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Supramolecular Synthons in Crystal Engineering. 3. Solid State Architecture and Synthon Robustness in Some 2,3-Dicyano-5,6-dichloro-1,4-dialkoxybenzenes[1]

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Abstract: Supramolecular synthons in crystals are structural units formed with intermolecular interactions. The assembly of an organic crystal is not just a geometrical interlinking with synthons but is often the consequence of compromise or mutual interference between adjacent synthons. Accordingly, synthon interference can be a major problem in systematic crystal engineering especially if it results in a lack of correspondence between molecular and crystal structures. Conversely, synthon robustness or the capacity to withstand interference is an essential attribute in crystal structure design. These ideas are illustrated with reference to the structural chemistry of a series of 1,4-disubstituted 2,3-dicyano-5,6-dichlorobenzenes and related compounds. The supramolecular synthons in this structural family are constructed with polarization-induced $C{\equiv}N\cdots Cl$ interactions. Synthon interference is analyzed in terms of the trade-off between these interactions on the one hand and hydrophobic and $C-H\cdots N$ interactions on the other. Topological relationships between these $C{\equiv}N\cdots Cl$ synthons and others containing stronger hydrogen bond interactions lead to similarities in the networks formed in the crystal structures of compounds, which at the molecular level, are widely disparate.

Introduction

An organic crystal is one of the best examples of a supermolecule in which mutual recognition of molecules is sharpened by geometrical factors and long-range structural periodicity to generate a near-perfect supramolecular array.[2−4] In the solid state, the rational design of supramolecular structure is referred to as crystal engineering and has important implications for the development of new materials with useful physical and chemical properties.[5]

Crystal engineering proceeds through the stages of observation of structural families, rationalization of observed crystal packings, prediction of new structures, and testing of predictions in structural design. In this context, it is possible to define a supramolecular synthon drawing from the conceptual relationship between crystal engineering and organic synthesis and recognizing that the crystal is a supramolecular entity. Supramolecular synthons are of significance in crystal engineering because they are the smallest structural units which contain all the information inherent in the recognition events through which molecules assemble into supermolecules. These synthons are therefore the algorithms which relate molecular and supramolecular structure.

A major difficulty in crystal engineering is the fact that the interactions which control crystal structures are numerous and weak. The lability and deformability of intermolecular interactions is a cause for concern, and closely related molecules can form widely different crystal structures. Therefore, robustness of supramolecular synthons is a critical issue, and the very concept of a supramolecular synthon would not be of any practical utility unless robustness were to hold. Only if supramolecular synthons are robust can the protocols for generating a particular combination of interactions be carried over from one molecule to another with generality.

The main features of the supramolecular synthon approach in crystal engineering have been recently described.[6] This and the succeeding paper[7] attempt to further justify this concept. Here, the accent will be on observation and rationalization of crystal packing and on the robustness of synthons derived from $C{\equiv}N\cdots Cl$ interactions in a series of crystalline 1,4-disubstituted 2,3-dicyano-5,6-dichlorobenzenes, **1**−**8**, and related compounds.

Experimental Section

Details of the preparation of the 2,3-dichloro-5,6-dicyano-1,4-dialkoxybenzenes **2**−**8** and crystal structure data for **1**−**6** and **8** are given in the supporting information.[8]

Results and Discussion

Cyano···Chloro Interactions. At the outset, it would seem that the use of interactions weaker than say $O-H\cdots O$ and $N-H\cdots O$ hydrogen bonds (that is, of energies less than 5 kcal/mol) in crystal engineering is largely self-defeating. Synthon robustness would appear to be a major casualty, even as

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(1) For Part 1 see ref 6. For Part 2 see: Thalladi, V. R.; Goud, B. S.; Hoy, V.J.; Allen, F. H.; Howard, J. A. K.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1996**, 401.

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(8) For the details of the crystal structure determination of the compounds **1**, **3**, **4**, **5**, and **8**, see the supporting information.

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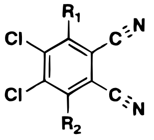
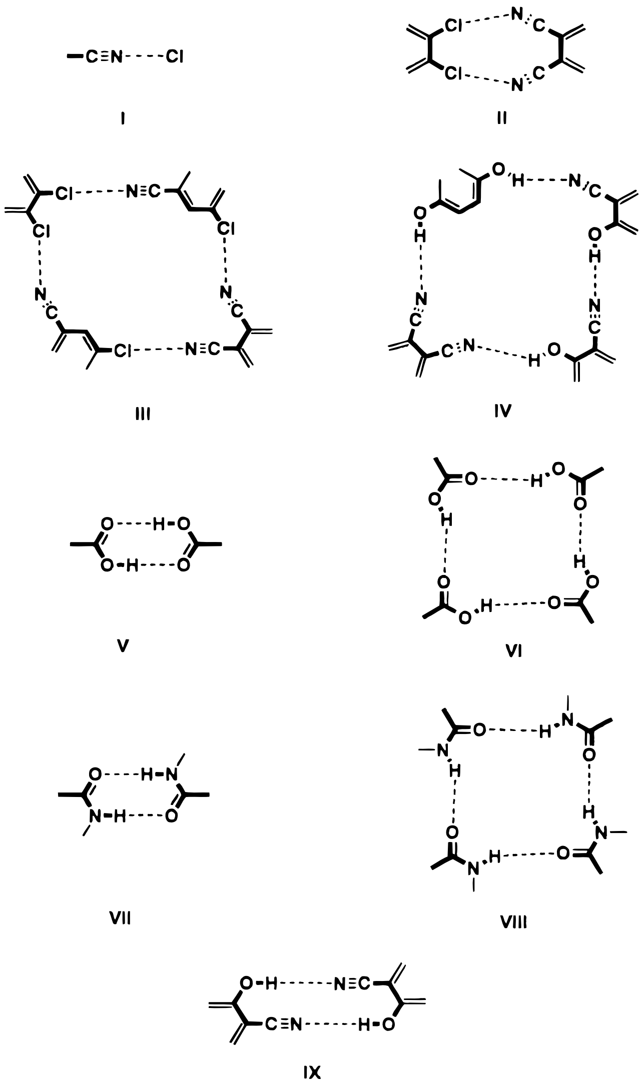


(1) $R_1 = R_2 = H$
(2) $R_1 = R_2 = OCH_3$
(3) $R_1 = R_2 = OC_2H_5$
(4) $R_1 = R_2 = n\text{-}OC_3H_7$
(5) $R_1 = R_2 = n\text{-}OC_4H_9$
(6) $R_1 = OH$, $R_2 = n\text{-}OC_8H_{17}$
(7) $R_1 = R_2 = n\text{-}OC_8H_{17}$
(8) $R_1 = R_2 = OH$

the very nature of some of these weaker interactions is still a matter of discussion and study.[5,6] The synthons used in this study are given in Chart 1.

Chart 1. Supramolecular Synthons Discussed in This Study



The motivation for the study of weaker interactions is that the scope of compounds which can be used for supramolecular construction is greatly enhanced, but because of their weakness, multipoint rather than single-point recognition is often the key to their succesful implementation. Here, we use the weak polarization induced C≡N···Cl interactions in crystal structure design. Studies with the CSD show that this interaction has definite length (N···Cl 3.00−3.50 Å) and angle (C≡N···Cl 100−180°) attributes and therefore a certain structure-defining ability which one might attempt to use in crystal engineering.[9]

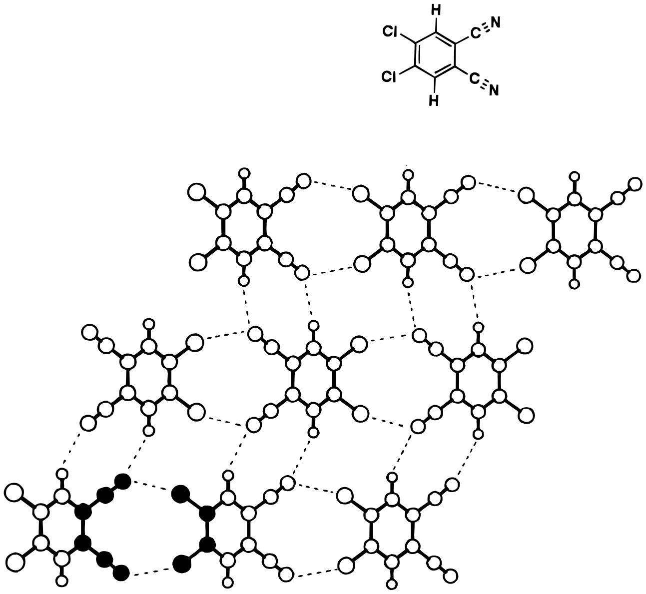
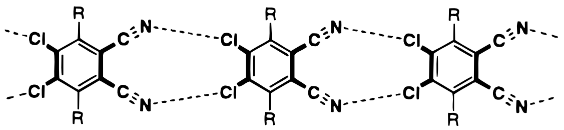


Figure 1. C≡N···Cl mediated molecular tapes in the crystal structure of compound **1**. Supramolecular synthon **II** is highlighted. Notice the C−H···N intertape connections.

Molecular Tapes in the Parent Hydrocarbon 1 and the Dimethoxy Derivative 2. The starting point for our crystal engineering exercise was the structure of 4-chlorobenzonitrile in which molecules are connected with C≡N···Cl interactions to form linear ribbons. The ribbons are laid side-by-side, but the lack of lateral interactions (along the C−H bond directions) leads to mistakes in their alignment, resulting in subtle disorder.[9] Noting that, in general, any control of supramolecular structure will improve with multipoint recognition, our attention was drawn to substituted 2,3-dicyano-5,6-dichlorobenzenes which were felt to be good candidates for the formation of C≡N···Cl mediated molecular tapes also shown in Chart 2.[10] Accordingly we prepared several 1,4-dialkoxy derivatives, **2**−**5**, the 1-hydroxy-4-(*n*-octyloxy) derivative **6**, the 1,4-bis(*n*-octyloxy) derivative **7**, and the 1,4-dihydroxy derivative **8**.

Chart 2. Tape Motif



The simplest member of the series is 1,2-dicyano-4,5-dichlorobenzene, **1**. The structure consists of molecular tapes which are constructed by linking the dimeric loop synthon **II** with spacer phenyl groups exactly as anticipated in Chart 2 (Figure 1). The 1,2,4,5-substitution pattern ensures that the tape is linear. The C≡N···Cl contacts are short and linear (N···Cl 3.21 Å, $\theta = 155.5°$). The tape pattern is stabilized by intertape C−H···N hydrogen bonding (C···N 3.47 Å; $\theta = 152.2°$) to generate sheets, and the three-dimensional structure is completed by stacking. This synthon **II** mediated tape structure is retained in 1,4-dimethoxy-2,3-dicyano-5,6-dichlorobenzene, **2** (Figure 2). Here, molecules are bisected by a 2-fold axis and the tape length

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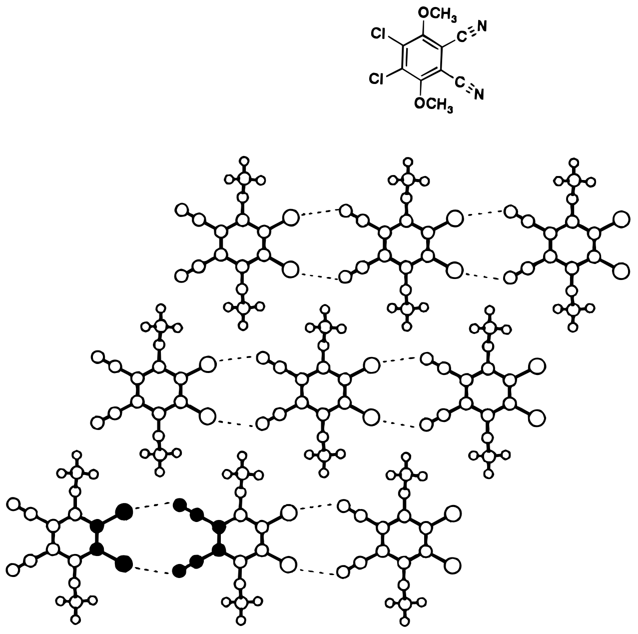

Figure 2. Crystal structure of compound **2** showing C≡N···Cl mediated molecular tapes. Synthon **II** is highlighted.

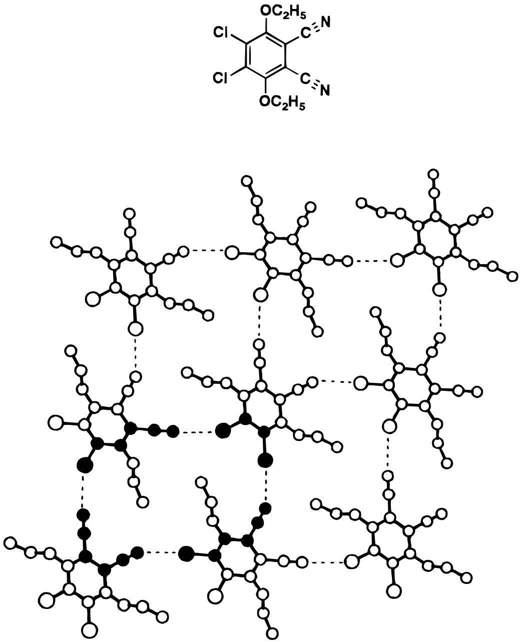

Figure 3. Tetrameric loop synthon **III** (highlighted) in the crystal structure of compound **3**. Notice the disposition of the ethoxy groups within the loop.

is along [010]. The C≡N···Cl contacts (N···Cl 3.10 Å, θ = 137.5°) are again short. Intertape C—H···N≡C hydrogen bonds (C···N 3.31 Å, θ = 96.8°), between methoxyl and cyano groups, are important. The three-dimensional structure is again generated by stacking (plane-to-plane perpendicular distance 3.67 Å). These two structures show that the synthon **II** based tape structure is a stable one but that additional intertape stabilization *via* C—H···N≡C hydrogen bonds could also be important.

Tetramer Structure in the Diethoxy Derivative 3. The structure is layered, each layer consisting of molecules connected to four others with short C≡N···Cl interactions (N···Cl 3.15 Å, θ = 153.5°; N···Cl 3.31 Å, θ = 170.3°). These contacts lead to the formation of the tetrameric loop synthon **III**, with the empty spaces in the square network being filled by the ethoxy groups (Figure 3). The shortest C···C distance between the ethoxy groups is 3.82 Å, and so these groups are reasonably well-packed. The tetramer-loop synthon **III** is more robust than the dimer-loop **II** (as observed in structures **1** and **2**) because the two distinct functionalities, namely, the cyano and chloro groups and the alkoxy groups, are structurally well-insulated unlike in **1** and **2** where the pendant groups (H atom in **1**, methoxy group in **2**) are C—H···N≡C hydrogen bonded to synthon **II**. Conceptually, one might even consider the ethoxy groups as being intercalated within a tubular host framework of cyano and chloro groups. It was therefore anticipated that this tetramer-loop synthon **III** would be carried over into the structure of the dipropoxy derivative.

Disordered and Ordered Forms of the Di-*n*-propoxy Derivative 4. Synthon **III** is retained as expected, but close-packing of the larger propoxy groups within a loop framework as compact as that found in compound **3** is now difficult. Two alternative structural compromises are observed in the dimorphs of this compound. In the *Pbcn* room temperature dimorph, there is a substantial elongation of loop **III** (N···Cl 3.82 Å, θ = 132°) in the direction of the (longer) propoxy substituents which are disordered (Figure 4a). The shortest C···C distance between propoxy substituents is 3.90 Å. In the terminology of host—guest complexes alluded to above, the host framework is distorted and the guest is disordered. In the *Pc* low-temperature ordered polymorph (Figure 4b), the tetramer-loop **III** is broken (N···Cl 3.34 Å, θ = 148.19°; N···Cl 3.59 Å, θ = 136.83°; N···Cl 3.59, θ = 112.44°; N···Cl 4.55Å, θ = 130.94°). There are two symmetry-independent molecules which differ only in the conformations of the propoxy groups. The closest C···C distances between propoxy groups are 3.23 and 3.26 Å, expectedly shorter than that found in compound **3** and in the disordered polymorph. More efficient close-packing of alkoxy groups has been achieved in the ordered polymorph at the expense of one of the four C≡N···Cl interactions in the tetramer-synthon **III** while in the disordered polymorph, the entropy contribution from the disordered propoxy groups compensates for the very long N···Cl distances.

Onset of Hydrophobic Interactions in the Di-n-butoxy Derivative 5. In any structural series, the existence of polymorphic modifications, especially ordered and disordered variants as seen in the dipropoxy derivative **4**, often signals the onset of a change in structure type. The alkoxy groups in the dibutoxy derivative **5** are definitely too long to be accommodated in the tetramer-loop **III** which is now broken in two (Figure 5). Of the four "original" links in the tetramer synthon, two have elongated to 6.081 Å while the two others (connecting glide-related molecules) have contracted to 3.18 Å (106.9°). Figure 5 shows clearly that this dissection of the tetramer synthon is caused by the approach of butoxy groups whose mutual disposition appears far less uneasy than in the dimorphs of compound **4**. Even so, these groups are not compactly packed, and they do not have the parallel sawtooth geometry characteristic of efficient hydrophobic interactions. For example, the shortest C···C distances between butoxy groups is still 3.90 Å (shortest H···H 2.62 Å). This is probably satisfactory for there was no evidence of a phase transition as was observed in compound **4**. The packing of the butoxy groups is still worth the two disrupted C≡N···Cl interactions in synthon **III**, and this structure represents the onset of alkyl···alkyl hydrophobic interactions in this family.

Three Types of Intermolecular Interactions in the Hydroxy(*n*-Octyloxy) Derivative 6. The *n*-octyl chain length in **6** ensures that hydrophobic interactions are the major determinants of the structure. Alkyl groups are compactly arranged, and the sawtooth conformation can be observed clearly (Figure 6). Synthon **II** reappears and with it the tape structure (N···Cl

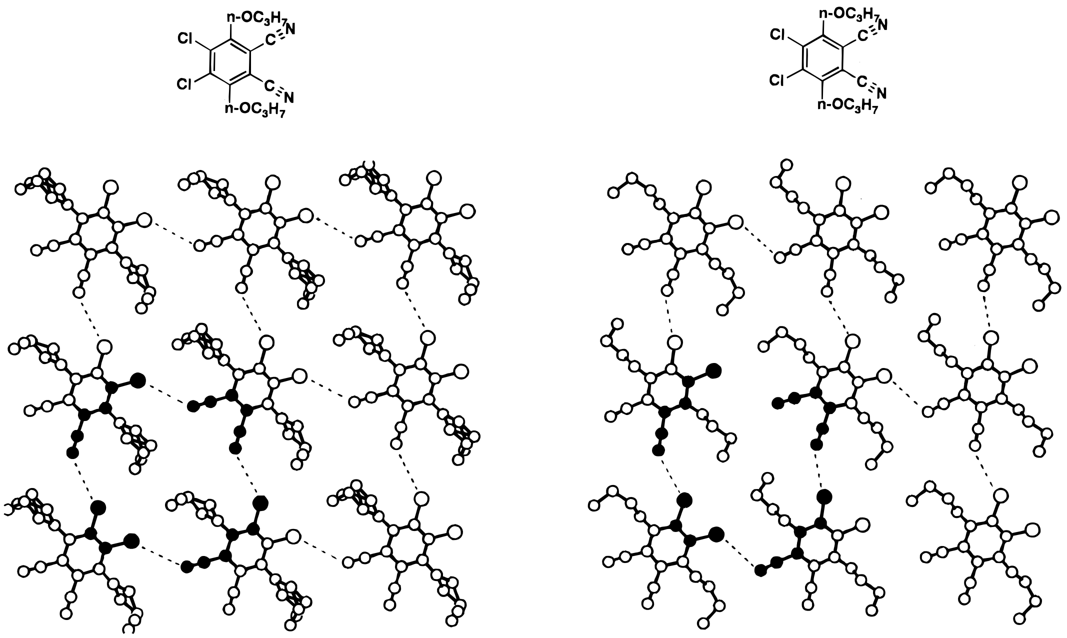

Figure 4. (a, left) Elongated tetrameric loop **III** in the room temperature form of compound **4**. Notice the disordered *n*-propoxy groups within the loop. (b, right) Broken tetrameric loop in the low-temperature form of compound **4**. The rupture of one C≡N···Cl interaction (compared to the room temperature form) is accompanied by the compensatory ordering of the *n*-propoxy group.

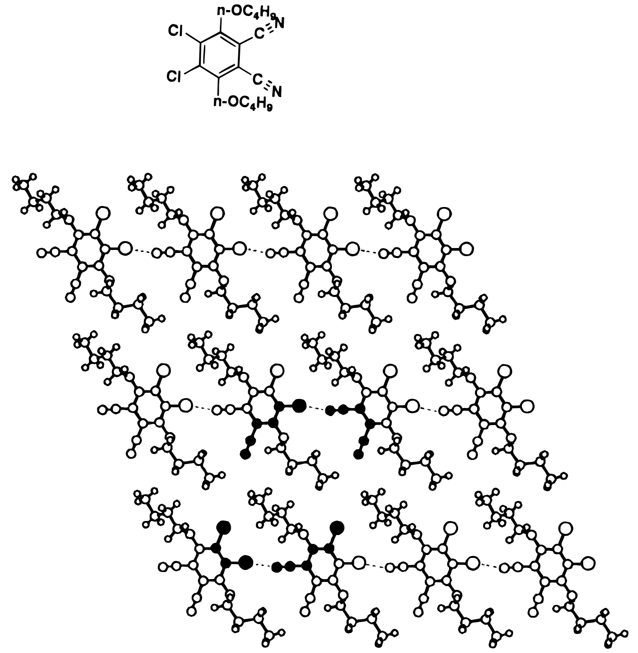

Figure 5. C≡N···Cl mediated linear chains in the crystal structure of compound **5**. Notice that the tetrameric loop **III** is now broken into two segments (highlighted).

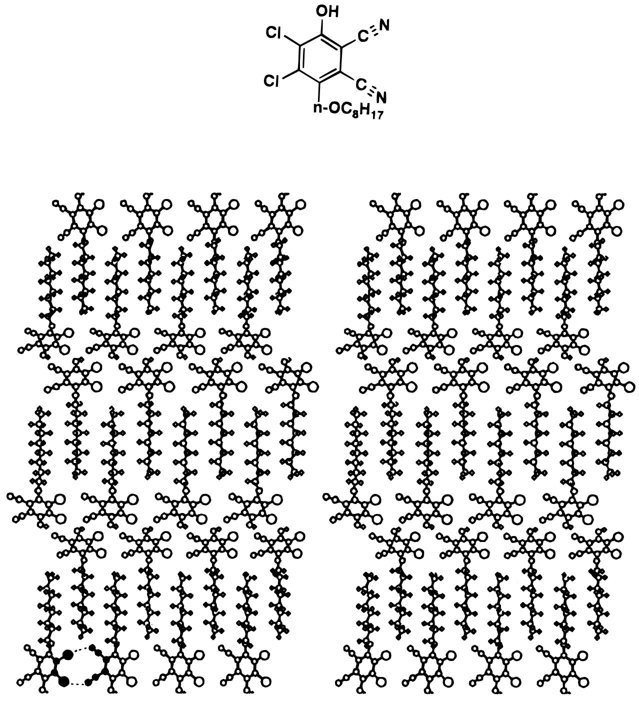

Figure 6. Stereoview of compound **6** showing tape and lamellar structures formed with C≡N···Cl interactions and close-packing of octyloxy groups.

3.40 Å, $\theta = 146.1°$; N···Cl 3.45 Å, $\theta = 132.4°$). However, this tape is stabilized for reasons which are different from those of **1** and **2**. It does not interfere with the close-packing of octyloxy groups (C···C 3.49 Å; H···H 2.55 Å), and further, adjacent tapes are connected with strong, helical C≡N···H—O hydrogen bonds (N···O, 2.79 Å, $\theta = 144.2°$) between phenolic and cyano groups. The bis(*n*-octyloxy) derivative **7** was anticipated to have the synthon **II** mediated tape structure. It was prepared as a liquid, and crystals were obtained with some difficulty *in situ*. However, even a unit cell could not be obtained.

Topological Analogies and the Structure of Dihydroxy Derivative 8. Though **8** is drastically different from **1**−**5** at the molecular level, there are similarities between the crystal structure of **8** (Figure 7) and **1**−**5**, especially the diethoxy derivative **3**. Molecules are again linked in tetramer loops (synthon **IV**), but these are formed *via* conventional N···H—O hydrogen bonds (N···O 2.75 Å, N···H 2.08 Å, $\theta = 160.2°$; N···O 2.76 Å, N···H 1.98 Å, $\theta = 148.5°$). One could visualize OH and Cl groups as $\delta+$ groups which make short contacts with the $\delta-$ cyano groups. In **3**, there are no OH groups and the tetramer is formed with N···Cl interactions. In **8**, the Cl group is unable to compete with the OH groups, and the tetramer is formed with C≡N···H—O hydrogen bonds. However, the vestigeal effects of the Cl groups are still seen in the form of three-center interactions (N···Cl 3.26 Å, $\theta = 104.2°$; N···Cl

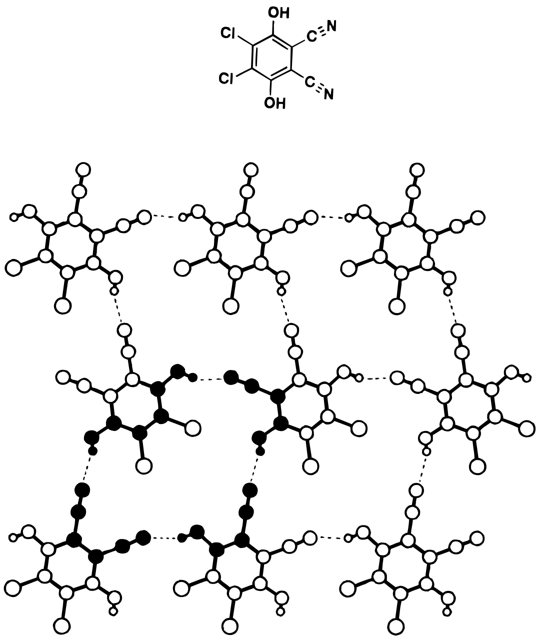

Figure 7. Tetrameric loop synthon **IV** in compound **8** formed with C≡N···H—O hydrogen bonds.

3.35 Å, $\theta = 121.3°$). The C≡N···Cl contact is, in effect, the chloro equivalent of a C≡N···H—O hydrogen bond. One notes that synthons **III** and **IV** are topologically similar and therefore have similar effects on crystal structure even though they are derived from rather dissimilar chemical functionalities.

Robustness of Supramolecular Synthons Formed by Strong and Weak Interactions. Robustness or lack of interference is a key prerequisite if the supramolecular synthon concept is to be useful in crystal engineering. In this study, there are only two structure types based on dimer synthon **II** and tetramer synthon **III**. The transition from one structure type to the other can be rationalized on the basis of the alkyl chain length. Surprisingly these structures that are based on a weak interaction like C≡N···Cl do not show more variability. Such an observation increases one's belief in synthon robustness and with it the utility of the supramolecular synthon concept in crystal engineering. Such robustness is common; for most molecules, one finds the same crystal structure regardless of the crystallization methods. This means that, at least in the late stages of nucleation (of which we know very little), the synthons must play an essential role. Why this should be so is not very clear. Perhaps the more gradual distance fall-off of electrostatic interactions results in early alignments of molecules into certain preferred recognition patterns (synthons) that are robust even in the presence of the subsequently established and the more energetically significant van der Waals interactions. Consequently, polymorphism is far less rampant than might be anticipated, and this means that a logic-based approach to crystal engineering with supramolecular synthons is viable and justified.

Synthons represent stable or robust design elements which define networks which hopefully remain invariant in a given family of crystal structures. The present study shows that relatively robust networks can be formed with interactions which are much weaker than conventional hydrogen bonds and makes a convincing case for the use of such fragile interactions in systematic supramolecular synthesis. Interestingly, the topological characteristics of the weak-interaction based-synthons **II** and **III** are similar to those of the commonly-observed strong-interaction-based synthons **IV**—**IX**.

A general issue in solid state supramolecular synthesis is the lack of 1:1 correspondence between molecular and supramolecular (crystal) structure. A given molecular structure can be associated with more than one crystal structure, and this problem of polymorphism is not very helpful in crystal engineering. However, the reverse situation can be quite helpful. This analysis shows that a given network may be associated with several precursor molecules, all of which self-assemble to produce supramolecular synthons which are compatible with or correspond to the network. This one-to-many correspondence between a crystal structure (defined as a network) and precursor molecular structures is distinctly advantageous because supramolecular targets are defined topologically in many practical applications.[11]

Conclusions

This work describes the two first steps in systematic crystal engineering, namely, observation and rationalization of crystal structures. The dissection of crystal structures into constituent supramolecular synthons facilitates a fuller analysis and enables the definition of target networks for subsequent structure design. Supramolecular synthons, even those formed with relatively weak interactions, are sufficiently robust, and this crucial observation justifies the use of the synthon concept in crystal engineering. Topological parallels between synthons and networks formed by strong and weak intermolecular interactions is another confirmation of synthon robustness. So, weak interactions may be used in crystal engineering. The following paper in this issue takes up the further questions of crystal structure prediction and design.

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Supporting Information Available: Crystallographic data, fractional atomic coordinates, bond lengths, bond angles, and anisotropic displacement parameters for compounds **1**, **3**, **4**, **5**, and **8** (29 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the Journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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