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Equilibrium Isotope Effects as a Probe of Nonbonding Attractions

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Nonbonding interactions that occur in host−guest systems and the active sites of enzymes are altered by isotopic substitutions.[1] For example, the binding affinities of caffeine isotopomers to human serum albumin vary considerably.[2,3] Variations in retention times among isotopologues were examined by Tanaka and Thornton using reverse-phase HPLC.[4] It was proposed that CH−aromatic interactions lower the CH vibrational frequency. These equilibrium isotope effects have not been explored computationally, although kinetic isotope effects (KIEs) have successfully been reproduced in simpler cases where the KIE is a result of nonbonding interactions.[5] We apply these techniques to a new class of isotope effects recently discovered in capsules[6] and show that the unusual isotope effects are related to the phenomena of "blue-shifting hydrogen bonds".[7] Similar equilibrium isotope effects (EIEs) on liquid−solid fractionations were also reported with porous host substances.[8]

The dimeric capsule $\mathbf{1}_2$ is a good host for small molecules and molecular pairs (Figure 1).[9−11] The internal size of the capsule is closely matched with the co-guest molecules, *p*-xylene and tetrachloromethane. Isotope effects on complex formations were determined by using NMR measurements: the equilibrium constant for *p*-xylene-d_{10} displacing the encapsulated *p*-xylene is 1.32 ± 0.04 in mesitylene-d_{12} solution; the equilibrium constant for the social isomerization with *p*-xylene-d_3, shown in Figure 2, is 1.35 ± 0.06.[6]

Two models, methane−benzene and methane−tetrachloromethane, were studied to determine the effect of isotopic substitution on the stabilities of these weakly bonded social isomers (Figure 2). Ab initio quantum mechanical calculations were performed with second-order Møller−Plesset perturbation theory (MP2)[12] and the 6-311++G(d,p) basis set in Gaussian 03.[13] This method gives reliable structures and potential energy surfaces for the complexes between benzene and methane, ethylene, and acetylene, as well as van der Waals (vdW) complexes.[14−16] The different orientations between methane and benzene, or between methane and tetrachloromethane, were computed, and the global minima were characterized by harmonic frequency analysis. The zero-point energies (ZPEs) were computed with different isotopic species. NMR shielding tensors were computed with the gauge-independent atomic orbital (GIAO) method.[17]

The resulting minima have C_{3v} geometries for both methane−benzene and methane−tetrachloromethane complexes (Figure 3). The binding energy for the single CH- - -π interaction (−0.85 kcal/mol) is stronger by 0.57 kcal/mol than that of the whole tripodal CH_3- - -Cl_3C vdW interactions (−0.28 kcal/mol).[18] The methane−benzene binding energy has been computed to be −1.45 kcal/mol with more accurate calculations.[15] The calculated NMR properties exhibited a strong shielding ($\Delta\delta = -2.72$ ppm) for the hydrogen contacting benzene and a very small change (−0.14 ppm) in the methane−CCl_4 complex, consistent with the experimental shielding ($\Delta\delta = -5.19$ ppm) resulting from four neighboring phenyl groups (Figure 1).

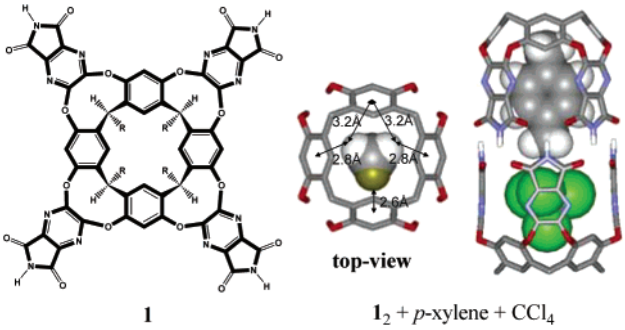

Figure 1. Half-capsule **1** (left), top view (middle), and side view (right) of the complexes of *p*-xylene and CCl_4 in the dimeric capsule $\mathbf{1}_2$ (the $C_{11}H_{23}$ chains (R) of the capsule are removed for clarity).

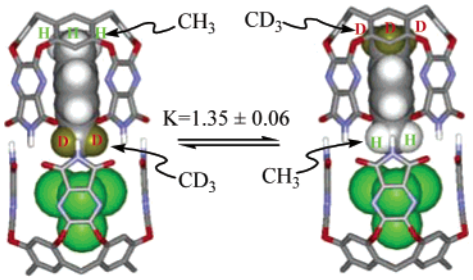

Figure 2. Equilibrium between two social isomers, one with the three deuteriums facing CCl_4 (left), and another with the three deuteriums facing resorcinarene (right).

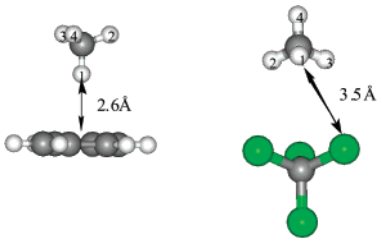

Figure 3. Calculated C_{3v} structures of methane−benzene and methane−tetrachloromethane complexes with MP2/6-311++G(d,p).

Isotopic fractionation can be explained by differences in their ZPEs (Table 1). For example, for the following hypothetical equilibrium, the change in ZPE is −13 cm^{-1} (−38 cal/mol).

$$CH_3D{\cdot}PhH + CH_4{\cdot}CCl_4 \rightleftharpoons CH_4{\cdot}PhH + CH_3D{\cdot}CCl_4$$

This value corresponds to an equilibrium constant at 298 K:

$$K = \exp(-\Delta G/RT) \approx \exp(-\Delta E_0/RT) = 1.07$$

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Table 1. Calculated ZPEs of Methane, Methane−Benzene Complex, and Methane−Tetrachloromethane Complex, Replacing Protium with One, Two, or Three Deuteriums

	ΔZPE (relative, kcal/mol)			
model	d_0	1-d_1	1,2-d_2	1,2,3-d_3
methane	0	−1.859	−3.749	−5.668
methane−benzene	0	−1.924	−3.822	−5.748
methane−CCl_4	0	−1.886	−3.800	−5.738

Table 2. Estimated ΔE_0 and Equilibrium Constants for *p*-Xylene-d_1, *p*-Xylene-d_2 and *p*-Xylene-d_3, and Co-guest CCl_4 in Capsule $\mathbf{1}_2$ with Methane, Methane−Benzene Complex, and Methane−Tetrachloromethane Complex Models, Replacing Protium with Deuterium at Positions 1, 2, and 3[a]

	ΔE_0 (cal/mol)			
	1-d_1	1,2-d_2	1,2,3-d_3	K(298 K)
p-xylene-d_1	−38			1.07
p-xylene-d_2	(−76)	−95		1.17
p-xylene-d_3	(−114)	(−143)	−170	1.33

[a] Numbers in parentheses are the simple multiples of ΔE of *p*-xylene-d_1 ("1-d_1" column), and *p*-xylene-d_2 ("1,2-d_2" column; i.e., $(-95) \times {}^3/_2$).

Assuming that the contacts in $\mathbf{1}_2$ + *p*-xylene + CCl_4 complexes are independent and additive, equilibrium constants for the social isomerizations with different isotopic substitutions can be estimated.[19] Even with such simple methods, the resulting equilibrium constants (1.33, Table 2) are surprisingly consistent with experimental results for *p*-xylene-d_3 ($K_{expl} = 1.35 \pm 0.06$, $\Delta G = -177 \pm 26$ cal/mol). Equilibrium constants of 1.07 and 1.17 are predicted for the social isomerizations in cases of *p*-xylene-d_1 and -d_2, respectively.

Harmonic frequency analysis indicates that the C−D stretching vibrational frequency in the methane-d_1 complex model increases by 12 cm^{-1} in the methane−benzene complex (2332 cm^{-1}, force constant = 7.09 mdyn/Å), compared with that in the methane−tetrachloromethane complex (2320 cm^{-1}, fc = 7.02 mdyn/Å).[20] On the other hand, the CH_3 rocking frequency in the methane-d_1 complex model decreases by 15.2 cm^{-1} in the methane−benzene complex (deuterium/protium, 94.2 cm^{-1}/109.5 cm^{-1}), compared to the 7.7 cm^{-1} decrease in the methane−tetrachloromethane complex (deuterium/protium, 53.9 cm^{-1}/61.7 cm^{-1}). Based on the ZPE definition (ZPE = $1/2\sum h\nu_i$; in the case of *p*-xylene-d_1, $\Delta\sum h\nu_i = -26.5$ cm^{-1}), the nine internal vibrational modes of the methane unit contribute 53% (−14.2 cm^{-1}) and the six intermolecular vibrational modes contribute the remaining 45% (−11.9 cm^{-1}). The total changes in benzene (30 modes) and tetrachloromethane (9 modes) vibrational frequencies upon complexations with methane are negligible (−0.5 cm^{-1}, 2%).[19] Thus, the close interactions of the methyl hydrogens and the surrounding π-systems in the capsule increase the force constant for C−H or C−D stretching and CH_3 rocking in the proximity of the capsule and shift the equilibrium balance toward complexation of the social isomer with the highest numbers of CD-π nonbonding attractions. There are classes of such interactions sometimes called "blue-shifting hydrogen bonds", where C−H stretching frequency shifts are small and opposite in sign to normal hydrogen bonds.[7,20] The CH−Ar interactions appear to be of this type.

In conclusion, the attraction between a methyl group and benzene is relatively large, due to the strong dispersion forces between methane and benzene. The CH_4−CCl_4 interaction is negligible, perhaps due to the low polarizability of CCl_4. The enclosed space of the capsule provides an environment to probe these differential nonbonding interactions. Even though the methyl groups of the guests inside the capsule still rotate rapidly at room temperature, the subtle differences between CH- - -π interactions ($-CH_3$·Ar)[21,22] and CH- - -Cl lone pair interaction ($-CH_3$·CCl_4) can be detected sensitively by either experiment or theory. The increases in CH stretching frequencies observed here upon CH- - -π interactions are in contrast to the decreased frequencies observed in Tanaka and Thornton et al.'s HPLC experiments[4] and recent studies of CH- - -O interactions in lipid bilayers.[23] The differences are under investigation.

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Supporting Information Available: Optimized structures and energies for all conformations discussed, binding energy calculations, calculated NMR shielding tensors, and harmonic vibrational frequencies of all modes (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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