

Does Size Really Matter? The Steric Isotope Effect in a Supramolecular Host-Guest System**

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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] Due to the anharmonicity of the C-H/D vibrational potential energy function and the lower ZPE of a C-D bond, the average C-D bond length is typically ~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 which 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 from a highly-charged supramolecular host.

The self-assembling $[\text{Ga}_4\text{L}_6]^{12-}$ 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 which 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 via 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 breakage (Figure 2).^[19] Due to the large distortion of the host framework required for guest exchange, 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.

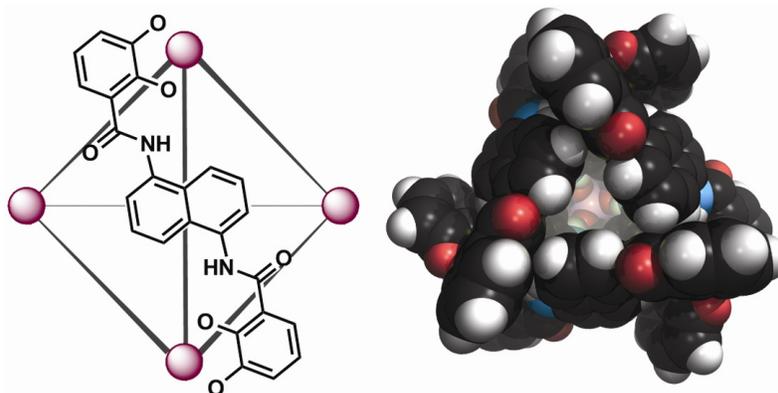


Figure 1. (Left) Schematic framework of **1**, only one ligand is shown for clarity. (Right) Space filling model of **1** as viewed down one of the C_3 -symmetric apertures in the host framework.

The displacement reaction of isotopologues of the cationic guest $[\text{CpRu}(\eta^6\text{-C}_6\text{H}_6)]^+d_n$ (**2-d_n**, Cp = η^5 -cyclopentadienyl) from host **1** was investigated. Modeling studies suggest that **2-d_n** passes through the sterically strained transition state for guest exchange in an orientation with all of the aromatic C-H/D bonds pointing toward the aperture host walls (Figure 2). This orientation, along with the rigid structure of **2-d_n**, maximizes contact between the host walls and guest C-H/D bonds and is thus expected to accentuate any KIEs in the exchange process.

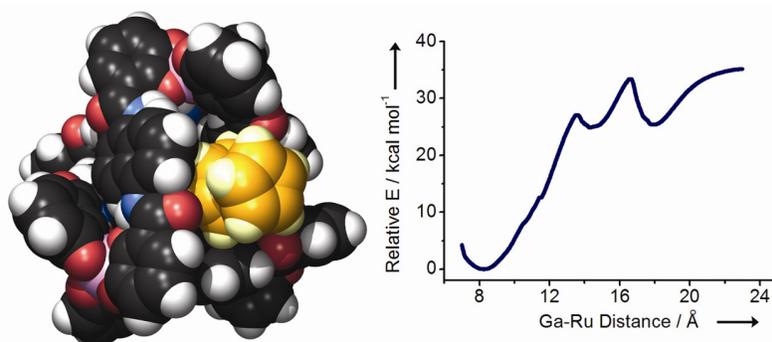
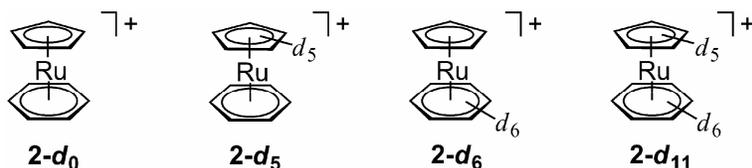


Figure 2. Calculations (MM3, CAChe) of the displacement of **2-d₀** from host **1** were carried out by increasing the distance between the Ru atom of **2-d₀** and a Ga atom of **1**.¹⁸ The calculated transition state (left) and energy profile (right) for the displacement process are shown. The increase in energy after guest ejection (>18 Å) is due to charge separation in the gas phase.

A series of **2-d_n** isotopologues (Scheme 1) and the corresponding $[\mathbf{2-d}_n \subset \mathbf{1}]^{11-}$ (where \subset denotes encapsulation) host-guest complexes were prepared. A D_2O solution of $[\mathbf{2-d}_n \subset \mathbf{1}]^{11-}$ was subjected to an excess of the more strongly binding guest PET_4^+ (under conditions sufficient for saturation in PET_4^+ , see supporting information) and the rate of guest exchange as PET_4^+ displaces the encapsulated **2-d_n** was followed by ^1H NMR. 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 K₂CO₃, pD 12.2) and unbuffered (pD 9) D₂O 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.



Scheme 1. [CpRu(η^6 -benzene)]- d_n^+ (**2-d_n**) guest isotopologues.

guest	unbuffered conditions ^a			buffered conditions ^b		
	k_{obs} ($\times 10^{-4}$ s ⁻¹)	k_{d_0}/k_{d_n}	IE/D(%) ^c	k_{obs} ($\times 10^{-4}$ s ⁻¹)	k_{d_0}/k_{d_n}	IE/D(%) ^c
2-d₀	6.15(4)	-	-	6.31(6)	-	-
2-d₅	6.28(5)	0.98(1)	0.4(2)	6.65(5)	0.95(1)	1.0(2)
2-d₆	6.60(5)	0.932(9)	1.2(2)	6.69(8)	0.94(1)	1.0(3)
2-d₁₁	6.92(4)	0.888(8)	1.1(2)	6.99(7)	0.90(1)	0.9(3)

Table 1. Average observed rate constants (k_{obs} ; reported as the weighted average of multiple kinetic experiments) kinetic isotope effects (k_{d_0}/k_{d_n}) and percent isotope effect per deuterium atom (IE/D) for ^a unbuffered (pD 9) and ^b buffered (100 mM K₂CO₃, pD 12.2) kinetic experiments monitoring the displacement of **2-d_n** from **1** by PET₄⁺ at 55 °C. ^c IE/D(%) = $[1 - (k_{d_0}/k_{d_n})^{1/n}] \times 100$, where n is the number of deuterium atoms.

These kinetic experiments show that deuteration of guest **2-d_n** results in faster displacement from the interior cavity 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 nearly all identical within experimental error, 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 **2-d₀** versus **2-d₆** was also measured and found to be $K_{d_0}/K_{d_6} = 0.96(1)$ (see supporting information), 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 at the transition state.

The rate accelerations observed upon deuteration of guest **2-d_n** 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, 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 which invokes changes in only C-H/D force constants and ZPEs (Figure 3) and allows for contributions to the IE from all C-H/D motions.^[22] As the guest **2-d_n** moves along the reaction coordinate to the transition state for guest exchange, the vibrational force constants of the aromatic C-H/D bonds increase due to constrictive interactions with the walls of **1** at the sterically strained transition state. This increase in force constants increases the energy difference between C-H and C-D ZPEs at the transition state, relative to the ground state, resulting in the observed inverse KIE. The ZPE model allows for contributions to the IE from all C-H/D vibrational modes. This type of analysis should be preferred in complex molecular systems such as these which are too large to be treated accurately with DFT-level calculations that can determine specific vibrational frequencies.

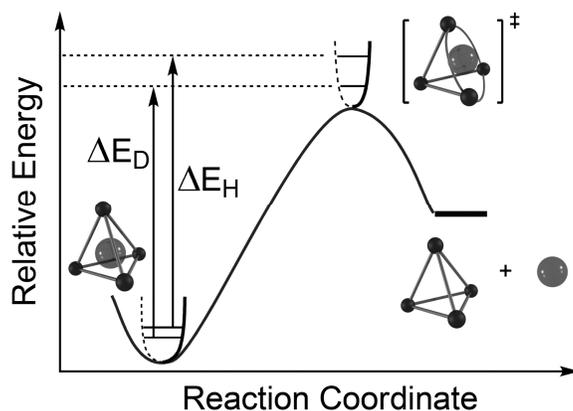


Figure 3. Proposed reaction coordinate diagram for the displacement of a guest from host **1**. An increase in guest C-H/D force constants when constricted at the strained transition state drives the CH and CD ZPEs further apart relative to the ground state, resulting in a larger activation energy for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

In conclusion, we have observed KIEs of up to 11% ($k_{d_0}/k_{d_n} = 0.89$) in the displacement reaction of guest **2-d_n** from the interior of the supramolecular host assembly **1**. We attribute the KIEs observed in the host-guest exchange process to differences in the relative C-H and C-D ZPEs resulting from an increase in guest C-H/D vibrational force constants 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 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.

References

- [1] Kohen, A.; Limbach, H. *Isotope Effects in Chemistry and Biology*; Taylor & Francis Group, LLC, 2006.
- [2] Wade, D. *Chem. Biol. Interact.* **1999**, *117*, 191-217.
- [3] Kuchitsu, K.; Bartell, L. S. *J. Chem. Phys.* **1962**, *36*, 2470-2481.
- [4] Allinger, N. L.; Flanagan, H. L. *J. Comp. Chem.* **1983**, *4*, 399-403.
- [5] Dunitz, J. D.; Ibberson, R. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1-4.
- [6] Melander, L.; Carter, R. E. *J. Am. Chem. Soc.* **1964**, *86*, 295-296.
- [7] Mislow, K.; Graeve, R.; Gordon, A. J.; Wahl, G. H., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1733-1741.
- [8] Sherrod, S. A.; Costa, R. L.; Barnes, R. A.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1565-1577.
- [9] Felder, T.; Schalley, C. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 2258-2260.
- [10] These types of KIEs have classically been explained in terms of a difference between C-H/D bond distances (a consequence of the anharmonicity of the potential function and the different zero point energies of the C-H/D bonds) and this is the context in which we frame our introduction. As we subsequently describe, these IEs are more fully explained by changes in force constants and the differences in coupling of C-H/D vibrational modes with the host deformation.
- [11] Caulder, D. L.; Powers, R. E.; Parac, T. N.; Raymond, K. N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1840-1843.
- [12] Pluth, M. D.; Johnson, D. W.; Szigethy, G.; Davis, A. V.; Teat, S. J.; Oliver, A. G.; Bergman, R. G.; Raymond, K. N. *Inorg. Chem.* **2008**, *48*, 111-120.
- [13] Parac, T. N.; Caulder, D. L.; Raymond, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 8003-8004.
- [14] Fiedler, D.; Pagliero, D.; Brumaghim, J. L.; Bergman, R. G.; Raymond, K. N. *Inorg. Chem.* **2004**, *43*, 846-848.
- [15] Biros, S. M.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12094-12095.
- [16] Hastings, C.; Pluth, M. D.; Biros, S. M.; Bergman, R. G.; Raymond, K. N. *Tetrahedron* **2008**, *64*, 8362-8367.
- [17] Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2005**, *38*, 349-358.
- [18] Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2009**, *42*, 1650-1659.
- [19] Davis, A. V.; Raymond, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 7912-7919.
- [20] Davis, A. V.; Fiedler, D.; Seeber, G.; Zahl, A.; van Eldik, R.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 1324-1333.
- [21] Leung, D. H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 9781-9797.
- [22] Hayama, T.; Baldrige, K. K.; Wu, Y.-T.; Linden, A.; Siegel, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 1583-1591.