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

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Abstract: A study was carried out, with use of the Cambridge Structural Database, to examine the role of CH/π interaction in the conformation of organic compounds. A number of short intramolecular CH/π distances have been disclosed in the crystal structure of these compounds. The structure was inspected to know whether the crystal conformation is a consequence of the so-called packing forces, or the CH/π interaction plays a role. The result has demonstrated that the CH/π interaction plays an appreciable role in controlling the conformation of organic compounds. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

It has been suggested that the CH/π interaction[1,2] plays important roles in supramolecular chemistry,[3,4] molecular recognition,[5] chiral discrimination,[6] self-assembly of complex molecules,[7] coordination chemistry[8] and protein biochemistry.[9] In a previous paper, we reported that the CH/π interaction plays a crucial part as a driving force of the crystal packing.[10] Here, a database study was carried out to understand the significance of the CH/π interaction in terms of the conformation of organic compounds.

METHOD

The Cambridge Structural Database[11] (CSD version 515, 181309 entries) was used. The method of exploring XH/π interactions in the crystal structure was reported earlier.[10] Thus, a computer program was written, by use of the CSD software, to find contacts between XH groups and π systems. Several kinds of distances (D_{pln}, D_{atm}, D_{lin}) and angle (θ, ω) parameters were defined to cover every possibility (Fig. 1).

Nonbonded atomic contact was sought between a XH and an sp^2 carbon, in compounds bearing six-membered carbon aromatic ring as a part of the structure, with appropriate cut-off values for the distance (D_{max}) and angle (θ, ω) parameters.

This paper is dedicated to the memory of the late Professor Sir Derek H. R. Barton, the founder of the concept of conformation in organic chemistry. The authors sincerely regret the immeasurable loss of an outstanding figure in the world of science.

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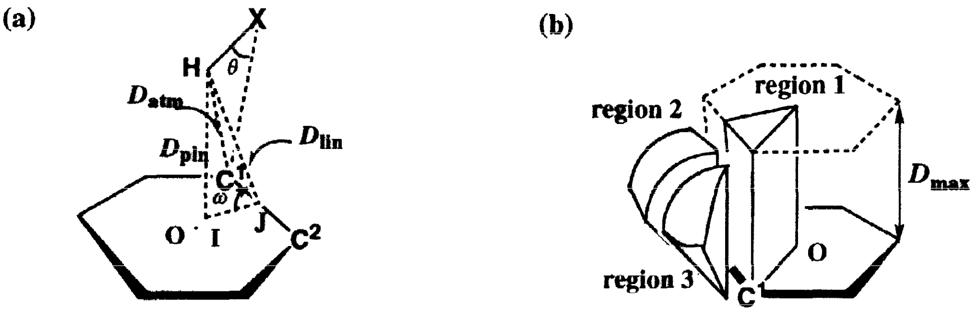


Fig. 1. Method for exploring XH/π contacts. (a) O: centre of the plane. C^1 and C^2: nearest and second nearest sp^2-carbons, respectively, to H. ω: dihedral angle defined by C^1OC^2 and HC^1C^2 planes. θ: $\angle HXC^1$. D_{pln}: H/π-plane distance (H/I). D_{atm}: interatomic distance (H/C^1). D_{lin}: 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 $D_{atm} < D_{max}$, $\theta < 60°$, $\omega = 180° - \phi$ (ϕ :HC^1I), $90° < |\omega| < 130°$ for region 3.

RESULTS

First, surveys were carried out, in the entire database, to search for short intramolecular and intermolecular XH/π contacts (X = C, O, N). In this study, D_{max} shorter than 3.05 Å [= 2.9 Å (1.2 Å for C-H plus 1.7 Å[12] for a half thickness of the aromatic molecule) x 1.05] was considered as relevant for the presence of CH/π interaction. Table 1 summarizes the results.

Table 1. XH/π Contacts Disclosed in the Crystal Structure of Organic Compounds.

	Entries[a]	Hits[b]	Percentage	Distances[c]	D_{atm}/Å[d]
Intramolecular interactions					
CH/Ar	32669	9520	29.1	22937	2.72±0.18
OH/Ar	8448	126	1.4	168	2.48±0.26
NH/Ar	8827	239	2.7	285	2.58±0.22
Intermolecular interactions					
CH/Ar		24523	75.1	112553	2.91±0.12
OH/Ar		431	5.1	512	2.80±0.21
NH/Ar		825	9.3	1059	2.78±0.19

[a] Number of entries bearing at least a XH (X = C, O, N) and an aromatic group (Ar). These numbers include entries lacking the hydrogen coordinates. Only error-free, non-disordered structures with $R < 0.10$ were accepted.[13] [b] Number of entries with at least a short XH/Ar contact. [c] Number of short XH/Ar distances. [d] Mean H/C atomic distance.

The number of organic compounds bearing at least a CH group and a six-membered aromatic moiety (Ar) was 32669. The number of entries with short CH/Ar intramolecular contacts (D_{max} = 3.05 Å) was 9520. These data give an estimation of ca. 29% of compounds which have at least one CH/Ar contact in their crystal structure. The corresponding values for OH/Ar and NH/Ar interactions are 1.4% and 2.7%, respectively. The mean H/C atomic distance is larger for the CH/Ar interaction than those of the OH/Ar and NH/Ar interactions. A similar result was obtained for the intermolecular interaction; in these cases the proportions of compounds with short CH/Ar contacts are ca. three times larger than those of the intramolecular interaction.

In Table 2, the data are arranged according to the number of covalent bonds (N) separating the C$\underline{H}$ and sp^2 carbon. The mean H/C$sp2$ interatomic distance is 2.63 Å for N = 4 (5-membered CH/π interaction) and increases on going to larger N, to a value of ca. 2.9 Å.

Table 2. Intramolecular CH/π Contacts Disclosed in the Crystal Structure of Organic Compounds.

N[a]	Hits[b]	Distances[c]	D_{atm}/Å[d]
4	4148 (4034)[e]	6960 (6665)	2.63±0.15 (2.62±0.14)
5	4958 (4589)	8310 (7451)	2.70±0.17 (2.67±0.14)
6	1991 (1679)	3011 (2439)	2.76±0.18 (2.70±0.15)
7	1127 (853)	1594 (1151)	2.83±0.16 (2.76±0.13)
8	685 (460)	877 (576)	2.87±0.15 (2.79±0.13)
9	555 (375)	730 (480)	2.88±0.14 (2.81±0.12)
10,11	593 (364)	770 (440)	2.92±0.13 (2.84±0.11)
12,13	331 (189)	418 (223)	2.91±0.13 (2.82±0.11)
14,15	116 (71)	165 (93)	2.90±0.13 (2.82±0.10)
>16	51 (30)	102 (55)	2.90±0.15 (2.80±0.14)

[a] Number of covalent bonds between the relevant H and C.

[b] Number of entries with short CH/Ar contact.

[c] Number of short distances.

[d] Interatomic distance D_{atm}.

[e] In the parentheses are data for a shorter cut-off, D_{max} = 2.9 Å.

The results show that short intramolecular CH/Ar distances are frequently found in organic crystals. This does not necessarily mean, however, that CH/π interactions are always responsible for the crystal conformation. In cases where an alkyl group is tertiary or at the bridgehead of a bicyclic structure, a CH group is compelled to be close to an adjacent aromatic ring. The crystal conformation may accommodate the CH/π geometry within the overall result of packing forces such as the van der Waals interaction, hydrogen bond, etc. To investigate the interactions involved, the H/π-interatomic distances were sought between CH_3 and the aromatic *ipso*-carbon. In these searches, all carbon atoms intervening the CH_3 and C$sp2$ are $sp3$-hybridized and are not involved in a cyclic structure (Fig. 2). Table 3 lists the results.

search 1

search 2

Fig. 2.

Table 3. H/π-interatomic distances between CH_3 and aromatic *ipso*-carbon.

	Ring size[a] (N)	Entries[b]	Hits[c]	Distances[d]	D_{atm}[e]
Search 1	5 (4)	287	49	56	2.62±0.07
Search 2	6 (5)	121	17	18	2.60±0.12

[a]Number of atoms consisting of the CH/C^{ipso} ring. [b]Number of entries (see text).[14] [c]Number of entries with short CH_3/C^{ipso} contact. [d]Number of short distances. [e]H/C^{ipso} interatomic distance.

The crystal structures were inspected to know whether the CH/π interaction is playing an important role or not. In a number of cases, among the hit entries, CH/π interaction appeared to be a motif of the crystal conformation. We do not pretend that the above results give a comprehensive view of the role of CH/π interaction. Inspection of the individual structures, however, suggests that the crystal conformations are not necessarily the results of only well-known packing forces such as the hydrogen bonding or Coulombic force.

An example is given in Fig. 3 for the crystal structure of procaterol hydrochloride hemihydrate.[15] A similar conformation was suggested to maintain in solution by NMR coupling data.

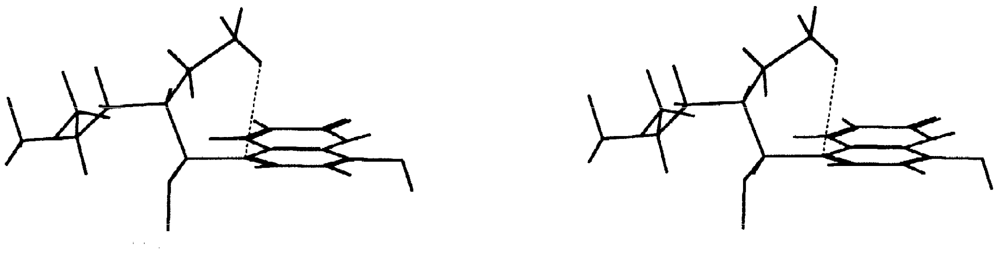


Fig. 3. Procaterol hydrochloride hemihydrate (stereo view), CSD Refcode BETXON. A dotted line indicates short CH/π contact.

Figure 4 is the crystal structure of *p*-phenylenetetrafluoro-*p*-phenylene-34-crown-10.[16] We see short CH/π contacts between methylene hydrogens and the aromatic rings.

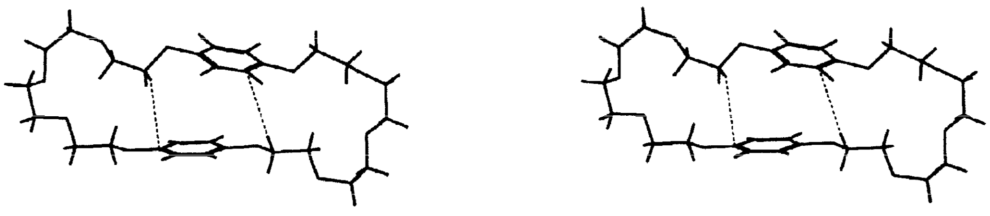


Fig. 4. *p*-Phenylenetetrafluoro-*p*-phenylene-34-crown-10 (stereo view), TIVYAY. Dotted lines indicate short CH/π contacts.

Figure 5 is the crystal structure of a benzazepinone derivative with antiischemic properties.[17] There we see short CH/π contacts in the molecule. Such a geometry has been suggested to maintain in solution.

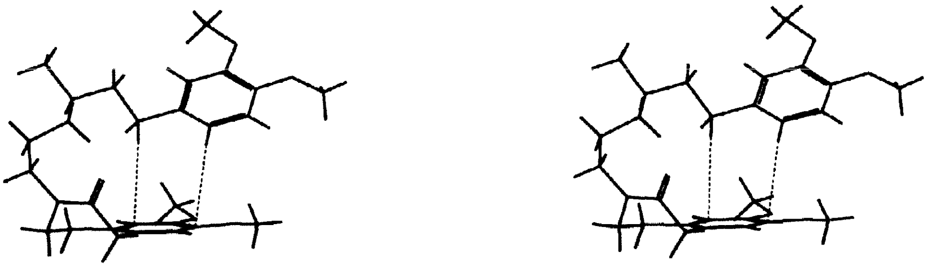


Fig. 5. 7,8-Dimethoxy-3-(3-((2-(3,4-dimethoxyphenyl)ethyl)methylaminium)propyl)-1,3,4,5-tetrahydro-2H-benzazepin-2-one chloride tetrahydrate (stereo view), JENHAL.

Figure 6 is the crystal structure[18] of *cis*-syn-bis((1-benzyloxycarbonyl)-5,6-dihydro-uracil-5,6-diyl). Note that the phenyl rings at the both termini of the molecule come close to each other.

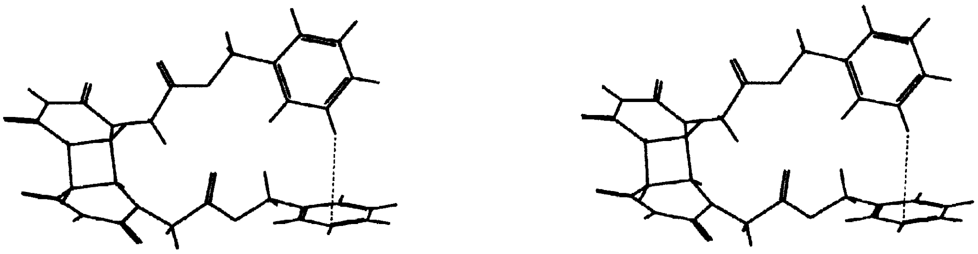
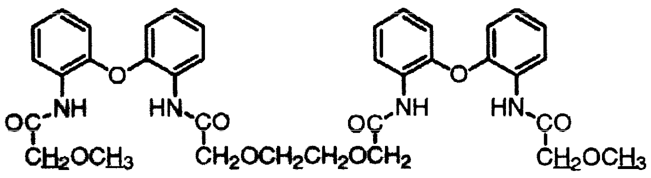


Fig. 6. *cis*-syn-bis((1-Benzyloxycarbonyl)-5,6-dihydro-uracil-5,6-diyl), (stereo view), ZUDFEJ.

Most interesting, among all, is probably the crystal structure of bis(2,2'-bis(2-methoxyethylamido)diphenyl ether) **1** reported by Stoddart et al.[19] Compound **1** has been shown to adopt an extensively coiled chain conformation with C_2 symmetry (Fig. 7). The structure is constrained by intramolecular hydrogen bonds (NH/O) and CH/π interactions involving methylene and methoxy hydrogens (underlined). Inspection of their NMR data suggests that the coiled structure is favoured also in solution.[20]



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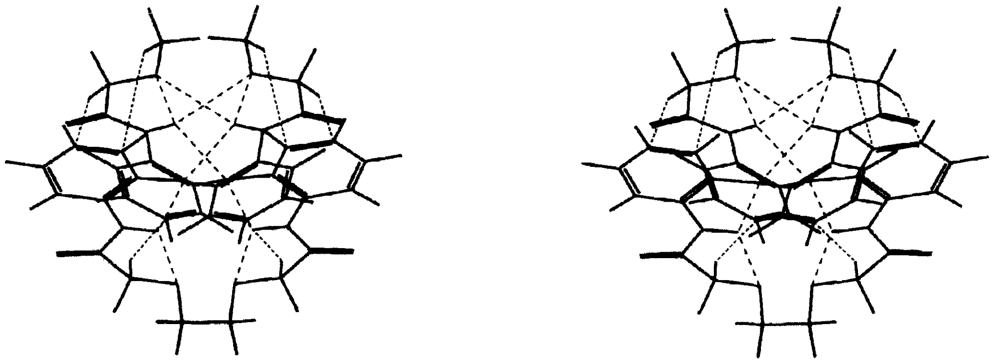


Fig. 7. Bis(2,2'-bis(2-methoxyethylamido)diphenyl ether) **1** (stereo view), TOJQUE. Dashed and dotted lines indicate hydrogen-bonds and CH/π contacts, respectively.

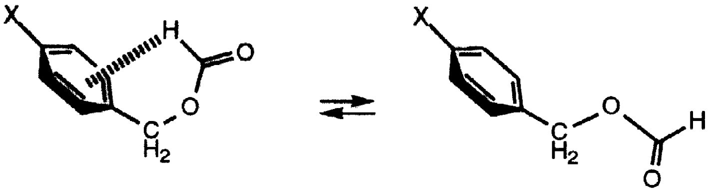
DISCUSSION

To summarize, the number of crystal structures with short intramolecular CH/π distance has been found appreciable. The proportion of compounds with H/Ar proximate structure has been shown to be larger for the CH/Ar than for the OH/Ar and NH/Ar interactions.[21] An explanation is that CH groups are abundant in organic molecules as compared to OH or NH. Another reason may be that OH and NH (hard acids) interact with O or N (hard bases) to form ordinary hydrogen bonds. In addition, in forming an OH/π bond, the OH and aromatic groups should position themselves in a manner unfavourable to the dipole/quadrupole interaction. The mean H/C atomic distance is larger for CH/Ar as compared to OH/Ar and NH/Ar interactions; thus the CH/π interaction is weaker than the OH/π or NH/π interaction. The CH/π distance has been found to be shortest in the 5-membered CH/π-bond and increases on going to a larger-membered interaction. We do not know the reason but it may be pointed out that formation of the 5-membered ring is entropically more favoured than forming the larger rings. Formation of the 5- or 6-membered ring is known to be general in the intramolecular hydrogen bonding,[22] OH/π[23] and CH/n[24] interactions.

Evidence has accumulated that the CH/π interaction plays a role in determining the conformation of organic compounds.[25] The following compounds have been reported to prefer a CH/π-contiguous conformation both in crystal and in solution: $ArSO_2CH_2Ar$, $ArSOCH_2Ar$,[26] aryl-*N*-(arylsulfonylmethyl)-*N*-methylcarbamates,[27] *N*, *N'*-[bis(α-tosylbenzyl)]urea,[28] 1-benzazocinone,[29] bisparaphenylene-25-crown-7,[30] *Z*-*N*-[1-(1-naphthyl)ethylidene]-1-phenyl-2-propylamine,[31] dibenzodiazocine esters[32] and a benzothiopyran derivative.[33] Shimohigashi et al. recently found the preference of alkyl/phenyl proximate geometry for a series of dipeptides

(D-Leu-L-Phe,[34] D-Arg-L-Phe,[35] D-Thr-L-Phe[36]) and discussed the results in the context of the CH/π interaction.[37] Kim et al. reported on the folded conformation of a peptide mimic 2-allyl-3-benzenepropanoate and attributed the result to the CH/π interaction.[38]

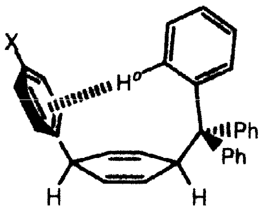
Partial charge transfer from the highest occupied π-orbital (HOMO) to the lowest unoccupied σ*-orbital (LUMO) of the CH bond stabilizes the CH/π interaction. The interaction is facilitated by elevation of the HOMO level or lowering the LUMO level.[39,40] Suezawa et al. compared the magnitude of nuclear Overhauser effect to estimate the conformational equilibria of benzyl formates **2** (Fig. 8).[41] Substitution of X from H by an electron-donating group has been found to be accompanied by an increase in the ratio of CH/π-interacted conformer, and vice-versa. Such an electronic substituent effect in the conformational equilibria has often been reported.



2 (interacted) **2** (free)

Fig. 8. Conformational equilibria of benzyl formate **2**.

Grossel et al. studied the crystal and solution conformation of *cis*-1,4-dihydro-4-tritylbiphenyls **3** (Fig. 9).[42] In non-substituted **3** (X = H), one of the aromatic proton of the trityl moiety is close to the π-plane of a phenyl ring of the biphenyl group (2.55 Å), while the distance in the *p*-bromo-derivative (**3**, X = Br) is appreciably shorter (2.48 Å).[43] This is reasonable since the acidity of the aromatic CH is greater in *p*-Br-**3** than in non-substituted **3**. The solution conformations have been reported to be similar to those in crystals and seem to reflect the subtle difference in the crystal structure: the ^{1}H NMR chemical shift of H^o in *p*-Br-**3** (δ 6.15) is higher than that of **3** (δ 6.3).



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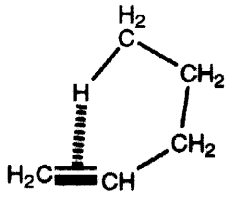
Hirota et al. reported on a potential role of the CH/π interaction in the conformation of 1-phenyl-2-propanol,[44] 1-pentene **4** and 1,5-hexadiene **5**;[45] the CH/π-interacted conformer has been shown to be most stable among a number of possible forms by ab initio calculations. Gung et al. also presented a rationale for the preference of a CH/π-interacted conformation of **5** by MP2/6-41G* calculations.[46] In view of the discussions as raised above, we conclude that the CH/π interaction plays an appreciable role in determining the conformation of organic compounds.



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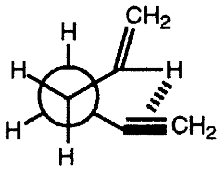

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