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Dramatic Acceleration of the Menschutkin Reaction and Distortion of Halide Leaving-Group Order

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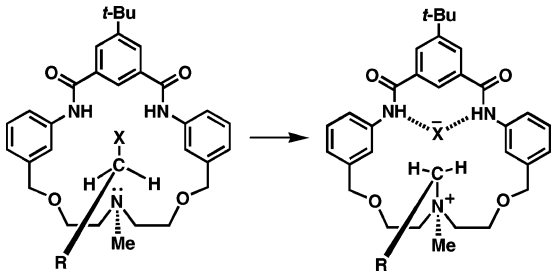

Compared to structurally related linear trialkylamines, a simple macrocyclic amine with an anion-binding cavity exhibits very large rate enhancements ($>10^5$) for stoichiometric N-alkylation with primary alkyl, allyl, and benzyl halides in the weakly polar solvent $CDCl_3$. There is also a major distortion of the halide leaving-group order. For example, with benzyl halides the relative leaving-group order with a control amine is Cl (1) < Br (71) < I (160), whereas the leaving-group order with the macrocyclic amine is I (0.4) < Cl (1) < Br (8.5). Reaction with the macrocyclic amine is inhibited by the addition of DMSO, which is unusual because the Menschutkin reaction is normally enhanced by the presence of a polar aprotic solvent. Competitive inhibition studies indicate that the reaction proceeds through a prereaction complex. Effective molarities for the subsequent unimolecular N-alkylation step with 4-*t*-butylbenzyl halides are 4-*t*-BuBnCl (62 000 M) > 4-*t*-BuBnBr (2200 M) > 4-*t*-BuBnI (35 M); thus, the free energy of activation is selectively decreased for organohalides having smaller and more charge dense leaving groups. Likely reasons for this selective enhancement effect are: (a) increased transition-state stabilization due to hydrogen bonding in the macrocyclic pocket and (b) reduced entropic penalty in the transition state due to an increased fraction of prereaction complexes that are oriented in a near attack conformation. The study suggests that it should be possible to develop highly reactive macrocyclic amines that selectively sense or scavenge carcinogenic haloalkanes from the atmosphere.

Introduction

The quaternization of a trialkylamine is known as the Menschutkin reaction.[1] The reaction is formally an alkyl group transfer, a process of central importance in biochemistry and a widely used strategy in organic synthesis. Numerous physical organic studies have been conducted on the Menschutkin reaction,[2] and it is a useful test system for theoretical methods.[3] To briefly summarize the basic features, two neutral molecules undergo an S_N2 reaction to produce an ion pair, a process that is accelerated by polar aprotic solvents, increased pressure, elevated temperature, and increased leaving-group ability.[4−6]

The literature contains a handful of structured molecular systems that exhibit an accelerated Menschutkin reaction.[7−9]

(1) Menschutkin, N. *Z. Phys. Chem.* **1890**, *6*, 41−57. Note that the chemistry literature contains a substantial number of citations with the German spelling Menschutkin, and also the English spelling Menshutkin.

(2) Abboud, J. M.; Notario, R.; Berrán, J.; Sola, M. H. In *Progress in Physical Organic Chemistry;* Taft, R. W., Ed.; Wiley: New York, 1993; Vol. 19, pp 1−182.

(3) Castejon, H.; Wiberg, K. B. *J. Am. Chem. Soc.* **1999**, *121*, 2139−2146.

(4) Wang, T.; Iou, Q. *Chem. Eng. J.* **2002**, *87*, 197−206.

(5) Abraham, M. H. In *Progress in Physical Organic Chemistry;* Streitwieser, A., Taft, R. W., Eds.; Wiley: New York, 1974; Vol. 11, pp 1−87.

(6) Taft, R. W.; Pienta, N. J.; Kamlet, M. J.; Arnett, E. M. *J. Org. Chem.* **1981**, *46*, 661−667.

(7) Purse, B. W.; Gissot, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 11222−11223.

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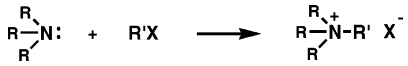
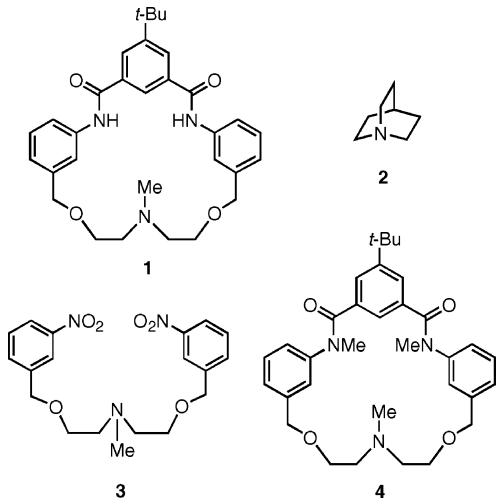


Here, we describe a relatively simple bifunctional macrocycle, **1**, that produces very large rate enhancements. Recently, we discovered that **1** is N-alkylated by methylene chloride solvent with a half-life of 2 min at 298 K, a rate that is about 50 000 times faster than that observed with structurally related, linear amines.[10,11] We have now measured reaction rates with other organohalides, and we find that macrocycle **1** reacts very rapidly with primary alkyl, allyl, and benzyl halides (i.e., RCH_2X). Furthermore, when compared to control amines **2**−**4** there is a major distortion of the halide leaving-group order. Although this nucleophilic substitution reaction is stoichiometric, the unprecedented reactivity of **1** is attributed to its hydrogen-bonding cavity, which produces some enzyme-like properties such as the formation of a prereaction complex and selective rate enhancement for organohalide substrates having smaller and more charge dense leaving groups. The small size of the reactants and the fact that the product is an internally solvated contact ion pair in a weakly polar solvent make it an experimentally and theoretically tractable bimolecular model for testing concepts in organic and enzyme catalysis.



Results and Discussion

Kinetic Studies. The reaction kinetics with 1-propyl, allyl, and 4-*tert*-butylbenzyl (4-*t*-BuBn) halides were monitored by ^{1}H NMR spectroscopy in $CDCl_3$ at 298 K. In each case, the corresponding quaternary ammonium salt was the only product formed, as determined by standard spectroscopic methods and X-ray crystallography. The starting amine concentrations were kept below 10 mM, which avoided kinetic complications due to product precipitation and product inhibition (i.e., noncovalent association of the ion-pair product with the starting amine).[12] Each reaction system exhibited bimolecular kinetics, and pseudo-first-order kinetics was observed when the electrophile was present in large excess. Thus, the reactions are first-order in nucleophilic amine and first-order in electrophilic organohalide.

In the Supporting Information (Table S1) is a listing of all the second-order rate constants that were measured in this study. As expected for an S_N2 process, the electrophile reactivity trend was 4-*t*-BuBn halide > allyl halide > 1-propyl halide.[13] Control amines **3** and **4** have very similar steric and electronic environments as macrocycle **1**, but they lack a hydrogen-bonding pocket. They are relatively unreactive at 298 K, and measurable rates could only be obtained with 4-*t*-BuBn halide as the electrophile. Therefore, the more reactive quinuclidine, **2**, was employed as the control amine with allyl and 1-propyl halides. Tables 1 and 2 show a selection of kinetic data that illustrate the major points. The most obvious result is the extremely high reactivity of macrocycle **1**. For example, reaction of 4-*t*-BuBnCl with macrocycle **1** is 160 000 times faster than that with control amine **3**; smaller rate enhancements are observed with 4-*t*-BuBnBr (12 000) and 4-*t*-BuBnI (220). Listed in Table 2 are leaving-group propensities, as measured by the ratio of rate constants with the different organohalides. The control amines **2**−**4** exhibit typical nucleophilic reactivity, with normal halide leaving-group orders. An example is the reactivity of amine **2**; with 4-*t*-BuBn halides, the relative leaving-group order is Cl (1) < Br (71) < I (160); with allyl halides, the relative leaving-group order is Cl (1) < Br (41) < I (110), and with 1-propyl halides, the relative leaving-group order is Cl (1) < Br (84) < I (140). In contrast, the leaving-group order with macrocycle **1** is very different. For example, with 4-*t*-BuBn halides the leaving-group order I (0.4) < Cl (1) < Br (8.5), which is similar to the order obtained when **1** reacts with allyl halides and 1-propyl halides. Inspection of the rate data shows that macrocycle **1** alters the inherent halide leaving-group order by selectively improving the leaving-group ability of Cl > Br > I (see, for example, the rate constant ratio k(**1**)/k(**3**) in Table 1).[14,15]

Although leaving-group tendencies in an S_N2 reaction are known to change with nucleophilic strength (which alters the structure of the transition state[16]), the large differences in

(8) (a) Heemstra, J. M.; Moore, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 1648−1649. (b) Heemstra, J. M.; Moore, J. S. *J. Org. Chem.* **2004**, *69*, 9234−9237. (c) Smaldone, R. A.; Moore, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 5444−5450.

(9) McCurdy, A.; Jimenez, L.; Stauffer, D. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10314−10321.

(10) Lee, J.-J.; Stanger, K. J.; Noll, B. C.; Gonzalez, C.; Marquez, M.; Smith, B. D. *J. Am. Chem. Soc.* **2005**, *127*, 4184−4185.

(11) For examples of N-alkylation with methylene chloride, see: (a) Nevstad, G. O.; Songstad, J. *Acta Chem. Scand. B* **1984**, *38*, 469−477. (b) Mills, J. E.; Maryanoff, C. A.; Cosgrove, R. M.; Scott, L.; McComsey, D. F. *Org. Prep. Proced. Int.* **1984**, *16*, 97−114. (c) Tal, S.; Salman, H.; Abraham, Y.; Botoshansky, M.; Eichen, Y. *Chem.−Eur. J.* **2006**, *12*, 4858−4862. (d) Ernst, R. D.; Harvey, B. G.; Oteri, O. J.; Arif, A. M. *Z. Kristallogr.* **2005**, *220*, 373−375.

(12) The alkylation products with unsubstituted benzyl halides tended to precipitate very quickly during the reaction; therefore, the more soluble 4-*tert*-butylbenzyl halides were employed instead.

(13) The calculational and kinetic isotope data reported in ref 10 are consistent with a classical S_N2 process, but with some of the organohalides we cannot rule out the possibility that the mechanism may involve two SET steps.

(14) Another example of selective improvement of leaving-group ability in the order Cl > Br > I is the ratio k(**1**)/k(**2**). With 4-*t*-BuBn halides, the values of k(**1**)/k(**2**) are 4-*t*-BuBnCl (55), 4-*t*-BuBnBr (6.5), and 4-*t*-BuBnI (0.15). In other words, 4-*t*-BuBnCl reacts with macrocycle **1** much faster than with **2**, whereas the ratio is reversed with 4-*t*-BuBnI.

(15) The leaving-group ability of fluoride in S_N2 reactions is about 200 times less than that of chloride. (McMurry, J. *Organic Chemistry;* 6th ed., Thomson-Brooks/Cole: Belmont, CA, 2004). The main reason is the high strength of the C−F bond (e.g., bond strengths are CH_3−F 108 kcal/mol, CH_3−Cl 84 kcal/mol, CH_3−Br 70 kcal/mol, and CH_3−I 56 kcal/mol). *t*-BuBnF reacts with macrocycle **1** in $CDCl_3$ with a rate constant of (5.63 ± 0.20) × 10^{-5} M^{-1} s^{-1} at 298 K. In contrast, no reaction with **2** could be detected at 298 K. To provide a point of comparison, the experiments with *t*-BuBnF were repeated at 323 K, where k_{rel}(**1**)/k_{rel}(**2**) = 100, which means that the rate enhancement for fluoride leaving group is greater than that for chloride (100- vs 55-fold).

(16) Lowry, T. H.; Richardson, K. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper: Cambridge, 1987; p 374.

TABLE 1. Second-Order Rate Constants (k) and Free Energies of Activation ($\Delta G^{\ddagger}$) for the Reaction of Macrocycle 1 and Control Amine 3 with 4-*tert*-Butylbenzyl Halides[a]

4-*t*-BuBnhalide	k(**1**) (M^{-1} s^{-1})	$\Delta G_1^{\ddagger}$ (kcal/mol)	k(**3**) (M^{-1} s^{-1})	$\Delta G_3^{\ddagger}$ (kcal/mol)	k(**1**)/k(**3**)	$\Delta\Delta G^{\ddagger}$ (kcal/mol)
4-*t*-BuBnCl	1.02 ± 0.12	17.4	$(6.58 \pm 0.62) \times 10^{-6}$	24.5	160 000	7.1
4-*t*-BuBnBr	8.70 ± 0.43	16.2	$(7.35 \pm 0.92) \times 10^{-4}$	21.7	12 000	5.5
4-*t*-BuBnI	0.44 ± 0.03	17.9	$(1.98 \pm 0.25) \times 10^{-3}$	21.1	220	3.2

[a] In $CDCl_3$ at 298 K.

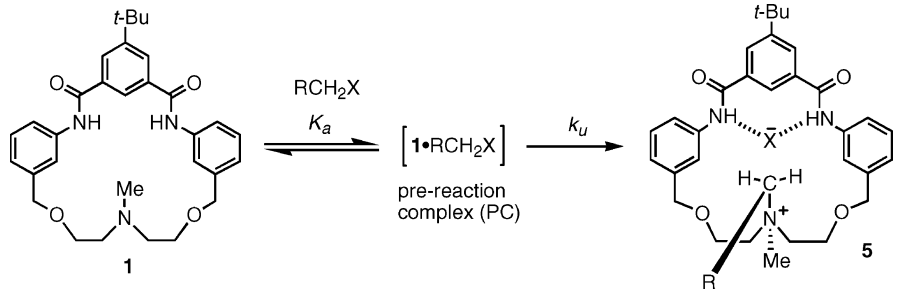


FIGURE 1. Proposed mechanism for reaction of RCH_2X with macrocycle **1**.

TABLE 2. Second-Order Rate Constants (k) and Leaving-Group Propensities[a]

amine	organohalide	k for organochloride (M^{-1} s^{-1})	ratio of rate constants Cl/Cl:Br/Cl:I/Cl
1	4-*t*-BuBn halides	1.02 ± 0.12	1.0/8.5/0.4
1	allyl halides	$(9.79 \pm 0.12) \times 10^{-2}$	1.0/8.4/2.5
1	1-propyl halides	$(4.20 \pm 0.73) \times 10^{-5}$	1.0/4.5/2.9
2	4-*t*-BuBn halides	$(1.87 \pm 0.48) \times 10^{-2}$	1.0/71/160
2	allyl halides	$(5.70 \pm 0.87) \times 10^{-3}$	1.0/41/110
2	1-propyl halides	$(6.40 \pm 0.09) \times 10^{-6}$	1.0/84/140
3	4-*t*-BuBn halides	$(6.58 \pm 0.62) \times 10^{-6}$	1.0/110/300
4	4-*t*-BuBn halides	$(1.95 \pm 0.62) \times 10^{-6}$	1.0/73/[b]

[a] In $CDCl_3$ at 298 K. [b] Not measured.

leaving-group order cannot be attributed solely to altered nucleophilicities, because each nucleophile is an sp^3 hybridized trialkylamine (this assumption is verified by other studies in the literature[4]). A more likely explanation for the observed change in reactivity is that the binding pocket in macrocycle **1** accelerates the reaction and distorts the halide leaving-group order by the mechanism shown in Figure 1. A central feature with this mechanism is association of the electrophilic organohalide with the macrocycle to form a prereaction complex. Evidence for this process is provided in the next section.

Evidence for a Prereaction Complex. The mechanism in Figure 1 involves a prereaction complex and therefore raises the possibility of saturation kinetics at high concentrations of electrophile. However, this effect was not observed with macrocycle **1**. For example, identical second-order rate constants were obtained for reaction of **1** (5.0 mM) with various concentrations of allyl chloride (60−500 mM). The fact that the rate does not plateau can be explained if the organohalide/**1** association constant is very low, which means that **1** is not saturated even when the concentration of electrophile is as high as experimentally possible. Thus, in this concentration regime, the involvement of a prereaction complex needs to be inferred by other methods,[17] such as a demonstration of competitive

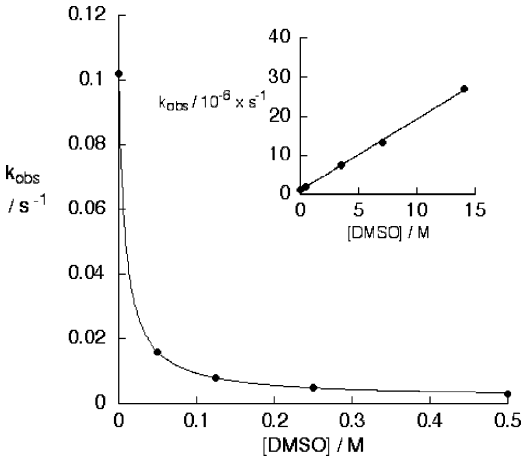


FIGURE 2. Effect of added DMSO inhibitor on pseudo-first-order rate constant for the reaction of macrocycle **1** (5 mM) with 4-*t*-BuBnCl (200 mM) in $CDCl_3$ at 298 K. Inset: Reaction of control **3** (5 mM) and 4-*t*-BuBnCl (200 mM) in $CDCl_3$ with increasing amounts of DMSO.

inhibition kinetics. This situation was recently encountered in related study by Heemstra and Moore,[8b] and we have employed a similar inhibition strategy to prove that macrocycle **1** forms a prereaction complex. In our case, the inhibitor is DMSO. As shown in Figure 2, the rate constant for the reaction of macrocycle **1** with 4-*t*-BuBnCl in $CDCl_3$ decreases with increasing amounts of added DMSO. This DMSO inhibition effect is unusual because the Menschutkin reaction is normally enhanced by the presence of a polar aprotic solvent.[4] For example, the reaction of 4-*t*-BuBnCl with control amine **3** is 21 times faster in DMSO than in $CDCl_3$ (inset in Figure 2). However, DMSO forms a 1:1 hydrogen-bonded complex with macrocycle **1** (observed in the solid and solution states[18]), and the association constant for **1**·DMSO is 160 M^{-1} in $CDCl_3$ at 298 K.[10] Thus, DMSO is an inhibitor that competes for the binding pocket in macrocycle **1**, and a computer-based nonlinear

(17) Prereaction complexes can also be identified using non-steady state kinetic analysis. Parker, V. D. *Pure Appl. Chem.* **2005**, *77*, 1823−1833.

(18) An X-ray crystal structure of **1** as its DMSO adduct (see the Supporting Information in ref 10) shows that the DMSO oxygen atom forms hydrogen bonds with the two NH residues in the macrocyclic cavity.

TABLE 3. Kinetic Data from DMSO Inhibition Studies[a]

organohalide	K_a[b] (M^{-1})	k_u[c] (s^{-1})	k_{in}[d] ($M^{-1}\,s^{-1}$)	$k(3)$[e] ($M^{-1}\,s^{-1}$)	EM[f] (M)
4-*t*-BuBnCl	3.3 ± 0.1	(4.1 ± 0.4) × 10^{-1}	(1.7 ± 0.5) × 10^{-2}	(6.6 ± 0.6) × 10^{-6}	62 000
4-*t*-BuBnBr	7.5 ± 1.4	1.6 ± 0.3	(9.1 ± 2.3) × 10^{-2}	(7.4 ± 0.9) × 10^{-4}	2200
4-*t*-BuBnI	17.3 ± 1.0	(7.0 ± 0.5) × 10^{-2}	(1.4 ± 0.4) × 10^{-2}	(2.0 ± 0.3) × 10^{-3}	35
allyl Cl	1.3 ± 0.1	(8.3 ± 0.6) × 10^{-2}	(1.4 ± 0.4) × 10^{-3}		
allyl Br	6.4 ± 1.2	(2.1 ± 0.4) × 10^{-1}	(2.8 ± 0.1) × 10^{-2}		
allyl I	19.0 ± 1.0	(1.4 ± 0.1) × 10^{-2}	(2.3 ± 0.7) × 10^{-3}		

[a] In $CDCl_3$ at 298 K. [b] **1**/Organohalide association constant. [c] Unimolecular rate constant for the prereaction complex. [d] Second-order rate constant for inhibited **1**/DMSO complex. [e] Second-order rate constant for reaction of organohalide with control **3**. [f] Effective molarity or $k_u/k(\mathbf{3})$.

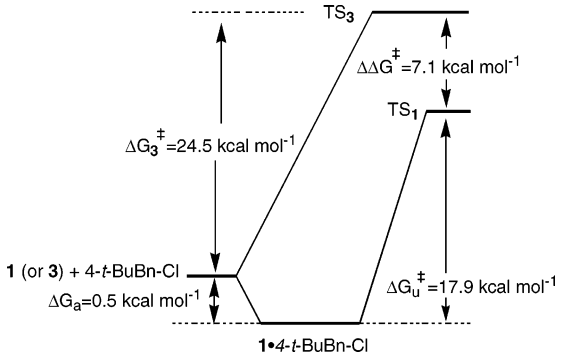
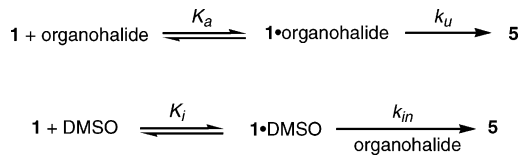


FIGURE 3. Reaction coordinate diagram for the reaction of 4-*t*-BuBnCl with macrocycle **1** or control amine **3**.

least-squares method was used to fit the curve in Figure 2 with the following reaction scheme for competitive inhibition. In this scheme, K_a is the association constant for formation of a 1:1 complex of **1** with the electrophilic organohalide (prereaction complex in Figure 1), k_u is the unimolecular rate constant for conversion of this complex into N-alkylated product **5**, and k_{in} is the second-order rate constant for reaction of the inhibited complex (**1**·DMSO, $K_i = 160\ M^{-1}$) with the organohalide.



In addition to the 4-*t*-BuBnCl curve in Figure 2, DMSO inhibition studies were conducted with the other two 4-*t*-BuBn halides and also the three allyl halides (Supporting Information). The kinetic variables, extracted by curve-fitting, are listed in Table 3. The data trends for the two electrophilic systems are very similar, and taken together they present compelling evidence for a prereaction complex.

Reaction Mechanism and Source of Acceleration. The results of this study support the mechanism proposed in Figure 1; that is, in the weakly polar solvent, $CDCl_3$, the electrophilic organohalide associates with macrocycle **1** to form a prereaction complex, which then undergoes unimolecular nucleophilic attack to give N-alkylated product, **5**, as a stabilized contact ion pair. The rate enhancement is clearly due to the ability of the hydrogen-bonding macrocycle in **1** to lower the free energy of activation. The kinetic data in Table 3 provide additional detail for the enhanced reactivity and altered leaving-group order. The organohalide affinities for **1**, K_a, are all quite weak, which explains the absence of saturation kinetics. In addition, the trend of K_a is 4-*t*-BuBnCl (3.3 M^{-1}) < 4-*t*-BuBnBr (7.5 M^{-1}) < 4-*t*-BuBnI (17.3 M^{-1}) and allyl Cl (1.3 M^{-1}) < allyl Br (6.4 M^{-1}) < allyl I (19.0 M^{-1}). In other words, macrocycle **1** associates with organoiodides the strongest and with organochlorides the weakest, which is opposite to the trend for relative rate enhancement (i.e., Cl > Br > I). Thus, the source of the selective acceleration is not the initial bimolecular association, but instead the subsequent unimolecular N-alkylation step. The data in Table 3 can be used to construct quantitative reaction coordinate diagrams. For example, Figure 3 shows the reactions of *t*-BuBnCl with macrocycle **1** and control amine **3**. The top pathway represents the S_N2 reaction with **3** and its single transition state (TS_3), whereas macrocycle **1** proceeds along the bottom pathway, through a prereaction complex, before crossing the transition state (TS_1). The observed acceleration of **1** over **3** ($\Delta\Delta G^{\ddagger} = 7.1$ kcal mol^{-1}) is the difference between TS_3 and TS_1.

Also provided in Table 3 are second-order rate constants $k(\mathbf{3})$ for control amine **3** and the calculated values of effective molarity (EM). EM is a measure of the enhancement that is gained when a bimolecular reaction is compared to an "intramolecular" process that uses the same mechanism.[19] Dividing the unimolecular rate constant, k_u, by the control amine second-order rate constant, $k(\mathbf{3})$, gives the following values of EM for reaction with 4-*t*-BuBn halides: 4-*t*-BuBnCl (62 000 M) > 4-*t*-BuBnBr (2200 M) > 4-*t*-BuBnI (35 M). Thus, the hydrogen-bonding macrocycle in **1** decreases $\Delta G^{\ddagger}$ for the unimolecular alkylation step in the order Cl > Br > I.[20]

How is $\Delta G_u^{\ddagger}$ selectively decreased with organohalides having smaller and more charge dense leaving groups? Elucidation of the fundamental factors that produce enzymatic catalysis remains a major intellectual topic in bioorganic chemistry.[21] Most likely, the major contribution is transition-state stabilization. Even though the solvent is weakly polar ($CDCl_3$), the macrocycle provides its own preorganized, polar solvation sphere,[22] and the energy of the dipolar transition state is lowered by stabilizing hydrogen bonds between the leaving halide and the macrocycle's two NH residues (Figure 4).[23] Furthermore, the strength of the

(19) Kirby, A. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 707−724.

(20) A similar but less dramatic correlation is seen when comparing leaving-group abilities for the Menschutkin reaction in aprotic and protic solvents. For example, moving from aprotic DMF to protic methanol enhances leaving-group ability in the order Cl > Br > I. Parker, A. J. *Chem. Rev.* **1969**, *69*, 1−32.

(21) Gao, J.; Ma, S.; Major, D. T.; Nam, K.; Pu, J.; Truhlar, D. G. *Chem. Rev.* **2006**, *106*, 3188−3209.

(22) The transition state of a typical Menschutkin reaction at ambient temperature in moderately polar solvents is characterized by $T\Delta S^{\ddagger}$ values of −9 to −11 kcal/mol (see ref 2). The highly negative $\Delta S^{\ddagger}$ is attributed to ordering of the solvent cage and a negative volume of activation, which explains why the reaction is promoted by high pressure.

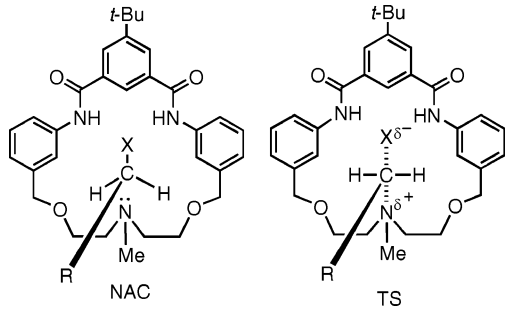


FIGURE 4. Structures of NAC and TS.

hydrogen bonds increases in the order $Cl^- > Br^- > I^-$.[24] There also may be differences in the entropy of activation. For example, the near attack conformation (NAC) hypothesis states that all enzyme-catalyzed reactions must proceed through a ground state NAC that approximates the structure of the transition state, but has not yet started bond forming and shortening.[25] Although formation of a prereaction complex (**1**·organohalide) is favored in the halide order of I > Br > Cl (see values for K_a in Table 3), it is possible that the fraction of prereaction complexes that adopt an NAC is higher when the organohalide has a smaller and more polar C−X bond (i.e., Cl > Br > I). Evidence for this statement are the results of high-level molecular modeling, which indicate that upon binding to macrocycle **1**, the organohalide is oriented by weak intermolecular interactions between its halogen atom and the macrocycle's NH residues, and also its CH_2 residues and the macrocycle's ether oxygens (Figure 4).[10,26] This would favor an NAC where the macrocycle's tertiary nitrogen is poised to attack the electrophilic CH_2 with a classic S_N2 trajectory. The relative contributions of these energy components to the overall value of $\Delta G_u^{\ddagger}$ cannot be determined from the experimental data, but they can be accessed with modern molecular dynamics simulations,[25] an exercise that is beyond the scope of this current experimental study.

(23) Activation of a halide leaving group by hydrogen bonding is a strategy that is employed by the family of enzymes known as *haloalkane dehydrogenases*. The first catalytic step in the enzymatic process involves attack of an organohalide by an active-site carboxylate nucleophile, and a significant fraction of the rate enhancement is attributed to two NH residues in the enzyme active site that form stabilizing hydrogen bonds with the halide leaving group. Dev-Kesavan, L.; Gao, J. *J. Am. Chem. Soc.* **2003**, *125*, 1532−1540.

(24) The halide association constants for macrocycle **1** in $CDCl_3$ at 298 K are F^- (1900 ± 400 M^{-1}) > Cl^- (620 ± 50 M^{-1}) > Br^- (140 ± 30 M^{-1}) > I^- (90 ± 15 M^{-1}), as determined by standard NMR titration experiments using tetrabutylammonium halides. The interaction is even stronger after the ion-pair product, **5**, is formed. Consider the salts obtained by N-alkylation of **1** with 4-*t*-BuBn halides; the ion-pair association constants in highly competitive DMSO-d_6 at 298 K are Cl^- (1360 ± 280 M^{-1}) > Br^- (136 ± 32 M^{-1}) > I^- (<10 M^{-1}) as determined by NMR dilution experiments.

(25) For discussions of near attack conformation, see: (a) Hur, S.; Kahn, K.; Bruice, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 2215−2219. (b) Schowen, R. L. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 1191−11932. (c) Hur, S.; Bruice, T. C. *J. Am. Chem. Soc.* **2003**, *125*, 10540−10542. (d) Shurki, A.; Strajbl, M.; Villa, J.; Warshel, A. *J. Am. Chem. Soc.* **2002**, *124*, 4097−4107. (e) Zhang, X.; Zhang, X.; Bruice, T. C. *Biochemistry* **2005**, *44*, 10443−10448. (f) Guo, H.; Cui, Q.; Lipscomb, W. N.; Karplus, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1508−1511. (g) Ranaghan, K. E.; Mulholland, A. J. *Chem. Commun.* **2004**, 1238−1239.

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Summary

While the literature contains many examples of bifunctional metal coordination complexes that can activate and attack phosphate and carboxylate esters,[27] there are very few uncharged organic molecules that exhibit such dramatic reaction enhancements (>10^5) as macrocyclic amine **1**.[28] Although stoichiometric, the Menschutkin reaction with **1** exhibits several kinetic features that are reminiscent of enzymes, namely, formation of a prereaction complex and substrate selectivity. There is a major distortion of the halide leaving-group order because of selective improvement of leaving-group ability in the order Cl > Br > I, and the EM for reaction with 4-*t*-BuBn halides is 4-*t*-BuBnCl (62 000 M) > 4-*t*-BuBnBr (2200 M) > 4-*t*-BuBnI (35 M). Likely reasons for the selective enhancement are: (a) increased transition-state stabilization due to hydrogen bonding in the macrocyclic pocket and (b) reduced entropic penalty in the transition state due to an increased fraction of prereaction complexes that are oriented in a near attack conformation. The small molecular size and structural simplicity of this bimolecular reaction system means that it should be possible to devise experimental and theoretical studies that determine the relative contribution of these fundamentally important reaction acceleration factors. A more practical goal is to develop highly reactive macrocyclic amines that selectively sense and scavenge carcinogenic haloalkanes from the atmosphere.

Experimental Section

Materials. The synthesis and characterization of compounds **1**, **3**, and **4** is described in the Supporting Information. Compound **2** was purchased from a commercial supplier and used as supplied.

Kinetic Measurements. A 5-mm NMR tube, containing a solution of macrocycle **1** in $CDCl_3$ (5 mM, 750 μL), was placed in an NMR spectrometer (500 MHz) and allowed to reach thermal equilibrium (298.0 ± 0.1 K). In certain cases, the solution also contained a specific concentration of DMSO inhibitor. After being shimmed, a starting spectrum was acquired, a very small aliquot of organohalide electrophile was added, and the reaction was monitored by periodic acquisition of a spectrum. The changes in peak intensity were monitored over time. Usually, the NH and *N*-methyl peaks of starting material (**1**) and product were well resolved, but changes in other peaks were also measured if possible. The concentrations of starting material and product at any time were calculated from the ratio of peak integrations. For relatively fast reactions (>95% complete within 4 h), the NMR tube remained in the NMR spectrometer throughout the run. For slower reactions, the NMR tube was stored at 298 K in an incubator oven and removed for periodic NMR acquisition. The curve fitting and extraction of kinetic data are described in the Supporting Information.

Anion Association with Macrocycle 1. A 10 mM solution of macrocycle **1** in $CDCl_3$ was prepared in a 5-mm NMR tube (solution volume 750 μL). Small aliquots of tetrabutylammonium halide stock solution (0.75 M) were added, and an ^1H NMR spectrum was acquired after each addition. Care was taken to avoid water absorption from the atmosphere. The changes in NH chemical

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shift were used to generate titration isotherms that were fitted to a 1:1 binding model using an iterative curve-fitting method.[29] In each case, the titration was repeated an average of three times.

Ion-Pair Association of the N-Alkylation Product of Macrocycle 1. General method: A stock solution of the N-alkylation product of **1** in DMSO-d_6 was prepared, and serial dilutions were made to cover the concentration range from 0.02 to 0.0002 M. The changes in NH chemical shift were used to generate titration isotherms that were fitted to the following equation:[29]

$$K_a = \alpha/(1 - \alpha)^2[c]$$

where $\alpha = (\delta - \delta_0)/(\delta_{max} - \delta_0)$, δ_0 is the initial chemical shift, δ is the chemical shift at each titration point, δ_{max} is the saturated chemical shift, and [c] is concentration of N-alkylation product.

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Supporting Information Available: Synthetic methods and spectral data, kinetic data, and curve fittings. This material is available free of charge via the Internet at http://pubs.acs.org.

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