A Deep Cavitand Provides a Structured Environment for the Menschutkin Reaction

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The Menschutkin reaction[1] results in the formation of quaternary ammonium salts by the action of alkyl electrophiles on tertiary amines. It has been studied extensively as a model S_N2 reaction because the charge that develops as the reaction proceeds makes the reaction's rate particularly sensitive to solvent.[2] Rate constants vary by orders of magnitude across a range of solvent polarity. Supramolecular chemistry provides many capsular host molecules which are ordered solvent cages for small guest molecules.[3] These structured environments can act to stabilize reactive species,[4−6] impart selectivity on reactions by geometric constraint,[7,8] and accelerate reactions.[8−14] We used the Menschutkin reaction to study the effects of structured environments[15−18] offered by cavitand **1** (Figure 1). Quinuclidine is bound within **1** and reacts with a variety of electrophiles; we report that the host facilitates the Menschutkin reaction, and we interpret the effect in terms of the reaction's fixed environment.

Cavitand **1** forms complexes with molecules of appropriate size, shape, and chemical complementarity.[19,20] The interior of the cavity is a π-electron rich surface similar to an ordered cage of benzene molecules. In contrast, the upper rim is a polar array of eight secondary amides rich in hydrogen bond donors and acceptors. The vase-like conformation is stabilized by a seam of hydrogen bonds that are also in position to interact with a guest molecule. Choline derivatives are among the best guests known for **1** and show association constants greater than 10^3, even in solvents that compete to occupy the cavity. The trimethylammonium "knob" is held by cation/π interactions, and polar groups are attracted to the cavitand's amide chain (Scheme 1.).

At millimolar concentrations, quinuclidine is a good enough guest to compete with acetone solvent; the nonpolar end of quinuclidine is located deep in the cavity (Figure 1). In its resting state, the cavitand is, on average, occupied with two molecules of acetone that exchange rapidly with the bulk solvent (Scheme 1). Through a partial unfolding mechanism, quinuclidine displaces the acetone,[21] with an association constant K_a of 40 M^{-1}. This complex then engages an electrophile RX in an S_N2 reaction, and we labeled this the accelerated rate constant k_{acc}. The product is the complex of an N-alkylquinuclidinium and **1**; it is tightly bound by **1**, with an association constant $K_{a,pdt}$ > 4000 M^{-1} (greater than the detection limits of a 600 MHz NMR spectrometer). In short, product inhibition prevents turnover, and the reactions are not catalytic.

We examined the reaction of the complex with alkyl electrophiles and compared these reactions to those of uncomplexed quinuclidine (Table 1). The electrophiles (16.9 mM) and quinuclidine (16.4 mM) in acetone-d_6 were monitored by NMR. Separate experiments determined the rate of the reaction in the presence and absence (k_{ctrl}) of **1** (12.3 mM). Experimental data were fit to kinetics simulations of the accelerated reaction using KinTekSim,[12−24] and regression analysis gave k_{acc}. The ratio of these rate constants provides a measure of the efficacy of **1** at facilitating the
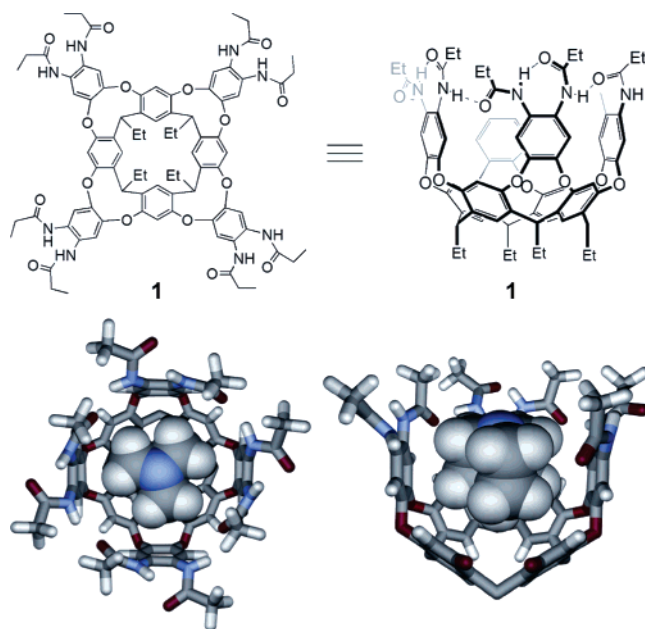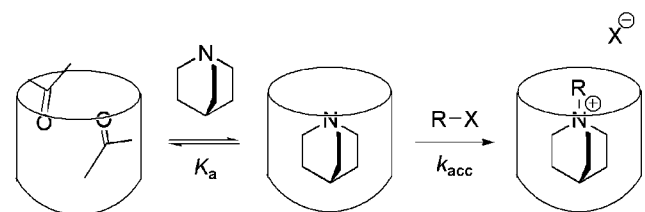

Figure 1. Deep cavitand **1** and an energy-minimized (Maestro; MM+) rendering of its complex with quinuclidine. Ethyl groups have been shown as methyl groups or omitted, and one cavitand wall of the model (side view) has been removed for clarity.

Scheme 1

Menschutkin reactions. A priori, there could have been inhibition of the reaction by the congested environment of the bound quinuclidine's nitrogen. Moreover, the 180° arrangement of nucleophile and leaving group is not without intermolecular steric clashes of alkyl groups and the amides.

Entries 1−4 (Table 1) illustrate the dependence of the rate enhancement on the nature of the leaving group. Bromobutane and chlorobutane exhibit the greatest rate enhancement, followed by butyl mesylate and butyl tosylate. The halide ions as leaving groups are well suited for solvation by the N−H donors of the amide groups at the cavitand periphery. The positive charge that develops on the quinuclidine can be stabilized by the carbonyl oxygens. Of course, a single amide cannot act simultaneously in both roles, but members of the cyclic array need only to twist slightly to bring their appropriate atoms near the reaction site. As the positive charge

Table 1. Alkylation of Quinuclidine in the Presence and Absence of **1**

| entry	electrophile	$k_{acc}/$ $M^{-1}min^{-1}$	$k_{ctrl}/$ $M^{-1}min^{-1}$	k_{acc}/k_{ctrl}
1	butyl chloride	0.44	3.3×10^{-4}	1300
2	butyl bromide	120	0.075	1600
3	butyl mesylate	0.68	4.5×10^{-3}	150
4	butyl tosylate	2.1	0.020	100
5	(bromomethyl)cyclopropane	47	0.065	720
6	neopentyl bromide	b	f	n.d.
7	isopropyl bromide	1.0	9.5×10^{-4}	1000
8	*threo*−2-bromo-3-methoxybutane	c	f	n.d.
9	*erythro*−2-bromo-3-methoxybutane	c	f	n.d.
10	*tert*-butyl bromide	0.014^d	f	n.d.
11	allyl chloride	84	0.11	760
12	allyl bromide	e	e	n.d.
13	benzyl bromide	e	e	n.d.
14	dichloromethane-$d_2{}^a$	0.29	4.3×10^{-4}	670

^{a} Used as solvent. ^{b} No reaction, even at 50 °C. ^{c} No reaction. ^{d} The products are isobutylene and quinuclidine hydrobromide. ^{e} Too fast to measure using this method. ^{f} Not measured. n.d. not determined.

develops on the nitrogen, the weak CH/π interactions between guest and host are "promoted" to stronger cation/π interactions, further stabilizing the transition state. The congested nature of the environment around the nucleophilic site is particularly suited to smaller leaving groups. The much larger mesylate and tosylate groups are less compatible with the mechanism of rate enhancement. When dichloromethane-d_2 was used as a solvent for quinuclidine and **1**, quaternization to yield (chlorodideuteriomethyl)quinuclidinium chloride was observed with a rate constant 670 times greater than that of the background reaction.[18]

A limited tolerance for steric crowding around the electrophilic site was also observed. Isopropyl bromide reacted with a 1000-fold rate constant enhancement, but the *erythro* and *threo* isomers of 2-bromo-3-methoxybutane were too congested to react (in addition to being electronically unfavorable). Bromomethyl cyclopropane reacted with a 720-fold rate constant enhancement, but neopentyl bromide was unreactive, even when heated at 50 °C. *tert*-Butyl bromide did not alkylate quinuclidine, but the cavitand did facilitate the elimination reaction, giving rise to isobutylene and protonated quinuclidinium. Benzyl and allyl bromides were highly reactive toward quinuclidine (the background rates were too fast to measure under these conditions), but allyl chloride showed a 760-fold acceleration.

A molecule **2** was prepared as an analogue of a single wall of cavitand **1**, with octyl chains appended for enhanced solubility. Four equivalents of **2** had no effect on the rate of the Menschutkin reaction of quinuclidine with butyl bromide. Accordingly, the rate enhancement by **1** was truly supramolecular in nature—it relied on the organization of **1** created during its synthesis.

Despite the increased steric congestion at the reaction center the complexed quinuclidine shows large rate accelerations. The organized environment is proposed as the key to the enhanced reactivity at hand. The translational freedom and many of the rotations of the solvent molecules are restricted when incorporated covalently into the host. Cavitand **1** positions both polar and nonpolar nanoenvironments appropriately for quinuclidine's Menschutkin

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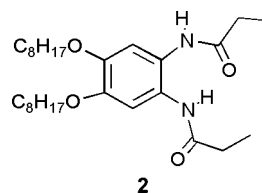
reaction transition state. The nucleophile and electrophile are not confined together by **1** as would be the case in a capsular host. Instead, this supramolecular effect increases the *intrinsic reactivity* of the reactants in a rate-determining step that is second order. These results contribute to a growing body of evidence that the structures providing the physical barriers of container molecules are not merely spectators in the reactions of molecules within molecules.

Supporting Information Available: Detailed descriptions of experimental methods, synthetic procedures, characterization of new compounds, and tabulated kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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