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CH/π Interaction in the Crystal Structure of Organic Compounds. A Database Study

Yoji Umezawa, Sei Tsuboyama,† Kazumasa Honda,†† Jun Uzawa,† and Motohiro Nishio*,†††

Institute of Microbial Chemistry, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141

†The Institute of Physical and Chemical Research (RIKEN), Wako, Saitama 351-01

††National Institute of Materials and Chemical Research, 1-1 Higashi, Tsukuba, Ibaraki 305

†††Department of Materials Science, Faculty of Engineering, Chiba University, 1-33 Yayoicho, Inage-ku, Chiba 263

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The CH/π interaction is a weak molecular force occurring between CH groups and π-groups. A study was carried out by use of the Cambridge Structural Database in order to obtain insights into the nature of the CH/π interaction and to examine its role in the crystal packing. The proportion of organic molecules bearing at least one CH/π interaction in their crystal structures has been found considerable. The CH hydrogen atoms tend to point toward the center of the aromatic ring. A number of short CH/π distances have been shown in the crystal structures of organic compounds. Moreover, the mean CH/π distance decreases as the acidity of the CH group increases. These results suggest that the CH/π interaction is not simply due to the dispersion force but involves other types of interactions, which are orientation-dependent and effective at wider ranges. It was suggested that the CH/π interaction constitutes one of the important factors in controlling the crystal packing of molecules.

The CH/π interaction is a weak hydrogen-bond-like force occurring between CHs (soft acids) and π-groups (soft bases).[1] It was reported that the CH/π interaction plays an important role in determining the conformation[2] and chiroptical property[3] of organic compounds,[1a] in chemistry of supramolecules such as host/guest complexes,[4] clathrates,[5] liquid crystals,[6] in coordination chemistry,[7] chromatographic phenomena,[8] chiral recognition,[9] self-assembly of complex molecules,[10] protein structures,[1b,1c,11,12] and enzyme biochemistry.[13] Here, a database study was carried out by use of the Cambridge Structural Database (CSD)[14] in order to understand the significance of the CH/π interaction in terms of the crystal packing of compounds.

Methods

Figure 1 shows the method of surveying CH/π contacts for a six-membered π-system. To participate in a CH/π interaction, the hydrogen atom should be positioned above the π-plane, since this interaction primarily originates from charge transfer of the π-electrons to the anti-bonding orbital of the C–H bond.[15] This, however, does not mean that the hydrogen should lie exactly above the aromatic ring. A C–H hydrogen can interact with the π-orbital in regions such as 2 and 3 [Fig. 1(b)], where the hydrogen atom is above the π-plane but slightly offset outside the ring. The distance of H to the π-plane, the distance between H and line C^1C^2, and the H/C^1 interatomic distance are defined as D_{pln}, D_{lin}, and D_{atm}, respectively. Thus, D_{hpi} corresponds to D_{pln}, D_{lin}, and D_{atm} for region 1, 2, and 3, respectively. The dihedral angle determined by the π-plane and the plane HC^1C^2, the $\angle HXC^1$ angle (X=C, O, etc.) are defined as ω and θ, respectively [Fig. 1(a)].

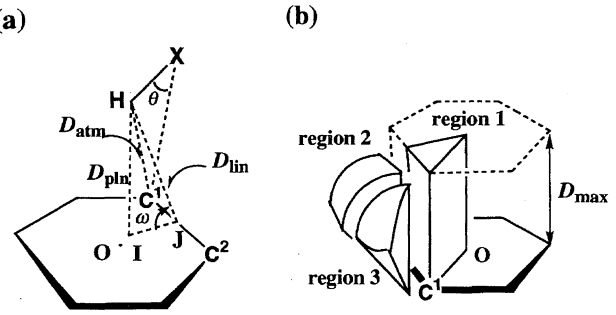

Fig. 1. Method of surveying CH/π contacts for a six-membered π-system. (a) O: center of the plane. C^1 and C^2: nearest and second nearest sp^2-carbons, respectively, to H. ω: dihedral angle defined by C^1OC^2 and HC^1C^2 planes. θ: $\angle HXC^1$. D_{pln}: H/π-plane distance (H/I). D_{atm}: interatomic distance (H/C^1). D_{lin}: distance between H and line C^1C^2 (H/J). (b) 1: region where H is above the aromatic ring. 2 and 3: regions where H is out of region 1 but may interact with π-orbitals. The program was run to search for H/π distance shorter than a cut-off value D_{max} in every region; $D_{pln} < D_{max}$, $\theta < 60°$, $|\omega| < 90°$ for region 1; $D_{lin} < D_{max}$, $\theta < 60°$, $90° < |\omega| < 130°$ for region 2, and $D_{atm} < D_{max}$, $\theta < 60°$, $50° < \phi < 90°$ for region 3 (ϕ: HC^1I). (θ should be smaller than 60° to avoid contact of the atom X to C^1).

Non-bonded atomic contact was sought between a CH and an aromatic π (C_{sp2}) atom with appropriate distance (D_{hpi}, D_{lix}, D_{liy})[16] and angle parameters (θ, ω). Positions of the hydrogens were normalized[17] according to the procedure in the CSD software. Only error-free, non-disordered structures with $R < 0.10$ were accepted.

The algorithm of the present procedure, composed of the CSD QUEST3D command system, is equivalent to that of our program (CHPI) previously written in order to study CH/π interactions in the protein structure.[1b,1c,11] To validate the present methods, several sets of coordinates among the hit entries were analyzed by CHPI to give consistent results.

Results and Discussion

As shown in Table 1, the number of organic compounds bearing at least a YCH_3 group (Y = any heavy atom) and a benzene moiety (Ar) is 19921 in the CSD (version 513: 167797 entries). The number of entries with YCH_3/Ar intermolecular contacts ($D_{hpi} < 2.9$ Å) has been found to be 7729. These values give an estimation of ca. 39% (ca. 54% for a longer cut-off value 3.05 Å: 2.9 Å +5%) of organic compounds which have at least one intermolecular YCH_3/Ar interaction in their crystal structures. The corresponding datum for YOH/Ar interaction is ca. 3% (ca. 4% for 3.05 Å cut-off). The proportion of compounds with H/Ar interacted structure seems to be greater for CH_3/Ar than for OH/Ar interaction.[18] One explanation is that the OH group is prone to make hydrogen bonds only with strong bases. The OH/π interaction requires that the relevant groups be arranged in a manner unfavorable to dipole(Y-OH)/quadrupole(Ar) interaction. The OH/π interaction is entropically handicapped compared to the CH_3/π interaction. In any event, the results show that CH/π interaction is abundant in organic crystals. This does not necessarily mean, however, that CH/π interactions are always responsible for the crystal packing. The crystal structures may accommodate the CH/π geometry within the overall framework of van der Waals and/or stronger molecular forces such as the conventional hydrogen bonds, OH/π,[19] NH/π,[20] or CH/O[21] interactions.

To obtain insight into the nature of the interaction, data were collected for a wide range of CH/π-plane distance (D_{pln} from 2.0 to 3.6 Å and D_{lix} from −1.2 to 1.2 Å). Figure 2 shows the result of a survey for the intermolecular CCH_3/Ar interaction.

In Fig. 2(a), positions of the hydrogen atoms are projected on XX/ZZ ($D_{lix} - D_{pln}$) plane.[22] Note that the C<u>H</u> atoms are concentrated at positions above the plane of the aromatic ring (D_{lix} from −1.2 to 0.0 Å). An intriguing feature is that many CH hydrogens are found inside the conventional van der Waals limit (ca. 2.9 Å: ca. 1.2 Å for C–<u>H</u> and ca. 1.7 Å for a half thickness of aromatic molecule).[23] Another interesting point is that the hydrogens are rather widely distributed (D_{pln} from 2.5 to 3.3 Å in the above D_{lix} range). The CH/π interaction seems to be effective at distances remoter than the van der Waals limit. This phenomenon is similar to what Desiraju, and Steiner and Saenger observed in their database studies of the CH/O hydrogen bond.[24] Figure 2(b) gives a projection of C<u>H</u> on the aromatic ($D_{lix} - D_{liy}$) plane.[25] This again shows that the hydrogens point towards the center of the aromatic ring. Figure 2(c) is a projection of the C<u>H</u>s on YY/ZZ ($D_{liy} - D_{pln}$) plane.[26] The hydrogen atoms are equally populated along line C^1C^2. The above facts imply that the CH/π interactions is not simply ascribed to the dispersion force (a short-range term), but involves other types of stronger forces which are directionally sensitive and effective at wider ranges of distance.

A survey was then carried out for intermolecular interactions of chloroalkanes $Cl_{4-n}CH_n$ (n = 1—3) with aromatic π-system. Table 2 summarizes the result. Short Cl_3CH/π and Cl_2CH_2/π distances (D_{hpi} <2.9 Å) were found in 12 and 37 entries, respectively. A search for $ClCH_3$/π interaction gave no hit; however, short $ClCCH_2$/π contacts were found in 37 entries.

The mean CH/π distance (D_{pln}) decreases from 2.73 Å for $ClCCH_2$/π to 2.65 Å for Cl_2CH_2/π, and then to 2.38 Å for Cl_3CH/π interactions, as the acidity of the CH group increases. The data for acetylenic CH/π[27] fall between those of chloroform and methylene chloride. The above results demonstrate that the electrostatic force contributes at least in interactions involving activated CH groups.

A systematic survey was then carried out for intermolecular CH/π contacts involving various types of CH groups (CH_3/Ar, CH_2/Ar, and CH/Ar) in organic compounds. Table 3 summarizes the results; interactions between aromatic CHs and an aromatic ring are also included. This latter type of interaction has long been known and is often referred to as the "edge-to-face Ar/Ar" or "T-shape π/π interaction."[28] The term "aromatic CH/π interaction" is more adequate in view of its nature.[1b,1c,29] As shown in Tables 3 and 4, the aromatic CH/π interaction is very often found in the crystal structure.

A histogram of the CH/π distances in the search is illustrated in Fig. 3. Note that there are many CH/π distances shorter than the accepted value of the sum of the van der Waals radii of the relevant nuclei (ca. 2.9 Å). The mean D_{hpi} distance depends on the cut-off value. However, the number of crystal structures bearing short CH/π contacts is considerable.[30]

Overconfidence of the above results may be unwise in view of the uncertainty in the determination of the exact position of the hydrogen atoms by X-ray diffraction method. We therefore examined entries studied by neutron diffraction. Table 4 lists the results.

Table 1. Proportion of Organic Compounds Bearing at Least One Intermolecular XH/Ar Contact (D_{hpi} <2.9 Å)[a] in the Crystal Structure

	No. of entries	No. of hits		Percentage	
YCH_3/Ar	19921	7729	(10793)[b]	39	(54)
YOH/Ar	7040	203	(311)	3	(4)
CCH_3/Ar	14530	4653	(6914)	32	(48)
COH/Ar	6530	182	(285)	3	(4)
$C(sp^3)CH_3$/Ar	10181	2698	(4369)	27	(43)
$C(sp^3)$OH/Ar	3290	114	(158)	3	(4)

Y = any nonhydrogen atom; C = any carbon atom; $C(sp^3) = sp^3$-carbon atom.

a) D_{hpi}: D_{pln}, D_{lin}, and D_{atm} for region 1, 2, and 3, respectively.

b) In the parentheses are data for a longer cut-off value 3.05 Å.

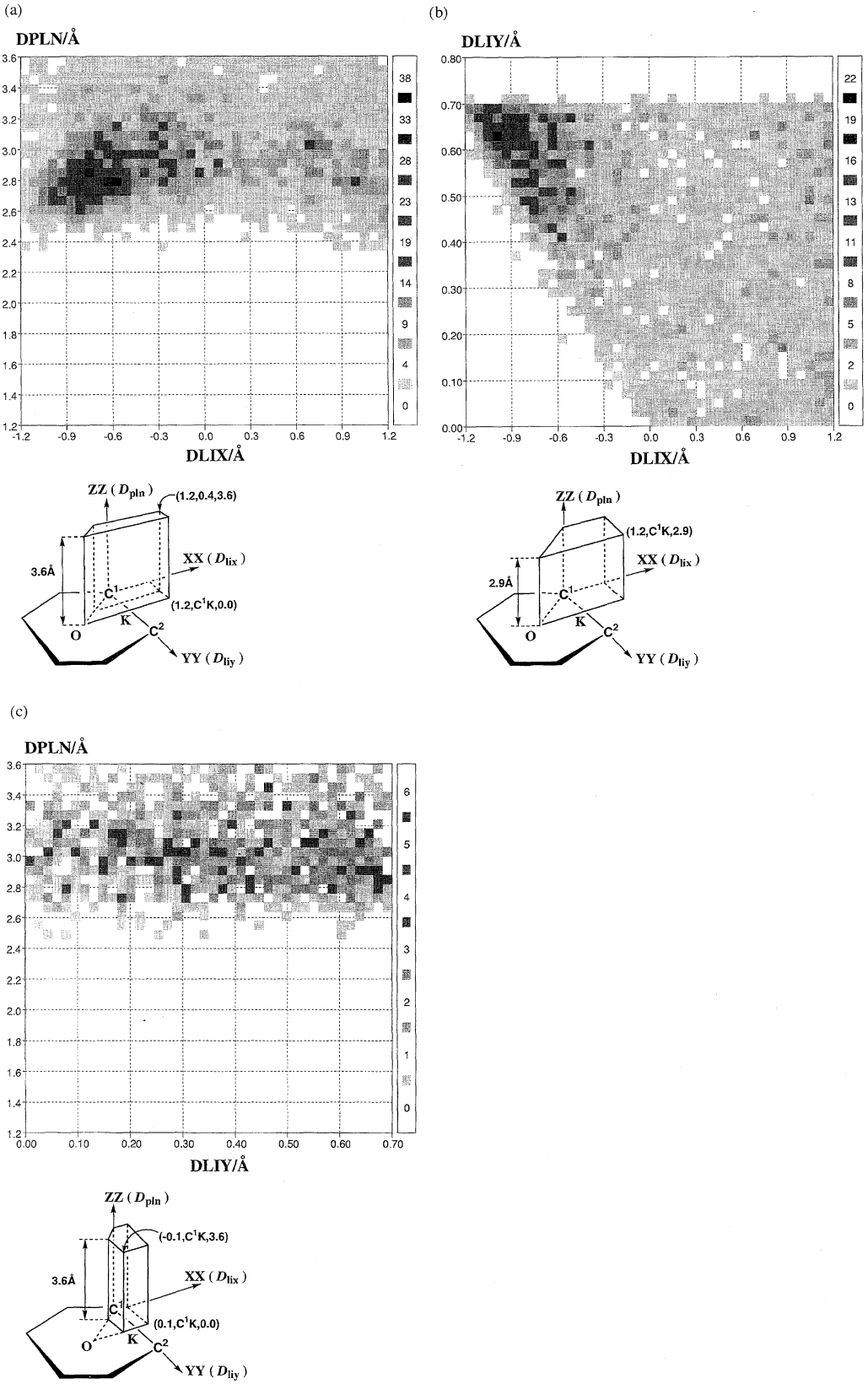

Fig. 2. Distribution of CH hydrogens for intermolecular CCH_3/Ar interaction projected on various planes (XX–ZZ, YY–ZZ, XX–YY). (a) Distribution of hydrogens projected on XX–ZZ ($D_{lix} - D_{pln}$) plane. Only hydrogens falling into the region $D_{liy} > 0.4$ Å are projected. D_{lix}: XX-axis portion of D_{lin}, or horizontal distance from line C^1C^2: $D_{lix} = D_{lin} \times \cos(180° - \omega)$. D_{liy}: distance from C^1 along line C^1C^2. $C^1K{=}C^2K$. (b) Distribution of hydrogens projected on XX–YY ($D_{lix} - D_{liy}$) plane. Only hydrogens with D_{pln} shorter than 2.9 Å are projeted. (c) Distribution of hydrogens projected on YY–ZZ ($D_{liy} - D_{pln}$) plane. Only hydrogens falling into the region 0.1 Å $> D_{lix} > -0.1$ Å are projected. Depicted by program CSD VISTA.

Table 2. Interactions of Chloroalkanes $Cl_{4-n}CH_n$ (n=1—3) with Aromatic π-System

	Hits[a]	Contacts[b]	D_{hpi}/Å[c]	D_{pln}/Å[d]	D_{atm}/Å[e]
Cl_3CH	12	14	2.58±0.24	2.38±0.16	2.70±0.14
Cl_2CH_2	37	52	2.73±0.14	2.65±0.15	2.79±0.13
$ClCCH_2$	37	43	2.75±0.12	2.73±0.14	2.83±0.11
$C_{sp}H$[f]	23	26	2.67±0.12	2.63±0.14	2.78±0.14

a) Number of entries with at least a CH/Ar intermolecular contact (<2.9 Å). b) Number of contacts (<2.9 Å) in the hit entries. c) Mean D_{hpi} distance (D_{pln}, D_{lin}, and D_{atm} for region 1, 2, and 3, respectively). d) Mean CH/π-plane distance (region 1). e) Mean interatomic distance. f) Acetylenic CH/Ar.

Table 3. Number of Intermolecular CH/Ar Interactions

CH	Hits[a]	Contacts[b]	D_{hpi}/Å[c]	D_{pln}/Å[d]	D_{atm}/Å[e]
CCH_3	4654	6772	2.78±0.10	2.75±0.10	2.85±0.11
C_2CH_2	3788	5518	2.77±0.10	2.74±0.11	2.84±0.11
C_3CH	995	1216	2.75±0.12	2.70±0.12	2.81±0.11
$(C_{sp2})_2CH$[f]	12440	32282	2.76±0.10		
YCH_3	7729	12270	2.77±0.10		
YCH_3	10793	21983	2.86±0.13	(3.05 Å cut-off)	
YCH_3	12406	31195	2.98±0.16	(3.2 Å cut-off)	

C = any carbon atom; Y = any nonhydrogen atom.
a) Number of entries with CH/Ar contact (for 2.9 Å cut-off value, unlesss otherwise noted). b) Number of observations with CH/Ar contact (2.9 Å cut-off, unless otherwise noted). c) Mean H/π distance: D_{hpi} (D_{pln}, D_{lin}, and D_{atm} for region 1, 2, and 3, respectively). d) Mean H/π-plane distance (region 1). e) Mean H/C interatomic distance. f) Aromatic CH/Ar interaction.

Table 4. Intermolecular CH/π Interactions in the Crystal Structure of Organic Compounds Determined by Neutron Diffraction

CH	Hits[a]	Contacts[b]	D_{atm}/Å[c]
CCH_3	6[d]	10	2.84, 2.90, 2.87, 2.87, 2.91, 2.90, 2.91, 2.91, 2.62, 2.94
C_2CH_2	7[e]	11	3.01, 2.92, 3.01, 2.85, 2.83, 2.88, 2.78, 2.77, 2.81, 2.79, 2.90
C_3CH	1[f]	2	2.89, 2.80
$(C_{sp2})_2CH$[g]	43[h]	110	2.82±0.10 (minimum, 2.60 Å)

Y = any nonhydrogen atom; C = any carbon atom.
a) Number of entries with CH/Ar contact (D_{hpi} <2.9 Å). b) Number of observations with CH/Ar contact (D_{hpi} <2.9Å). c) H/C_{sp2} interatomic distance. d) Refcode in the CSD: DIMNAP01, DURENE03, DURENE04, HYDNST01, HYDNST02, MPIMZR01. e) Refcode: ACENAP03, ANTMET01, BABCOW01, COCNBZ01, FUDVUV02, HYTPRD01, PHALNC01. f) Refcode: CUXTOE. g) Aromatic CH/Ar interaction. h) Refcode: ACENAP03, ANTMET01, BENZEN, BENZEN01, BIKBEC01, BORMUQ01, BZAMID02, BZAMID03, CADKEX01, CBOATZ02, COPTCY01, CUSGAY01, DBEZLM02, DEKMUB01, DIMNAP01, FLUANT01, HDYNTS01, HYQHCL01, HYTPRD01, LIHPAL01, LIHPAL02, LTYRHC10, LTYROS11, MCPROP01, MNPHCY03, MPIMZR01, NINDOD01, OPHDAH01, PHALNC01, PHENAN13, PIHFRB10, PIMCRC01, PIMHCO10, PPCRHZ01, PSULHZ11, PYRENE02, RESORA13, SULAMD04, TERPHE03, TERPHO11, TOLSAM03, TOLSAM12, TRIPHE11

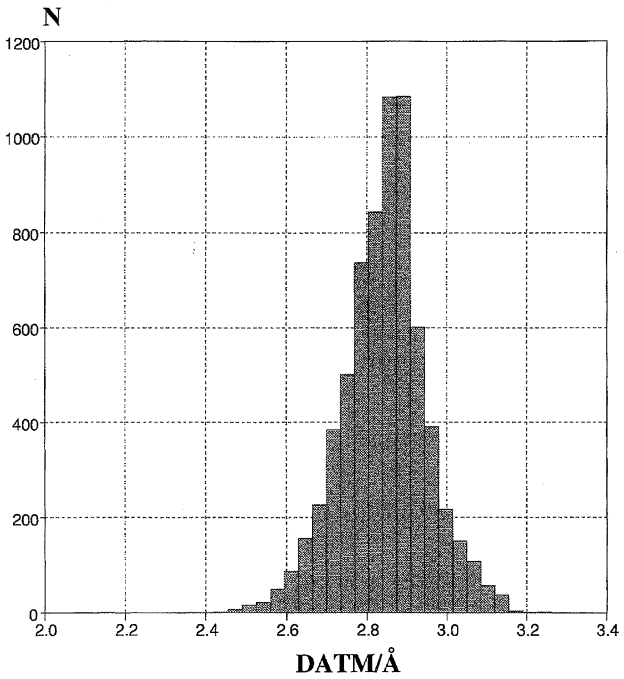

Fig. 3. Number of observations plotted against H/C interatomic distance D_{atm} for intermolecular CCH_3/Ar interaction (D_{max} = 2.9 Å).

The CH/π distances do not significantly differ from those determined by X-ray studies. Every hit was inspected to know whether the CH/π interaction is playing a crucial role or not. In the above cases CH/π interaction appeared to be an important motif of the crystal packing. In other words, the crystal structures are not necessarily consequences of the dominant influence of only other molecular forces.

An example is given in Fig. 4 for the crystal structure of 1, 5-dimethylnaphthalene **1**. (Chart 1)[31] One molecule of **1** is surrounded by many other molecules with use of two types of CH/π interactions: CH_3/π (2.87, 2.99, and 2.94 Å) and aromatic CH/π (2.90 and 2.84 Å), thus forming an extensive network.

Figure 5 shows the crystal structure of resorcinol **2**. (Chart 2)[32] Each molecule of **2** forms three aromatic CH/π bonds (2.77, 2.92, and 2.78 Å) and two hydrogen bonds (OH/O: 1.73 and 1.76 Å).

Figure 6 shows the crystal structure of L-phenylalanine hydrochloride **3**. (Chart 3)[33] We see CH/π contacts around

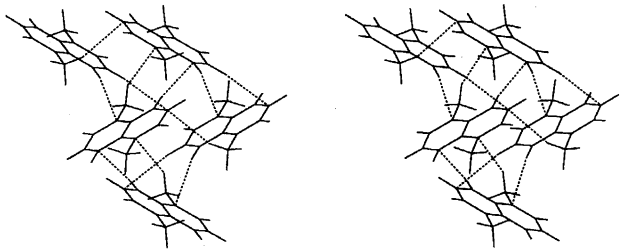

Fig. 4. Stereo view of 1,5-dimethylnaphthalene **1** (CSD refcode DIMNAP01). Dotted lines indicate CH/π bonds (D_{hpi} < 2.9 Å).

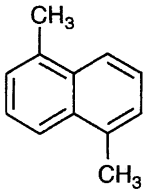

Chart 1. 1,5-Dimethylnaphthalene **1**.

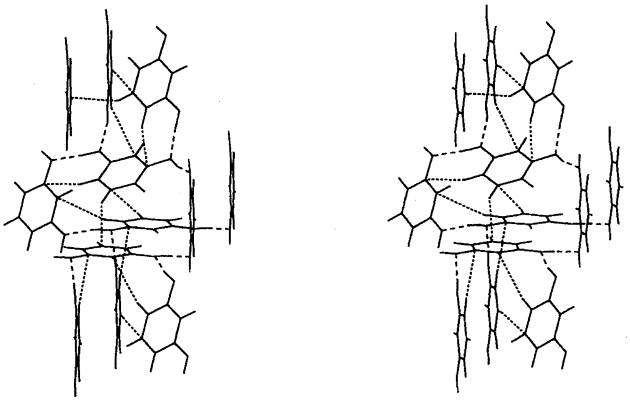

Fig. 5. Stereo view of resorcinol **2** (CSD refcode RESORA13). Dotted and dashed lines indicate CH/π contacts and hydrogen-bonds, respectively.

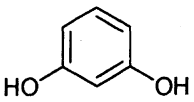

Chart 2. Resorcinol **2**.

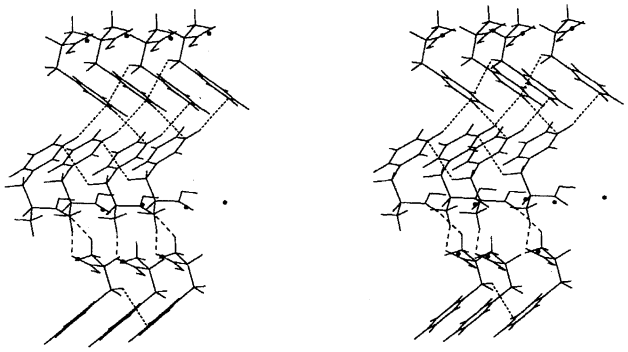

Fig. 6. Stereo view of L-phenylalanine hydrochloride **3** (CSD refcode PHARNC01). Dotted and dashed lines indicate CH/π bonds and hydrogen-bonds, respectively. Black circles represent chlorine ions.

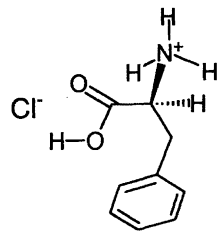

Chart 3. L-Phenylalanine hydrochloride **3**.

a molecule of **3**, together with hydrogen bonds: a CH_2/π (2.90 Å), an aromatic CH/π (2.75 Å) and two salt bridges (N^+H_3/O=C: 2.48 and 2.49 Å). The CH_2/π interaction is often found in protetin structures (with use of a β-hydrogen of the side-chain).

To summarize, the CH/π interaction seems to play an important part in controlling the crystal packing of many compounds, in cooperation with other molecular forces.

Conclusion

The proportion of crystal structures having CH/π interaction has been found to be significant. The CH hydrogen atom tends to point toward the center of the aromatic ring. Many of the CH/π distances are shorter than the sum of the van der Waals radii of H and C_{sp2}. Moreover, CH/π interaction seems to be effective beyond the van der Waals limit, falling off more slowly with distance. The mean CH/π distance decreases as the acidity of the hydrogen atom increases. Inspections of the structures determined by neutron diffraction suggested that the crystal structures were not the consequences of only well-known packing forces such as the van der Waals interaction or hydrogen bonding (hard acid versus hard base). Available evidence in the literature such as thermochemical data[34] and substituent effects on NMR and IR spectra,[35] conformational equilibria,[36] and thermodynamic data[37] demonstrate that the CH/π interaction is not merely a conventional dispersion force. According to theory[1,15,38] and experimental results, we believe that the CH/π interaction is largely originating by a charge transfer process from the π system to the antibonding orbital of the C–H bond. Superimposed on this effect is the London dispersion force. The electrostatic force, though not very important, also contributes. In view of the foregoing discussions, it seems reasonable to suggest that the CH/π interaction (soft acid versus soft base) contributes in controlling the crystal packing of compounds.[39] Implications of the concept in supramolecular design are evident.

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