A cavitand stabilizes the Meisenheimer complex of S_NAr reactions†

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A deep cavitand binds amine nucleophiles and accelerates their subsequent S_NAr reactions by solvating the intermediate Meisenheimer complex.

Deep cavitands offer hosts with an organized gradient of solvent polarity for guests. The bottom of the cavity is composed of rigid aromatic walls and is nonpolar, while the upper rim features secondary amides and is polar.[1] The amides are capable of donating or accepting hydrogen bonds through simple rotations about single bonds. Accordingly, the microenvironment of the cavitand is poised to perturb reaction rates relative to those occurring in bulk solvent outside and we report here its effects on nucleophilic aromatic substitution (S_NAr) reactions.

These reactions have long been known to exhibit strong solvent effects as a result of the dipolar nature of the Meisenheimer complex intermediate and the transition states that flank it.[2] For the reaction of neutral nucleophiles with electron poor aromatics, the rates of S_NAr adduct formation increase with increasing solvent polarity:[2,3] reactions in DMSO, for example, are 50 times faster than those in cyclohexane.[3] Here we compare the influence of the supramolecular host **1** (Fig. 1) relative to reactions occurring in the nonpolar, bulk solvent *p*-xylene. A clear enhancement in rates of reaction of amine nucleophiles surrounded by **1** was observed. We propose this effect largely results from the ability of the secondary amide groups of the cavitand interior to solvate the charges developing in the transition state.

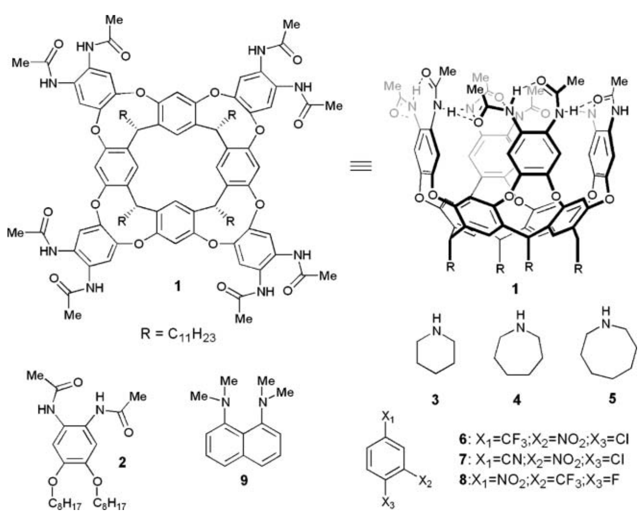

Fig. 1 Cavitand host, wall mimic, amine guests, and aromatic substrates.

The binding of amines **3–5** (Fig. 1) in **1** was demonstrated by proton NMR resonances in the far upfield region of the spectra. The 8 aromatic host walls bestow magnetic shielding effects on the amine guest. Guest **3** has low affinity, K_a = 14 M^{-1} for the host and the larger amines **4** and **5** show K_a's of 40 M^{-1}. Though the affinities are low, the barriers to exchange are high and separate signals are seen for free and bound guests in the spectra. The patterns of the bound guest resonances require that the amine nitrogens are near the open end of **1**, in the circle of amides of the host (Fig. 2).

The S_NAr reactions were followed by ^1H NMR, in the absence or presence of stoichiometric amounts of **1** in d_{10}-*p*-xylene. For reactions in the presence of **1**, separate signals were also observed for the bound and free S_NAr products (Fig. 3, example of reaction between **4** and **6**). Initial formation of S_NAr adducts at sub-millimolar concentrations led to the immediate displacement of encapsulated amines due to the stronger binding of the products to **1** (Fig. 3). Accordingly, product inhibition precludes efficient turnover (true catalysis). Furthermore, the generation of acid during the course of the S_NAr reactions led to protonated amine reactants which also compete strongly for cavitand binding (Fig. 3). To remove this complication, all experiments were carried out in the presence of "proton sponge" **9**.

The initial rate (velocity) of product formation, V_{ctrl}, was 0.21 mM h^{-1} for the background reaction of piperidine **3** with **6**, and an accelerated rate, V_{acc}, of 2.7 mM h^{-1} was observed in the

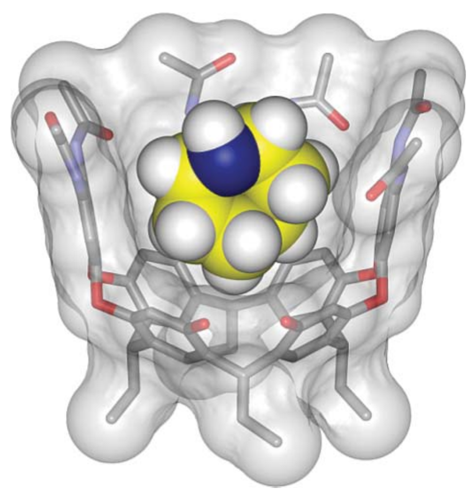

Fig. 2 Molecular model of encapsulated **4** with front cavitand wall removed for viewing ease (Spartan, molecular mechanics force field).

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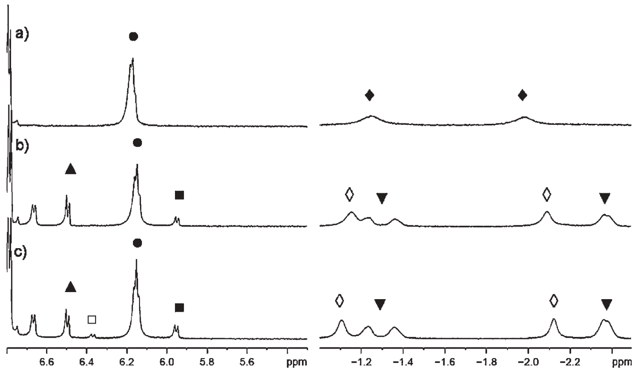

Fig. 3 Progress of S_NAr reaction between **4** and **6** in the presence of **1** as followed by ^1H NMR (600 MHz, d_{10}-*p*-xylene, 300 K). a) t = 0, before addition of **6**; b) t = 17 min; c) t = 98 min (●: methine protons of **1** vase; ♦: encapsulated **4**; ▲: starting material **6**; ■: aromatic proton of bound S_NAr product; □: aromatic proton of free product; ◇: bound **4** in fast exchange with protonated bound **4**; ▼: encapsulated product).

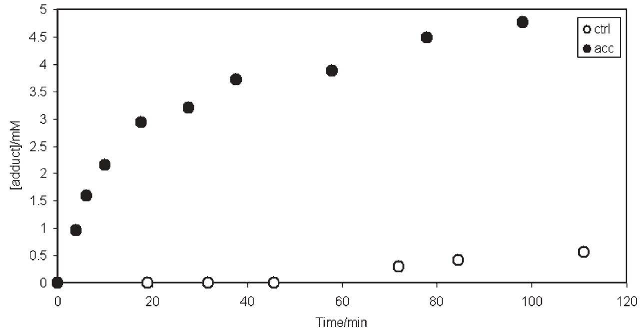

Fig. 4 Acceleration of S_NAr reaction between **4** and **6** with **1**. Conditions: [**1**] = 10 mM; [**4**] = 21 mM; [**6**] = 10 mM; [**9**] = 21 mM (○: background reaction (ctrl) in the absence of **1**; ●: accelerated reaction (acc)).

presence of **1**, corresponding to a 12-fold rate enhancement (Table 1). Additionally, a V_{ctrl} of 3.5 mM h^{-1} for the reaction of **3** with **7** was obtained, while V_{acc} was too fast to determine accurately by NMR, indicating a significant rate enhancement (Table 1). In order to trace the acceleration to the inner microenvironment of **1**, rather than the increased concentration of polar amides in solution, the reaction of **3** with **6** was followed in the presence of four equiv. of cavitand wall mimic **2** (Fig. 1). The rate in the presence of **2** was identical to the background rate, confirming the specific effect of the host cavity on the rate (see supporting information).

Molecular modeling suggests hydrogen bonding interactions are possible between the amides of **1** and the *ortho* NO_2 substituent of the anionic portion of the intermediate formed from **6**. To probe this possibility, we investigated the influence of **1** on the reaction of **3** with **8**. In **8**, the *para* NO_2 substituent is too far away from the amides of **1** to hydrogen bond. In this case, an S_NAr reaction was observed only in the presence of **1** (Table 1), indicating that rate acceleration does not result solely from interactions with the *ortho* NO_2 groups.

The reaction of amines **3**–**5** with substrate **6** in the absence of **1** had identical reaction rates (Table 1). However, with the stronger binding nucleophiles **4** and **5**, initial rate enhancements were accelerated by ~40 to ~70-fold in the presence of **1**, with the greatest enhancement observed for the reaction of **4** with **6** (Table 1, Fig. 4). The accelerated rate constants, k_{acc}, were determined for S_NAr reactions with substrate **6** by regression analysis using KinTekSim software.[4] The accelerated rate constants were 100–400 times greater than those of the background rate constants, k_{ctrl}. We attribute this to the ability of the polar amide upper rim to stabilize the dipolar TS (Fig. 5).[5] Cation–π interactions between the aromatic walls of **1** and the developing positive charge on the amine may also play a role.[6]

A mechanistic interest in the solvent dependency of S_NAr reactions is apparent in the literature.[7] In the present work, we have shown for the first time the influence of a polar supramolecular environment on these classic reactions, and report an accelerating effect, and combined molecular recognition with enhancement of chemical reactivity.[8] The stabilization of polar transition states with polar groups in enzyme acitve sites is well-documented,[9] even for Meisenheimer intermediates.[10] Accordingly, this work is of relevance to enzyme mimetics.

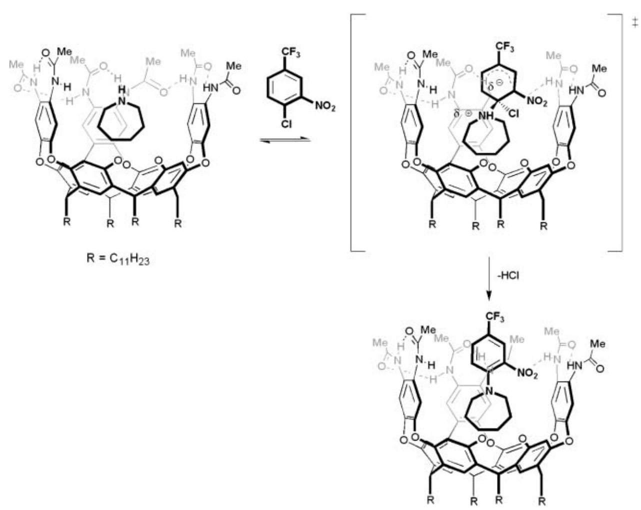

Fig. 5 S_NAr reaction between **4** and **6** in **1**.

Table 1 Initial rates (V) and rate constants (k) for accelerated (acc) and control (ctrl) S_NAr reactions[a]

Rxn	V_{acc}/mM h^{-1}	V_{ctrl}/mM h^{-1}	V_{acc}/V_{ctrl}	k_{acc}/M^{-1} s^{-1} [d]	k_{ctrl}/M^{-1} s^{-1}	k_{acc}/k_{ctrl}
3 + **6**	2.6	0.21	12	0.03	0.0003	100
3 + **7**	n.d.[b]	4.4	n.d.	n.d.	0.006	n.d.
3 + **8**	0.27	n.r.[c]	n.d.	n.d.	n.r.	n.d.
4 + **6**	14	0.21	67	0.12	0.0003	400
5 + **6**	7.3	0.21	35	0.06	0.0003	200

[a] In d_{10}-*p*-xylene at 300 K; accelerated reactions were carried out with stoichiometric **1**. [b] Too fast to monitor by NMR, even at 288 K. [c] No reaction over 4 days. [d] Error limit ±30%, as determined by fitting error.

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Notes and references

1 D. M. Rudkevich, G. Hilmersson and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 12216.

2 (*a*) P. M. E. Mancini, R. D. Martinez and L. R. Vottero, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1133; (*b*) N. S. Nudelman, *J. Chem. Soc., Perkin Trans. 2*, 1987, 951; (*c*) J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, 1955, **77**, 5051.

3 C. Reichardt, in *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, Germany, 2003, pp. 173–174.

4 K. S. Anderson, J. A. Sikorski and K. A. Johnson, *Biochemistry*, 1988, **27**, 7395.

5 L. Forlani, *J. Phys. Org. Chem.*, 1999, **12**, 417.

6 (*a*) F. Hof, L. Trembleau, E. C. Ullrich and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2003, **42**, 3150; (*b*) P. Ballester, A. Shivanyuk, A. R. Far and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 14014.

7 (*a*) O. Banjoko and I. A. Babatunde, *Tetrahedron*, 2004, **60**, 4645; (*b*) P. M. E. Mancini, A. Terenzani, C. Adam and L. R. Vottero, *J. Phys. Org. Chem.*, 1999, **12**, 430; (*c*) P. M. Mancini, G. Fortunato, C. Adam, L. R. Vottero and A. J. Terenzani, *J. Phys. Org. Chem.*, 2002, **15**, 258; (*d*) N. S. Nudelman, M. Savini, C. E. S. Alvaro, V. Nicotra and J. Yankelevich, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1627; (*e*) O. Acevedo and W. L. Jorgensen, *Org. Lett.*, 2004, **6**, 2881; (*f*) C. Arnone, G. Consiglio, V. Frenna and D. Spinelli, *J. Org. Chem.*, 1997, **62**, 3093; (*g*) O. Banjoko and I. A. Babatunde, *Tetrahedron*, 2005, **61**, 8035; (*h*) J. Rebek, Jr., *Tetrahedron*, 1979, **35**, 723.

8 (*a*) S. Richeter and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 16280; (*b*) A. Gissot and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 7424; (*c*) B. W. Purse, A. Gissot and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2005, **127**, 11222; (*d*) Y. Zhu and D. G. Drueckhammer, *J. Org. Chem.*, 2005, **70**, 7755; (*e*) J. Wolfe, A. Muehldorf and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1991, **113**, 1453; (*f*) T. S. Snowden, A. P. Bisson and E. V. Anslyn, *J. Am. Chem. Soc.*, 1999, **121**, 6324; (*g*) R. Grotzfeld, N. Branda and J. Rebek, Jr., *Science*, 1996, **271**, 487.

9 For examples, see: (*a*) A. Kienhöfer, P. Kast and D. Hilvert, *J. Am. Chem. Soc.*, 2003, **125**, 3206; (*b*) D. C. Carlow, S. A. Short and R. Wolfenden, *Biochemistry*, 1998, **37**, 1199; (*c*) H. Park and S. Lee, *J. Chem. Theory Comput.*, 2006, **2**, 858; (*d*) D. T. Major, K. Nam and J. Gao, *J. Am. Chem. Soc.*, 2006, **128**, 8114.

10 M. M. Benning, K. L. Taylor, R.-Q. Liu, G. Yang, H. Xiang, G. Wesenberg, D. Dunaway-Mariano and H. M. Holden, *Biochemistry*, 1996, **35**, 8103.