The CH···π interaction as an important factor in the crystal packing and in determining the structure of clathrates†

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Crystal structures in the Cambridge Structural Database (CSD) were examined to investigate the role of the CH···π interaction in the crystal packing and the structure of clathrates. More than 77% of organic crystals have been found to bear CH···π interatomic distances shorter than 3.05 Å. Database subsets were edited by monitoring the entire CSD with the structure of included solvents ($CHCl_3$, CH_2Cl_2, $MeNO_2$, MeCN, MeOH, Me_2CO, DMSO, DMF, 1,4-dioxane, benzene, toluene and *p*-xylene). A great many of the examined compounds have been shown to bear short CH···π distances among themselves and between supramolecular components. A variety of different solvents (protic, dipolar aprotic as well as non-polar) has been found to be included by CH···π interactions. The crystal structures were retrieved and examined in detail for clathrates of 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol and 1,1′-binaphthyl-2,2′-dicarboxylic acid in complexation with their specific guests. The results are discussed in the context of the CH···π interaction in controlling the specific structure of supramolecular aggregates.

Introduction

Consequences of non-covalent forces in chemistry and structural biology have stimulated interest in exploring a variety of such intermolecular interactions. By far the most significant and strongest of the non-covalent forces is the hydrogen bond.[1] The conventional hydrogen bond, X–H···Y, occurs when X and Y are electronegative atoms such as O and N. In other words, the ordinary hydrogen bond is an interaction working between a hard acid and a hard base. This contrasts with weaker hydrogen bonds such as XH···π (X = O or N) and CH···X (X = O or N) interactions; the former is a hard acid–soft base combination while the latter is a soft acid–hard base interaction.[2,3] The CH···π interaction,[4] in this context, can be regarded as the weakest extreme of hydrogen bonds, which occurs between a soft acid and a soft base. Available data in the literature such as the substituent effect on conformational equilibria,[5] crystal packing[6] and equilibrium of supramolecular complexes[7] demonstrate that the CH···π interaction is not merely a conventional van der Waals force but has a hydrogen-bond-like property. High-level *ab initio* MO calculations supporting the concept were published recently.[8] The enthalpy of a single unit CH···π interaction is the smallest (around 1 kcal mol^{-1})[8,9] of these weak hydrogen bonds. However, the CH···π interaction has been shown to play significant roles in various fields of chemistry: *e.g.*, in determining the conformation of molecules,[10] crystal packing[6,11,12] and in assembling molecular units into an organized supramolecular structure.[13] An important role for the CH···π interaction in the structure of proteins[14] and DNA[15] has also been suggested.

Previously, we reported on the role of the CH···π interaction in several inclusion compounds such as cyclodextrin complexes, calix[4]arene complexes and pseudorotaxanes.[16] Here we present evidence, obtained by a systematic database study, that the CH···π interaction generally plays an important role in the crystal packing and in determining the structure of clathrates.

Method

The Cambridge Structural Database[17] (CSD version 5.19, June 2000 release: 215 403 entries) was used. The method of exploring CH···π interactions in the crystal structures deposited in the CSD was reported in detail in our previous papers.[11,16] To participate in a CH···π interaction, the hydrogen atom should be positioned above the π-plane. This, however, does not mean that the hydrogen should lie exactly above the aromatic ring. A CH group can interact with the π-group in regions where the hydrogen atom is above the π-plane but slightly offset outside the ring. Several kinds of distance and angle parameters were therefore defined to cover every possibility (Fig. 1). Here, we chose the aromatic C_6 ring since this is by far the most extensively studied π-system and in view of its importance in materials chemistry and structural biology. In practice, the program QUEST3D was used to locate CH···π contacts

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† A comprehensive literature list for the CH···π interaction is available on the following website: http://www.tim.hi-ho.ne.jp/dionisio

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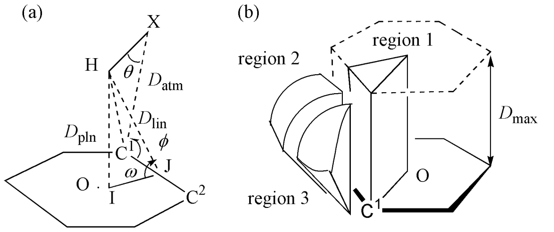

Fig. 1 Method of surveying CH···π contacts. (a) O: centre of the plane. C^1 and C^2: nearest and second nearest sp^2-carbons, respectively, to H. ω: dihedral angle defined by C^1OC^2 and HC^1C^2 planes. θ: $\angle HCC^1$. D_{pln}: H–π-plane distance (H–I). D_{atm}: interatomic distance (H–C^1). D_{lin}: 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 a H–π distance shorter than a cut-off value D_{max} in every region: $D_{pln} < D_{max}$, $\theta < 60°$, for region **1**; $D_{lin} < D_{max}$, $\theta < 60°$, $90° < |\omega| < 130°$ for region **2**, and $D_{atm} < D_{max}$, $\theta < 60°$, $50° < \varphi < 90°$ for region **3** (φ: HC^1I).

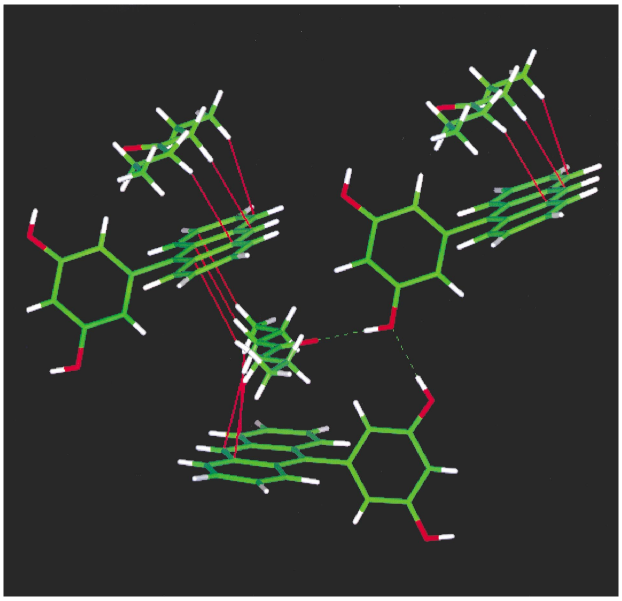

Fig. 2 Crystal structure of 9-(3,5-dihydroxyphenyl)anthracene–heptan-4-one clathrate (CSD refcode REKMAV). Red dotted lines and blue dashed lines indicate CH···π and hydrogen bonds, respectively.

within the above constraints. A short interatomic distance [D_{max} 3.05 Å: 2.9 Å (1.2 Å for C–H plus 1.7 Å for a half thickness of the aromatic group) × 1.05] was considered to be relevant for the presence of a CH···π interaction. The C–H bond distance was normalized to the standard value (1.083 Å) in the CSD QUEST3D software.

Results and discussion

First, short CH–Csp^2 interatomic contacts were sought in the entire database for organic compounds‡ with at least a six-membered carbon aromatic ring. We found many crystal structures bearing short CH···π contacts. Fig. 2 gives a typical example: 9-(3,5-dihydroxyphenyl)anthracene–heptan-4-one clathrate[18] (CSD refcode REKMAV). It is remarkable that the guest is sandwiched by aromatic rings of the host involving many CH···π bonds.

The proportion of structures§ bearing at least a short intermolecular CH···π distance (D_{max} 3.05 Å) has been found to be *ca.* 77% (30226/39458) for organic crystals. This is a modest estimate since in the above 39458 entries are included structures without hydrogen coordinates. Further, CH···π interactions may occur at longer distances.[8]

Table 1 CH···π interactions disclosed in various solvates

Solvent	DB[a]	Hit 1[b] (ratio 1)	Hit 2[c] (ratio 2)
$CHCl_3$	98	91 (93%)	25 (26%)
CH_2Cl_2	160[d]	155 (97)	90 (56)
$MeNO_2$	54	46 (85)	23 (43)
MeCN	122[d]	112 (92)	69 (57)
MeOH	201[d]	189 (94)	94 (47)
Me_2CO	94	93 (99)	73 (78)
DMF	55	54 (98)	40 (80)
DMSO	48	39 (81)	31 (65)
1,4-Dioxane	55	52 (95)	38 (69)
Benzene	192[d]	185 (96)	145 (76)
Toluene	66	64 (97)	25 (38)[e]
p-Xylene	36	36 (100)	25 (69)[e]

[a] Number of crystal structures (bearing hydrogen coordinates) in the database subset. [b] Number of entries bearing short CH···π contacts (D_{max} 3.05 Å). [c] Number of entries bearing short CH(guest)···π(host) contacts (D_{max} 3.05 Å). [d] Entries were limited to organic structures with no disorder and R <10%. [e] Only interactions involving the guest CH_3 were counted.

Next, a series of database subsets were edited by monitoring the entire CSD with the structure of included solvents ($CHCl_3$, CH_2Cl_2, $MeNO_2$, MeCN, MeOH, Me_2CO, DMSO, DMF, 1,4-dioxane, benzene, toluene and *p*-xylene). Short CH···π contacts were then searched in these solvates. Table 1 lists the number of entries bearing short CH···π distances in these database subsets. We note that most crystal structures have CH···π contacts (column 3: ratio 1 = 81–100%).¶

Column 4 of Table 1 summarizes the results for interactions unveiled between the guest CH and host π-groups. We note that a variety of solvents are included by CH···π interactions (ratio 2 = 38–80% except for $CHCl_3$). The proportion of hits was exceptionally small for the chloroform solvates. We do not know the exact reason but it may be that $CHCl_3$ has only one CH atom, while the other solvents bear more than two CHs as the hydrogen donor. In support of this, ratio 2 for the CH_2Cl_2 solvates is about double (56%) that of $CHCl_3$ (26%). Furthermore, toluene is included at a ratio (38%), about half that of the *p*-xylene complexes (69%). Toluene bears only one CH_3 whereas xylene has two methyl groups.

Typical results are given in Fig. 3 for solvates of (a) nitromethane,[19] (b) acetonitrile,[20] (c) 1,4-dioxane[21] and (d) benzene.[22] Note that the guest molecules are effectively included in the crystal lattices by CH···π bonds. There are, of course, crystals showing no CH···π contacts. In these cases other types of molecular forces such as hydrogen bond, π–π stacking,[23] electron donor–acceptor,[24] CH···O,[25] CH···F,[26] OH···π[27] or NH···π[28] interactions, *etc.* may predominate.

A considerable effort has been made over the past few decades to explore the use of clathrates in the stabilization and separation of compounds and in the design of new materials.[29] In the hope of throwing some light on the mechanism of inclusion phenomena, we examined the crystal structure of typical host–guest complexes. The clathrands studied here are 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol **1** and 1,1′-binaphthyl-2,2′-dicarboxylic acid **2**.

1,1,6,6-Tetraphenylhexa-2,4-diyne-1,6-diol

The crystal structure was analyzed for clathrates composed of a wheel-and-axle type compound 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol **1** and several guest molecules. Compound **1** is known as an excellent clathrand and has been extensively studied by Toda and Akagi.[30] Our analysis showed a number of

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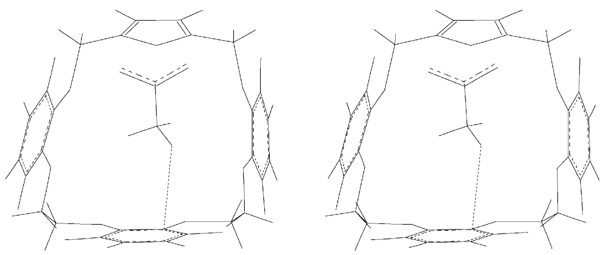
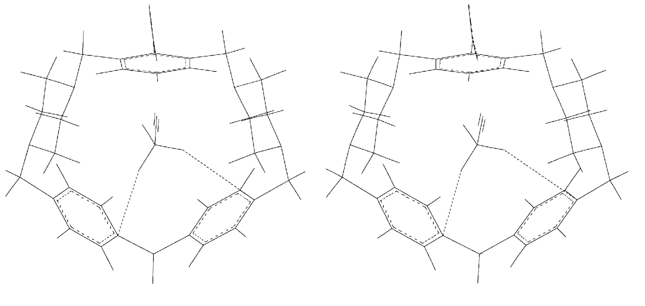
‡ Structures with no disorder, no coordinate errors and R <10%.

§ These compounds are not necessarily the host–guest complexes. Many short contacts have been noted between the same molecules.

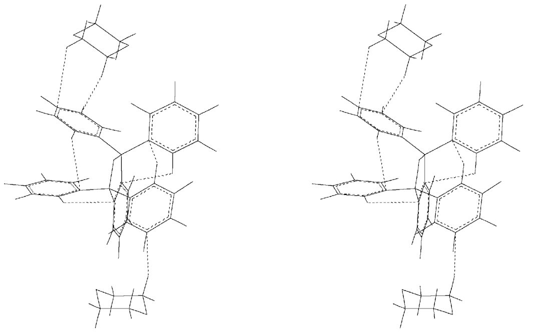
¶ Short contacts have been noted between host molecules as well as between the supramolecular units.



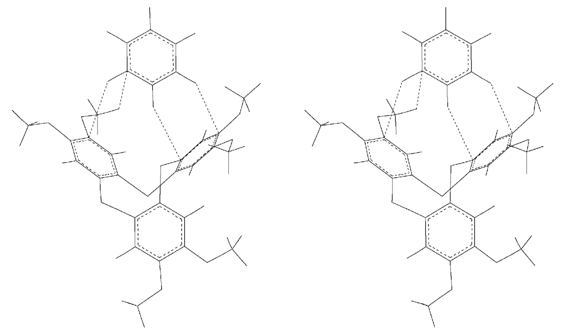
a) Nitromethane (NETKOM)



b) Acetonitrile (ZEJHUR)



c) 1,4-Dioxane (NOQFOO)

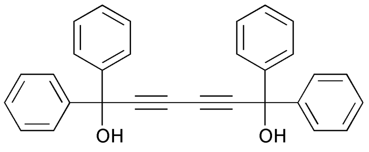


d) Benzene (HMTHBZ)

Fig. 3 Crystal structures of clathrates (stereoviews). Dotted lines indicate $CH\cdots\pi$ short contacts. (a) Furotribenzo-21-crown-7–nitromethane clathrate (NETKOM). (b) Nitro-1(1,3),5,7(1,4)-tribenza-3,9(1,4)-dipiperazinacyclodecaphane–acetonitrile clathrate (ZEJHUR). (c) 1,3-Dihydro-1,1,3,3-tetraphenylisobenzofuran–1,4-dioxane clathrate (NOQFOO). (d) 2,3,7,8,12,13-Hexamethoxy-5,10,15-trithiatribenzo[*a*,*d*,*g*]cyclononene–benzene solvate (HMTHBZ).

short intermolecular distances between **1** and its guest in six clathrates (Table 2). In Fig. 4 an example is given.

In Fig. 4, many $CH\cdots\pi$ interactions are shown between aromatic CHs of a host and the π-rings of another host molecule. This type of interaction has long been known and is often referred to as edge-to-face or T-shape Ar–Ar (π–π) interaction.[35] We prefer this to be termed 'aromatic $CH\cdots\pi$ interaction', in view of its nature.



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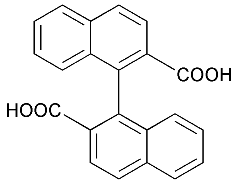

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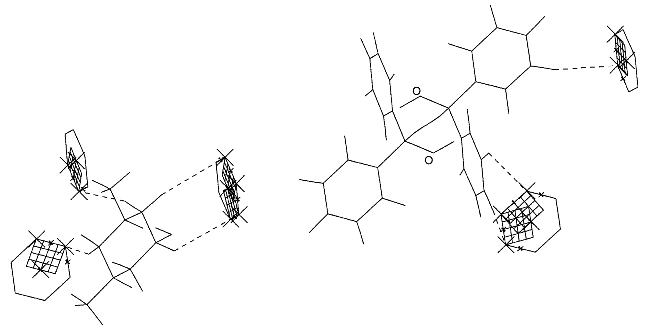

Fig. 4 Crystal structure of 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol–bis(*cis*,*cis*,*cis*-3,5-dimethylcyclohexanol) clathrate (VEMLAA). Shaded planes represent aromatic rings interacting with a CH.

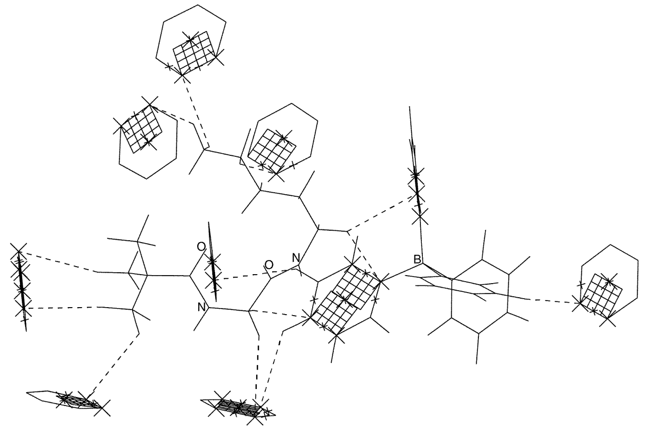

Fig. 5 Crystal structure of *N*-(*tert*-butylcarbonylglycylaminoethyl)-*N*-(ethyl)ammonium tetraphenylborate pseudo-peptide (JOFHUH) Shaded planes represent aromatic rings interacting with a CH.

Since we felt from the literature[36] and the program search that tetraphenylborates bear many interactions of this type, a database subset was edited and surveyed for organic salts ‡ having Ph_4B^- as the anion component. We found many compounds to have short $CH\cdots\pi$ contacts (106/106, D_{atm} 2.89 ± 0.14 Å, 1292 distances; 90/106 for the aromatic $CH\cdots\pi$, D_{atm} 2.81 ± 0.11 Å, 377 distances). An example is given in Fig. 5.[37] The abundance of $CH\cdots\pi$ interactions in these salts may explain the reason why good crystals can often be grown using tetraphenylborate.

1,1′-Binaphthyl-2,2′-dicarboxylic acid

Weber and co-workers systematically studied various types of synthetic clathrands in order to find principles that govern the specificity of the inclusion phenomena.[38] 1,1′-Binaphthyl-2,2′-dicarboxylic acid **2** is a typical clathrand from the many which exhibit good host properties. It is noteworthy that every compound that Weber and co-workers reported bears *aromatic*

Table 2 CH···π contacts in clathrates composed of **1** and various guests

CSD refcode	Guest	D_{atm}/Å (aliphatic CH···π)	D_{atm}/Å (aromatic CH···π)
BABKAQ[31]	Acetone	2.78	
BABKAQ10[32]	Acetone	2.84, 2.96	
KERSAB[33]	Nicotine	2.77, 2.98	2.77, 3.04
SOGHAX[34]	Benzophenone	2.86	2.70, 2.72, 2.92, 2.97
VEMKUT[34]	[a]	2.79, 2.89, 2.95	
VEMLAA[35]	[b]	2.93, 3.05, 2.85, 3.05	

[a] 3,5-Dimethylcyclohexanone. [b] 3,5-Dimethylcyclohexanol.

Table 3 CH···π contacts in clathrates composed of **2** and various guests

CSD refcode	Guest[a]	Mp/°C[b]	D_{atm}/Å
CILLUE[39]	MeOH (1 : 2)	146	2.81, 2.81, 3.12[c]
CILMAL[39]	EtOH (1 : 2)[c]	88	3.11
CILMIT[39]	Butan-2-ol (1 : 1)	92	2.86, 3.04
CILMOZ[39]	Ethylene glycol	165	2.76, 2.89, 2.93
CITRUS10[40]	Imidazolium		2.74, 2.85
CITSAZ10[40]	Imidazolium		2.93, 2.97, 3.04
CIWJEX10[41]	DMSO (1 : 1)	155	2.73, 2.90, 2.95, 3.03
CIWJIB10[41]	DMF (1 : 2)	117	2.62, 2.68, 2.78, 2.80, 2.83, 2.88, 3.11
DOGXUS[41]	C_6H_5Br (1 : 1)	116	2.81, 2.90, 2.93
TANDAN[42]	*tert*-Butanol (1 : 1)[c]	141	3.13, 3.16, 3.19, 3.35

[a] In parentheses is the stoichiometry of the host–guest ratio. [b] The beginning of the clathrate decomposition as demonstrated by either onset of opacity or release of the gaseous guest component. [c] Distances obtained for a longer cut-off value D_{max} 3.2 Å.

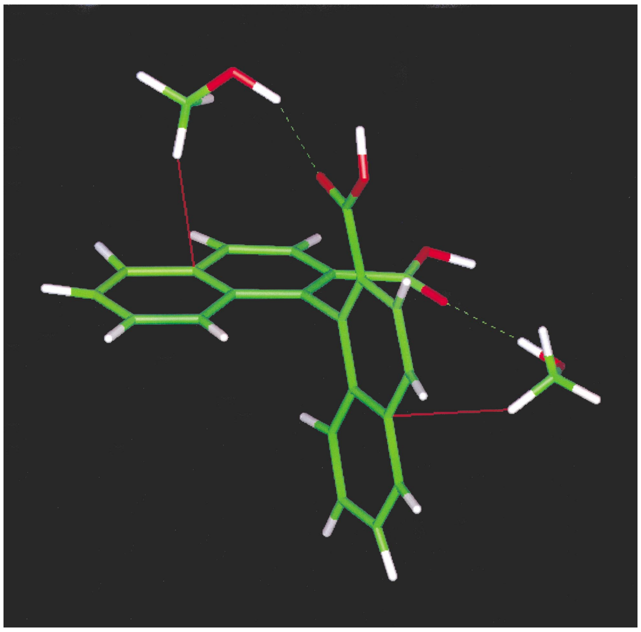

Fig. 6 Crystal structure of 1,1′-binaphthyl-2,2′-dicarboxylic acid–methanol clathrate (CILLUE). Red dotted lines and blue dashed lines indicate CH···π and hydrogen bonds, respectively.

moieties in the molecule. Compound **2** represents an example and binds a variety of guest solvents:[39] alcohols, amides and aprotic solvents such as acetonitrile, nitromethane and dimethyl sulfoxide. Short CH···π distances have in fact been found between **2** and various guest molecules (Table 3). Fig. 6 illustrates a typical example.

The principle governing the stability of host–guest complexes has not been well elucidated. Hydrogen bonding, dipole–dipole interaction, shape and dimension of the cleft, topological requirements of the guests and symmetry of the whole crystal structure are important. The results must be interpreted with caution. It is pertinent to comment, however, on several features reported in their paper.[39] The methanol clathrate decomposes at 146 °C, which is 70 degrees higher than the boiling point of the solvent. Three close CH···π contacts have in fact been found in the crystal structure between the host and the guest methanol, while in the ethanol complex we see only one such short distance (Table 3). The thermal decomposition point of the ethanol clathrate is 88 °C; this is only 10 degrees higher than the boiling point of ethanol. They also reported that complexes of **2** with acetylacetone, acetonitrile, nitromethane, dimethylformamide and dimethyl sulfoxide are very stable. This seems reasonable since CH hydrogens in the above dipolar aprotic molecules are weakly acidic and thus are more liable to undergo the CH···π interaction. The higher branched homologues have also been shown to be preferred guest components. The guest preference in these cases may emerge, at least partly, as a result of more extensive CH···π bonds. Toluene and bromobenzene, which are neither polar nor protic, are also included. We see three host–guest CH···π contacts in the crystal structure of the **2**–C_6H_5Br complex.

Conclusion

To summarize, a number of H–C distances shorter than the sum of the van der Waals radii of CH and aromatic sp^2 carbon have been disclosed in a variety of crystal structures. It is worthy of note that the most effective clathrands reported thus far[18–22,30–34,36–43] have *aromatic* groups in their structures. This is reminiscent of the experience of organic chemists that generally an aromatic compound has a higher melting point and is easier to crystallize than its aliphatic analogue. In view of this and available data in the literature, we conclude that the CH···π interaction plays an important role in determining the stability of organic crystals. The implication of this is obvious for the design of useful clathrands,[44] crystal engineering,[45] catenation,[46] self-assembly,[47] optical resolution,[48] liquid crystals,[49] solid state reaction[50] and so on.

According to theory and experimental results, the CH···π interaction results largely from the dispersion force.[51,52] Electrostatic forces also contribute,[8,52] in particular for interactions involving polar CH groups such as those in chloroform or acetylene derivatives.[53] Superimposed on this mechanism, we believe, is a charge transfer process from the π system to the antibonding orbital of the C–H bond.[54] The enthalpy of a one-pair CH···π interaction is small; however, a unique feature of this type of attractive force is that a number of CH groups can simultaneously participate and cooperate in the interaction with π-bases.[55] The total energy of the interaction may become considerable by organizing the relevant groups into a favourable supramolecular arrangement. Moreover, this type of interaction is entropically advantageous in that CH and π-groups are generally arranged in a certain symmetric chemical structure. These points are crucial in understanding the role of the $\mathrm{CH}\cdots\pi$ interaction. Another significant point is that the $\mathrm{CH}\cdots\pi$ interaction is effective in protic media such as water,|| unlike the ordinary hydrogen bond and electrostatic interactions, as well as in nonpolar media unlike the so-called "hydrophobic effect". This type of molecular force has long been known but was imprecisely attributed in the past to non-specific apolar interactions such as the van der Waals force or the so-called packing force. We suggest that a considerable part of conventional nonpolar interactions should be re-examined in the context of a new paradigm, the $\mathrm{CH}\cdots\pi$ interaction.

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|| This is important when considering biochemical processes.

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