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Occurrences of bimolecular C-H···O synthons in organic crystal structures in the Cambridge Database

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Abstract

The control of molecular aggregation in the solid state is a current challenge in crystal engineering and materials chemistry. Supramolecular retrosynthesis via recurring synthons is an attractive strategy for the design and self-assembly of target crystal structures. This database study deals with occurrences of two- and three-point intermolecular C-H···O hydrogen bonded synthons in fragments of DAD, DDA and DDD type in organic crystals, where D=C(sp^2)-H and A=O-atom. The number of hits with fragments DAD>DDA>>DDD (2606, 1485, 461 hits). Two-point recognition synthon DA•AD occurs more frequently in DAD and DDA structures (225, 111 hits) than DD•AA motif in DDA and DDD structures (34, 5 hits). Three-point recognition synthons DAD•ADA, DDA•AAD and DDD•AAA are extremely rare (3, 0, 1 hits). These frequency data are rationalised in terms of the molecular complexity of fragments, the overriding preference for centrosymmetric packing, and the stringent requirements of donor-acceptor and solubility match in binary crystals. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Supramolecular synthon; C-H···O hydrogen bond; Cambridge Structural Database; Multipoint recognition

1. Introduction

Crystal engineering, the design and premeditated self-assembly of molecules in the solid state [1], may be carried out through retrosynthesis with supramolecular synthons,

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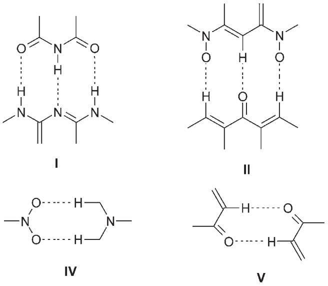
defined as structural units in crystals mediated by hydrogen bonds and other intermolecular interactions [2]. Crystal engineering via strong O-H···O and N-H···O hydrogen bonds [3], as well as through their multi-point recognition motifs, is well established. For example, molecular recognition through synthon I between barbiturate–melamine components can be tailored to produce supermolecules with linear tape, crinkled tape and rosette architectures depending on the nature of pendant alkyl groups [4]. Supramolecular synthons mediated through weak hydrogen bonds (C-H···O, C-H···N) [5] and heteroatom interactions [6] have emerged in complementary strategies. In contrast to the strong and robust O-H···O synthons (7–15 kcal/mol), C-H···O interactions show variable hydrogen bond geometry and recognition motifs in crystals because of their weakness (1–4 kcal/mol). The inherent weakness of C-H···O based synthons may be overcome by multi-point recognition to achieve a degree of repetitivity and structural control. For example, DAD•ADA synthon II (D=C(sp^2)-H, A=O-atom), a C-H···O surrogate of I, is a recurring motif in complexes of dibenzylidene ketones and 1,3,5-trinitrobenzene [7]. A combination of strong and weak hydrogen bonds, as in trithiocyanuric acid-4,4′-bipyridine (synthon III) [8] and carboxylic acid-phenazine [9], have also been used.

Synthons I to V



Molecular recognition through multipoint C-H···O hydrogen bonding continues to elicit interest. The highly selective complex formation between 2,4,7-trinitrofluorenone and 2,6-dimethylnaphthalene is ascribed to the numerous, strong C-H···O hydrogen bonds ($d<2.6$ Å, $\theta>140°$) in this crystal structure, compared to the complex with 2,7-dimethylnaphthalene in which only one C-H···O interaction could be classified as strong [10]. In the 1:1 complex of 3,5-dinitrobenzoic acid and 4-(N,N-dimethylamino)benzoic acid, the structure is stabilised by an interplay of carboxylic acid O-H···O homo-dimer, two-point C-H···O synthon IV between NMe_2 and NO_2 groups, and π···π interactions [11]. While these studies highlight the structural role of C-H···O interactions, they deal with synthons observed in specific crystal structures. The advantage of employing the statistical approach to study weak intermolecular interactions and crystal engineering with multi-point recognition synthons have been reviewed elsewhere [12]. In a combined database and computational study of C-H···O hydrogen bonded dimer synthon V in 1,4-benzoquinone and related molecules [13], it was found that this centrosymmetric synthon occurs in 53 accurate crystal structures ($R<0.07$). The mean geometry of C-H···O interactions in cyclic motif V (H···O 2.47(2) Å, ∠C-H···O 165.7(9)°) is shorter and more linear compared to noncyclic interactions (2.58(2) Å, 148(2)°). The computed binding energy of V is 4.5 kcal/mol, with each C-H···O contributing 1.5 kcal/mol. The balance stabilisation accrues from electrostatic interactions and cooperative effects.

The probabilities of formation, or recurrence frequency, of 75 bimolecular O-H···O/N and N-H···O/N synthons extracted from the Cambridge Structural Database (CSD) were reported recently [14]. The present study was carried out to search the CSD for molecules with fragments DAD 1, DDA 2 and DDD 3 that form two- and three-point C-H···O synthons VI–XIV (Figs. 1 and 2). The objective of this CSD study was to find out occurrences of various two- and three-point bimolecular motifs (e.g. DA•AD, DD•AA, DAD•ADA, DDD•AAA) and the nature of molecules that they occur in. This study on the occurrences of C-H···O based bimolecular synthons complements the analysis by Allen et al. [14] in which strong hydrogen-bonded synthons were considered.

2. Methods

The Cambridge Structural Database (CSD, version 5.19, April 2000 update, 215 403 entries) [15] was searched for crystal structures with fragments 1–3. The vbt command (variable bond type) was used to define double/aromatic and single/double bonds in these fragments. Individual sub-databases were created for each of these fragments for further retrieval. The following screens were applied: atom coordinates present (153), insist on perfect match (85), no disorder (35), error free structures (33), *R* factor ≤0.10 (88) and organic compounds only (57). The three sub-databases of fragments 1–3 were searched for intermolecular contacts in motifs VI–XIV (Fig. 2) in the range 1.8<H···O (*d*)<3.0 Å and 120<∠C-H···O (*θ*)<180° [5] with the C-H distance neutron-normalised (1.083 Å, HNORM). The *d*-*θ* data were analysed and displayed using VISTA, a built-in program

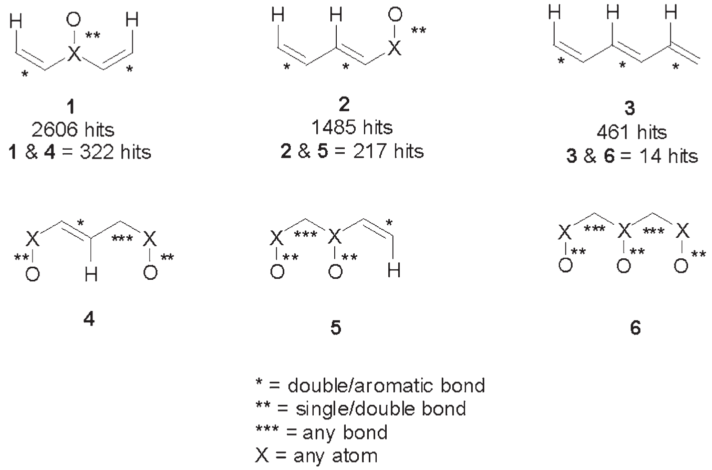


Fig. 1. Chemical structures of fragments DAD 1, DDA 2, DDD 3, ADA 4, AAD 5 and AAA 6 used to search the CSD. Duplicate refcodes are not removed from the number of hits mentioned for these sub-databases.

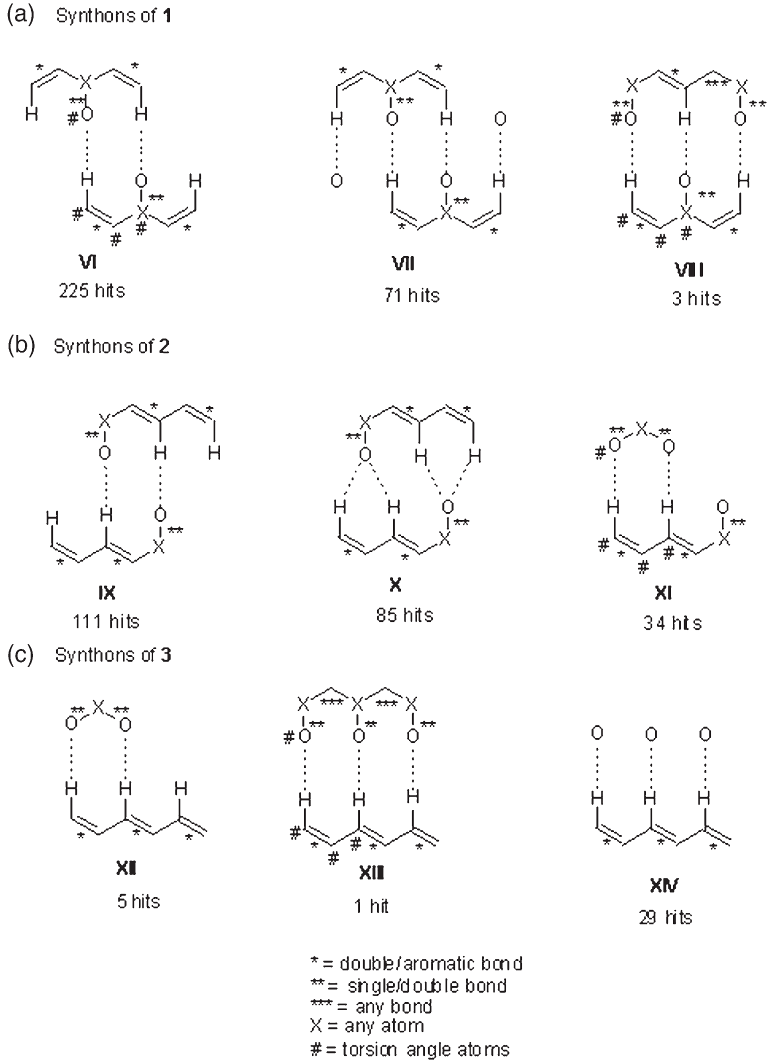


Fig. 2. Some two- and three-point C-H···O supramolecular synthons VI–XIV with dotted lines representing hydrogen bonds. The search criteria are: 1.8< H···O<3.0 Å, 120<∠C-H···O<180°. Duplicate structures were removed from the number of hits mentioned for each motif.

in the CSD. Duplicates hits were removed manually except when they correspond to polymorphs in which case the different crystal structures were retained for analysis.

3. Results

The nature of donor C-H groups in this study was restricted to phenyl and alkenyl type. The acidity of C(sp^2)-H groups is sufficiently enhanced [16] and cyclic synthons are easily constructed with this moiety because the C=C-H angle is 120°. While cyclic motifs are also possible with C(sp^3)-H groups, such donors are largely unactivated. Alkyne C-H donors are very acidic, but they are unable to form intermolecular cyclic synthons for geometric reasons (C≡C-H angle is 180°). Therefore, C(sp^2)-H donors are an excellent category of molecules to study bimolecular supramolecular synthons with C-H···O hydrogen bonds. Another reason for selecting alkenyl and phenyl donors is that the sub-databases are of a statistically significant size (500–2500 hits) and yet small enough so that a few selected entries may be examined manually. A random sampling of hits is an essential part of any database study.

The results are analysed and discussed for DAD fragment 1, DDA fragment 2 and DDD fragment 3, where D refers to an alkenyl or phenyl C-H donor and A to an O-acceptor bonded to any atom X through a single or double bond (Fig. 1). Liberal distance and angle cut-off criteria have been employed for C-H···O contacts [5] so that crystal structures with both good (short d, linear θ) and deformed (long d, bent θ) geometries are retrieved automatically. It is advisable to remove structures with bad geometries manually rather than miss out hits that could be chemically relevant.

3.1. Synthons of DAD fragment 1

The CSD contains 2606 crystal structure entries with fragment 1. A search of this sub-database of 2606 hits for dimer synthon VI with no centrosymmetry imposed in the search query gave 230 hits, of which 5 duplicates were removed manually. The C-H···O interactions in VI exhibit the roughly inverse d-θ correlation characteristic of a hydrogen bond [5] (Fig. 3a) and furthermore the dimer motif generally adopts a centrosymmetric arrangement (225/265 contacts, Fig. 3b). Histograms of H···O distance (d), ∠C-H···O (θ) and X-C-C-O torsion (τ, atoms marked with # in VI) have distributions (Supplementary data, S1–S3, www.elsevier.nl/gej-ng/10/15/30/38/59/65/show/index.htt) similar to those observed by Bovenkamp et al. [13] for synthon V. A third of motifs VI (74/225) have a nearly planar configuration (τ<20°). The two terminal C-H groups that are free in synthon VI are hydrogen bonded to different O-atoms (synthon VII) in 71/225 cases. A three-point recognition synthon (DAD•ADA) was constructed as shown in VIII with the donor C-H and acceptor O-atoms in the complementary fragment 4 being defined the same way as in 1–3. Synthon VIII is rare (3 hits, NIXJOT, PEVKIK01, TECSAV) in a sub-database of 322 crystal structures with both DAD and ADA molecular fragments present. Refcodes NIXJOT and PEVKIK01 (Figs. 4 and 5) are 2:1 complexes of 1,3,5-trinitrobenzene with 2,6-dibenzylidenecyclohexanone and dibenzylideneacetone [7] and TECSAV (Fig. 6) is a 1:1 complex of anthracene and 2,7-dinitro-9,10-anthraquinone [17]. The hydrogen bond metrics for these refcodes are listed in Table 1.

3.2. Synthons of DDA fragment 2

Dimer synthon IX is the most common aggregation motif in molecules with fragment 2, being present in 111 structures out of 1485 hits. In 41/111 hits, the motif adopts a near-planar arrangement (τ<20°). Bifurcated C-H···O synthon X, obtained by sliding the

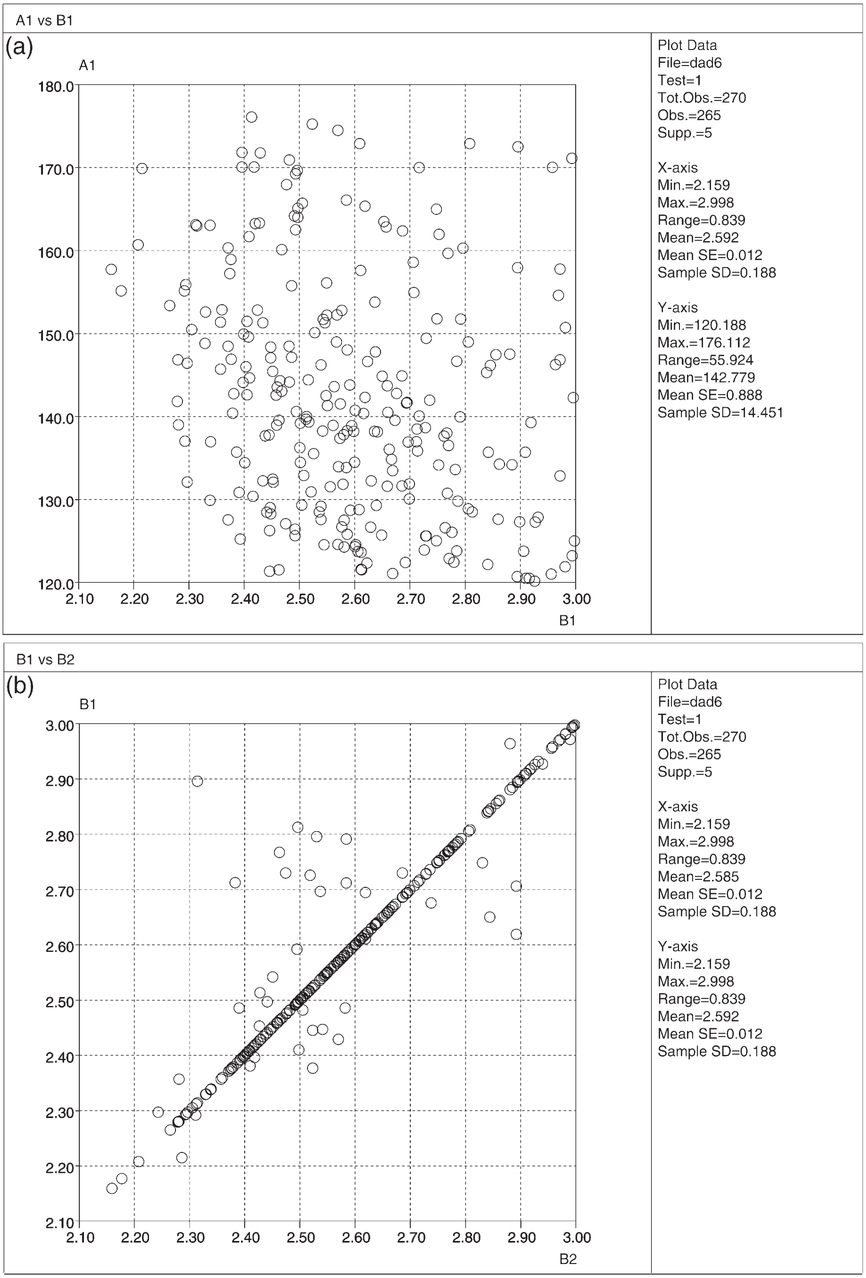


Fig. 3. C-H···O interactions in synthon VI. (a) distance-angle (B1–A1) scatterplot (correlation coefficient −0.24). (b) B1–B2 scatterplot (225/265 contacts along the diagonal).

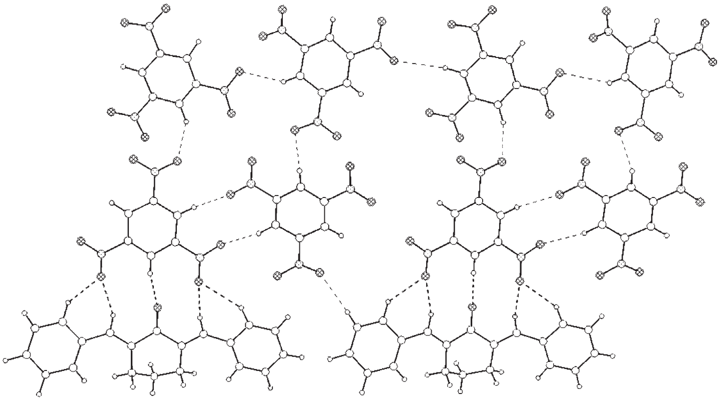


Fig. 4. Crystal packing in NIXJOT, 2,6-dibenzylidenecyclohexanone-1,3,5-trinitrobenzene (1:2). C-H···O interactions that are part of synthon VIII are shown as bold dash lines. Synthon with A molecules is shown, B molecules form the same synthon with similar metrics (Table 1).

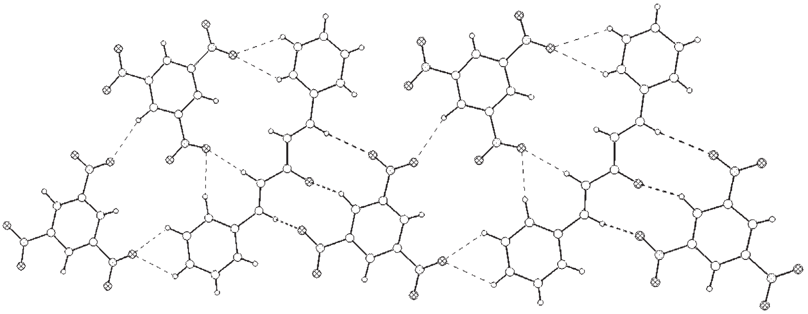


Fig. 5. Crystal packing in PEVKIK01, dibenzylideneacetone-1,3,5-trinitrobenzene (1:2). C-H···O interactions that are part of synthon VIII are shown as bold dash lines.

molecular components in IX towards one another, is a recurring motif in 85 crystal structures. The two adjacent C-H donors in fragment 2 can hydrogen bond to acceptors of CO_2, NO_2, NO_3 and ClO_4 type (synthon XI, 34 hits), as exemplified through refcode FOHLAP, 3-acetoacetyl-2-chromenone [18], in which lactone moiety is the acceptor (Fig. 7). DD•AA synthon XI is reminiscent of two-point recognition between NMe_2 and NO_2 groups (synthon IV) [11]. However, three-point recognition, DDA•AAD is not present in any crystal structure among the 217 hits which have both these fragments, 2 and 5.

3.3. Synthons of DDD fragment 3

The sub-database with fragment 3 is the smallest with only 461 hits; 14 hits have have both DDD and AAA molecular fragments, 3 and 6. Hydrogen bonding with CO_2/NO_2 groups (synthon XII) is present in 5 structures while the elusive DDD•AAA motif XIII occurs in only one crystal structure. In refcode ZOKZII [19], 1,7-

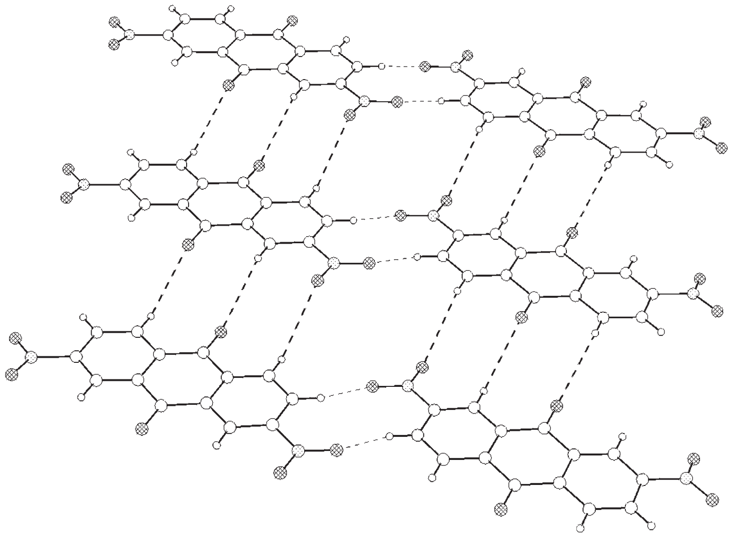


Fig. 6. Crystal packing in TECSAV, 2,7-dinitro-9,10-anthraquinone-anthracene (1:1). C-H···O interactions that are part of synthon VIII are shown as bold dash lines.

Table 1
C-H···O hydrogen bond geometry in some synthons discussed in this paper[a]

Refcode	Synthon	H···O (d), Å	∠C-H···O (θ), °	X-C-C-O (τ), °
NIXJOT (A and B)	VIII	2.38, 2.52, 2.30	142.7, 137.6, 161.6	13.9, 12.4
		2.35, 2.42, 2.52	151.0, 124.4, 145.7	20.8, 6.3
PEVKIK01	VIII	2.32, 2.54, 2.65	134.0, 129.6, 153.9	36.9, 17.2
TECSAV	VIII	2.69, 2.73, 2.81	126.8, 125.6, 126.8	38.1, 45.6
FOHLAP	XI	2.42, 2.43	154.5, 144.7	18.6
ZOKZII	XIII	2.46, 2.35, 2.55	171.4, 153.0, 146.7	1.6, 7.7
BCBANN	XIV	2.96, 2.88, 2.67	146.3, 126.9, 131.0	49.6, 5.2

[a] C-H distance is neutron-normalised (1.083 Å), τ is torsion angle between atoms marked # in Fig. 2.

bis(dimethylamino) heptamethinium picrate (Fig. 8), the constituent atoms in synthon XIII are almost co-planar (τ=1.6, 7.7°, Table 1). Given the small number of structures retrieved with this fragment, the restriction that the complementary AA or AAA fragment is covalently bonded in a finite array was removed. In 29 structures the three C-H donors of fragment 3 are bonded to any three O-acceptors from the same or different molecules (synthon XIV). While many of these structures have bifurcated C-H···O contacts, some contain the motif with single interactions as shown for refcode BCBANN [20], syn-1,6:8,13-bis-carbonyl[14]annulene (Fig. 9). The C-H···O interactions in non-cyclic synthon XIV are longer and with little d-θ correlation (Supplementary data, S4, www.elsevier.nl/gej-ng/10/15/30/38/59/65/show/index.htt) when compared with Fig. 3a. Such an observation, namely that C-H···O interactions in a cyclic motif have better hydrogen bond geometry than single contacts, is with precedent [7,13].

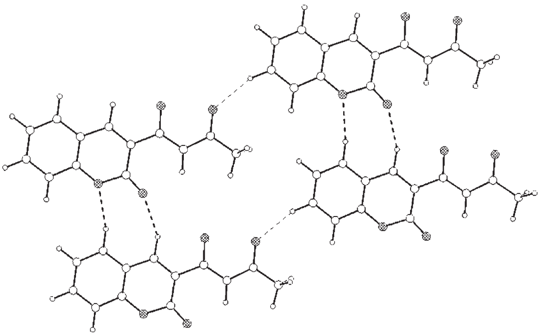


Fig. 7. Crystal packing in FOHLAP, 3-acetoacetyl-2-chromenone. C-H···O interactions that are part of synthon XI are shown as bold dash lines.

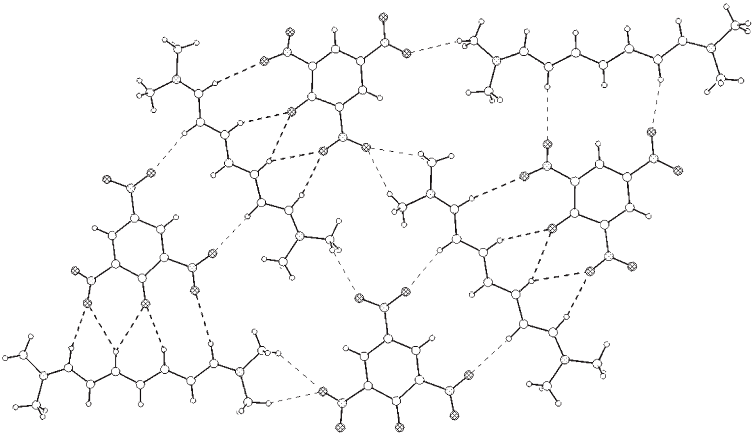


Fig. 8. Crystal packing in ZOKZII, 1,7-bis(dimethylamino)heptamethinium picrate (1:1) in (101) layer. C-H···O interactions that are part of synthon XIII are shown as bold dash lines.

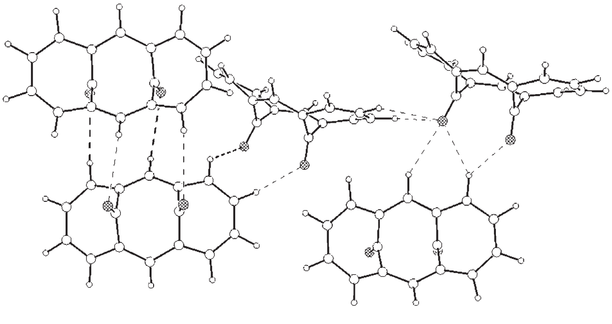


Fig. 9. Crystal packing in BCBANN, syn-1,6:8,13-bis-carbonyl[14]annulene. C-H···O interactions that are part of synthon XIV are shown as bold dash lines.

4. Discussion

The occurrence of fragments 1, 2 and 3 in decreasing order (2606, 1485 and 461 hits) is a consequence of increase in molecular complexity from DAD to DDA to DDD structures. Synthesis of molecules wherein a phenol or a ketone is flanked by vinyl or phenyl group (fragment 1) may be routinely carried out by condensation with an aldehyde followed by dehydration. Diene- and triene–ketones and acids (fragment 2) are also easily synthesised but they lack the symmetry present in 1 and are therefore fewer in number. Fragment 3, present on the periphery of polycyclic aromatic hydrocarbons or in polyene molecules, is rare in molecular crystals.

Studies by Desiraju et al. [7,21] on the recurrence of synthon II in dibenzylidene ketone-1,3,5-trinitrobenzene complexes is the only example on crystal engineering with three-point C-H···O synthon. Here, molecular complexation results from the deliberate co-crystallisation of complementary molecules with the donor and acceptor groups positioned correctly to form a cyclic hydrogen bonded array. Further, a proper matching of solubility, an essential requisite in any binary crystallisation experiment, was favourable in these cases. Because the twin criteria of geometry- and solubility-match must be simultaneously fulfilled in two-component molecular crystals, synthons VIII, XI, XII and XIII are much less frequent compared to ring motifs that result from recognition between the same fragments, as in VI, VII, IX and X. The frequent occurrence, or robustness, of the latter C-H···O synthons is because they result from self-complementarity, generally occur about an inversion centre, and are reasonably strong (3–5 kcal/mol) on the energy scale of weak interactions.

5. Conclusions

The occurrences of various bimolecular C-H···O synthons have been archived from a database of >200,000 crystal structures. These frequency data show that DA•AD synthon is formed to about the same extent in DAD (225/2606 hits) and DDA (111/1485 hits) structures because of the strong tendency for centrosymmetric (or pseudocentric) packing in crystals. Consequently, DAD•ADA (3/322 hits) and DDA•AAD (0/217 hits) target motifs have to be obtained in competition with centrosymmetric packing arrangements that are far more favoured. On the other hand, retrosynthesis via DDD•AAA synthon (1/14 hits), even though more difficult in terms of molecular synthesis, may be easier to manipulate supramolecularly because alternative centrosymmetric packing arrangements are not possible here. Thus, while DAD, ADA and DDA, AAD molecular fragments are more frequent in the CSD, crystal engineering with three-point synthon DDD•AAA has the advantage that competition from the centrosymmetric DA•AD motif is avoided. To conclude, a potential strategy for crystal synthesis emerges from this CSD study.

Triply hydrogen bonded complexes are interesting systems to study secondary electrostatic interactions in molecular recognition [22,23]. They are relevant not only for crystal engineering but also provide building blocks for tailored materials. The presence of persistent 2D lamellar networks [24] offer an approach for simplifying the difficult challenge of 3D structural control into the easier goal of tuning the third dimension [25]. Such a strategy has application in host-guest complexes, crystalline clathrates and organic pillared materials.

Supplementary material has been deposited with this manuscript. The material is available for download at the following site www.elsevier.nl/gej-ng/10/15/30/38/59/65/show/index.htt.

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