Crossing the threshold from accelerated substitution to elimination with a bifunctional macrocycle†‡

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A previously reported macrocyclic amine with anion binding amide residues can be N-alkylated at highly accelerated reaction rates to give quaternary ammonium products. This present study examines the reactivity with 1,2-disubstituted ethanes. Accelerated substitution is observed with 1,2-dichloroethane (5000 times faster than analogous control amines); whereas, accelerated elimination is the outcome with 3-halopropionitriles (10 000 times faster than analogous control amines). The structure of the protonated form of the macrocycle is analyzed by X-ray diffraction. The rates of elimination for 3-chloro, 3-bromo and 3-iodopropionitrile were measured and the relative order of second-order rate constants with triethylamine was 1 : 43 : 182 which reflects the expected order of leaving group abilities. In the case of the macrocycle, the relative order of second-order rate constants was 1 : 29 : 61. The macrocyclic cavity preferentially stabilizes the charge developing on the smaller and more basic Cl^- leaving group. The kinetic data are consistent with a bimolecular *syn* elimination mechanism.

Introduction

The emerging interest in organocatalysis has lead to increased attention on the development of bifunctional molecules that have both Lewis basic and acidic sites.[1] This research topic also overlaps with more mature efforts to prepare synthetic mimics of enzyme active-sites.[2] In terms of molecular design, a major challenge is to construct scaffolds that hold multiple functional groups in close proximity but do not allow strong intramolecular interaction between the activating residues.[3] Inspection of the literature indicates that macrocyclic scaffolds have been employed.[4] Recently, we discovered that macrocyclic amine **1** can be N-alkylated at highly accelerated reaction rates to give the quaternary ammonium product **4** (Fig. 1).[5,6] This substitution reaction is known as the Menschutkin reaction,[7] and the reaction rates with **1** are $>10^4$ times faster than structurally related acyclic amines. Mechanistic studies indicate that the two amide residues in macrocycle **1** activate the halide leaving group by hydrogen bonding,[8] and allow simultaneous nucleophilic attack by the macrocyclic nitrogen. After the carbon–halogen bond breaks, the halide remains strongly associated with the cationic ammonium product as a contact ion-pair. Because amines can also act as bases, we wondered if macrocycle **1** could also accelerate a mechanistically related elimination reaction. Here we examine the reactivity with 1,2-dichloroethane and 3-halopropionitriles and report highly accelerated substitution chemistry with the former and elimination with the latter.

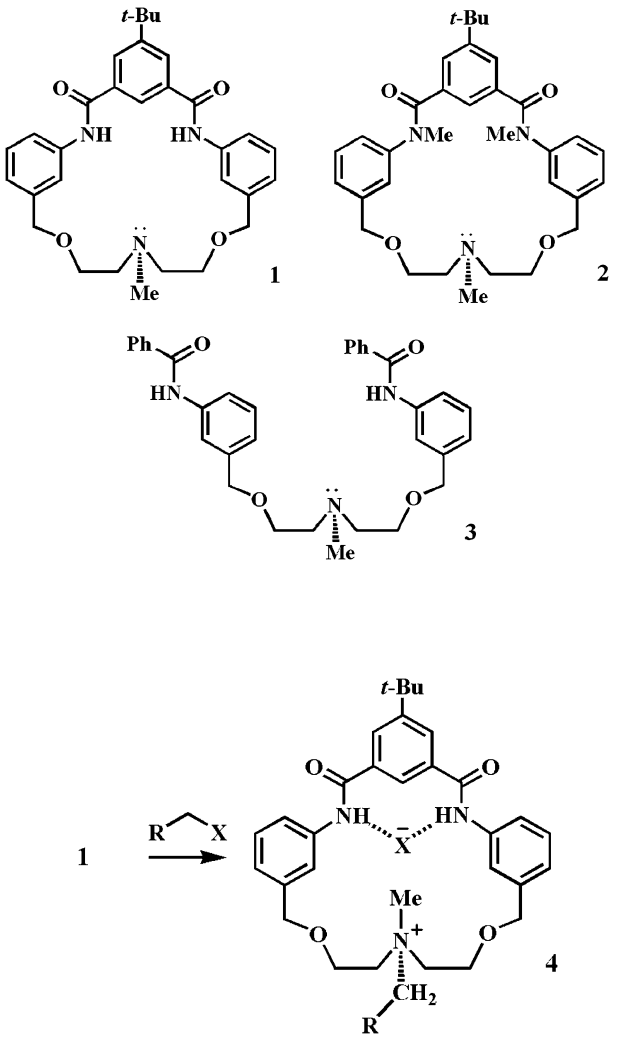

Fig. 1 Substitution reaction with macrocycle **1**.

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† Dedicated to Professor Jerry Atwood on the occasion of his 65th birthday.

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Results and discussion

Substitution with 1,2-dichloroethane

Industrial production of 1,2-dichloroethane, a known carcinogen, exceeds 8 billion kilograms annually in the United States, primarily for the manufacture of PVC.[9] Methods that effectively sense its presence or remove it from waste streams would thus be beneficial. Therefore, we investigated the reactivity of macrocycle **1** with 1,2-dichloroethane.

NMR studies showed that treatment of **1** with 1,2-dichloroethane produces the substitution product **5** quantitatively (Fig. 2). The spectra in Fig. 3 show the concomitant conversion of **1** into product **5**. Characteristic spectral features of amine alkylation are the splitting of the signal for the diastereotopic benzylic protons (4′) and the significant downfield shift of the protons on carbons alpha to the cationic ammonium (6′ and 9′). Another noteworthy observation is that the signals for the starting material remain unchanged as the reaction progresses, indicating that the starting material and ion-pair product do not interact extensively. The reaction of **1** in neat 1,2-dichloroethane under pseudo-first-order conditions was measured by monitoring the appearance of product with HPLC to obtain a second-order rate constant of 5.3×10^{-6} M^{-1} s^{-1} at 298 K. The rates of reaction were also measured for two control amines, the macrocycle **2**, which has no anion binding affinity because both amide protons have been substituted with methyl groups, and acyclic **3**, which contains two amide NH groups but is less preorganized than macrocycle **1**. The second-order rate constant for **1** is about 5000 times faster than cyclic control amine **2**, and 650 times faster than the acyclic control amine **3** (Table 1). These accelerations are similar to those observed previously with 1-chloropropane.[6]

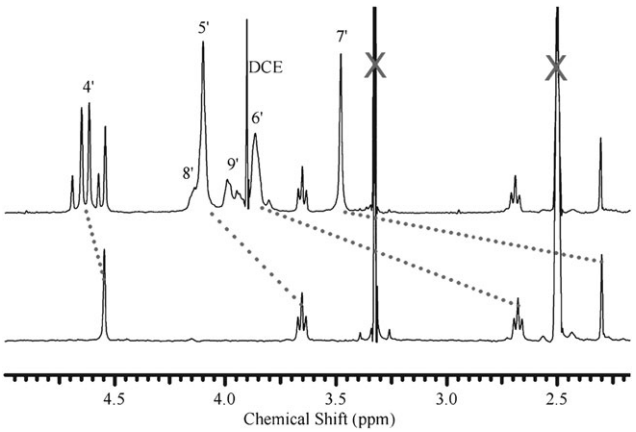

Fig. 3 Reaction of **1** with 1,2-dichloroethane (DCE). The bottom spectrum shows unreacted **1**. The top spectrum is at 80% conversion of **1** into **5** (see Fig. 2 for atom labels). The large peaks at 2.5 and 3.3 ppm are DMSO and water, respectively.

Elimination with 3-halopropionitrile

An alternative outcome with 1,2-disubstituted ethanes is elimination, and we assumed that by introducing a stronger electron withdrawing substituent, we would cross the threshold from substitution to elimination.[10] Therefore, the 3-halopropionitrile series was examined with the expectation that the withdrawing effect of the nitrile group would acidify the adjacent protons,[11] and produce the relatively stable conjugated elimination product, acrylonitrile (Fig. 4).[12]

The peaks of acrylonitrile product were easily observed by ^{1}H NMR allowing a facile method to measure the reaction kinetics. In contrast to the alkylation product **5**, the protonated macrocycle **6** is in rapid exchange with unreacted amine **1** (Fig. 5). Protons 5, 6 and 7 track downfield as the reaction progresses and the concentration of **6** and acrylonitrile increases, however there is no change in the signal for benzylic protons 4. The identity and structure of the protonated

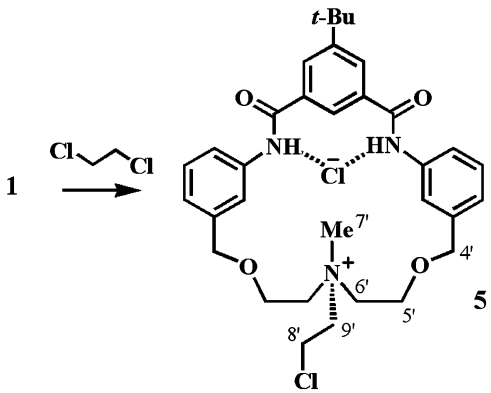

Fig. 2 Reactivity of **1** with 1,2-dichloroethane.

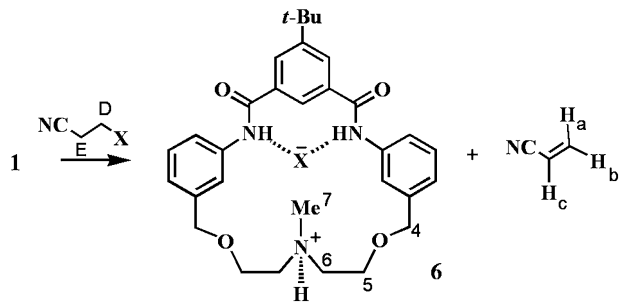

Fig. 4 Reaction of **1** with 3-halopropionitrile.

Table 1 Second-order rate constants, k

Organohalide	k(**1**) (M^{-1} s^{-1})	TEA[c] (M^{-1} s^{-1})	k(**2**) (M^{-1} s^{-1})	k(**3**) (M^{-1} s^{-1})
1,2-Dichloroethane[a]	$(5.3 \pm 0.9) \times 10^{-6}$	NA[d]	$(9.9 \pm 3.1) \times 10^{-10}$	$(8.1 \pm 0.3) \times 10^{-9}$
3-Chloropropionitrile[b]	$(1.2 \pm 0.1) \times 10^{-3}$	$(4.5 \pm 0.7) \times 10^{-4}$	$<10 \times 10^{-10}$	$(8.6 \pm 0.3) \times 10^{-7}$
3-Bromopropionitrile[b]	$(3.4 \pm 0.1) \times 10^{-2}$	$(1.9 \pm 0.1) \times 10^{-2}$	NA[d]	NA[d]
3-Iodopropionitrile[b]	$(7.3 \pm 1.6) \times 10^{-2}$	$(8.2 \pm 0.1) \times 10^{-2}$	NA[d]	NA[d]

[a] Neat 1,2-dichloroethane at 289 K. [b] In 1,2-dichlorobenzene at 289 K. [c] TEA = triethylamine. [d] NA = not available.

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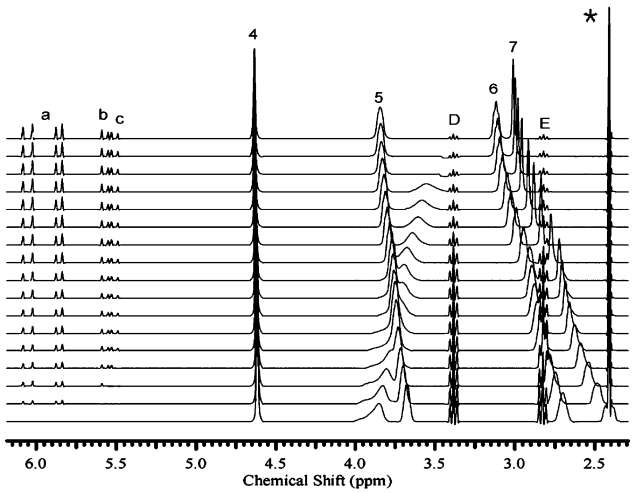

Fig. 5 Reaction of **1** with 3-bromopropionitrile over the course of 10 hours. The integration of product peaks (protons *a*, *b* and *c*) is compared to *p*-xylene (denoted by the asterisk), which was used as a standard (atom labels are shown in Fig. 4).

macrocyclic amine was confirmed by X-ray diffraction of **7**, an analogue of **6** (X = Cl) that lacks the *tert*-butyl group. The structure in Fig. 6, shows the N–Me group pointing into the

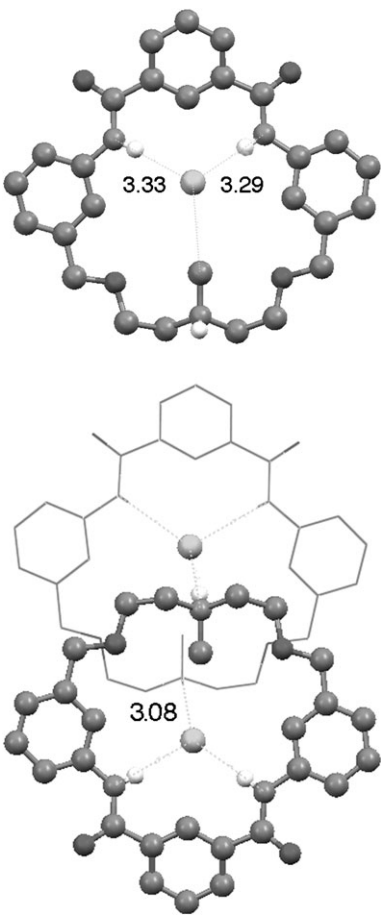

Fig. 6 X-Ray crystal structure of ion-pair **7** (an analogue of **6** with no *tert*-butyl group and X = Cl) showing N···Cl distances (Å) and ellipsoids at 50% probability; (top) monomer, (bottom) off-set dimer.

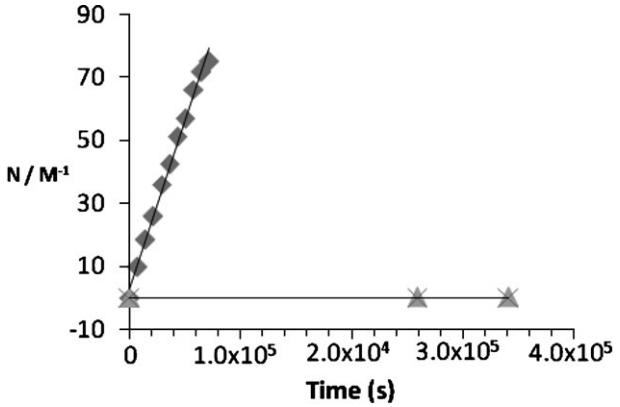

Fig. 7 Second-order plots of reactions with **1**, **2** and **3** with 3-cloropropionitrile at 298 K in 1,2-dichlorobenzene: ◆ is macrocycle **1**, ▲ is **2**, and × is **3**. The slope of the line provides the second-order rate constant in units of M^{-1} s^{-1}. The value of *N* in the vertical axis is defined by eqn (1) in the Experimental section.

macrocycle which leads to a circular arrangement of two partially positive NH residues and six CH residues (three Ar–H and three alkyl–H) around the Cl^- anion (solid-state distances for one of the two ion-pairs in the unit cell (Å): N···Cl 3.29, 3.32; aromatic C···Cl 3.31, 3.68, 3.76; N–Me C···Cl 3.38). The ammonium NH residue is directed towards the Cl^- in a neighboring molecule, such that the solid-state packing is an off-set dimer of two cofacial **7** molecules that are connected by two intermolecular H···Cl hydrogen bonds (Fig. 6).

Compared to the control amines **2** and **3**, macrocycle **1** is $>10^6$ and 10^3 times faster, respectively (Fig. 7). Clearly, the presence of the two NH residues greatly promotes the elimination reaction and the effect is enhanced by the preorganization provided by the macrocycle. To gauge the effect of the macrocycle on halide leaving group ability, the rates of elimination for 3-chloro, 3-bromo and 3-iodopropionitrile were measured using **1** and compared to triethylamine a control amine that reacts at experimentally useful rates.[13] The relative order of second-order rate constants with triethylamine was 1 : 43 : 182 which reflects the expected order of leaving group abilities (Table 1). In the case of macrocycle **1**, the relative order of second-order rate constants was

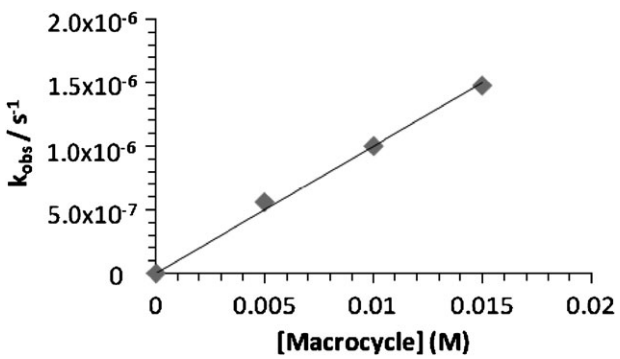

Fig. 8 Observed pseudo-first order rate constants for the reaction of **1** (5–15 mM) with 3-chloropropionitrile (150 mM) in 1,2-dichlorobenzene at 298 K.

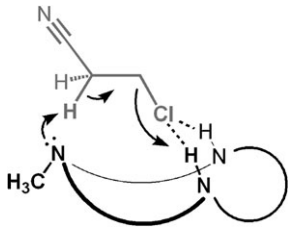

Fig. 9 Proposed bimolecular *syn* elimination mechanism.

1 : 29 : 61. Dividing the second-order rate constants for elimination induced by **1** by the rate constants for triethylamine leads to the following reactivity ratios; **1**/triethylamine = 2.7 (Cl) > 1.8 (Br) > 0.9 (I). In other words, compared to triethylamine, macrocycle **1** accelerates the elimination of HCl by a factor of three, with less of an effect on the elimination of HBr and HI.

When the reaction of **1** and 3-chloropropionitrile is performed under pseudo-first-order conditions, a first-order dependence on macrocycle is clearly observed (Fig. 8), indicative of a mechanism in which only one macrocycle participates in the transition state. Additional facts are the previously reported evidence for a pre-reaction complex,[6] the observed chloro-selectivity of the elimination reaction, the propensity of 3-chloropropionitrile to be in a *trans* configuration in low dielectric solvents,[14] and the inability of macrocycle **1** to associate with 3-halopropionitrile when it adopts a *cis* conformation.[15] Taken together the data is consistent with a *syn* elimination mechanism as shown in Fig. 9.

Conclusions

Not only does macrocycle **1** undergo accelerated substitution reactions with organohalides, it also can also dramatically accelerate eliminations with appropriately acidic 1,2-disubstituted ethanes. In both reactions, the anion binding NH residues in macrocycle **1** enhance the halide leaving group ability in the order Cl > Br > I. The macrocyclic cavity is able to best stabilize the charge developing on the smaller and more basic Cl^- leaving group. The kinetic data is consistent with a bimolecular *syn* elimination mechanism.

Experimental

Compounds **1**, **2** and **3** were available from a previous study.[6]

Substitution kinetics

tert-Butyl macrocycle **1** (or control amines **2** or **3**) was placed in three different 20 mL vials containing 1,2-dichloroethane (concentration of **1** is 5 mM) and kept in an isothermal incubator at 298.0 ± 0.1 K when not under analysis. At specific time intervals, 50 μL aliquots were removed and immediately added to methanol (at least 0.95 mL) to stop the reaction. The amounts of starting material **1** and product **5** in each aliquot were determined by analytical HPLC with detection at 210 and 277 nm using a photodiode array detector. Eluents A (acetonitrile) and B (80 mM ammonium acetate) were used in a linear gradient (75% A to 77% B in 6 min). For this reaction the pseudo-first-order rate equation applies:

$$\ln(a/(a - x)) = k_1 t$$

where 'a' is the initial concentration of the amine and 'x' is the concentration of product **4** at time t. The second-order rate constant, k_2, is thus k_1 divided by 25.3, which two times the concentration of 1,2-dichloroethane, 12.7 M at 298 K, a correction due to the statistical factor of two chlorine leaving groups.

Elimination kinetics

A 5 mm capped NMR tube containing a solution of amine base (**1, 2 or 3**) in 1,2-dichlorobenzene (0.012 M) was placed in an NMR spectrometer and allowed to come to thermal equilibrium (298.0 ± 0.1 K). After the spectrometer was shimmed, the appropriate 3-halopropionitrile was added (0.01 M) and spectra were taken at set intervals of 30 seconds to 1 hour. The NMR tube was never removed from the instrument during the course of the experiment. The growth of product peak intensity was monitored over time by comparing the integration to an internal *p*-xylene methyl peak.

The second-order kinetic rate constant was determined using eqn (1), which is the linearized form of a second-order rate expression.

$$\frac{\ln[([B]/[B]_0)/([A]/[A]_0)]}{([B]_0 - [A]_0)} = kt \qquad (1)$$

Here [B] and [A] are the concentration of the reagents at time t and $[B]_0$ and $[A]_0$ are the starting concentrations; [B] and [A], were directly monitored by NMR. The slope of the line provides the second-order rate constant in units of $M^{-1}\ s^{-1}$. Plotting the left side of eqn (1) (which is equal to N) against time yields the second-order rate constant, k.

X-Ray crystal structure

Crystallographic summary: triclinic, space group $P\bar{1}$, $C_{27}H_{30}ClN_3O_4$, FW = 495.99, Z = 4 in a cell of dimensions a = 11.0581(3), b = 13.2036(3), c = 18.3085(5) Å; α = 99.027(1), β = 104.128(1), γ = 102.882(1)°, V = 2463.12(11) Å^3, D_c = 1.338 Mg/m^3, $F(000)$ = 1048. The structure was refined on F^2 to R_w = 0.1765, conventional R = 0.0639 (16 272 reflections with $I > 2\sigma(I)$, and a goodness of fit = 1.109 for 731 refined parameters. The asymmetric unit is comprised of two macrocyles. Each macrocycle contains a Cl anion. There is disorder present in both macrocycles and it is more severe in the first macrocycle, C1–C27. There are alternate positions for the linker C24, O2, C25, C26 and for the bridge C1, C2, as well as methyl group C27. Site occupancy for the first group is 0.845(6) and for the group C1, C2, C27, the site occupancy factor is 0.826(5). In the second macrocycle the disorder is located at atoms C30 and O5. The site occupancy factor is 0.813(8).

Acknowledgements

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13 The elimination rates with control amines **2** and **3** are too slow for accurate studies of leaving group effects. Triethylamine is more basic and more reactive, which allows the comparative studies to be conducted in a practical time-frame.

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