ORGANIC LETTERS

2007
Vol. 9, No. 15
2883−2886

Isotope Effects as Probe of *Constrictive* and *Intrinsic* Binding in Hemicarceplexes

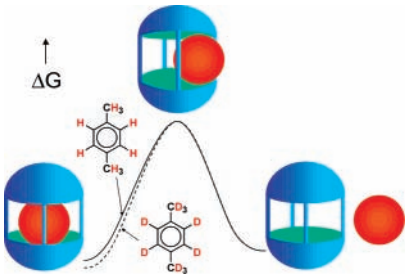
Yong Liu[†] and Ralf Warmuth*

Department of Chemistry and Chemical Biology, Rutgers—The State University of New Jersey, Piscataway, New Jersey 08854

warmuth@rutgers.edu

Received May 10, 2007

ABSTRACT



Kinetic isotope effects (KIE) of hemicarceplex dissociation for naphthalene and *p*-xylene hemicarceplexes with partially and fully deuterated guests have been measured. The KIEs are consistent with the absence of steric effects in the transition states of hemicarceplex dissociation, which supports an earlier interpretation of constrictive binding energy in hemicarceplexes as being primarily controlled by different forms of gating.

Hemicarceplexes and rotaxanes have in common the mechanical bonding (constrictive binding) between host and guest or wheel and dumbbell, respectively.[1] Cram defined constrictive binding energy in hemicarceplexes as the steric interactions that a guest encounters during passage through one of the host's size-restricted openings.[2] In rotaxanes, it is the energy needed to slip the wheel over the dumbbell's stopper.[3] Constrictive binding prevents diffusional dissociation of the complexes even in the absence of intrinsic binding interactions (Figure 1).[2]

Constrictive binding in hemicarceplexes is partially controlled by gating. In a series of computational experiments, Houk and co-workers analyzed hemicarceplex dissociation and identified different forms of gating.[4] Gating enlarges one or more openings in the host shell through conformational changes involving the OCH_2O spanners (French door gating) and the linkers (Sliding door gating and unwrapping). Beyond this, steric interactions resulting from a mismatch between the shape and size of the portal and the guest's cross-section and solvent effects become important.[5]

An interesting way to probe constrictive binding is measuring steric kinetic isotope effects (SKIE). The physical origin for a steric isotope effect is the smaller zero point energy (ZPE) of the C−D bond as compared to that of a C−H bond. In combination with the anharmonicity of the vibrational potential, this decreases the mean bond length and vibrational amplitude upon isotopic substitution leading

[†] Current address: Early Development Analytical Research, Merck Research Laboratories, RY818-C204, Rahway, NJ 07065.

(1) Fyfe, M. C. T.; Raymo, F. M.; Stoddart, J. F. In *Stimulating Concepts in Chemistry*; Voegtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, Germany, 2000; pp 211−220.

(2) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717−7727.

(3) Raymo, F. M.; Houk, K. N.; Stoddart, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 9318−9322.

(4) (a) Nakamura, K.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 1853−1854. (b) Houk, K. N.; Nakamura, K.; Sheu, C.; Keating, A. E. *Science* **1996**, *273*, 627−629. (c) Sheu, C.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 8056−8070.

(5) (a) Cram, D. J.; Blanda, M. T.; Paek, K.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7765−7773. (b) Yoon, J.; Cram, D. J. *Chem. Commun.* **1997**, 1505−1506.

10.1021/ol071090g CCC: $37.00
Published on Web 06/26/2007

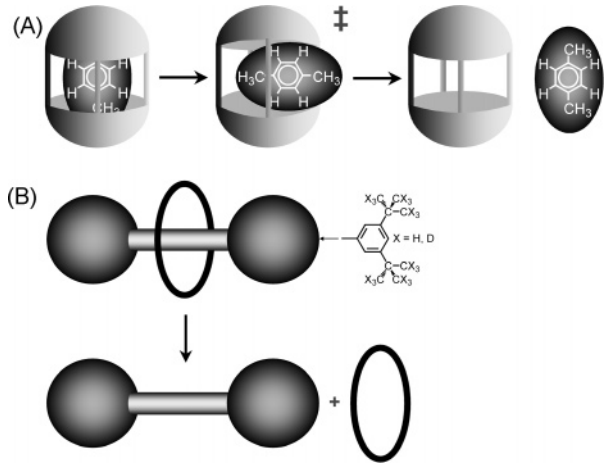


Figure 1. Dissociation of hemicarceplexes (A) and rotaxanes (B) involving the breaking of a mechanical bond.

to a bond length difference of ~0.005 Å.[6,7] In fact, KIEs on the deslipping reaction of rotaxanes have been reported recently by Schalley and support high sensitivity of the constrictive binding energy toward changes in the cross-section of the stoppers (Figure 1B).[8]

Here, we report kinetic isotope effects (KIEs) on hemicarceplex dissociation, which show major differences between constrictive binding in rotaxanes and hemicarceplexes and which further support the importance of gating for the kinetic stability of hemicarceplexes.

In light of the substantial KIE ($k \sim 0.91$) for the deslipping reaction of rotaxanes,[8] we were surprised to find no difference in the dissociation rate constants of hemicarceplexes **1⊙Naph** and **1⊙Naph**-d_8 (Figure 2), even though the barrier

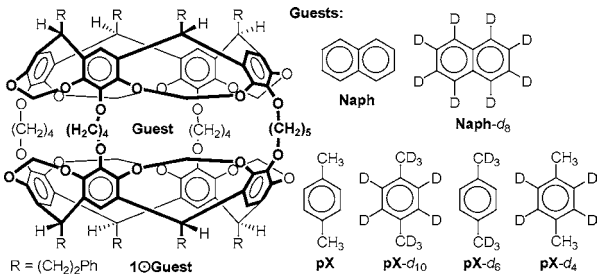


Figure 2. Isotopomeric hemicarceplexes.

(E_a = 24 kcal/mol) is similar to that of the deslipping (Figure S17, Supporting Information). Furthermore, when we investigated *p*-xylene hemicarceplexes **1⊙pX** and **1⊙pX**-d_{10}, it was the larger nonlabeled guest that escaped the fastest, even though the measured KIE was very small k_H/k_D = 1.05 (Table 1, Figure 3). NMR experiments support that hemicarceplex dissociation in nitrobenzene yields **1**⊙nitrobenzene. Mechanistically, this guest exchange can proceed via a slow, rate-determining decomplexation yielding empty **1** followed by a fast complexation of one solvent molecule **S** (eq 1).[9]

Table 1. Dissociation Rate Constant k_{diss} (s^{-1}) of *p*-Xylene Hemicarceplexes at 120 °C in Nitrobenzene and KIE (k_H/k_D)

hemicarceplex	k_{diss} ($\times 10^{-4}$)	Δk_{diss} ($\times 10^{-4}$)	isotopomer pair	k_H/k_D
1⊙pX	1.868	0.018	H10/D10	1.05
1⊙pX-d_4	1.848	0.015	H10/D6	1.05
1⊙pX-d_6	1.785	0.016	D4/D10	1.04
1⊙pX-d_{10}	1.775	0.019	D6/D10	1.01
			H10/D4	1.01
1⊙pX[a]	3.5	0.1		

[a] In mesitylene-d_{12}/4-chlorotoluene (50:1 v/v).

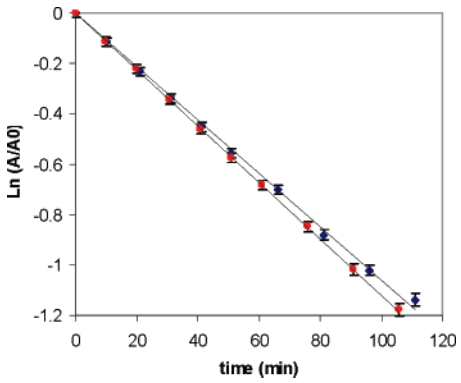


Figure 3. Semilogarithmic kinetic plots for the decomplexation of **1⊙pX** (red) and **1⊙pX**-d_{10} (blue) at 120 °C in nitrobenzene.

Alternatively, a solvent molecule may enter **1** to form a transient termolecular complex **1⊙Guest+S** followed by egress of the guest (eq 2). If the first step were rate-determining, the latter mechanism could explain the absence of steric isotope effects in hemicarceplex dissociation.

$$\mathbf{1{\odot}Guest} \xrightarrow[\text{slow}]{-\mathbf{Guest}} \mathbf{1} \xrightarrow[\text{fast}]{+\mathbf{S}} \mathbf{1{\odot}S} \qquad (1)$$

$$\mathbf{1{\odot}Guest} \xrightarrow{+\mathbf{S}} \mathbf{1{\odot}Guest{+}S} \xrightarrow{-\mathbf{Guest}} \mathbf{1{\odot}S} \qquad (2)$$

We dismiss mechanism (2) based on the fact that in mesitylene-d_{12}/4-chlorotoluene (50:1 v/v) decomplexation of **1⊙pX**, which yields **1**⊙4-chlorotoluene, is faster than in nitrobenzene (Table 1). If mechanism (2) would operate, the reaction should have been substantially slower, since mesitylene is too large to fit into **1** and the concentration of

(6) Wade, D. *Chem. Biol. Interact.* **1999**, *117*, 191−217. (b) Lacks, D. J. *J. Chem. Phys.* **1995**, *103*, 5085−5090.

(7) (a) Bartell, L. S.; Kuchitsu, K.; deNeui, R. J. *J. Chem. Phys.* **1961**, *35*, 1211−1218. (b) Bates, F. S.; Keith, H. D.; McWhan, D. B. *Macromolecules* **1987**, *20*, 3065−3070. (c) Liu, Y.; Warmuth, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 7107−7110.

4-chlorotoluene is 65-fold lower than that of nitrobenzene in neat nitrobenzene. The latter observations also exclude a third mechanism, in which guest egress and solvent encapsulation take place simultaneously.

In order to account for the measured KIEs with mechanism (1), we initially considered that a binding isotope effect (BIE) may have compensated the expected steric effects in the transition state (TS). A BIE that decreases the barrier of the unlabeled relative to that of the deuterated guest may arise from blue-shifted C−H···π-interactions in the ground state that are lost in the TS.[11] This increases the ZPE difference in the ground state relative to that of the TS. For example, Rebek and co-workers observed recently an equilibrium isotope effect between social isomers A and B, which was explained with blue-shifted C−H···π-interactions between the guest's methyl group and the resorcinarene π-faces as opposed to red-shifted C−H···Cl interactions between the two guests (ΔZPE = $1/2\Delta\Sigma h\nu_i$ = 59 cm^{-1}; Figure 4).[12,13]

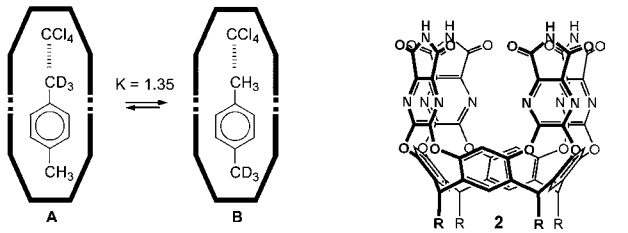


Figure 4. Equilibrium isotope effects in social isomers $\mathbf{2}_2$ + *p*-xylene-d_3 + CCl_4 (**A** and **B**).[11,12]

Complexation-induced upfield shifts of guest protons in the *p*-xylene hemicarceplex suggest that the guest's methyl groups are located inside a host's cavitand and are able to form similar C−H···π-interactions. Loss of these interactions in the TS region may have caused the inverted SKIE in the hemicarceplex (Figure 1A). In order to dissect contributions of the aryl C−H/D bonds, which should lead primarily to different steric interactions in the TS, from those of the methyl groups, we included hemicarceplexes **1**⊙**pX**-d_4 and **1**⊙**pX**-d_6, with partially deuterated guests in our investigation (Table 1). The essentially identical dissociation rate constants for **1**⊙**pX**-d_4 and **1**⊙**pX** and for **1**⊙**pX**-d_6 and **1**⊙**pX**-d_{10} must be interpreted with the absence of SKIEs in the dissociation of the *p*-xylene hemicarceplex and also of the naphthalene hemicarceplex. This suggests that steric interactions in the TS are minimal in hemicarceplexes of this kind and supports Houk's interpretation of constrictive binding energy in hemicarceplexes as being primarily controlled by conformational changes of the host (gating).[4] Indeed, Houk's approach for computing constrictive binding energy supports that French door gating substantially lowers the dissociation barrier for both hemicarceplexes (Figures S18 and S19, Supporting Information).[4c] Thus, contrary to rotaxanes, in which steric interactions between wheel and stopper strongly contribute to the height of the constrictive barrier, the dissociation rate of hemicarceplexes at elevated temperature is primarily controlled by changes in host conformational energy required to enlarge an opening in the host shell such that guest passage is essentially without friction.

The second interesting observation of this extended study is the very small isotope effect for pairs **1**⊙**pX**/**1**⊙**pX**-d_6 and **1**⊙**pX**-d_4/**1**⊙**pX**-d_{10} ((KIE = 1.05 and 1.04, Table 1). These KIEs probe the difference in the interactions of methyl C−H bonds in ground and transition state and are about 1 order of magnitude smaller than the equilibrium isotope effect (K = 1.35) observed between social isomer **A** and **B** (Figures 1A and 4).[12]

An IR analysis of **1**⊙**pX**-d_4, **1**⊙**pX**-d_6, and **1**⊙**pX**-d_{10} shows that incarceration results only in a very small net blue-shift of the CD_3 stretching vibrations relative to those in CCl_4 consistent with the very small KIE in pairs **1**⊙**pX**/**1**⊙**pX**-d_6 and **1**⊙**pX**-d_4/**1**⊙**pX**-d_{10} (Table 2).[14] Even though other internal and intermolecular vibrational modes, which could not be analyzed in our case, also contribute to the ZPE difference,[11] our results point toward considerable differences in the binding modes of hydrocarbon guests inside Rebek's self-assembled capsules and Cram's hemicarcerands. Both belong formally to the same family. Yet, small structural and electronic differences between both resorcinarenes

Table 2. C−D-stretching Vibrations (cm^{-1}) of Free and Encapsulated *p*-Xylene Isotopomers and Encapsulation Induced Shift (in Parentheses)[a]

hemi-carceplex	ν(CD) B_{3u}	ν(CD) B_{2u}	$\nu_{as}(CD_3)_{ip}$	$\nu_{as}(CD_3)_{oop}$	$\nu_s(CD_3)$
pX-d_4[b]	2268	2245			
1⊙**pX**-d_4	2266	2251			
	(−2)	(+6)			
pX-d_6[b]			2229	2207	2131
1⊙**pX**-d_6			2243	2195	2129
			(+14)	(−12)	(−2)
pX-d_{10}	2269	2242	*c*	2206	2120
1⊙**pX**-d_{10}	*c*	*c*	*c*	2197	2118
				(−9)	(−2)

[a] Assignment based on ref 10 and DFT calculations. [b] Reference 10. [c] Frequency could not be determined due to overlap.

(8) Felder, T.; Schalley, C. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2258−2260.

(9) Formation of **1**⊙nitrobenzene by heating empty **1** in nitrobenzene to 120 °C is orders of magnitude faster than the measured dissociation rate constants in Table 1.

(10) Julien-Laferriere, S.; Lebas, J.-M. *Spectrochim. Acta, Part A* **1971**, *27A*, 1337−1350.

(11) Zhao, Y.-L.; Houk, K. N.; Rechavi, D.; Scarso, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 11428−11429.

(12) Rechavi, D.; Scarso, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 7738−7739.

(13) For spectroscopic observation of CH···π-interactions in gas-phase benzene complexes, see: Hobza, P.; Špirko, V.; Havlas, Z.; Buchhold, K.; Reimann, B.; Barth, H.-D.; Brutschy, B. *Chem. Phys. Lett.* **1999**, *299*, 180−186.

(14) Essentially no differences in the frequency of the C−D stretching vibrations of **pX**-d_{10} in nitrobenzene and CCl_4 were observed.

resulting from the different spanners and different restriction of the guest's tumbling motions by the capsule express themselves in the CH$\cdots\pi$-interactions between host and guest.

Acknowledgment. We thank Mr. Xuejun Liu (Rutgers, The State University of New Jersey, Piscataway, NJ) for recording MALDI-MS spectra and the National Science Foundation for support of this research (Grant No. CHE-0518351).

Supporting Information Available: Experimental procedures, compound characterization, FT-IR, ^{1}H and ^{13}C NMR spectra of hemicarceplexes, kinetic plots, and energy surfaces for hemicarceplex dissociation. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071090G