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CH/π Interactions as Demonstrated in the Crystal Structure of Host/Guest Compounds. A Database Study

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Abstract—Crystal structures deposited in the Cambridge Structural Database (CSD) were examined, by use of our program CHPI, for several kinds of clathrates in order to know the role of the CH/π interaction in host/guest chemistry. These include cyclodextrin complexes, calix[4]arene complexes, cryptophane complexes and pseudorotaxanes. A number of short CH/π distances have been shown in the crystal structure of these compounds. The result was discussed in view of the role of the CH/π interaction in controlling the specific structure of supramolecules. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

The CH/π interaction is a weak hydrogen bond occurring between CH groups (soft acids) and π-systems (soft bases).[1] It has been suggested that the CH/π interaction play important roles in determining the conformation[2,3] and chiroptical property[4] of organic compounds, in stereoselective reactions[5] and chiral recognitions.[6] The CH/π interaction also plays a role in the solid structure of supramolecules such as clathrates (lattice-inclusion[7] or cavity-inclusion type[8]) and mesogenic compounds.[9] Recently, we reported that the CH/π interaction plays a crucial part in controlling the crystal packing[10] of organic molecules.[11] Importance of the CH/π interaction in biochemistry (protein,[12] DNA[13]) has also been suggested.

To investigate the significance of the CH/π interaction in host/guest chemistry, crystal data deposited in the Cambridge Structural Database (CSD)[14] were examined for several kinds of macrocyclic compounds in complex with their specific guests.

Method

The method of exploring CH/π interactions in the crystal structure was reported earlier. In short, a program was written, by use of the CSD QUEST3D command system, to find interatomic contacts between CH groups and π systems. To participate in a CH/π interaction, the hydrogen should be positioned above the π plane. Several kinds of parameters were thus defined to cover every possibility (Fig. 1). Interatomic contact, between a CH and an aromatic π (C), was sought within cut-off values for reasonable distance and angle parameters.

First, database subsets were edited from the CSD (version 515, 181309 entries) for several series of clathrates by surveying the entire database; only structures bearing 3D screen[‡] and hydrogen coordinates were collected. Next, nonbonded short atomic contacts were sought between CHs and Csp^2 within the sub-databases.

Results

The compounds examined were cyclodextrin complexes, calix[4]arene complexes, cryptophane complexes and pseudorotaxanes.

Cyclodextrin complexes

Capability of cyclodextrins (CD) to form inclusion complexes with various compounds is well known.[15] The

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Keywords: CH/π interaction; crystal structure; host/guest; supramolecules; CSD.

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[‡] Screens used in the QUEST3D searches were 57, 153, 85, 35, −54, 88, and 33. The C–H bond length was normalized to 1.083 Å.

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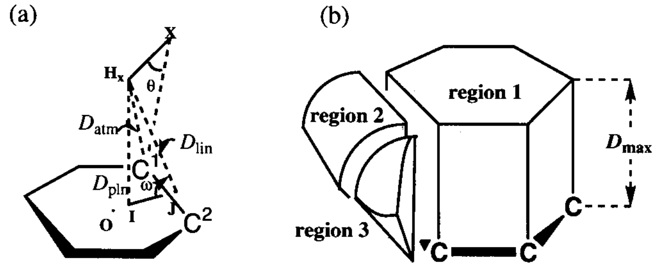

Figure 1. Method of surveying CH/π contacts. (a) O: centre of the plane. C^1 and C^2: nearest and second nearest sp^2-carbons, respectively, to H. ω: dihedral angle defined by C^1OC^2 and HC^1C^2 planes. θ: $\angle HXC^1$. D_{pln}: H/π-plane distance (H/I). D_{atm}: interatomic distance (H/C^1). D_{lin}: 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_{max}=3.05 Å unless otherwise noted): $D_{pln}<D_{max}$, $\theta<60°$, for region 1; $D_{lin}<D_{max}$, $\theta<60°$, $90<|\omega|<130$ for region 2, and $D_{atm}<D_{max}$, $\theta<60°$, $50°<\phi<90°$ for region 3 (ϕ: HC^1I).

crystal data of complexes composed of α or β-CD derivatives and aromatic guests were retrieved from the CSD and analyzed.[§] Short H/π contacts were disclosed in 12 entries (D_{atm}=2.89±0.14 Å,[||] 24 observations) between the host and the aromatic guests. Table 1 lists the results.

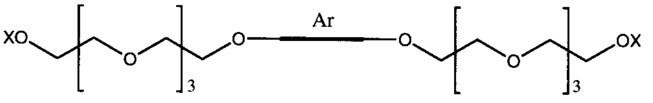

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Fig. 2 illustrates an example. Thus, Stoddart et al. reported a synthesis of catenanes from dimethylated CD (DM-β-CD) and polyethers **1**.

Complexation occurred more strongly as the effective surface of the aromatic ring (Ar) of the ligand **1** increases. Upfield H NMR chemical shift changes were shown for hydrogens of the glucose moiety of DM-β-CD on complexation, indicating that the aromatic part of the guest is effectively included in the host CD. A catenane product was obtained by cyclizing the pseudorotaxane **1**/DM-β-CD. The crystal structure of the catenated cyclodextrin (Ar=4,4′-biphenyl, Fig. 2) revealed that the aromatic unit of the synthetic macrocycle is close to the CH groups inside the wall. Short H/π distances [D_{atm} 2.93 Å (D_{pln} 2.78), 2.72 (2.70) and 2.77 (2.61)] were in fact found between hydrogens in DM-β-CD and the biphenyl part of the partner. The results indicate that CH/π interaction is an important factor controlling the self-assembly of the molecules

Harata studied the thermodynamics of complex formation in water for hexakis(2,6-di-*O*-methyl)-α-CD with aromatic guests such as substituted benzoic acids, phenols and anilines.[25] Negative values were obtained, in every case, for $\Delta H°$ and $\Delta S°$. The result indicated that the tight binding of the guests forms the complexes with the host; the driving force of the complex formation is enthalpic in origin and is by no means regulated by the so-called hydrophobic interaction. To summarize, the complexation of aromatic molecules with cyclodextrins seems to be due to the CH/π interaction, at least in part.

Calix[4]arene complexes

A number of calix[4]arenes have been reported as potent synthetic macrocycles to include various types of organic guests in crystals,[26] whereby an important role of the CH/π interaction was suggested.[27] The finding has been supported by a force-field calculation of the pyridine complex of a *p-t*-butylcalix[4]arene derivative;[28] thus the crystal structure was reproduced only when contribution of the CH/π interaction was taken into account. NMR,[29] mass spectral[30] and thermodynamic data of various calixarene complexes have

Table 1. Distances between CHs of the host cyclodextrins and sp^2 carbons of the aromatic guests

CSD Refcode	Guest	D_{atm}/Å
ACDHBA (α)[16]	p-$C_6H_4(OH)COOH$	2.90, 2.96, 3.15
ACDPNP (α)	p-$C_6H_4(OH)NO_2$	2.82, 2.96, 3.09, 3.00
GELKEN10 (β)[17]	m-$C_6H_4(OH)I$	2.82, 2.98
GETPAW (β)[18]	(*R*)-Fenoprofen	2.93
GETPEA (β)	(*S*)-Fenoprofen	3.12
HEHJEJ (β)[19]	Diclofenac	2.65, 2.77 2.89, 2.75
JEJWOK (α)[20]	(*R*)-1-Phenylethanol	3.10
JEJXAX (α)	(*S*)-1-Phenylethanol	3.02
JUMYUL (α)[21]	o-$C_6H_4(OH)F$	2.71
KOFJEU (β)[22]	*t*-Butyl benzyl alcohol	2.99
WAGHAN (β)[23]	2-Naphthoic acid	2.69, 2.98
YAPSEN10 (β)[24]	Cyclophane[a]	2.72, 2.77, 2.93

[a] DM-β-CD catenated with [2]-15,22-dioxo-2,5,8,11,26,29,32,35-octaoxa-14,23-diaza(15.15.0)paracyclophane.

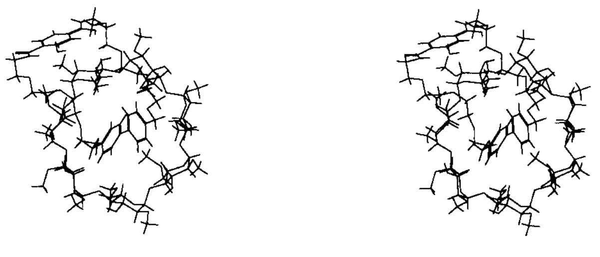


Figure 2. Stereo view of [2]-catenane composed of DM-β-CD and [2]-15,22-dioxo-2,5,8,11,26,29,32,35-octaoxa-14,23-diaza(15.15.0)paracyclophane (CSD refcode YAPSEN10).

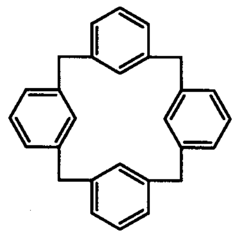
[§] Only those bearing hydrogen coordinates were retrieved.

[||] The mean distance±standerd deviation.

Table 2. CH/π contacts in calix[4]arene derivatives complexed with chloroform or methylene chloride

CSD refcode	Guest	D_{atm}/Å
HAGFEA[34]	$CHCl_3$	2.52
YAPTAK[35]	CH_2Cl_2	2.69, 2.77, 2.97, 3.08
YEBFAM[36]	CH_2Cl_2	2.74, 2.96, 2.94, 3.04
YOCPUB[37]	CH_2Cl_2	2.86, 3.03, 3.08
ZELDID[38]	CH_2Cl_2	2.32, 3.08
ZIDNUV[39]	CH_2Cl_2	2.40, 2.60, 2.64, 2.76, 2.91

shown that the CH/π interaction plays a role in maintaining the structure of these compounds in solution as well as in gas phase.



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A survey for inclusion complexes bearing common partial structure **2** disclosed a number of short intermolecular H/π distances: aliphatic CH/π interaction (D_{atm}=2.91±0.14 Å,[‖] 404 observations in 81 entries) as well as aromatic CH/π interaction[31,32,33] (2.91±0.14 Å,[‖] 159 observations in 39 entries). In these cases, a number of guests have been found in the crystal lattice.

The interaction involving chloroform or methylene chloride was examined (Table 2). In HAGFEA we found a very short CCl_3H/host distance (2.52 Å). In five entries were disclosed 18 short Cl_2CH_2/host contacts (2.83±0.22 Å[‖]). The mean H/π distance seems to decrease as the acidity of the CH hydrogen increases; this is consistent with our earlier results.

Cryptophane complexes

Collet et al. studied the inclusion property of cryptophanes derived from cyclotriveratrylene. Cryptophane C (**3**, n=2) was expected, from CPK model considerations, to effectively include chloroform. Contrary to the expectation, however, methylene chloride was found to bind much more tightly to cryptophane C than chloroform.

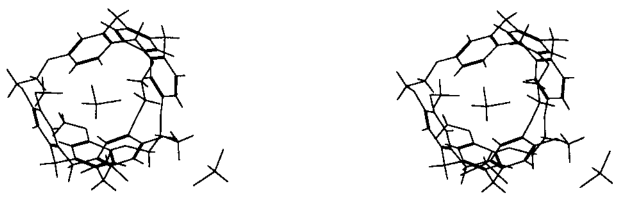
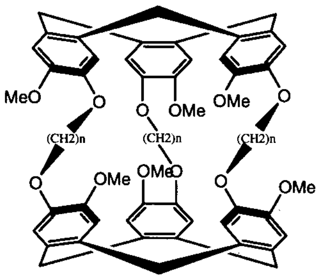


Figure 3. Stereo view of cryptophane C/CH_2Cl_2 complex (CSD refcode CUSCEY).



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The crystal structure of methylene chloride complex of cryptophane C[40] (CUSCEY) was retrieved and analyzed by our program ($D_{\max}$=3.6 Å). CH/π interatomic distances between the two hydrogens (H^1 and H^2) of the guest methylene chloride and the three aromatic rings of the host are 2.70, 3.40 and 2.96 Å for H^1/Ar and 3.26, 3.44 and 2.96 Å for H^2/Ar (Fig. 3). In the complex of CH_2Cl_2 with a stereoisomer cryptophane D (DIJJUB)[41] have also been noted short CH/π distances (D_{atm} 2.93 and 2.90 Å for H^1/Ar, 2.80, 2.83 and 3.01 Å for H^2/Ar). The guest methylene chloride was reported to be tightly bound in solution by NMR (complexation-induced upfield shifts of CH_2 were 4.39 and 4.20 ppm, for cryptophane C and D, respectively). It might well be that CH/π interaction is responsible for the tight binding of CH_2Cl_2 with use of its two hydrogens. Chloroform, on the other hand, bears only one hydrogen that interacts with the cryptophanes.

Cryptophane E (**3**, n=3) bearing a larger cavity was expected, by CPK model, to form a stable complex with carbon tetrachloride. Experimentally, however, cryptophane E binds $CHCl_3$ by two orders of magnitude more strongly than CCl_4.[42] we analyzed the structure of the E/$CHCl_3$ complex (SEDPOG). Distances between the carbon of the included guest and six carbons of a benzene ring are 4.00, 4.11, 4.03, 4.26, 4.12 and 4.11 Å. Clearly, the C–H bond of chloroform points to the center of the aromatic ring. The effective binding of $CHCl_3$ may thus be due to its CH; such a hydrogen atom is absent in carbon tetrachloride.

Pseudorotaxanes

Pseudorotaxanes, rotaxanes and catenanes are novel classes of compounds, which show interesting physicochemical properties. Stoddart, Williams and their co-workers extensively studied these types of compounds.

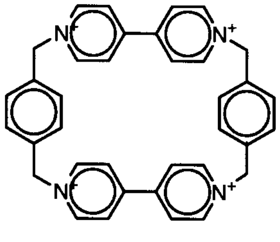

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Table 3. CH/π interactions in crystal structure of pseudorotaxanes and rotaxanes

Refcode	CH/π contacts[a]	ArCH/π contacts[b]
HAYBEO	–	2.73, 2.81
KIRTEK	–	2.74, 2.76
SOVKOD[43]	3.07	2.99
SOVKUJ	3.29	2.72
SOVLEU	–	2.80
TEYLUE	2.87	2.88, 2.90
TEYMAL	–	2.95
TOPQIY[44]	2.88, 2.89	2.73, 2.88
VONHUB	–	2.74
VOTNEX	–	2.74
VOTNIB	–	2.92
VOTNOH[45]	–	2.89
VOTPAV	–	2.87
ZOPDAJ[46]	–	2.71
ZORHAP[47]	–	2.67
ZORHET	–	2.85

[a] CH/π distances (aliphatic CH) between the host and guest.
[b] CH/π distances (aromatic CH).

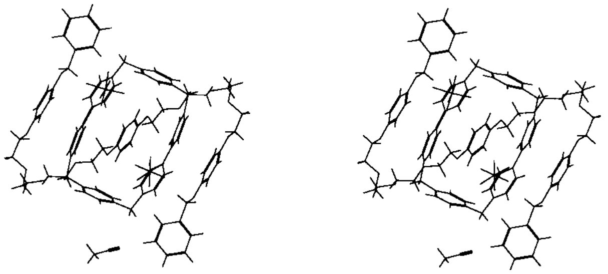

Figure 4. Stereo view of a pseudorotaxane (CSD refcode SOVKUJ).

The compounds examined were pseudorotaxanes and rotaxanes bearing the common partial structure cyclobis(paraquat-*p*-phenylene) cyclophane **4** as the host molecule (Fig. 4). The contacts are found either between the components or between the adjacent supramolecular units (in Table 3, only interactions between the host and guests are listed). The aromatic CH/π interaction seems to dominate in these types of compounds, especially for interactions between the guest and the host.[#]

The crystal conformation of these compounds has been reported to maintain in solution. It therefore seems probable that the CH/π interaction plays an appreciable role in the process of self-assembly of complex molecules.

Discussion

Understanding of weak molecular interactions is indispensable in supramolecular chemistry.[48] In the present study a number of H/C distances shorter than the sum of the conventional van der Waals radii of CH and C (aromatic) have been found in a variety of inclusion compounds. The spectral data show that in many cases the crystal structure is maintained in solution. It therefore seems that the CH/π interaction plays a crucial part in determining the stability of host/guest complexes and in assembling the molecular units into an organized supramolecular structure. Available data in the literature (substituent effect on crystal structures[49] and NMR spectra,[50] stereoselectivity in chemical reactions,[51] conformational equilibria,[52] formation constants of supramolecular complexes[53] and thermochemical data[54]) demonstrate that the CH/π interaction is not merely a conventional dispersion force. Recent high-level ab initio calculations[55] support this. This type of interaction has been known but was broadly ascribed in the past to the nonspecific apolar forces such as the van der Waals force or the so-called packing force.[¶] We conclude that recognition of a specific molecular force, the CH/π interaction, is important in understanding chemistry of molecular assemblies.

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[#] Note added in proof: These workers already noticed the importance of CH/π interaction in their papers.

[¶] Incorporation of bulky groups is a prerequisite for designing good clathrands. The bulky group is always an aromatic one.

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