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How is the CH/π interaction important for molecular recognition?†

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Received (in Cambridge, UK) 12th December 2003, Accepted 28th January 2004
First published as an Advance Article on the web 10th February 2004

***Ab initio* calculations illustrate that CH/π attractions significantly contribute to host–guest complexation, but are not always a direct factor in molecular recognition.**

Attractive CH/π interactions[1] have received considerable attention as a principal factor governing molecular recognition and self-assembly, as accumulated in the database on CH/π proximate arrangements in crystal structures of host–guest complexes.[2] Experimental attempts have been made to assess the importance of CH/π interactions.[3,4] Recent theoretical calculations reveal that the magnitude of CH/π interactions is in the range 1.5–5.6 kcal mol^{-1}.[5–10] To address the role of CH/π interactions in molecular recognition, a resorcinol cyclic tetramer (**1**) was considered as a typical host and its interactions with alcohols were theoretically investigated with the Hartree–Fock (HF) and second-order Møller–Plesset perturbation (MP2) methods.[11] We report that CH/π attractions themselves are not always a direct factor in molecular recognition, despite the significant contribution to stabilization.

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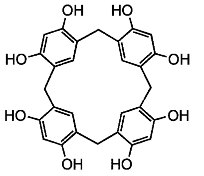

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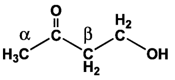

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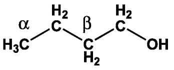

It has been known that 3-oxo-1-butanol (**2**) forms a stronger complex with **1** than 1-butanol (**3**) does.[12] This has been explained as the effect of the carbonyl group in **2** which enhances CH/π interactions by increasing the acidity of C–H groups. To confirm this effect, intermolecular interaction energies (INT) were first calculated for the simplified model system, $XH_2C–H + C_6H_6$ (X = CH_3 and CHO), at the HF and MP2 levels with the 6-31+G(d,p) basis set, by varying only the intermolecular distance *r* (Fig. 1). The CH acidity of $XH_2C–H$ increases as X changes from CH_3 to CHO, as shown by the MP2 natural charge density distributions, $C^{-0.79}–H^{+0.26}$ for X = CHO and $C^{-0.68}–H^{+0.23}$ for X = CH_3; these distributions agree well with those of $C^{-0.76}–H^{+0.26}$ and $C^{-0.67}–H^{+0.23}$ calculated for **2** and **3**, respectively. As Fig. 1 shows, the $XH_2C–H + C_6H_6$ system is much more stabilized at the MP2 level than at the HF level. This indicates that the major intermolecular attraction is due to the dispersion force (electron correlation). The equilibrium distance *r* for X = CHO is 0.1 Å shorter at the MP2 level than that for X = CH_3. Accordingly, the INT of −3.6 kcal mol^{-1} for X = CHO is 1.0 kcal mol^{-1} [13] more attractive at the MP2 level than the value of −2.6 kcal mol^{-1} for X = CH_3. This trend was even unchanged at the CCSD(T)/aug-cc-pVDZ//MP2/aug-cc-pVDZ level (ΔINT = 1.0 kcal mol^{-1}). It is interesting that the INT difference agrees with the observed free energy difference of 1.3 kcal mol^{-1} favoring **1** + **2** over **1** + **3**.[12]

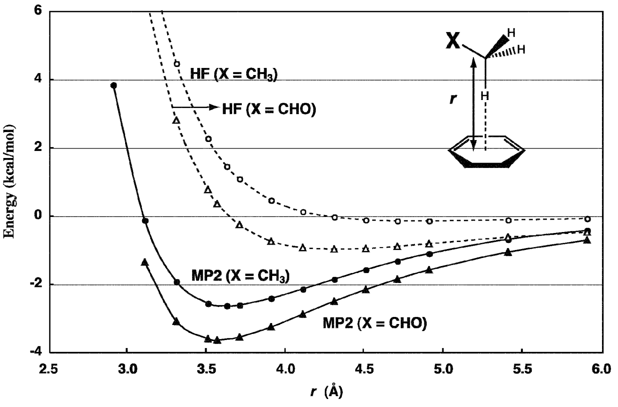

Fig. 1 Intermolecular interaction energies calculated at the HF and MP2 levels with the 6-31+G(d,p) basis set.

The INT difference can be analyzed by expressing INT as a sum of electrostatic (ES), exchange (EX), polarization (PL), charge transfer (CT), their mixed (MIX), and dispersion (DISP) energies, according to the energy component analysis developed by Kitaura and Morokuma.[14,15] As shown by previous *ab initio* calculations of related systems,[5–10] DISP is the major source of the CH/π attraction (Table 1). A noticiable finding is that DISP stabilizes the $XH_2C–H + C_6H_6$ complex to the same extent for X = CHO and CH_3. It is the smaller ES attraction that is mainly responsible for molecular recognition and makes the X = CHO case 1.0 kcal mol^{-1} more stable.

We return to the complexes of **1** + **2** and **1** + **3**. These fully optimized structures at the MP2/6-31G(d) level are shown in Fig. 2 as **a** (**1** + **2**) and **b** (**1** + **3**). The binding energy (BE) is expressed as a sum of INT and intramolecular deformation (DEF) energies.[16] BE values are given in Table 2, which are corrected for basis set superposition errors (BSSE) with the counterpoise method.[17] In both **a** and **b**, host **1** encapsulates guests **2** and **3** inside its π electron-rich bowl-shaped cavity consisting of four benzene rings in the way that CH/π interactions are maximized. It is not surprising that **a** has 0.1–0.3 Å shorter C–H···π distances[18] than **b**, since the carbonyl group in **2** increases the acidity of C–H groups at both α- and β-positions. As Table 2 shows, however, almost identical BE values were calculated for **a** and **b**. This trend was unchanged at the MP2/6-31+G(d,p)//MP2/6-31G(d) level. To evaluate the stabilization due to CH/π interactions, we replaced the CH_2CH_2OH part in **2** and **3** by a H atom and calculated BE. Upon this replacement, **a** has 2.1 kcal mol^{-1} larger BE than **b**. This result confirms that CH/π interactions are indeed stronger in **a**. However, it also suggests that the advantage in CH/π attractions is diminished by the interaction between the CH_2CH_2OH part and **1**. As Fig. 2 shows, the O–H

Table 1 Energy component analysis for the $XH_2C–H + C_6H_6$ complex at the MP2/6-31+G(d,p) level in kcal mol^{-1}

	X = CHO	X = CH_3	Δ
ES	−2.62	−1.25	−1.37
EX	3.90	3.31	0.59
PL	−0.73	−0.58	−0.15
CT	−0.55	−0.27	−0.28
MIX	0.36	0.25	0.11
DISP	−3.99	−4.09	0.10
INT[a]	−3.63	−2.63	−1.00

[a] INT = ES + EX + PL + CT + MIX + DISP.

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† Electronic supplementary information (ESI) available: optimized cartesian coordinates. See http://www.rsc.org/suppdata/cc/b3/b316280j/

DOI: 10.1039/b316280j

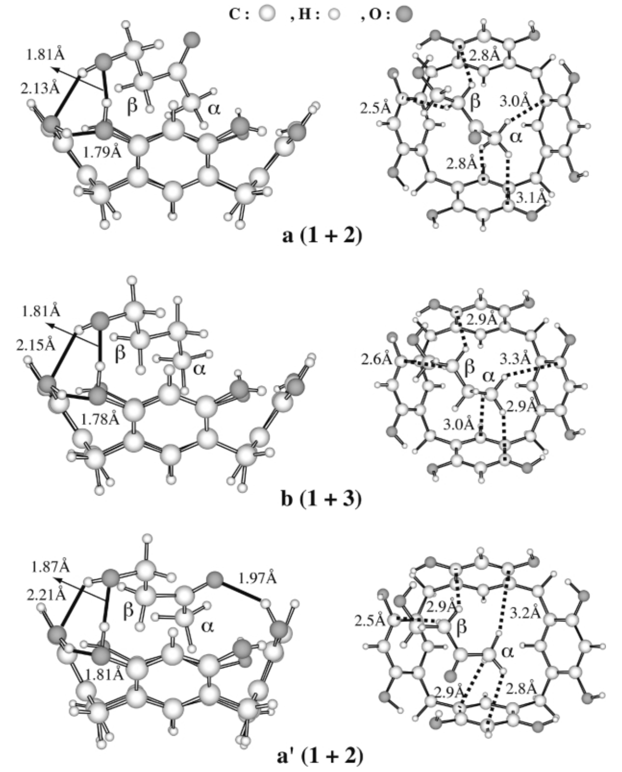

Fig. 2 Two views of optimized MP2/6-31G(d) geometries. CH/π interactions (dotted lines) and OH/O hydrogen bonds (solid lines).

Table 2 Binding energies (BE = INT + DEF) of **a**, **b**, and **a′** calculated at the MP2/6-31G(d) level in kcal mol^{-1}

	a	**b**	**a′**
INT	−16.3	−15.6	−20.4
DEF	3.8	3.2	7.6
BE	−12.5	−12.4	−12.8
BE^a	−12.9^a	−12.5^a	−14.2^a

^{a} Values for the complexes solvated by $CHCl_3$.

group in the CH_2CH_2OH part forms a cyclic hydrogen bond with **1**. However, this is accompanied by considerable molecular deformation (Table 2). As a result, **a** and **b** differ little in BE. Obviously, this conflicts with the experimental observation.

Thus, an alternative complex **a′**, having an additional hydrogen bond (1.97 Å), was considered for **1** + **2** (Fig. 2),[19] which was once discarded in the experimental study.[12] The complex **a′** has slightly larger BE than **a**.[20] As Table 2 shows, however, the BE of **a′** is significantly enhanced in $CHCl_3$ (ε = 4.9), according to the calculations of solvation by the Onsager method.[21] As a result, in $CHCl_3$, **a′** has 1.7 kcal mol^{-1} larger BE than **b**. This BE difference agrees well with the value of 1.3 kcal mol^{-1} observed in $CHCl_3$.[12] This is ascribed to the large dipole moment of 5.62 D for **a′** *vs.* 3.99 D for **a** and 3.70 D for **b**. In this context, we suggest that the BE difference between **a′** and **b** (that is, molecular recognition) is further enhanced by increasing the polarity of the solvent.[22]

In summary, CH/π interactions significantly contribute to the host–guest complexation. However, it is not always true that the interactions are a direct factor in molecular recognition.

S. R. thanks a JSPS research fellowship for Young Scientists. This work was supported by the grand-in-aid for NAREGI Nanoscience Project and Scientific Research on Priority Area (A) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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