface.

It is clear that overall there is broad correlation between cation size and yield of 4-nitrobenzonitrile. 4-Nitrobenzonitrile was obtained in 28% yield when 4.0 g of $Fe^{3+}\beta$ zeolite was used compared with 24% when 2 g was used. Therefore, we thought that more experimental work needed to be done using $Fe^{3+}\beta$ as a catalyst with the hope that the *para*-selectivity could be increased further. We hoped that the benefits to be gained from such study would justify the extra amount of work required.

**Table 4.13: Selectivity and yield relationship of cation radius and cavity negative charge balance in nitration of benzonitrile with a $HNO_3$/TFAA/$M^{n+}\beta$ system**

| Entry | $M^{n+}\beta$ | Radius/Å[a] | 4R/e[b] | Yield (%)[c] | |
|---|---|---|---|---|---|
| | | | | 4-NBN | 3-NBN |
| 1 | $H\beta$ | 0.01 | 0.04 | 24 | 76 |
| 2 | $Al^{3+}\beta$ | 0.53 | 0.71 | 22 | 77 |
| 3 | $Fe^{3+}\beta$ | 0.64 | 0.85 | 24 | 77 |
| 4 | $In^{3+}\beta$ | 0.80 | 1.07 | 15 | 85 |
| 5 | $Ce^{3+}\beta$ | 1.03 | 1.37 | 15 | 85 |
| 6 | $La^{3+}\beta$ | 1.06 | 1.41 | 14 | 87 |
| 7 | $Zn^{2+}\beta$ | 0.74 | 1.48 | 17 | 80 |
| 8 | $Cd^{2+}\beta$ | 0.97 | 1.94 | 22 | 78 |
| 9 | $Hg^{2+}\beta$ | 1.02 | 2.04 | 11 | 34 |
| 10 | $K^{+}\beta$ | 1.38 | 5.52 | 0 | 7 |

[a] cation radius.
[b] e is the number of negative charges to be balanced.
[c] Yields calculated by quantitative GC using tetradecane as an internal standard.

## 4.14. Nitration of benzonitrile with a TFAA/$HNO_3$/$Fe^{3+}\beta$ system

A series of experiments was conducted in which the quantity of $Fe^{3+}\beta$ was varied from 0.1-4.0 g in nitration of benzonitrile (9.5 mmol) using TFAA (25 mmol) and $HNO_3$ (19 mmol) in DCM under reflux for 4 h. The results are recorded in Table 4.14.

**Table 4.14:** **Nitration of benzonitrile over a $HNO_3$/TFAA/$Fe^{3+}$β system**[a]

| Fe$^{3+}$β (g) | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **0.10** | 21 | 22 | 58 | 78 | 101 |
| **0.25** | 0 | 23 | 77 | 100 | 100 |
| **0.50** | 0 | 23 | 78 | 100 | 101 |
| **1.0** | 0 | 23 | 78 | 100 | 101 |
| **2.0** | 0 | 24 | 77 | 100 | 101 |
| **4.0** | 0 | 28 | 73 | 100 | 101 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), TFAA (25 mmol, 3.5 ml) and zeolite Fe$^{3+}$β in DCM (20 ml) was heated under reflux for 4 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] 100 - BN %.

It was found that the yield of nitrobenzonitriles was 80%, including 22% of 4-nitrobenzonitrile, when 0.1 g of Fe$^{3+}$β was used. Under such condition around 21% of benzonitrile was recovered unreacted. The yield of nitrobenzonitriles was quantitative when more catalyst (0.25-4 g) was used, and the yield of 4-nitrobenzonitrile was in the range of 23-28%. However, the *para/meta* ratio in most cases was the same. The highest *para/meta* selectivity was achieved when 4 g of Fe$^{3+}$β was used as a catalyst. However, a high yield (81%) and a high *para/meta* ratio could be achieved by using only 0.1 g of catalyst but the reaction was not complete and *ca.* 21% of BN was recovered and a longer reaction time might be needed to achieve a quantitative yield of NBNs. It was concluded that Fe$^{3+}$β can be used catalytically in small amount to enhance the reaction of benzonitrile to provide a quantitative yield of nitrobenzonitriles with reasonable *para*-selectivity.

## 4.15. Nitration of benzonitrile over dealuminated zeolite Hβ

We have previously shown that nitration of benzonitrile over various $M^{n+}\beta$ zeolites produced nitrobenzonitriles quantitatively. 4-Nitrobenzonitrile was produced in up to 28% yield when $Fe^{3+}\beta$ was used as a catalyst. Dealumination of zeolites often results in greater *para*-selectivity when the zeolites are used to catalyse aromatic substitution reactions. Therefore, attempts were made to dealuminate a sample of Hβ (Si/Al = 12.5) with the hope of further improvement in *para*-selectivity in nitration of benzonitrile. Dealumination is the process of removing aluminium from a zeolite framework. This process increases the acid strength of individual sites and the hydrothermal stability of the zeolite structure by increasing the Si/Al ratio. However, the capacity of the zeolites for cation-exchange is decreased.[41] Therefore; the reasons for dealumination are to reduce the number of active sites at the surface of zeolite in an attempt to push the reaction to take place selectively within the pores of the zeolites. As a result, the zeolite pore pushes selectivity towards the *para*-isomer. Therefore, we attempted to use dealumination to make a difference between the internal and external surface activity.

Two batches of dealuminated Hβ were prepared by leaching Hβ (Si/Al = 12.5) with HCl; the first batch was treated with 4 M HCl and the second one with 8 M HCl. Reactions with the two dealuminated Hβ catalysts were conducted under identical conditions, and compared against non-dealuminated Hβ. The results obtained are recorded in Table 4.15.

The dealuminated Hβ samples gave identical conversions and overall yields of nitrobenzonitriles as the original sample. However, the selectivity towards the *para*-isomer was reduced, especially with Hβ dealuminated with 8M HCl, unless a large quantity of zeolite was used. This suggests that either few acid sites remained in the solid due to a significant proportion of the aluminium having been removed or that the amount of extra-framework alumina deposited in the pores was sufficient to cause significant hindrance to diffusion.

**Table 4.15:** **Nitration of benzonitrile over dealuminated Hβ zeolite**[a]

| Treatment of Hβ | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **No treatment** | 0 | 24 | 76 | 100 | 100 |
| **4 M** | 2 | 18 | 79 | 99 | 98 |
| **8 M** | 1 | 8 | 90 | 97 | 102 |
| **8 M**[d] | 2 | 17 | 82 | 98 | 101 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml) in TFAA (25 mmol, 3.5 ml) and zeolite Hβ (Si/Al= 12.5; 2.0 g) in DCM (20 ml) was heated under reflux for 4 h.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] 100 - BN %.

[d] Catalyst (4 g) was used.

It was concluded that there was no benefit to be gained in terms of selectivity towards the *para*-isomer when dealuminated Hβ was used. Therefore, we decided to use passivated Hβ in an attempt to improve the selectivity of reaction towards the *para*-isomer.

## 4.16. Nitration of benzonitrile over passivated Hβ

Passivation of the external surface of zeolites can lead to significant desirable changes to their catalytic and sorption properties.

The structural characteristic of greatest interest for catalysis by zeolites is the channel system because of the well-known shape-selective properties of zeolites. The size and dimensionality of these channel systems result in molecules being subjected to different diffusion resistances, thus ultimately controlling the selectivity of the reaction. Although the channel system has a large internal surface area, it has been shown that the external surface area of zeolite is much greater than would be expected if it were assumed to be a perfectly spherical particle.[41] Because the external surface is fully accessible to all molecules, it behaves catalytically in a non-shape selective manner, and it is therefore of great interest to study the effects of passivation in order to promote the shape-selective reactions. One way to achieve this is to deposit Si on the zeolite. This treatment has the most important secondary effect of narrowing or blocking entrances to pores and thus modifying the diffusion resistances experienced by different molecules, either reducing the pore diameter or increasing the diffusion path length, respectively.

Passivation of external surface sites can be achieved by a number of techniques. One method passivates by sorbing bulky, strong base molecules such as methylquinoline onto the zeolite. The bulkiness ensures that the molecule does not enter into the pores of the zeolite, thus possibly poisoning the internal sites of the zeolite. Another method involves removal of external acid sites by using chelating agents such as ethylenediaminetetraacetate (EDTA). It has also been extensively reported that treatment with molecules such as silanes, disilanes or $SiCl_4$ can result in a modification of the internal surface of a zeolite.[42] However, passivation of exclusively external surface sites accompanied by modification of the pore opening is generally only achieved using silane compounds. The silicon source is usually a bulky silane derivative such as tetramethoxysilane (TMOS), tetraethoxysilane (TEOS) or trimethylchlorosilane (TMCS).

There are many reports in the literature on the use of such methods and these have been reviewed elsewhere.[42-46] In general, there is consensus that the most important effect of silanisation is not so much the inertisation of external surface acid sites, which occurs readily, but rather the changes in the diffusion properties of the zeolite by either narrowing or blocking the pore openings. In the latter case, the resultant greater diffusion path length mimics the effect of using a larger crystal size as far as catalytic shape selectivity of the zeolite is concerned.

Passivation of the external surface of zeolite Hβ was performed at room temperature by treatment of calcined Hβ zeolite with an excess of pure trimethylchlorosilane (TMCS) in dichloromethane. The mixture was stirred at room temperature for 5 min and solvent and excess reagent were then removed by a dry nitrogen stream. The passivated zeolite was dried in an air oven at 120 °C for 2-6 h then crushed to a powder form. The zeolite was used in nitration reactions as fresh as possible. No attempt was made to measure the internal and external acidity of zeolite after the silanisation process.

As a test case, nitration of benzonitrile (9.5 mmol) with nitric acid (19 mmol) and TFAA (25 mmol) over passivated Hβ (2 g) in dichloromethane (20 ml) was attempted for 2 h under reflux conditions. The reaction mixture was worked-up and analysed by quantitative GC using tetradecane as an internal standard. The results clearly indicated that the yield of nitrobenzonitriles was quantitative, including a 33% yield of 4-nitrobenzonitrile, the highest yield obtained so far.

Our attention was next turned to the possibility of using less of this passivated catalyst or to see if 2 g of catalyst was actually necessary for good results. Therefore, a series of experiments was conducted under similar conditions expect that the quantity of passivated Hβ was varied from 0.1 to 2.0 g. The results obtained are recorded in Table 4.16 and represented graphically in Figure 4.12.

**Table 4.16: Effect of quantities of passivated Hβ on nitration of benzonitrile[a]**

| **Passivated Hβ (g)** | **Yield (%)[b]** | | | **Conversion[c]** | **Mass Balance (%)** |
|---|---|---|---|---|---|
| | **BN** | **4-NBN** | **3-NBN** | | |
| **0.10** | 40 | 15 | 45 | 60 | 100 |
| **0.25** | 4 | 30 | 65 | 96 | 99 |
| **0.50** | 5 | 31 | 65 | 95 | 101 |
| **1.0** | 0 | 33 | 67 | 100 | 100 |
| **2.0** | 0 | 33 | 67 | 100 | 100 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml) TFAA (25 mmol, 3.5 ml) and passivated zeolite β (Si/Al= 12.5) in DCM (20 ml) was heated under reflux for 2 h.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] 100 - BN %.

The results showed that 1 g of catalyst gave almost identical results with those obtained with 2 g. Using 0.25 or 0.50 g of catalyst produced *ca.* 31% of 4-nitrobenzonitrile, along with only *ca.* 4% of unreacted starting material. However, using only 0.10 g of catalyst gave only 15% of 4-nitrobenzonitrile and a total conversion of only 60%. In this case, therefore, the selectivity towards the *para*-isomer was significantly lower than for all the other amounts. It is clear that with 0.25 g or more of passivated catalyst nitration of benzonitrile (9.5 mmol) is complete within 2 hours and gives a good selectivity for the *para*-isomer.

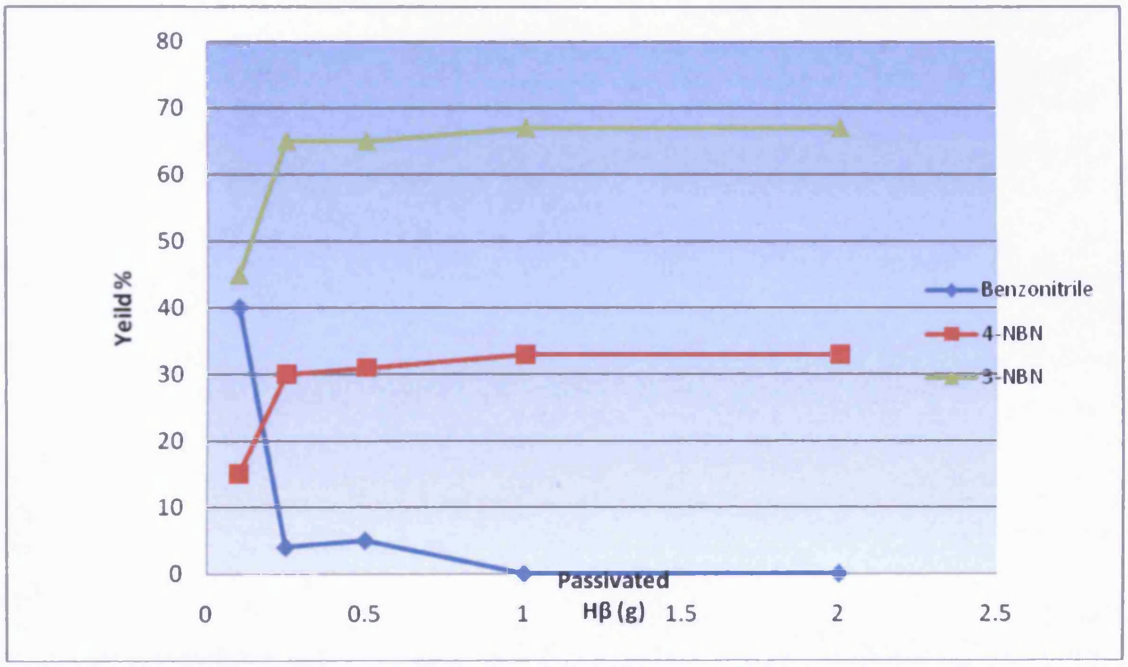


**Figure 4.11: Effect of quantities of passivated Hβ on nitration of benzonitrile**

We thought that allowing a longer reaction time might push the reaction using 0.1 g of passivated catalyst to completion. Therefore, we attempted nitration of benzonitrile using 0.10 g of zeolite Hβ for reaction times from 2 to 6 h. Each reaction was carried out under identical conditions side by side using the same batch of passivated Hβ. The reactions were worked-up and analysed quantitatively by GC. The results are recorded in Table 4.17.

**Table 4.17: Effect of reaction time on nitration of benzonitrile using passivated Hβ[a]**

| Time (h) | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **2** | 40 | 15 | 45 | 60 | 100 |
| **3** | 38 | 15 | 47 | 62 | 100 |
| **4** | 38 | 15 | 48 | 62 | 101 |
| **6** | 40 | 15 | 46 | 60 | 101 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), TFAA (25 mmol, 3.5 ml) and passivated Hβ (Si/Al = 12.5, 0.1 g) in DCM (20 ml) was heated under reflux for the stated reaction time.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] 100 - BN %.

It was hoped that increasing the reaction time would bring an increase in yield of nitrobenzonitriles. However, almost identical results were obtained regardless of the reaction time. The reason for that is not clear but possibilities include decomposition or escape of nitrating reagent within 2 h or that the quantity of Hβ (0.10 g) becomes totally deactivated either by blocking of the pores or through interaction with trifluoroacetic acid produced in the reaction. Whatever the precise explanation, it appeared that 0.10 g of catalyst was not enough to catalyze the reaction and it would be better to use 0.25-1.0 g.

The results obtained so far indicated that the maximum yield of 4-nitrobenzonitrile was 24% when Hβ itself without passivation was used as a catalyst. Zeolite $Fe^{+3}\beta$ was found to give even better yield (28%) than Hβ, albeit when a rather large quantity of catalyst was used. Also, it had been revealed that passivated Hβ gave the highest yield of 4-NBN (33%). It was of interest to see what effect passivated $Fe^{+3}$β might have on the selectivity of the reaction. Therefore, $Fe^{+3}$β was passivated as described before for Hβ and then used as a catalyst in nitration of benzonitrile. We attempted reaction using various quantities of passivated $Fe^{3+}$β (0.10–1.0 g) under identical conditions. The results obtained are recorded in Table 4.18.

**Table 4.18: Nitration of benzonitrile over various quantities of passivated $Fe^{+3}$β zeolite[a]**

| Passivated $Fe^{+3}$β | Yield (%)[b] | | | Conversion[c] | Mass Balance (%) |
|---|---|---|---|---|---|
| | BN | 4-NBN | 3-NBN | | |
| **0.10** | 22 | 20 | 60 | 78 | 100 |
| **0.25** | 6 | 24 | 70 | 94 | 100 |
| **0.50** | 4 | 24 | 71 | 96 | 99 |
| **1.0** | 2 | 26 | 73 | 98 | 101 |

[a] A mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml), TFAA (25 mmol, 3.5 ml) and passivated $Fe^{+3}$β (Si/Al = 12.5) in DCM (20 ml) was heated under reflux for 2 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] 100 - BN %.

Using 0.10 g of catalyst gave a 20% yield of 4-nitrobenzonitrile with a selectivity similar to that in the reaction carried out with passivated Hβ (Table 4.16) but the reaction proceeded to a greater conversion within the time. The yield of nitrobenzonitriles was high (94-98%) when 0.25-1.0 g of catalyst was used. However, the *para*-selectivity was lower than that with passivated Hβ. As a conclusion passivated and non-passivated Hβ were chosen as catalysts for further experiments.

## 4.17. Nitration of other deactivated mono-substituted benzenes

In order to investigate the generality of the nitration reaction, other deactivated benzenoid compounds, namely nitrobenzene, benzaldehyde, acetophenone, butyl phenyl ketone (valerophenone), *tert*-butyl phenyl ketone (pivalophenone), benzoic acid, methyl benzoate, ethyl benzoate, butyl benzoate, *N*,*N*-dimethylbenzamide, methylsulfonylbenzene and (trifluoromethyl)benzene (Figure 4.12), were chosen as substrates.

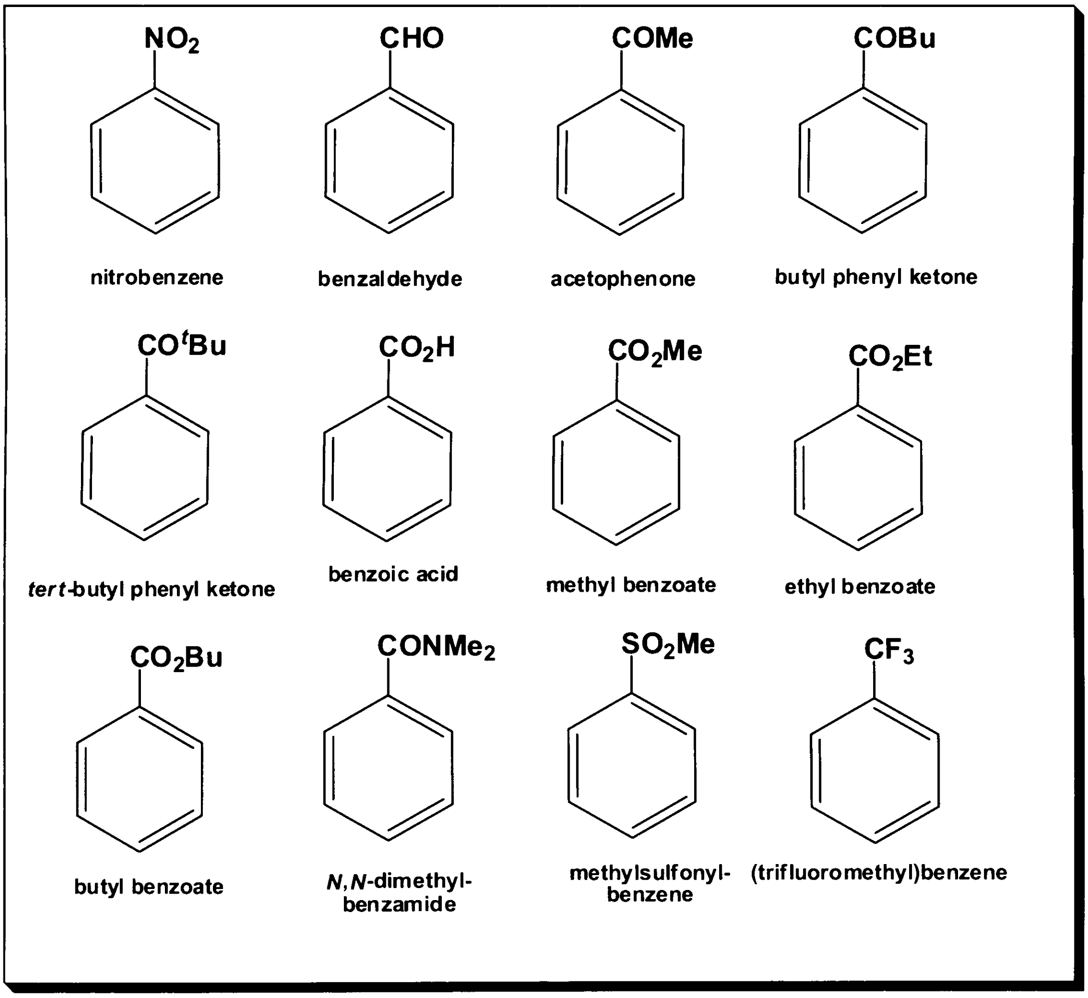
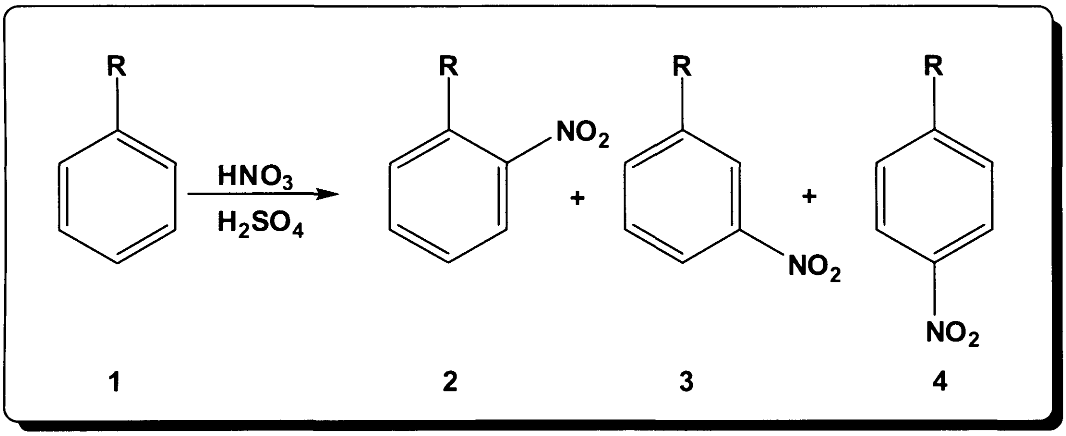


**Figure 4.12: Deactivated mono-substituted benzenes**

The first task was to carry out traditional nitration reactions, using mixed acids, of the chosen substrates (Figure 4.12). The reason for that was to obtain a baseline of results to allow comparison with the results that would be obtained in the case of zeolite catalysed reactions and to compare the results with ones previously reported.[1,16]

Each nitration reaction was carried out under identical conditions. Therefore, nitration reactions of compounds of the general type **1**, using a mixture of nitric and sulfuric acids in the ratio of 1:2, were attempted at 0 °C (Scheme 4.8). The expected products from such reactions are shown in Scheme 4.8.



**Scheme 4.8: Traditional nitration of deactivated mono-substituted benzenes using mixed acids**

In order to allow quantification of each reaction mixture, a pure sample of at least one isomeric product is required. Therefore, crude products from each reaction were purified by crystallisation, using a mixture of diethyl ether and hexane (1:3), and/or using column chromatography (silica gel; ether/hexane in the ratio of 1:3) to give pure samples of the corresponding *meta*-nitro compounds. The purity of the *meta*-nitro products was confirmed by $^1$H NMR spectroscopy. Response factors for the *meta*- isomers were measured using GC and it has been assumed that response factors are the same for the *ortho*- and *para*-isomers. Quantitative $^1$H NMR was used to analyze the mixture from nitration of acetophenone since the GC peaks for *meta*- and *para*-nitroacetophenones overlapped. Having successfully measured the response factors (Table 4.23), each reaction was analysed by GC using tetradecane as an internal standard. The results obtained are recorded in Table 4.19.

**Table 4.19: Nitration of mono-substituted benzenes 1 using a mixture of $HNO_3$ and $H_2SO_4$ according to Scheme 4.8**[a]

| **R** | **Yield (%)**[b,c] | | | **Mass Balance (%)** |
|---|---|---|---|---|
| | **2** | **3** | **4** | |
| **CN** | 17 (17) | 80 (81) | 2 (2) | 99 (100) |
| **$NO_2$** | 6 (5) | 91 (94) | 2 (1) | 99 (100) |
| **CHO** | 22 (19) | 72 (72) | 1 (9) | 95 (100) |
| **COMe**[d] | 0 (0) | 75 (83) | 0 (0) | 75 (83) |
| **COBu**[e] | 18 | 27 | 0 | 100[f] |
| **$CO^{t}Bu$** | 33 (30) | 41 (44) | 26 (26) | 100 (100) |
| **$CO_2H$** | 27 (17) | 72 (81) | 1 (2) | 100 (100) |
| **$CO_2Me$** | 20 | 69 | 3 | 93 |
| **$CO_2Et$** | 20 (28) | 78 (68) | 3 (3) | 101 (99) |
| **$CO_2Bu$** | 20 | 74 | 2 | 96 |
| **$CONMe_2$** | 2 | 82 | 0 | 84 |
| **$SO_2Me$** | 7 | 90 | 0 | 97 |
| **$CF_3$** | 8 | 91 | 2 | 101 |

[a] To a stirred mixture of $HNO_3$ (9.5 mmol) and $H_2SO_4$ (19 mmol) the appropriate substrate (9.5 mmol) was added and the mixture stirred for 10 minutes at 0 °C.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] Figures in parentheses are the reported results for similar reactions.[1,16]

[d] The mixture was analysed by $^{1}H$ NMR spectroscopy.

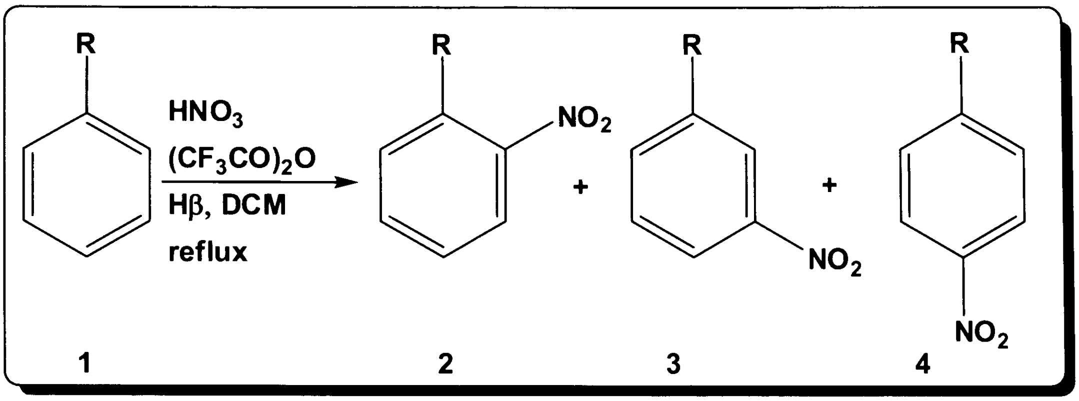
[e] Reaction was carried out using only nitric acid rather than mixed acid. A similar reaction with mixed acid was aggressive and none of the expected products was detected by GC.

[f] Including *ca.* 55% of the starting material.

The results recorded in Table 4.19 clearly indicated that traditional nitration of deactivated mono-substituted aromatics **1** gave quantitative yields of nitro products in which the *meta*-isomers were the predominate ones in all cases. In the case of acetophenone, the *meta*-isomer was the only product identified. Also, moderate yields of the *ortho*-isomers (up to 33%) were produced in most cases. Generally, the *para*-isomers were formed in very low yields, with only one exception (nitration of *tert*-butyl phenyl ketone). This last case has been attributed to possible non-planarity of the carbonyl group and benzene ring,[47] which may also explain why pivalophenone is much more reactive towards nitration than acetophenone.[48]

In order to investigate the effect of catalyst, we planned to study nitration reactions of deactivated mono-substituted benzenes **1** in the presence of zeolite catalysts. The conditions applied were the ones that produced the highest yields of NBNs and provided relatively high selectivity towards the *para*-isomer. These procedures were simple, involving a short reaction time, a small quantity of catalyst and an excess of reagents. Two types of zeolite Hβ were chosen as catalysts, namely zeolite Hβ (Si/Al = 12.5) and its passivated form, which were the ones previously tested with benzonitrile and were the most effective catalysts in terms of yield and selectivity.

Therefore nitration reactions of **1** (9.5 mmol) were conducted using nitric acid (19 mmol) and TFAA (25 mmol) over zeolite Hβ and its passivated form (0.25 g) in DCM (20 ml) under reflux conditions for 4 h (Scheme 4.9). The results with Hβ and its passivated form are recorded in Tables 4.20 and 4.21, respectively.



**Scheme 4.9: Nitration of deactivated mono-substituted benzenes 1 over a $HNO_3$/TFAA/Hβ system**

The results recorded in Tables 4.20 and 4.21 showed that nitration of deactivated aromatics **1** was general and gave quantitative yields of nitro products in most cases. The results also revealed the fact that both types of zeolite Hβ did enhance the *para*-selectivity in such nitration reactions. Nitration of benzonitrile, butyl phenyl ketone, *tert*-butyl phenyl ketone and benzoic acid gave the highest *para*-selectivity, with yields of *para*-isomers in the range of 21-37%. It was also clear that none of the *ortho*-products were obtained in the case of benzonitrile, nitrobenzene, acetophenone, benzoic acid and *N*,*N*-dimethylbenzamide.

**Table 4.20: Nitration of mono-substituted benzenes 1 over a $HNO_3$/TFAA/zeolite Hβ system according to Scheme 4.9[a]**

| R | Yield (%)[b] | | | Mass Balance (%) |
|---|---|---|---|---|
| | 2 | 3 | 4 | |
| CN | 0 | 76 | 24 | 100 |
| $NO_2$ | 0 | 92 | 7 | 99 |
| CHO | 10 | 76 | 14 | 100 |
| COMe[c] | 0 | 67 | 15 | 82 |
| COBu | 10 | 52 | 30 | 92 |
| CO$^t$Bu | 38 | 26 | 36 | 100 |
| $CO_2H$ | 0 | 75 | 21 | 96 |
| $CO_2Me$ | 4 | 85 | 10 | 99 |
| $CO_2Et$ | 8 | 77 | 12 | 97 |
| $CO_2Bu$ | 10 | 75 | 13 | 99 |
| $CONMe_2$[d] | 0 | 18 | 10 | 28 |
| $SO_2Me$ | 2 | 94 | 2 | 98 |
| $CF_3$ | 3 | 90 | 7 | 100 |

[a] A mixture of **1** (9.5 mmol), nitric acid (19 mmol, 0.8 ml), TFAA (25 mmol, 3.5 ml) and Hβ (Si/Al = 12.5, 0.25 g) in DCM (20 ml) was heated under reflux for 4 h.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] The mixture was analysed by $^1H$ NMR spectroscopy.
[d] Low mass balance presumably due to formation of other unidentified products.

**Table 4.21: Nitration of mono-substituted benzenes 1 over a $HNO_3$/TFAA/passivated zeolite Hβ system according to Scheme 4.9**[a]

| R | Yield (%)[b] | | | Mass Balance (%) |
|---|---|---|---|---|
| | 2 | 3 | 4 | |
| CN | 0 | 67 | 33 | 100 |
| $NO_2$ | 0 | 90 | 8 | 98 |
| CHO | 12 | 73 | 15 | 99 |
| COMe[c] | 0 | 70 | 17 | 87 |
| COBu | 10 | 50 | 33 | 93 |
| CO$^t$Bu | 37 | 26 | 37 | 100 |
| $CO_2H$ | 0 | 78 | 24 | 102 |
| $CO_2Me$ | 4 | 85 | 10 | 99 |
| $CO_2Et$ | 8 | 78 | 13 | 99 |
| $CO_2Bu$ | 11 | 72 | 14 | 97 |
| $CONMe_2$[d] | 0 | 19 | 11 | 30 |
| $SO_2Me$ | 2 | 93 | 3 | 98 |
| $CF_3$ | 3 | 91 | 8 | 102 |

[a] A mixture of **1** (9.5 mmol), nitric acid (19 mmol, 0.8 ml), TFAA (25 mmol, 3.5 ml) and passivated Hβ (Si/Al = 12.5, 0.25 g) in DCM (20 ml) was heated under reflux for 4 h.

[b] Yields calculated by quantitative GC using tetradecane as an internal standard.

[c] The mixture was analysed by $^1$H NMR spectroscopy.

[d] Low mass balance presumably due to formation of other unidentified products.

Within the ester and ketone series, it is clear that the role of the steric effect of the substituent in enhancing the *para*-selectivity was not so straightforward. For example, the yields of *para*-isomers in the case of butyl phenyl ketone and *tert*-butyl phenyl ketone were quite similar, which was not expected. The reason for that is not clear, but it may be that in the confines of the zeolite pores the transition state for reaction of *n*-butyl phenyl ketone necessitates twisting the carbonyl group somewhat out of conjugation with the benzene ring, as in the case of the *tert*-butyl phenyl ketone. This could have the effect of reducing the deactivating effect of the substituent, resulting in a faster and intrinsically less selective reaction and also transforming the substituent into something more like an activating and *ortho/para* directing group. It is possible that in the case of *tert*-butyl phenyl ketone the twisting out of alignment is further enforced, which could help to explain the much higher than expected proportion of *ortho*-substituted product in this case. However, it is worth noting that the proportion of *para*-substituted product for each of these two ketones was quite high and that in the case of *tert*-butyl phenyl ketone it is the highest we have yet recorded within this series of deactivated substrates. Indeed, the *meta*-substituted product was the minor product in this case.

Methylsulfonylbenzene, nitrobenzene and (trifluoromethyl) benzene gave the lowest *para*-selectivities, presumably due to the powerful *meta*-directing and deactivating nature of such substituents. In the case of *N,N*-dimethylbenzamide the yield was low due to formation of other products that were not identified.

The results obtained with *tert*-butyl phenyl ketone were very interesting. The *ortho*-isomer was produced in high yield even in the absence of the catalyst (33%) and was even higher in the presence of zeolite (37%). The reason for this observation is not clear but presumably because *ortho*-product was produced quickly. Therefore, if this is true slowing down the reaction could lead to an increase in the *para*-product at the expense of the *ortho*-isomer. One possibility to slow down the reaction to enhance the *para*-selectivity is to use a less reactive nitrating reagent such as propionyl nitrate, which may be more selective. However, such reagent was not reactive enough in the case of benzonitrile and only starting material was recovered and this makes this possibility unlikely. However, we decided to use this reagent in nitration of *tert*-butyl phenyl ketone over Hβ in DCM under reflux. It was found that nitration of *tert*-butyl phenyl ketone over $HNO_3/(EtCO)_2O/H\beta$ in DCM under reflux for 4 h gave the corresponding nitro isomers in 81% yield, with *ortho/meta/para* proportions of 30/23/28 (Table 4.22). The GC indicated the presence of 18% of unreacted starting material. The results revealed that no high *para*-selectivity was obtained under the conditions tried. In order to force the reaction to completion the previous experiemt was carried out but for a longer reaction time (8 h). Indeed, under such conditions the reaction was complete but the *para*-selectivity was not exceptional, with *ortho/meta/para* proportions of 36/27/37 (Table 4.22). It seems that this is the maximum that could be achieved under the conditions tried.

The second possibility is to conduct the reaction at lower temperatures, which may enhance the selectivity. Therefore, we decided to investigate nitration of *tert*-butyl phenyl ketone with $HNO_3$/TFAA/Hβ in DCM at a lower temperature rather than reflux conditions. Two identical experiments were carried at room temperature and at 0 °C. The results obtained are also recorded in Table 4.22.

The results obtained were unexpected in that the *ortho*-isomer was produced in even higher yields (*ca.* 42%) compared with 38% under reflux conditions. We also attempted nitration of *tert*-butyl phenyl ketone in relatively higher boiling point solvents such as chloroform and dichloroethane under reflux conditions. The results obtained were very similar to the ones produced when DCM was the solvent under reflux conditions (Table 4.22). Also, using chloroacetyl nitrate as the reagent over Hβ in DCM under reflux conditions gave very similar results to those obtained with trifluoroacetyl nitrate under similar conditions (Table 4.22).

**Table 4.22: Nitration of *tert*-butyl phenyl ketone with $HNO_3/(RCO)_2O/H\beta$ systems under various reaction conditions[a]**

| Reagent | Solvent | Temp. (°C) | Yield (%)[b] | | | Mass Balance (%) |
|---|---|---|---|---|---|---|
| | | | *ortho* | *meta* | *para* | |
| $HNO_3/H_2SO_4$ | ---- | 20 | 33 | 41 | 26 | 100 |
| TFAA | DCM | reflux | 38 | 26 | 36 | 100 |
| TFAA[c] | DCM | reflux | 37 | 26 | 37 | 100 |
| TFAA | DCM | 20 | 42 | 27 | 31 | 100 |
| TFAA | DCM | 0 | 42 | 26 | 32 | 100 |
| TFAA | $CHCl_3$ | reflux | 38 | 26 | 36 | 100 |
| TFAA | DCE | reflux | 38 | 30 | 32 | 100 |
| $(ClCH_2CO)_2O$ | DCM | reflux | 36 | 26 | 37 | 99 |
| $(CH_3CH_2CO)_2O$[d] | DCM | reflux | 30 | 23 | 28 | 99 |
| $(CH_3CH_2CO)_2O$[e] | DCM | reflux | 36 | 27 | 37 | 100 |

[a] A mixture of *tert*-butyl phenyl ketone (9.5 mmol), nitric acid (19 mmol, 0.8 ml), acid anhydride (25 mmol) and zeolite Hβ (Si/Al = 12.5, 0.25 g) in solvent (20 ml) was stirred for 4 h using the appropriate reaction conditions.
[b] Yields calculated by quantitative GC using tetradecane as an internal standard.
[c] Results obtained from use of passivated Hβ zeolite
[d] Starting material was recovered (18%).
[e] The reaction carried out for 8 h.

## 4.18. Conclusion

Proton and cation-exchanged forms of zeolites are able to catalyse and improve the *para*-regioselectivity in the nitration reaction of benzonitrile using a nitric acid/acid anhydride/zeolite system. No reaction takes place with the same system in the absence of the zeolite. The reaction produces a quantitative yield of nitrobenzonitriles comprising only 3- and 4-nitrobenzonitriles, with no

2-nitrobenzonitrile produced in most cases under the conditions tried. Trifluoroacetic and chloroacetic anhydrides were found to be the most active of the anhydrides tried. Also, zeolite Hβ with a Si/Al ratio of 12.5 was the most active of the catalysts tried and also gave high *para*-selectivity. The highest yield of 4-nitrobenzonitrile (33%), with a *para*/*meta* ratio of *ca.* 0.50, was obtained using passivated Hβ. Furthermore, heating easily regenerates the zeolite, which can be reused up to six times to give results similar to those obtained with a fresh sample of the catalyst.

The process was found to be general for the nitration of monosubstituted deactivated aromatic compounds and gave significantly increased proportions of *para*-substituted isomers compared with the results obtained from the traditional mixed acid method.

It is recognised that trifluoroacetic anhydride's volatility, toxicity and cost may render it unattractive for larger scale commercial processes, but in our previous work with acetic anhydride alone it has been shown that acetic acid could be recovered quantitatively, and recovery should be equally easy with the more volatile trifluoroacetic acid.

## 4.19. Experimental Section

### 4.19.1. General experimental

Commercial Hβ zeolites were purchased from Zeolyst International and were freshly calcined at 550 °C for a minimum of 18 h prior to use. Benzonitrile, nitrobenzene, benzaldehyde, acetophenone, butyl phenyl ketone, *N*,*N*-dimethylbenzamide, benzoic acid, methylsulfonylbenzene, butyl benzoate, (trifluoromethyl)benzene, sulfuric acid and acid anhydrides were purchased from

Aldrich Chemical Company and used without purification. Nitric acid (100%) was purchased from BDH Laboratory Supplies.

Methyl benzoate and ethyl benzoate were prepared according to the literature procedure,[49] by reaction of benzoic acid with the appropriate alcohol in the presence of sulfuric acid as a catalyst, and their structures were confirmed by NMR spectroscopy.

Product mixtures from the nitration reactions of deactivated mono-substituted benzenes **1** were subjected to gas chromatography using a Shimadzu Gas Chromatograph fitted with a ZEBRON ZB-5 (5% phenyl polysiloxane) 30 m length column. The GC conditions used for analysis were: 70 °C for 1 min ramped to 250 °C at 20 °C/min and held for 3 min. The injection temperature was 250 °C and the detection temperature was 250 °C. Tetradecane was used as an internal standard.

GC was the method of choice, unless otherwise indicated, to quantify the product mixtures and to determine the yield (%) and the total mass balance.

### 4.19.2. GC Analytical procedure

All available expected isomeric products [purchased from Aldrich Chemical Company (99% purity), or obtained following purification following traditional nitration reactions] were injected into the GC individually to record the retention time for each product (see Table 4.23). For details see Chapter 3; Section 3.24.

**Table 4.23: Retention time for each standard**

| Expected products | Retention time (min) |
|---|---|
| **Tetradecane (TD)** | 5.09 |
| **Benzonitrile (BN)** | 1.40 |
| **2-Nitrobenzonitrile (2-NBN)** | 4.51 |
| **3-Nitrobenzonitrile (3-NBN)** | 4.87 |
| **4-Nitrobenzonitrile (4-NBN)** | 4.74 |
| **Nitrobenzene (BN)** | 3.58 |
| **1,3-Dinitrobenzene (1,3-DNB)** | 5.37 |
| **1,4-Dinitrobenzene (1,4-DNB)** | 5.21 |
| **1,2-Dinitrobenzene (1,2-DNB)** | 5.58 |
| **Benzaldehyde** | 2.12 |
| **3-Nitrobenzaldehyde** | 4.61 |
| **4-Nitrobenzaldehyde** | 4.61 |
| **Acetophenone (AP)** | 2.72 |
| **3-Nitroacetophenone (3-NAP)** | 5.46 |
| **4-Nitroacetophenone (4-NAP)** | 4.30 |
| **butyl phenyl ketone** | 4.71 |
| **3-Nitrobutyl phenyl ketone** | 7.33 |
| **4-Nitrobutyl phenyl ketone** | 7.24 |
| ***tert*-butyl phenyl ketone** | 3.77 |
| **2-Nitro *tert*-butyl phenyl ketone** | 6.29 |
| **3-Nitro *tert*-butyl phenyl ketone** | 6.59 |
| **4-Nitrophenyl *tert*-butyl ketone** | 6.44 |
| **Benzoic acid (BA)** | 3.77 |
| **3-Nitrobenzoic acid (3-NBA)** | 6.40 |
| **4-Nitrobenzoic acid (4-NBA)** | 6.28 |
| **Methyl benzoate** | 2.46 |
| **Methyl 3-nitrobenzoate** | 5.74 |
| **Methyl 4-nitrobenzoate** | 5.52 |
| **Ethyl benzoate** | 2.91 |

**Continued: Table 4.24: Retention time for each standard**

| | |
|---|---|
| **Ethyl 3-nitrobenzoate** | 6.41 |
| **Ethyl 4-nitrobenzoate** | 6.22 |
| **Butyl benzoate** | 4.92 |
| **Butyl 3-nitrobenzoate** | 7.38 |
| **Butyl 4-nitrobenzoate** | 7.26 |
| ***N*,*N*-Dimethylbenzamide** | 4.93 |
| ***N*,*N*-Dimethyl-3-nitrobenzamide** | 7.63 |
| ***N*,*N*-Dimethyl-4-nitrobenzamide** | 7.54 |
| **Methyl phenyl sulfone** | 5.02 |
| **Methyl 3-nitrophenyl sulfone** | 7.57 |
| **Methyl 4-nitrophenyl sulfone** | 7.38 |
| **(Trifluoromethyl)benzene** | 1.34 |
| **2-Nitro(trifluoromethyl)benzene** | 2.43 |
| **3-Nitro(trifluoromethyl)benzene** | 1.94 |
| **4-Nitro(trifluoromethyl)benzene** | 1.77 |

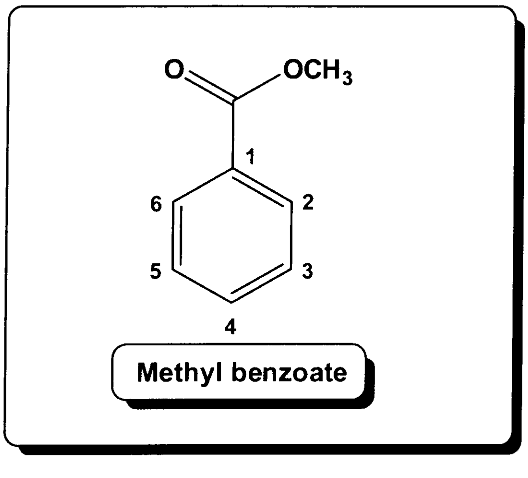
### 4.19.3. Typical nitration procedure: nitration of benzonitrile using nitric acid, trifluoroacetic anhydride and zeolite catalyst

Trifluoroacetic anhydride (25 mmol, 3.5 ml) was added to a stirred mixture of benzonitrile (9.5 mmol), nitric acid (19 mmol, 0.8 ml) and zeolite Hβ (Si/Al = 12.5, quantity as stated in tables in the results section) in DCM (20 ml). The flask was equipped with a water condenser fitted with a calcium chloride tube and was heated under reflux conditions for the stated reaction time. The reaction mixture was cooled to room temperature and analytical grade acetone (*ca.* 10 ml) was then added and the mixture was stirred for 5 min. The zeolite was removed by suction filtration and washed with copious amounts of acetone. The mother liquors were combined in a 100 ml volumetric flask.

The yields and compositions of product mixtures were analysed by quantitative GC using tetradecane as the internal standard. The conversion and yields of 3-NBN, 4-NBN and other isomers are recorded in tables. Results from variation of the procedure and use of different substrates of the general formula **1** are also recorded in tables. Details of the procedures are recorded in footnotes to the tables.

### 4.19.4. Preparation of methyl benzoate

Methyl benzoate was prepared according to the literature procedure.[49] A mixture of benzoic acid (10.0 g, 82 mmol), absolute methanol (35 ml, 27.7 g, 360 mmol) and concentrated sulfuric acid (1 ml) was heated under reflux conditions for 4 h. The excess methanol was removed under reduced pressure. The residue obtained was diluted with diethyl ether (50 ml) and then washed with saturated aqueous solution of sodium carbonate (2 x 30 ml). The organic layer was separated, washed with water (30 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue obtained was purified by simple distillation to give methyl benzoate (10.0 g, 73 mmol; 90%) as a colourless oil.

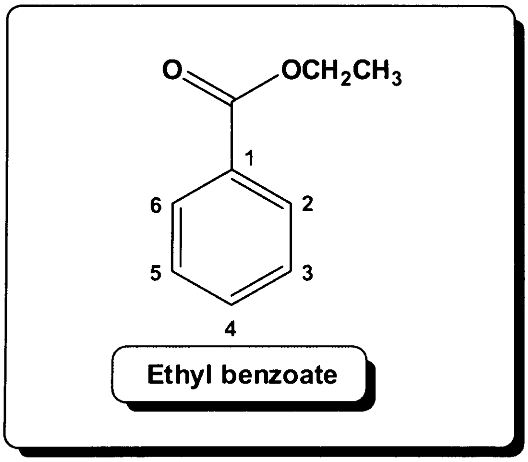


$^1$H NMR ($CDCl_3$): $\delta = 8.05$ (d, $J = 7.5$ Hz, 2 H, H-2/H-6), 7.55 (t, $J = 7.5$ Hz, 1 H, H-4), 7.44 (apparent t, $J = 7.5$ Hz, 2 H, H-3/H-5), 3.92 (s, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$): $\delta$ = 167.0 (s, C=O), 132.9 (d, C-4), 130.2 (s, C-1), 129.6 (s, C-2/C-6), 128.4 (d, C-3/C-5), 25.1 (q, $CH_3$).

### 4.19.5. Preparation of ethyl benzoate

Ethyl benzoate was prepared according to the literature procedure.[49] The procedure was identical with that described for the preparation of methyl benzoate in which ethanol (39.8 g, 50 ml, 357 mmol) was used instead of methanol and the mixture was refluxed for 6 h. Pure ethyl benzoate (10.2 g, 68 mmol; 83%) was obtained.



$^{1}$H NMR ($CDCl_3$): $\delta$ = 7.95 (d, $J$ = 7.6 Hz, 2 H, H-2/H-6), 7.44 (t, $J$ = 7.6 Hz, 1 H, H-4), 7.32 (apparent t, $J$ = 7.6 Hz, 2 H, H-3/H-5), 4.27 (q, $J$ = 7.0 Hz, 2 H, $CH_2$), 1.29 (t, $J$ = 7.0 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$): $\delta$ = 166.6 (s, C=O), 132.8 (d, C-4), 130.5 (s, C-1), 129.5 (s, C-2/C-6), 128.3 (d, C-3/C-5), 60.9 (t, $CH_2$), 25.1 (q, $CH_3$).

### 4.20. References

1. G. A. Olah, R. Malhotra and S. C. Narang, *Nitration Methods and Mechanisms*, VCH, New York, 1989.

2. R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990.

3. C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Bell, London, 1969.

4. P. B. delaMare and J. H. Ridd, *Aromatic Substitution, Nitration and Halogenation*, Butterworths, London, 1959.

5. K. Schofield, *Aromatic Nitration*, Cambridge University press, Cambridge, 1980.

6. B. Gigante, A. Prazeres, M. Marcelo-Curto, A. Cornelis and P. Laszlo, *J. Org. Chem.*, 1995, **60**, 3445.

7. B. Carvalheiro, P. Laszlo, A. Cornelis and M. Marcelo-Curto, *PCT Inc. Appl.* WO 94/19310, 1994.

8. G. A. Olah, R. Malhotra and S. C. Narang, *J. Org. Chem.*, 1978, **43**, 4628.

9. G. Hammond and K. Douglas, *J. Am. Chem. Soc.*, 1959, **81**, 1184.

10. A. R. Hajipour and A. E. Ruoho, *Tetrahedron Lett.*, 2005, **46**, 8307.

11. H. Suzuki and T. Murashima, *J. Chem. Soc., Perkin Trans. 1*, 1994, 903.

12. R. R. Bak and A. J. Smallridge, *Tetrahedron Lett.*, 2001, **42**, 6767.

13. J. Almog, A. Klein, A. Sokol, Y. Sasson, D. Sonenfeld and T. Tamiri, *Tetrahedron Lett.*, 2006, **47**, 8651.

14. J. C. Oxley, J. L. Smith, J. S. Moran, J. N. Canino and J. Almog, *Tetrahedron Lett.*, 2008, **49**, 4449.

15. M. F. A. Dove, B. Manz, J. Montgomery, G. Pattenden and S. A. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1589.

16. H. E. Zieger and B. Lee, *Tetrahedron lett*, 1990, **46**, 2707

17. Y. Yuan, J. Nie, Z. Zhang and S. Wang, *Appl. Catal. A: Gen.*, 2005, **295**, 170.

18. J. H. Clark, *Acc. Chem. Res.*, 2002, **35**, 791.

19. J. H. Clark, *Catalysis of Organic Reactions using Supported Inorganic Reagents*, VCH, New York, 1994.
20. L. Delaude, P. Laszlo and K. Smith, *Acc. Chem. Res.*, 1993, **26**, 607.
21. K. Smith, In: *New Aspects of Organic Synthesis II*, eds. Z. Yoshida and Y. Ohshiro, Kadonsha, Tokyo and VCH, Weinheim, 1992, p. 43.
22. M. Butters In *Solid Supports and Catalysts in Organic Synthesis*, ed. K. Smith, Ellis Horwood, Chichester, 1992.
23. K. Smith, In *Catalysis of Organic Reactions*, eds. M. G. Scaros and M. L. Prunier, Marcel Dekker, New York, 1991, p. 91.
24. K. Smith and G. A. El-Hiti, *Curr. Org. Synth.*, 2004, **1**, 253.
25. K. Smith and G. A. El-Hiti, *Curr. Org. Chem.*, 2006, **10**, 1603.
26. K. Smith, S. D. Roberts and G. A. El-Hiti, *Org. Biomol. Chem.*, 2003, **1**, 1552.
27. K. Smith, G. A. El-Hiti, A. J. Jayne and M. Butters, *Org. Biomol. Chem.*, 2003, **1**, 1560.
28. K. Smith, G. A. El-Hiti, A. J. Jayne and M. Butters, *Org. Biomol. Chem.*, 2003, **1**, 2321.
29. K. Smith, G. M. Ewart, G. A. El-Hiti and K. R. Randles, *Org. Biomol. Chem.*, 2004, **2**, 3150.
30. K. Smith, G. A. El-Hiti, M. E. W. Hammond, D. Bahzad, Z. Li and C. Siquet, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2745.
31. K. Smith, M. Butters, W. E. Paget, D. Goubet, E. Fromentin and B. Nay, *Green Chem.*, 1999, **1**, 83.
32. K. Smith, A. Musson and G. A. DeBoos, *J. Org. Chem.*, 1998, **63**, 8448.
33. K. Smith, S. Almeer and S. J. Black, *Chem. Commun.*, 2000, 1571.

34. K. Smith, S. Almeer, and C. Peters, *Chem. Commun.*, 2001, 2748.

35. K. Smith, S. Almeer, S. J. Black and C. Peters, *J. Mater. Chem.*, 2002, **12**, 3285.

36. K. Smith, M. D. Ajarim and G. A. El-Hiti, *Top. Catal.*, 2009, **52**,1696.

37. K. Smith, T. Gibbins, R. W. Millar and R. P. Claridge, *J. Chem. Soc. Perkin Trans. 1*, 2000, 2753.

38. K. Smith, M. D. Ajarim and G. A. El-Hiti, *Catal. Lett.*, 2010, **134**, 270.

39. M. Alotaibi, Ph. D. Thesis, Cardiff University, Cardiff, UK, 2008.

40. G. M. Ewart, Ph. D. Thesis, Swansea University, Swansea, UK, 2006.

41. J. H. Koegler, H. van Bekkum and J. C. Jansen, *Zeolites*, 1997, **19**, 262.

42. Y. Murakami, *Stud. Surf. Sci. Catal.*, 1989, **44**, 177.

43. M. Niwa, H. Itoh, S. S. Kato, T. Hattori and Y. Murakami, *J. Chem. Soc., Chem. Commun.*, 1982, 819.

44. Hibino, M. Niwa and Y. Murakami, *J. Catal.*, 1991, **128**, 551.

45. F. Chu, C. F. Keweshan and E. F. Vansant, *Stud. Surf. Sci. Catal.*, 1989, **6**, 749.

46. C. T. O'Connor, K. P. Möller and H. Manstein, *Kona*, 2007, **25**, 230.

47. S. D. Barker, R. K. Norris and D. Randles, *Aust. J. Chem.*, 1981, **34**, 1875.

48. R. B. Moodie, *Organic Reaction Mechanism*, 1982, 231.

49. A. I. Vogel, *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Harlow, 1989.