Programming recognition arrays through double chalcogen-bonding interactions.

Nicolas Biot and Davide Bonifazi*

Dedicated to Prof. Alain Krief on the occasion of his 75th birthday.

[*] N. Biot, Prof. Dr. D. Bonifazi
School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, United Kingdom; E-mail: bonifazid@cardiff.ac.uk

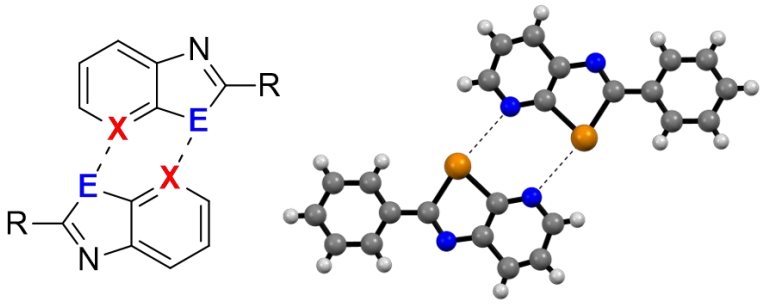
[**] D.B. gratefully acknowledges Cardiff University and the EU through the MSCA-RISE funding scheme (project INFUSION) for the financial support. The authors also acknowledge the use of the Advanced Computing @Cardiff (ARCCA) at Cardiff University, and associated support services. N.B. thanks Dr. Benson Kariuki for the training to use the X-ray diffractometer and data treatment.

Full experimental details and characterization data, spectroscopic measurments and computational studies details are gathered in the Supporting Information. Supplementary crystallographic data for compounds **11_{Se} (1584366)**, **11_{Te} (1584370)**, **12_{Se} (1584376)**, **12_{Te} (1584372)**, **13_{Se} (1584369)**, **13_{Te} (1584371)**, **14_{Se} (1584203)**, **14_{Te} (1584374)**, **15_{Se} (1584204)**, **15_{Te} (1584377)**, **16_{Se} (1584378)**, **16_{Te} (1584367)**, **17_{Se} (1584368)**, **17_{Te} (1584375)**, **18_{Te} (1584373)** and **$(13_{Te})_2$.HDFIO (1584205)** can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Keywords: recognition algorithm / chalcogen bonding / SBIs / Te / Se / supramolecular chemistry / solid-state arrangement / self-assembly.

Abstract: In this work, we have programmed and synthesized a recognition arrays constructed around a chalcogenazolo-pyridine scaffold (**CGP**) that, through the formation of frontal double chalcogen-bonding interactions, associates into dimeric EX-type complexes. The reliability of the double chalcogen bonding interaction has been shown at the solid-state by X-ray analysis, depicting the strongest recognition persistence for the Te-congener. The high recognition fidelity, chemical and thermal stability and easy derivatization at the 2-position makes **CGP** a convenient motif for constructing supramolecular architectures through programmed chalcogen-bonding interactions.

Figure to Table of Content



Introduction

The essence of supramolecular chemistry gravitates around the use of the principle of molecular recognition to engineer functional architectures.[1] This implies the storage of bonding information in a recognition arrays that, through the formation of a specific array of intermolecular non-covalent interactions drives the programmed association of molecules into complex architecture.[2]

In recent years, a class of weak interactions has increasingly attracted the attention of chemists: secondary-bonding interactions (SBIs).[3] A SBI is generally described as n^2(X) $\rightarrow$ σ^*(E-EWG) donation (X···E-EWG), where X, E and EWG stand for the electro-donating atom, polarizable atom and electron withdrawing group, respectively. Halogen bonding is certainly the most recognized SBI,[3b, 4] and its use has been largely demonstrated in both materials science[5] and biochemistry.[6] Structures containing electron-deficient chalcogen atoms can also give rise to SBIs, known as chalcogen bonding.[7] Recent examples describe the use of chalcogen bonds to master architectures at the solid-state,[8] to promote anion recognition and transport,[7d, 9] in catalysis[10] and macrocyclic synthesis.[11] Our group recently entered in the field while preparing benzo-1,3-chalcogenazoles organic phosphors.[12] When crystallized, these molecules underwent formation of polymeric structures through intermolecular N···E interactions (E = Se or Te).[8]

In the majority of these examples, the self-assembly process is driven by the formation of single X···E contacts (for the aromatic derivative see Fig. 1). Arrays featuring a programmed combination of multiple chalcogen-bonding interactions are very rare. Striking examples include the bidentate chalcogen donors (*i.e.*, of E···X···E type) reported by the groups of Matile[9a, 10a, 10b] and Taylors,[9b] and the bifurcated X···E···X type motif from Reid and co-workers.[13] To the best of our knowledge, only one example of a double EX-type array has been conceived to date by Vargas-Baca and co-workers, in which the E and X atoms are linked as first nearest neighbors (FNN) (Fig. 1).[14]

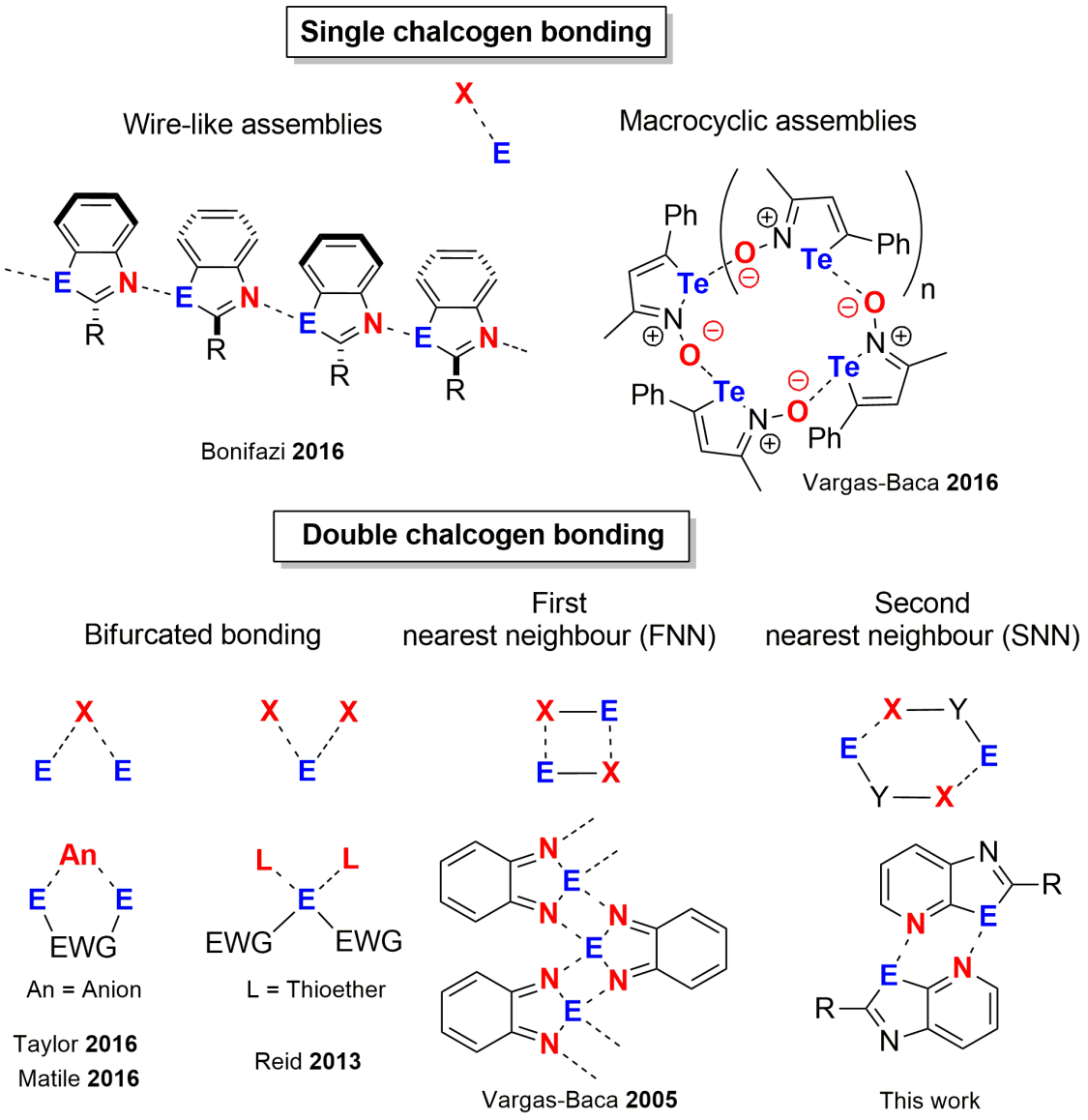


Fig. 1. Single and double chalcogen-bonding interactions.

Building on the results with the benzo-1,3-chalcogenazole scaffolds,[8] in this work we report about molecular motifs leading to double chalcogen-bonded EX-type arrays with high recognition fidelity, chemical and thermal stability and easy derivatization.[7a] Provided that a carbon atom is replaced by a basic heteroatom (X) in the benzenoic ring of a benzochalcogenazole,[8] one can expect to program a recognition motif giving a double chalcogen-bonded array (Fig. 1). Thus, we conjectured that the β-fusion of a chalcogenazole to a pyridine ring to give a chalcogenazolo[5,4-*β*]pyridine unit (abbreviated here as **CGP**, Fig. 2) should lead to a self-complementary

motif that, through the peripheral exposition of second nearest neighbouring (SNN) chalcogen-bonding donor (E) and acceptor (X) atoms, can undergo dimerization. To validate this recognition ability, we used electrostatic surface potential (ESP)[7d, 15] and estimated the value ($V_{s,max}$) at the point of the highest charge for both donor and acceptor atoms.[7d, 15] The ESPs of models for the Se- and Te-doped **GCP**s are shown in Figure 2.

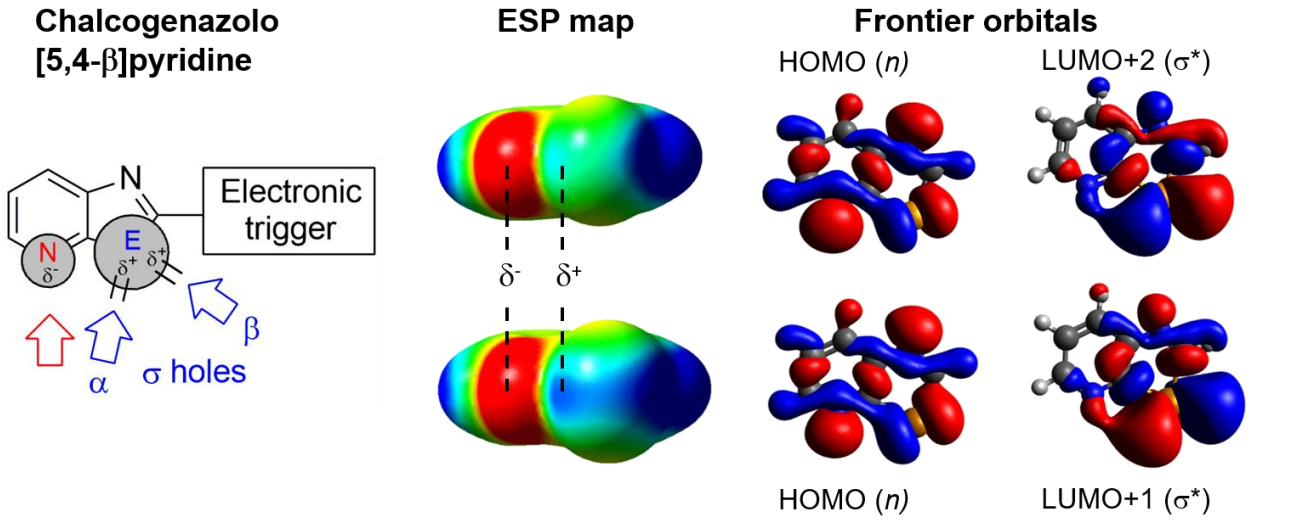
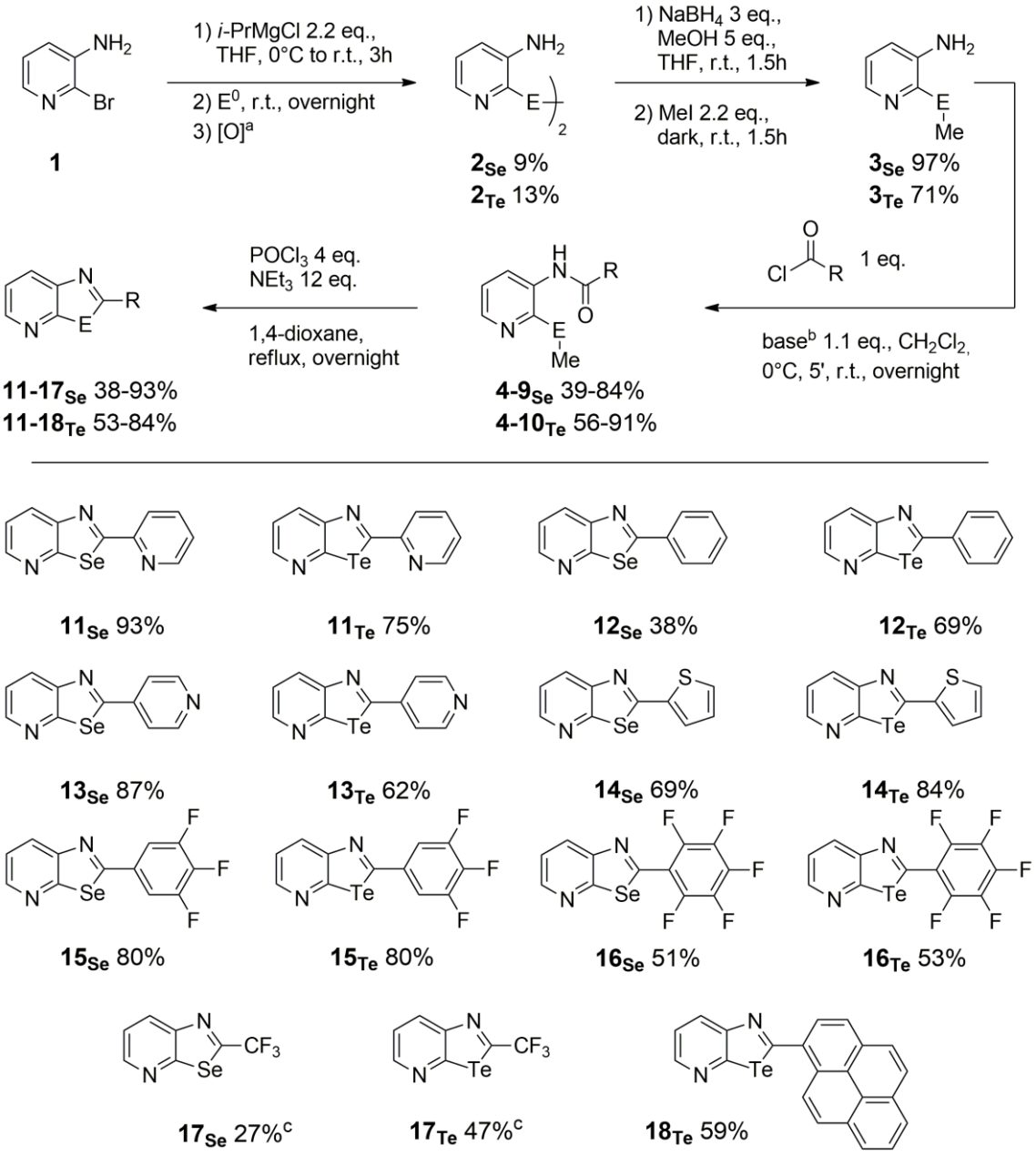


Fig. 2. ESP (calculated using Gaussian 09 at B97-D3/def2-TZVP level of theory)[7d] mapped on the van-der-Waals surface of the CGP motifs (Se top and Te bottom) along with the relevant molecular orbitals involved in the interactions.

As expected, electron deficient σ-holes(α) and σ-holes(β) are present[8] on the chalcogen atom, with that in α being the depleted region engaging into the non-covalent array through $n^2 \rightarrow \sigma^*$ orbital delocalization[7e] (for the molecular orbitals see Fig. 2). The calculated $V_{s,max}$ values are +5.4 and +10.5 kcal mol^{-1} for the σ-holes(α) of the Se and Te congeners, respectively. $V_{s,max}$ values of similar magnitude were obtained for the pyridyl N atom of both Se and Te derivatives (-28.7 and -27.8 kcal mol^{-1}, respectively), whereas weaker potentials were found for the chalcogenazole N atom (-26.5 and -25.1 kcal mol^{-1}, respectively). Building on these computational results, one can envisage that the chalcogen interactions will be preferentially established through the pyridyl

N atom. We thus engineered Se- and Te-containing **CGP**s bearing different substituents at the 2-position (Scheme 1).



Scheme 1. Synthetic route for preparing the **CGP** synthone through the dehydrative cyclization reaction. E = Se or Te; a) for $\mathbf{2_{Se}}$ $K_3Fe(CN)_6$ in H_2O for 10 min, while for $\mathbf{2_{Te}}$ air bubbling in a buffered NH_4Cl aqueous solution for 2h; b) dry pyridine was generally used as base at the exception of $\mathbf{4_E}$, $\mathbf{5_{Se}}$ and $\mathbf{8_{Te}}$ for which dry Et_3N was used; c) $(CF_3CO)_2O$ was used and the yield calculated over two steps.

At the synthetic planning level, we contemplated the dehydrative cyclization reaction[12] as the key synthetic step. The synthesis commenced with the reaction of 2-bromo-3-aminopyridine **1** with two equivalents of *i*-PrMgCl that, upon addition of the relevant chalcogen powder (Se^0 or Te^0), afforded the corresponding dichalcogenide $\mathbf{2_E}$ after oxidation (Scheme 1). Reductive cleavage of the dichalcogenide

using $NaBH_4$ in MeOH gave the corresponding pyridylchalcogenolate that, in the presence of MeI, could be transformed into the relevant pyridine derivative $\mathbf{3_E}$. Starting from $\mathbf{3_E}$, we could synthesize a series of Se- ($\mathbf{4_{Se}}$–$\mathbf{9_{Se}}$) and Te-bearing amides ($\mathbf{4_{Te}}$–$\mathbf{10_{Te}}$) with very good yields upon reaction with the appropriate acyl chloride. Following the cyclisation protocol recently developed by us ($POCl_3$ in the presence of Et_3N under reflux in 1,4-dioxane),[8, 12] we could prepare 2-substituted Se- ($\mathbf{11_{Se}}$–$\mathbf{17_{Se}}$) and Te-congeners ($\mathbf{11_{Te}}$–$\mathbf{18_{Te}}$) in good to excellent yields (38-93%). Different aromatic moieties were successfully inserted ($\mathbf{12_E}$, $\mathbf{15_E}$, $\mathbf{16_E}$ and $\mathbf{18_E}$), as well as heterocyclic rings, like thiophenyl ($\mathbf{14_E}$) and pyridyl ($\mathbf{11_E}$ and $\mathbf{13_E}$) substituents (Scheme 1). All structures were fully characterized by ^1H- and ^{13}C-NMR spectroscopy, IR, and HR-Mass spectrometry (SI).

The association properties of the **CGP** derivatives were probed at the solid state by means of X-ray analysis (Fig. 3) of the single crystals obtained by slow evaporation of a $CHCl_3$ solution. As conjectured in our programming strategy, one can notice that the molecule $\mathbf{12_{Te}}$ associates into dimers, $(\mathbf{12_{Te}})_2$, through double N···Te interactions ($d_{N...Te}$ = 3.006 Å), involving the chalcogen σ-hole(α) and the pyridyl N atom. In the array, both **CGP** and phenyl moieties are co-planar and undergo antiperiplanar π-π stacking arrangements. Substitution of the phenyl ring with other heterocycles ($\mathbf{11_{Te}}$, $\mathbf{13_{Te}}$ and $\mathbf{14_{Te}}$) does not alter the recognition fidelity of the **CGP** algorithm, which in all cases gave double N···Te arrays. Notably, when passing to pentafluorophenyl ($\mathbf{16_{Te}}$) derivative, a shortening of the N···Te distance to 2.971 Å for dimers $(\mathbf{16_{Te}})_2$ was observed. This can be rationalized considering the increasing electronegativity of the 2-substituents that, enhancing the $V_{s,max}$ value of the σ-hole(α) (from +7.71 for $\mathbf{12_{Te}}$ to +14.1 for $\mathbf{16_{Te}}$), enhance the electrostatic contribution of the interaction (Table 1).[7d, 7e, 16]

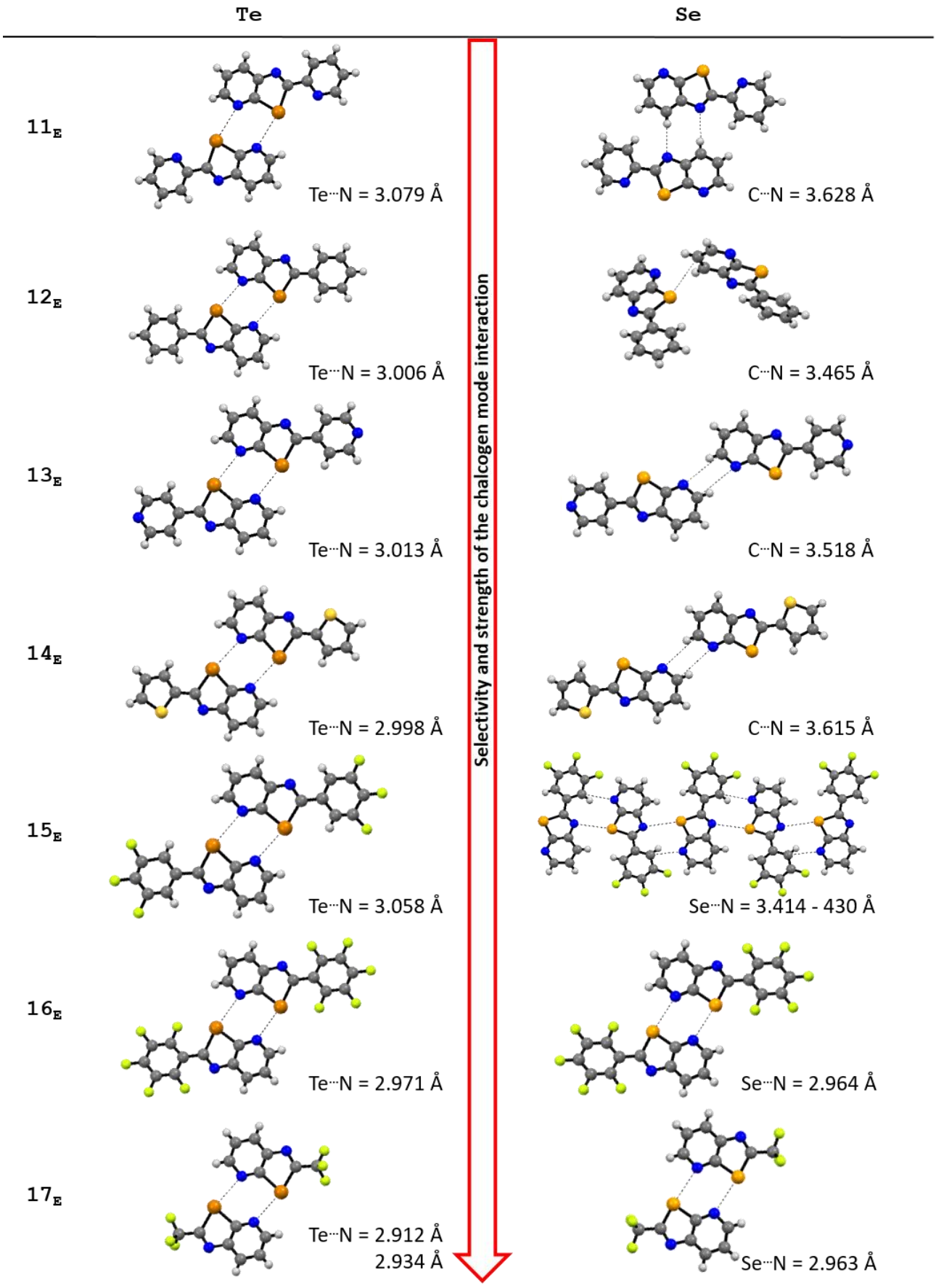
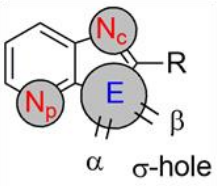
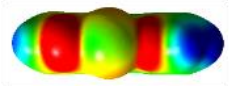
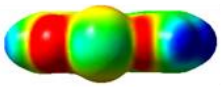
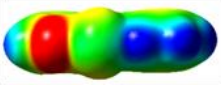
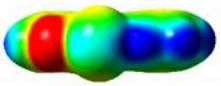
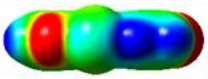
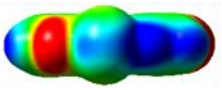
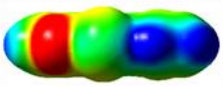
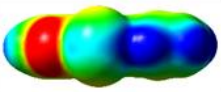
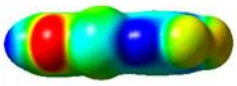
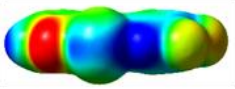
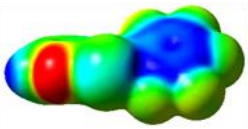
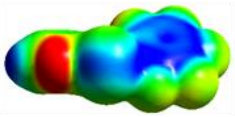
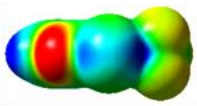
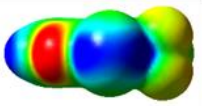


Fig. 3. Solid-state recognition mode and length of the relevant shortest non-covalent interactions.

Table 1. Calculated[15] ESP and $V_{s,max}$ values.



Entry	ESP		$V_{s,max}$ (kcal mol^{-1})			
	Se	Te	E	N_c	N_p	σ-hole (α)
11_E			Se	-19.4	-32.0	-0.36
			Te	-18.5	-32.0	+5.67
12_E			Se	-19.4	-30.7	-2.29
			Te	-17.9	-30.0	+7.71
13_E			Se	-15.1	-26.8	+7.09
			Te	-13.9	-26.1	+12.5
14_E			Se	-24.1	-30.5	+3.70
			Te	-22.3	-29.6	+9.53
15_E			Se	-13.6	-25.9	+7.84
			Te	-12.1	-25.9	+13.4
16_E			Se	-23.1	-26.6	+8.30
			Te	-22.0	-26.0	+14.1
17_E			Se	-24.1	-23.6	+12.7
			Te	-23.6	-23.0	+19.1

To further corroborate this effect, we have also prepared 2-trifluoromethano derivative **18_{Te}**. As expected, the presence of the CF_3 moiety further shifts the $V_{s,max}$ value of the σ-hole(α) to +19.1, shortening the N···Te distance to 2.912-2.934 Å, thus increasing the strength of the association. When programming the **CGP** moiety with Se atoms, a certain variability of the recognition behavior was

observed instead. For instance, no N···Se SBIs have been detected for the Se congeners, **11_{se}-14_{se}**. Rather, molecules **11_{se}**, **13_{se}** and **14_{se}** arrange into dimeric species through double H-bonding interactions involving the N atom of either the chalcogenazole unit (**11_{se}**) or that of the **CGP** (**13_{Se}** and **14_{se}**) moiety. Conversely, only Se···π contacts were present in the crystal architecture of **12_{se}**. SBIs appear in the crystal structure of 2-substitued trifluorophenyl derivative (**14_{se}**), where rod-like polymers are formed through weak N···Se interactions ($d_{N...Se}$ = 3.414-3.430 Å) involving the chalcogenazole N atom.[8] Only the pentafluorophenyl (**16_{Se}**) and trifluoromethano (**17_{Se}**) derivatives gave dimeric complexes (**16_{Se}**)$_2$ and (**17_{Se}**)$_2$, both held by double N···Se contacts ($d_{N...Se}$ = 2.964 and 2.963 Å, respectively). This suggests that, for the less polarizable Se atom, only motifs bearing strong electron-withdrawing groups lead to chalcogen-bonded arrays (Table 1).

Next, we envisaged exploiting this recognition system to control the solid-state arrangement of polycyclic aromatic hydrocarbons (PAHs). We anticipated that the conjugation of the **CGP** moiety to a PAH should constrain the aromatic core to pair in flat complexes, leveling the aromatic cores in the same plane. As a model PAH, we used pyrene, known to organize in terraced herringbone architectures at the solid state.[17] Single-crystals X-ray diffraction of **18_{Te}** (Fig. 4) revealed the formation of dimeric complexes (**18_{Te}**)$_2$, where the **CGP** motifs frontally couple through double N···Te bonds ($d_{N...Te}$ = 3.046 Å). Being the **CGP** moiety almost coplanar to the pyrenyl ring (torsion angle N2-C1-C3-C4 of 10°), the two pyrenyl cores essentially lie on the same plane. In the three-dimensional arrangement, the dimers are held together by parallel π-π stacking interactions (3.428 Å), with an offset of 3.155 Å (Fig. 4).

Finally, we challenged the **CGP** recognition motif to form co-crystals integrating two components held by orthogonal non-covalent interactions. In identifying a suitable ditopic molecular module, we inferred that molecule **13_{Te}**, with its basic pyrid-4-yl moiety, could orthogonally establish halogen-bonding interactions in the presence

of an appropriate donor. This consideration guided us to co-crystallize **13$_{Te}$** and hexadecafluoro-1,8-diiodooctane (**HDFIO**)[18] in a 2:1 ratio.

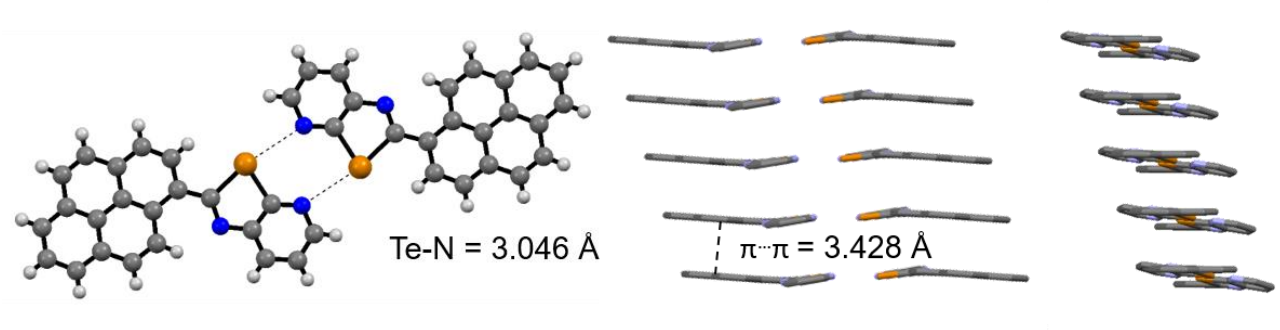


Fig. 4. Chalocogen-bonding pairing of pyrene at the solid state.

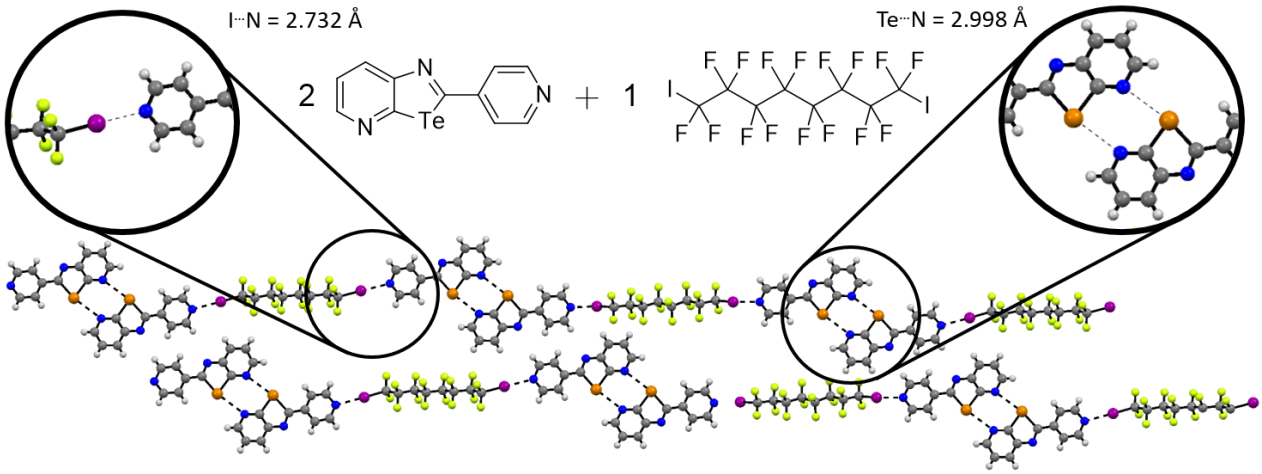


Fig. 5. Orthogonal chalcogen- and halogen-bonding interactions at the solid-state.

X-ray analysis revealed the formation of a polymeric [(**13$_{Te}$**)$_2$•**HDFIO**]$_n$ chains, in which the two components are held together through the two types of SBIs. Within the assembly, molecule **13$_{Te}$** forms dimers (through double N···Te interactions, $d_{N...Te}$ = 2.998 Å) that, in turn, sandwich ditopic **HDFIO** through N···I interactions ($d_{N...I}$ = 2.732 Å) established through the pyrid-4-yl moieties. Notably, the supramolecular assembly segregates, forming multilayered aromatic stacks interconnected by the perfluorinated chains. At the molecular level, the columnar arrangement develops from the quasi-parallel π-π stacking of (**13$_{Te}$**)$_2$.

In conclusion, we have programmed a recognition motif constructed around a **CGP** scaffold that, through the formation of double chalcogen interactions, associates in dimeric EX-type complexes. The reliability of the double chalcogen bonding interaction has been shown by X-ray analysis of single crystals, which depicted the strongest recognition persistence for the Te-congeners. Increasing the electrophilic nature of the chalcogen atom strengthens the electrostatic contribution of the interaction, shortening the N···E distance. Conjugation of the Te-**CGP** unit to a pyrene, allows the leveling of the aromatic cores, forming flatten complexes. Exceptionally, the recognition array also proved to be orthogonal to halogen-bonds, allowing the formation of the first integrated co-crystals expressing both SBIs. The recognition algorithm discussed in this paper represents the first target on the route toward the full exploitation of this interaction in molecular recognition. Future challenges would be to apply this principle to program triply- and quadruply-chalocogen-bonded arrays for the construction of operative supramolecular architectures, featuring functional properties in materials science and biochemistry.

References

[1] J.-M. Lehn, *From Molecular to Supramolecular Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, **2006**.

[2] J.-M. Lehn, *Science* **2002**, *295*, 2400-2403.

[3] a) N. W. Alcock, in *Advances in Inorganic Chemistry and Radiochemistry, Vol. 15* (Eds.: H. J. Emeléus, A. G. Sharpe), Academic Press, **1972**, pp. 1-58; b) T. M. Beale, M. G. Chudzinski, M. G. Sarwar, M. S. Taylor, *Chem. Soc. Rev.* **2013**, *42*, 1667-1680; c) Á. M. Montaña, *ChemistrySelect* **2017**, *2*, 9094-9112; d) M. Fourmigué, P. Batail, *Chem. Rev.* **2004**, *104*, 5379-5418.

[4] a) P. Metrangolo, G. Resnati, *Science* **2008**, *321*, 918-919; b) L. C. Gilday, S. W. Robinson, T. A. Barendt, M. J. Langton, B.

R. Mullaney, P. D. Beer, *Chem. Rev.* **2015**, *115*, 7118-7195; c) M. Erdelyi, *Chem. Soc. Rev.* **2012**, *41*, 3547-3557; d) A. Mukherjee, S. Tothadi, G. R. Desiraju, *Acc. Chem. Res.* **2014**, *47*, 2514-2524.

[5] R. Bertani, P. Sgarbossa, A. Venzo, F. Lelj, M. Amati, G. Resnati, T. Pilati, P. Metrangolo, G. Terraneo, *Coord. Chem. Rev.* **2010**, *254*, 677-695.

[6] a) M. Cametti, B. Crousse, P. Metrangolo, R. Milani, G. Resnati, *Chem. Soc. Rev.* **2012**, *41*, 31-42; b) P. Metrangolo, G. Resnati, *Nat. Chem.* **2012**, *4*, 437-438.

[7] a) C. Cohen-Addad, M. S. Lehmann, P. Becker, L. Parkanyi, A. Kalman, *J. Chem. Soc., Perkin Trans. 2* **1984**, 191-196; b) A. F. Cozzolino, P. J. W. Elder, I. Vargas-Baca, *Coord. Chem. Rev.* **2011**, *255*, 1426-1438; c) J. Fanfrlik, A. Prada, Z. Padelkova, A. Pecina, J. Machacek, M. Lepsik, J. Holub, A. Ruzicka, D. Hnyk, P. Hobza, *Angew. Chem. Int. Ed.* **2014**, *53*, 10139-10142; d) G. E. Garrett, G. L. Gibson, R. N. Straus, D. S. Seferos, M. S. Taylor, *J. Am. Chem. Soc.* **2015**, *137*, 4126-4133; e) D. J. Pascoe, K. B. Ling, S. L. Cockroft, *J. Am. Chem. Soc.* **2017**, *139*, 15160-15167; f) T. Chivers, R. S. Laitinen, *Chem. Soc. Rev.* **2015**, *44*, 1725-1739;.

[8] A. Kremer, A. Fermi, N. Biot, J. Wouters, D. Bonifazi, *Chem. Eur. J.* **2016**, *22*, 5665-5675.

[9] a) S. Benz, M. Macchione, Q. Verolet, J. Mareda, N. Sakai, S. Matile, *J. Am. Chem. Soc.* **2016**, *138*, 9093-9096; b) G. E. Garrett, E. I. Carrera, D. S. Seferos, M. S. Taylor, *Chem. Commun.* **2016**, *52*, 9881-9884; c) J. Y. C. Lim, I. Marques, A. L. Thompson, K. E. Christensen, V. Félix, P. D. Beer, *J. Am. Chem. Soc.* **2017**, *139*, 3122-3133.

[10] a) S. Benz, J. Mareda, C. Besnard, N. Sakai, S. Matile, *Chem. Sci.* **2017**; b) S. Benz, J. López-Andarias, J. Mareda, N. Sakai, S. Matile, *Angew. Chem. Int. Ed.* **2017**, *56*, 812-815; c) P. Wonner, L. Vogel, M. Düser, L. Gomes, F. Kniep, B. Mallick, D. B. Werz, S. M. Huber, *Angew. Chem. Int. Ed.* **2017**, *56*, 12009-

12012; d) P. Wonner, L. Vogel, F. Kniep, S. M. Huber, *Chem. Eur. J.* **2017**, *23*, DOI: 10.1002/chem.201704502.

[11] a) P. C. Ho, P. Szydlowski, J. Sinclair, P. J. W. Elder, J. Kubel, C. Gendy, L. M. Lee, H. Jenkins, J. F. Britten, D. R. Morim, I. Vargas-Baca, *Nat. Commun.* **2016**, *7*, 11299; b) P. C. Ho, J. Rafique, J. Lee, L. M. Lee, H. A. Jenkins, J. F. Britten, A. L. Braga, I. Vargas-Baca, *Dalton Trans.* **2017**, *46*, 6570-6579.

[12] A. Kremer, C. Aurisicchio, F. De Leo, B. Ventura, J. Wouters, N. Armaroli, A. Barbieri, D. Bonifazi, *Chem. Eur. J.* **2015**, *21*, 15377-15387.

[13] A. Jolleys, W. Levanson, G. Reid, *Dalton Trans.* **2013**, *42*, 2963-2972.

[14] a) A. F. Cozzolino, I. Vargas-Baca, S. Mansour, A. H. Mahmoudkhani, *J. Am. Chem. Soc.* **2005**, *127*, 3184-3190; b) A. F. Cozzolino, J. F. Britten, I. Vargas-Baca, *Cryst. Growth Des.* **2006**, *6*, 181-186; c) A. F. Cozzolino, I. Vargas-Baca, *J. Organomet. Chem.* **2007**, *692*, 2654-2657.

[15] a) T. Clark, M. Hennemann, J. S. Murray, P. Politzer, *J. Mol. Model.* **2007**, *13*, 291-296; b) J. S. Murray, P. Lane, P. Politzer, *Int. J. Quantum Chem.* **2007**, *107*, 2286-2292; c) P. Politzer, J. S. Murray, T. Clark, *Phys. Chem. Chem. Phys.* **2013**, *15*, 11178-11189; d) F. De Vleeschouwer, M. Denayer, B. Pinter, P. Geerlings, F. De Proft, *J. Comput. Chem.* **2017**, DOI: 10.1002/jcc.25099.

[16] P. L. Bora, M. Novák, J. Novotný, C. Foroutan-Nejad, R. Marek, *Chem. Eur. J.* **2017**, *23*, 7315-7323.

[17] G. R. Desiraju, A. Gavezzotti, *J. Chem. Soc., Chem. Commun.* **1989**, 621-623.

[18] a) V. Amico, S. V. Meille, E. Corradi, M. T. Messina, G. Resnati, *J. Am. Chem. Soc.* **1998**, *120*, 8261-8262; b) A. Lunghi, P. Cardillo, T. Messina, P. Metrangolo, W. Panzeri, G. Resnati, *J. Fluorine Chem.* **1998**, *91*, 191-194.