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Does Size Really Matter? The Steric Isotope Effect in a Supramolecular Host–Guest Exchange Reaction**

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Isotope effects (IEs), which arise from differences in zero-point energies (ZPEs) between a parent and isotopically substituted bond, have been used extensively by chemists to probe molecular interactions and reactivity.[1,2] The anharmonicity of the C−H/D vibrational potential energy function and the lower ZPE of a C−D bond make the average C−D bond length approximately 0.005 Å shorter than an equivalent C−H bond.[3–5] It is this difference in size that is often invoked to explain the observation of secondary, inverse kinetic isotope effects (KIEs) in chemical processes that proceed through a sterically strained transition state. This so-called "steric isotope effect" (SIE) has been observed in processes such as the racemization of *ortho*-substituted biphenyls[6] and phenanthrenes,[7] ring-flipping of cyclophanes,[8] and more recently in the deslipping of rotaxanes,[9] where substitution of the sterically less demanding deuterium for protium results in rate accelerations for these processes.[10] Herein, we use deuterium substitution in a cationic guest molecule to probe the sensitivity limits of the guest-exchange process with a highly charged supramolecular host.

The self-assembling $[Ga_4L_6]^{12-}$ supramolecular host (**1**, Figure 1) is composed of six ligands (L = 1,5-bis(2,3-dihydroxybenzamido)naphthalene) that span the edges of a tetrahedron and four Ga metal centers that sit at the vertices.[11,12] The host assembly **1** has a hydrophobic interior cavity that can encapsulate a variety of monocationic[13,14] and neutral[15,16] guest molecules, and has been shown to mediate the chemical reactivity of encapsulated guests.[17,18] Guest molecules can exchange between the interior and exterior of the host assembly through one of four C_3-symmetric apertures (Figure 1) in the ligand framework, which expand and contract to accommodate guest exchange without Ga−L bond cleavage (Figure 2).[19] The large distortion of the host framework required for guest exchange means that drastically different exchange rates are observed for guests of different size and shape.[20] These observations prompted us to investigate whether the tiny difference between C−H and C−D bond lengths is enough to produce a measurable effect on the guest-exchange kinetics. In other words, just how much does guest size matter? The KIEs observed in this study demonstrate that host **1** is able to distinguish between guests with even as small a structural difference as isotopic substitution.

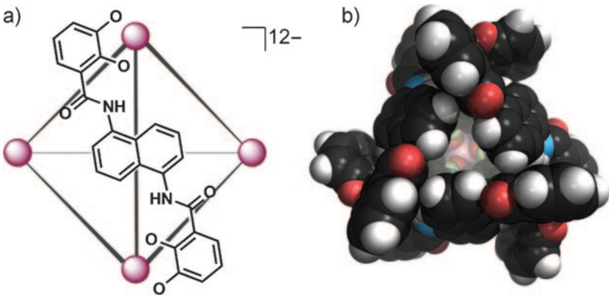

Figure 1. a) Schematic framework of **1**, only one ligand is shown for clarity. b) Space-filling model of **1** as viewed down one of the C_3-symmetric apertures in the host framework.

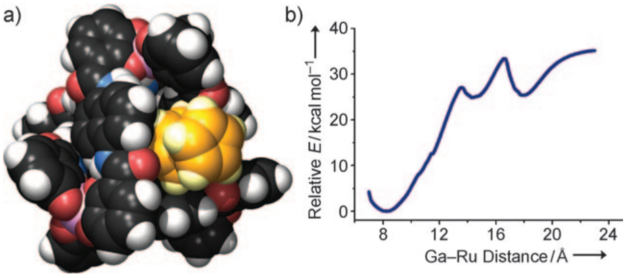

Figure 2. Calculations (MM3, CAChe) of the displacement of $[D_n]$-**2** from host **1** were carried out by increasing the distance between the Ru atom of $[D_n]$-**2** and a Ga atom of **1**.[18] The calculated transition state (a) and energy profile (b) for the displacement process are shown. The increase in energy after guest ejection (> 18 Å) arises from charge separation in the gas phase. See the Supporting Information for an animation of the guest-exchange process.

The displacement reaction of isotopologues of the cationic guest $[D_n][CpRu(\eta^6\text{-}C_6H_6)]^+$ ($[D_n]$-**2**, Cp = η^5-cyclopentadienyl) from host **1** was investigated. Modeling studies suggest that $[D_n]$-**2** passes through the sterically strained transition state for guest exchange in an orientation with all of the guest aromatic C−H/D bonds pointing toward the aperture host walls (Figure 2). This orientation, along with the rigid structure of $[D_n]$-**2**, maximizes contact between the host walls and guest C−H/D bonds and is thus expected to accentuate any KIEs in the exchange process.

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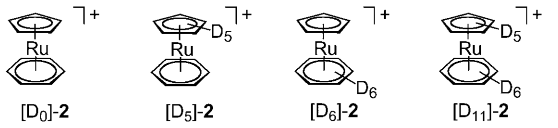

Scheme 1. $[D_n][CpRu(\eta^6\text{-benzene})]$ ($[D_n]$-**2**) guest isotopologues.

A series of $[D_n]$-**2** isotopologues (Scheme 1) and the corresponding $[[D_n]\text{-}\mathbf{2}\subset\mathbf{1}]^{11-}$ (where ⊂ denotes encapsulation) host–guest complexes were prepared. A solution of $[[D_n]\text{-}\mathbf{2}\subset\mathbf{1}]^{11-}$ in D_2O was subjected to an excess of the more strongly binding guest PEt_4^+ (under conditions sufficient for saturation in PEt_4^+, see the Supporting Information) and the rate of guest exchange as PEt_4^+ displaced the encapsulated $[D_n]$-**2** was followed by ^{1}H NMR spectroscopy. Guest egress from **1** has previously been shown to be rate-limiting in the guest-exchange process.[20,21] The observed rate constants for the guest-exchange process were obtained by plotting the concentration of encapsulated PEt_4^+ versus time and fitting the data to a first-order exponential function. Kinetic experiments for each substrate were carried out in both buffered (100 mM K_2CO_3, pD 12.2) and unbuffered (pD 9) D_2O solutions to exclude the possibility that small differences in pD or ionic concentration between host–guest complex solutions were responsible for the observed rate changes. The average observed rate constants (k_{obs}) and KIEs ($k[D_0]/k[D_n]$) are listed in Table 1.

Table 1: Average observed rate constants (k_{obs}),[a] kinetic isotope effects ($k[D_0]/k[D_n]$), and percentage isotope effects per deuterium atom (IE/D)[b] for displacement of $[D_n]$-**2** from host **1** by PEt_4^+.

Guest	Unbuffered conditions[c] k_{obs} [$\times10^{-4}$ s^{-1}]	$k[D_0]/k[D_n]$	IE/D(%)[b]	Buffered conditions[c] k_{obs} [$\times10^{-4}$ s^{-1}]	$k[D_0]/k[D_n]$	IE/D(%)[b]
$[D_0]$-**2**	6.15(4)	–	–	6.31(6)	–	–
$[D_5]$-**2**	6.28(5)	0.98(1)	0.4(2)	6.65(5)	0.95(1)	1.0(2)
$[D_6]$-**2**	6.60(5)	0.932(9)	1.2(2)	6.69(8)	0.94(1)	1.0(3)
$[D_{11}]$-**2**	6.92(4)	0.888(8)	1.1(2)	6.99(7)	0.90(1)	0.9(3)

[a] Rate constants are reported as the weighted average of multiple kinetic experiments (see the Supporting Information for rate constants for each kinetic experiment). [b] $\text{IE/D}(\%) = [1-(k[D_0]/k[D_n])^{1/n}]\times100$, where n is the number of deuterium atoms. [c] Kinetic experiments were carried out in D_2O at 55 °C in both unbuffered (pD 9) solution and buffered (100 mM K_2CO_3, pD 12.2) solution.

These kinetic experiments show that deuteration of guest $[D_n]$-**2** results in an inverse KIE, that is, faster displacement of the deuterated guest from the interior of host **1**. Deuteration at either the Cp ring or the benzene ring has a measurable impact on the guest-exchange kinetics and the calculated IE per deuterium atom (IE/D) values, which are all statistically identical within approximately two standard deviations, suggest that deuteration at either position has a roughly equal effect on the rate of guest ejection. When both rings are perdeuterated, KIEs of up to 11% are observed. The equilibrium IE for encapsulation of $[D_0]$-**2** versus $[D_6]$-**2** was also measured and found to be $K[D_0]/K[D_6] = 0.96(1)$ (see the Supporting Information), thus excluding the possibility that the observed KIEs result from a ground-state effect where deuterated substrates are more weakly bound to the interior of **1** ($K[D_0]/K[D_6] > 1$). The KIEs must therefore be a result of host–guest interactions in the transition state.

The rate accelerations observed upon deuteration of guest $[D_n]$-**2** can be explained in terms of the SIE: the slightly shorter C–D bonds in the deuterated guest molecules require a smaller distortion of the host aperture during guest ejection, thus allowing deuterated guests to more easily squeeze through the sterically strained aperture at the transition state. Although the SIE may be a convenient way to explain the observed rate accelerations, we present a more general explanation that invokes changes in the vibrational potential energy functions (i.e., vibrational force constants) at the sterically strained transition state (Figure 3). As the guest $[D_n]$-**2** moves along the reaction coordinate to the transition state for guest exchange, the vibrational (guest C–H/D stretches, wags, etc.) potential functions steepen and become narrower because of constrictive host–guest interactions at the sterically strained transition state. Similar changes in guest C–H/D force constants upon encapsulation have previously been invoked to explain equilibrium IEs in other host–guest systems.[22] This steepening increases the relative spacing between the vibrational ZPEs for the protiated versus deuterated guests at the transition state, compared to the ground state. Since deuterated guests will have lower vibrational ZPE levels because of their larger mass, a smaller activation energy for deuterated guest molecules consistent with the experimentally observed inverse KIEs is observed. This model rationalizes the observed KIEs based only on changes in the shape of vibrational potential energy wells and the mass difference between isotopologues, and allows for contributions to the IE over all modes of guest C–H/D vibration.[23] Such a general analysis should be preferred in complex molecular systems such as these that are too large to be treated accurately with DFT-level calculations that can determine specific vibrational contributions to the IE.

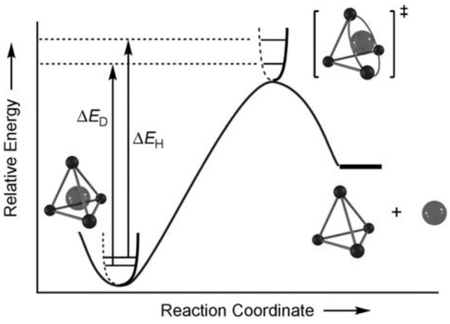

Figure 3. Proposed reaction coordinate diagram for the displacement of a guest from host **1**. An increase in guest C–H/D force constants when constricted at the sterically strained transition state drives the CH and CD ZPEs further apart relative to the ground state, thus resulting in a larger activation energy for the ejection of a protiated guest ($\Delta E_H > \Delta E_D$).

Finally, this model obviates the need to invoke the smaller apparent size of a C–D versus C–H bond, a size difference that may not always be valid.[5]

The model presented above rationalizes the observed KIEs on the basis of enthalpic changes; however, it should be noted that entropic contributions to the IE cannot necessarily be discounted.[24,25] In the case of primary IEs in which covalent C–H/D bonds are broken, it is exclusively enthalpic effects that dominate, but for supramolecular systems in which the IE arises from weak, noncovalent interactions, entropy (e.g., losses in configurational entropy at the transition state) may also contribute to the IE. The KIEs observed in this study are too small to allow for an accurate examination of the temperature dependence of the IE, but we are currently exploring this topic in similar host–guest systems.

In conclusion, we have observed KIEs of up to 11% ($k[D_0]/k[D_n] = 0.89$) in the displacement reaction of guest $[D_n]$-**2** from the interior of the supramolecular host assembly **1**. We attribute the KIEs observed in the host–guest exchange process to increases in the relative spacing of guest C–H/D vibrational ZPE levels. These increases arise from a steepening of the vibrational potential energy functions at the sterically strained transition state. The dramatic guest stabilization and catalysis previously observed in this host[17,18] has much to do with guest binding and exchange. The latter process occurs through dilation of the host aperture, and this study has shown that the exquisite dependence on guest architecture at the transition state for exchange leads to a significant isotope effect.

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