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Authors: Rong Cao and Giuseppe Resnati

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The Relevance of Size Matching in Self-assembly: Impact in Regio- and Chemoselective Cocrystallizations

Dedicate to Prof. Jane S. Murray on the Occasion of her 65th Birthday

Jing–Xiang Lin,^{a,b} Andrea Daolio,^c Patrick Scilabra,^c Giancarlo Terraneo,^c Hongfan Li,^a Giuseppe Resnati^{c,*} and Rong Cao^{a,*}

^[a] Dr. H. Li, Prof. R. Cao

State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter; Chinese Academy of Sciences;

Fuzhou 350002, P. R. China;

E-mail: rcao@fjirsm.ac.cn (R.C.)

^[b] Dr. J.-X. Lin

The School of Ocean Science and Biochemistry Engineering, Fujian Polytechnic Normal University (formerly called Fuqing Branch of Fujian Normal University);

Fuqing, 350300, P. R. China;

^[c] Dr. A. Daolio, P. Scilabra, Prof. G. Terraneo, Prof. G. Resnati

NFMLab; Department of Chemistry, Materials and Chemical Engineering "Giulio Natta; Politecnico di Milano;

via Mancinelli 7; 20131 Milano, Italy;

E-mail: giuseppe.resnati@polimi.it (G.R).

Abstract: Decamethonium diiodide is reported to perform the chemo- and regio-selective encapsulation of *para*-dihalobenzenes via competitive formation of halogen bonded cocrystals starting from solutions containing also *ortho* and *meta* isomers. Selective caging in the solid occurs even when excess *ortho* and *meta* isomers, or a mixture of them, are present in solution. A prime matching between the size and shape of the dication and the formed dianions plays a key-role in enabling for the selective self-assembly, as proven by successful encapsulation of halogen bond donors as weak as 1,4-dichlorobenzene and by the results of cocrystallization trials involving mismatching tectons. Encapsulated *para*-dihalobenzenes guest molecules can be removed quantitatively by heating the cocrystals under reduced pressure and be recovered as pure materials. The residual decamethonium diiodide can be recycled with no selectivity reduction.

Supramolecular chemistry deals with the recognition, organization, and self-assembly of molecules into zero-, one-, two-, or three-dimensional architectures. The engineering of these processes poses tremendous challenges but offers unprecedented opportunities for a plethora of functional properties.¹ Supramolecular self-assembly is affected by both energetic and geometric features. For instance, the effectiveness and selectivity of a host material in coordinating quest molecules depend on the balance between the strength of host/quest interactions and the size and shape complementary of the two modules. These two aspects and the importance of their synergistic action for effective binding became apparent since the early stages of supramolecular chemistry, when the recognition of different cations by crown-ethers and kryptands²

or of neutral molecules by calixarenes³ and cyclodextrins⁴ begun to be studied.

We decided to assess to what extent the effect of dimensional matching of interacting modules on self-assembly processes⁵ can be influential enough to enable the formation of heteromeric adducts when the inter-components attractive interactions are weak, specifically as weak as the halogen bonds (HaBs)⁶ formed by unactivated chloro- and bromocarbons. We proved the importance of size and shape matching of starting components in regioselective self-assembly processes and investigated its hierarchical effectiveness relative to intercomponents interactions strength. Specifically, in this paper we report that 1,4-dichloro- and 1,4-dibromobenzene (1a,b), two weak HaB donors,7 self-assemble with 1,10bis(trimethylammonium)decane diiodide (decamethonium diiodide, 2b) and afford the 1:1 cocrystals 1a·2b and 1b·2b (Scheme 1). In these adducts, the linear, trimeric and supramolecular dianions I ... X–C₆H₄–X···I are formed via long and weak C–X···I HaBs (X = CI and Br). The dication length (viz. N^+-N^+ separation) is similar to the supramolecular dianions



Scheme 1. Structural formulas of used tectons.

length (viz. I -- I separations) and we suggest that this size matching effect plays a major role in driving the self-assembly processes. This hypothesis is confirmed by the fact that when there is a size or shape mismatching between the dication of 2 and the supramolecular dianion given by 1, cocrystals are formed only occasionally and only if the inter-component interactions are strong. Out of fifty one attempted cocrystal formations starting from mismatching modules, no cocrystal was obtained starting from the p-, m-, and o-dichlorobenzenes 1a,d,g, only one cocrystal from the corresponding dibromobenzenes 1b,e,h and five cocrystals from the three isomeric diiodobenzenes 1c,f,i. These results and the formation of halogen bonded cocrystals 1a·2b and 1b·2b from the weak HaB donors **1a**,**b**,^{7,8} prove here that a prime matching of the metrics of interacting components can enable for the self-assembly of components when the weak inter-component interactions fail in driving the process. The practical relevance of the size matching principle is demonstrated by its exploitation in isomer separations via regioselective self-assembly processes. Precisely, 1,4-dihalobenzenes 1a-c have been separated in nearly quantitative yields from solutions containing the respective 1,3- or 1,2-isomers 1d-i via regioselective cocrystal formation with decamethonium diiodide 2b. Importantly, the process occurs effectively also starting from mixtures containing all the three isomeric dihalobenzenes and from mixtures wherein the 1,4-isomer is a minor component (e.g., mixtures where the p/o isomer ratio is 1:3).

The HaB donor ability of a halocarbon increases moving from fluorine to iodine.^{7,8} Consistent with this trend, a Cambridge Structural Database (CSD) search of crystals containing C₆H₅-Cl, -Br, and -I reveals that the percentage of entries wherein the haloarene is halogen bonded is highest with C₆H₅I and lowest with C_6H_5CI (Table S1). 1,4-Dihalobenzenes **1a-c** behave similarly and no adduct is found in the CSD for 1,4dichlorobenzene. A further confirmation of the weak HaB donor ability of unactivated chlorobenzene derivatives comes from the comparison of values of the surface electrostatic potential at the halogen σ -hole (V_{S,max}). σ -Holes with highly positive potentials are more likely to serve as strong HaB donors. V_{S,max} is 5.3, 12.2, and 17.3 kcal·mol⁻¹ in C₆H₅-Cl, -Br, and -I, respectively,^{7a-c,9} and similar trends are shown by other halobenzenes (V_{S,max} is 18.4, 27.2, and 35.9 kcal·mol⁻¹ in the corresponding pentafluorinated derivatives and 19.6 and 25.7 kcal·mol⁻¹ in 1,4-Br₂- and 1,4-I₂-C₆H₄).

Despite their poor HaB donor ability, p-dichloro- and pdibromobenzene (1a,b) afford the cocrystals 1a·2b and 1b·2b in nearly guantitative yields and high purity (Figures 1 and S25) on isothermal evaporation of chloroform/methanol solutions containing equimolar amounts of decamethonium diiodide (2b) and dihalobenzenes **1a**,**b**. The homogeneity of obtained crystal batches was proven by powder X-ray diffraction patterns (PXRD) (Figures S30 and S31). Single crystal X-ray analyses revealed that **1a**,**b·2b** are isostructural with **1c·2b**¹⁰ (Figure 2) despite the non-minor differences in the attractive intermolecular interactions in the three cocrystals (Figure 3). This is consistent with the fact that the size and shape matching of dication molecules and dianions supramolecules has a major role in driving the self-assembly and determining the cocrystal architectures.



Figure 1. Representation (Mercury 4.1.0) of the crystal structure of 1a·2b. Top, two different views of the confinement of a supramolecular dianion p-Cl₂-C₆H₄·2l⁻ in the space circumscribed by decamethonium dications. Bottom, partial view of the crystal packing along *c* axis. HaBs are red dotted lines. Color codes: White, hydrogen; grey, carbon; blue, nitrogen; green, chlorine; violet, iodine.



Figure 2. Representation (Mercury 4.1.0) of the superimposed crystal structures of cocrystals **1a·2b** (green) **1b·2b** (brown) and **1c·2b** (purple). Decamethonium dications and supramolecular dianions are in ball and stick and space filling representation, respectively.Figure Caption.

Similar to other cocrystals where decamethonium diiodide, and shorter or longer α , ω -dionium dihalides, encapsulate size matching HaB donors,¹¹ anions are fastened close to nitrogens at the endings of the polymethylene chain by electrostatic attraction and N⁺-C-H···I - hydrogen bonds (HB) (e.g., three HBs with an average length of 312.1 pm are present in 1a·2b). lodides are thus conveniently spaced to pin dihalobenzenes 1a,b at either halogen atoms. Linear, trimeric, and supramolecular dianions I ... X-C₆H₄-X...I are formed via long and weak C-X···I HaBs (X = CI and Br) (Table 1). The X···I separations are 369.3(7), 359.2(4), and 352.2(5) pm in 1a·2b, 1b·2b, and 1c·2b; the corresponding normalized contacts (N_c)¹² are 0.94, 0.90, and 0.85, respectively, confirming that HaBs are weaker in 1a·2b than in 1c·2b and have an intermediate strength in 1b·2b. Cocrystal 1a·2b is the first adduct formed by a dichlorobenzene (Table S1). Importantly, supramolecular dianions I ···X–C₆H₄–X···I sit in their position within a rectangular parallelepiped shaped cavity defined by four dication molecules (Figures 1 and S25) and the N⁺–N⁺ and I – I separations are guite similar, their difference being at most 36 pm. Hirshfeld surfaces of para-dihalobenzene tectons in

cocrystals **1a-c·2b** give an insight in the varying relevance of different supramolecular interactions present in these isostructural lattices (Figure 3). The faint red spots on the extension of the C–Cl bonds in **1a** correspond to the long and weak C–Cl···I HaBs in **1a·2b** and contrast with the intense red spots on the elongation of C–I bonds in **1c** (corresponding to close and strong C–I···I HaBs in **1c·2b**). Numerous hydrogen bonds are also evidenced; for instance, the N⁺–C–H···I interactions mentioned above.

Table 1. Selected structural parameters for cocrystal 1a-c·2b.

Cocrystal	Nc Value of X…l [−] HaB	C – X ····I [−] Angle (°)	l⁻ — l⁻ Separation (pm)	N⁺ — N⁺ Separation (pm)
1a·2b	0.94	178.49	1361.2	1397.3
1b·2b	0.90	179.64	1373.6	1398.6
1c·2b	0.85	179.96	1402.6	1402.3

To systematically verify at what extent the size and shape matching favors or determines self-assembly processes in the absence of strong inter-component interactions, cocrystal formation trials are performed starting from HaB donors and acceptors with different steric and electronic features. *Ortho-, meta-*, and *para-*dihalobenzenes **1a-i** are used to assess the effect of the size/shape of the trimeric dianions possibly formed on self-assembly (linear *vs.* angled trimers formed from *para vs. ortho/meta* isomers). Octa- and dodecamethonium diiodides **2a** and **2c** are employed to evaluate the effect of N⁺ — N⁺ separations shorter and longer than that of **2b**, and *n*-alkyl-trimethylammonium iodides **2d-f** are used as two units of these ammonium salts are chemically and metrically equivalent to one unit of diammonium salts **2a-c**.

The results of all crystallization trials are summarized in Tables S3 and S4. The eighteen trials involving dichlorobenzene isomers 1a,d,g afford only the size matching cocrystal 1a·2b, i.e., C-CI-I HaBs are not strong enough to entail cocrystal formation in the absence of the size and shape matching of the components. The eighteen trials involving dibromobenzenes 1b,e,h afford the matching cocrystal 1b·2b and the mismatching cocrystal 1b-2c. In contrast, the eighteen trials involving diiodobenzenes 1c,f,i afford the matching cocrystal 1c·2b and five mismatching cocrystals, namely 1f,i·2b, 1f,i·2c, and 1i·2d. Clearly, the C-I---I HaBs formed by unactivated iodoaromatics are strong enough to occasionally drive the formation of heteromeric adducts also in the absence of the components size matching. Single crystal X-ray analysis of 1b·2c, 1f,i·2b, and 1i-2d (Tables S8 and S9; Figures S26-S29) was possible and showed that mismatching modules result in crystal packings, and sometimes even stoichiometries, different from size matching cocrystals 1a-c·2b.





Figure 3. Hirshfeld surface of *p*-dichloro-, *p*-dibromo- and *p*-diiodo-benzene units in cocrystals **1a-c-2b** (left, middle and right, respectively).

The applicative usefulness of size and shape matching effect in driving self-assembly processes is shown by the regioselective adducts formation enabled by the greater affinity of **2b** for *para*-dihalobenzenes **1a-c** than for *meta* and *ortho* isomers **1d-i**.

Isothermal evaporation of chloroform/methanol solutions containing equimolar amounts of 2b, 1a, and 1d, or of 2b, 1a, and 1g affords the 1a 2b adduct as pure crystalline material and in nearly quantitative yields (Table S5, Figure S16), while the dichlorobenzenes 1d and 1g remaining in solution. Analogously, solutions containing 2b and the dibromobenzene isomers (i.e., solutions of 2b, 1b, and 1e, or of 2b, 1b, and 1h) afforded exclusively cocrystal 1b·2b (Figure S17), and solutions containing 2b and the diiodobenzene isomers (i.e., solutions of 2b, 1c, and 1f, or of 2b, 1c, and 1i) afforded exclusively cocrystal 1c·2b (Figure. S20). Clearly, the selective cocrystal formation enabled by size and shape matching between decamethonium cation and supramolecular anions formed by pdihalobenzenes allows for quantitative, facile, and scalable separation of regioisomeric dihalobenzenes. This is the case also when crystallizations are performed from solutions containing an excess of the mismatching isomer (e.g., a 1:3 ratio between the matching and the mismatching dihalobenzenes (Figures S18 and S19)).

As mentioned above, the N⁺—N⁺ and I —I separations match in all three cocrystals **1a-c·2b**. Cocrystal formation from solutions containing **2b** and **1a**, **1b**, and **1c**, may afford solid solutions¹³ (wherein the **1a/1b/1c** content is a function of the respective concentration in solution). Alternatively, a single pure cocrystal may be formed via chemoselective inclusion in the adduct of the strongest HaB donor if the different strength of the HaBs present in the pure cocrystals **1a-c·2b** is influential. Indeed, **1c·2b** is formed from the four-tectons solution containing equimolar amounts of **2b**, **1a**, **1b**, and **1c** and from the threetectons solutions (containing **2b**, **1a**, and **1c** or **2b**, **1b**, and **1c**) while **1b·2b** is selectively formed from the three-tectons solution containing **2b**, **1a**, and **1b** (Table S6, Figures S21-S24).

In order to demonstrate the practical usefulness of regioand chemoselective cocrystallizations described above, the pure 1a-c·2b cocrystals were heated under vacuum to remove dihalobenzene molecules namely to prove the potential of decamethonium diiodide (2b) as a reusable agent for the separation of mixtures of o-/m-/p-dihalobenzenes and of pwith different dihalobenzenes halogen atoms. Thermogravimetric analyses of 1a-c·2b cocrystals (Figures S34-S36) showed that the corresponding dihalobenzenes were released (at ambient pressure) in quantitative yields. Gram scale tests on 1a-c·2b cocrystals revealed that the dihalobenzene sublimation from the cocrystals was better performed under

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reduced pressure (0.05 mmHg) and it was quantitative after ~10 hours at 160 °C for **1a** and at 220 °C for **1b,c**. The three dihalobenzenes were recovered as highly pure and crystalline materials on cooling the vapors, while the residual decamethonium diiodide **2b** was a whitish powder which could be reused for selective cocrystal formation without further purification and with no decrease in the efficiency and selectivity of the self-assembly.

In conclusion, this paper exemplifies the utility of supramolecular chemistry and crystal engineering in preparing heteromeric cocrystals for useful applications. It is proven how the size and shape matching between cocrystal components can drive self-assembly processes. Specifically, we have described: - the formation of cocrystals between HaBs acceptor and poor donor modules of decamethonium diiodide 2b and p-dichloro- or p-dibromobenzenes 1a,b; - the regioselective formation of cocrystals between 2b and p-dihalobenzenes 1a-c in the presence of respective ortho and meta isomers 1d-f and 1g-i and even of an excess of them. The relevance of the strength of inter-component interactions (specifically the C-X--I HaB) in driving self-assembly processes is displayed by the cocrystal formation between mismatching components when strong C-I---I HaBs are present. The relative relevance of the size and shape matching vs. the strength of inter-component interactions in processes is drivina self-assembly clarified by the chemoselective cocrystal formation from solutions containing 2b and three matching partners 1a-c. The applicative value of reported regio- and chemoselective cocrystallizations is demonstrated by the quantitative separation of mixtures of o-/m-/p-dihalobenzenes and of different p-dihalobenzenes and the recovery of pure dihalobenzenes and decamethonium component (for possible reuse). It can be expected that the established heuristic principles will enable for identifying other tectons which undergo selective self-assembly processes in the absence of strong inter-component interactions.

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- [12] N_c is defined as D_{ij}/(r_{vdWi} + r_{vdWj}), where D_{ij} is the experimental distance between halogen atom i and nucleophilic atom j, and r_{vdwl}/r_{vdWj} are the van der Waals radii of *i/*j; if j is an anion, r_{Pj}, the Pauling ionic radius of j, substitutes for r_{vdWj}. N_c allows different interactions lengths to be compared in a more reliable way than by using absolute separation values. Ncs smaller than 1 correspond to attractive interactions and the smaller Nc is, the stronger the interaction.
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Entry for the Table of Contents



Selective cocrystallization: Decamethonium diiodide demonstrate region- and chemoselective cocrystallization with *para*dihalobenzenes over its isomers thanks to the size/shape matching effect and hierarchical halogen bonds, which make it a promising reagent for resolving dihalobenzene mixtures.

ORCID identification number(s) for the author(s) of this article:

Jing-Xiang Lin: 0000-0002-5519-4047

Andrea Daolio: 0000-0003-3571-3935

Patrick Scilabra: 0000-0003-1972-620X

Giancarlo Terraneo: 0000-0002-1225-2577

Giuseppe Resnati: 0000-0002-0797-9296

Rong Cao: 0000-0002-2398-399X