

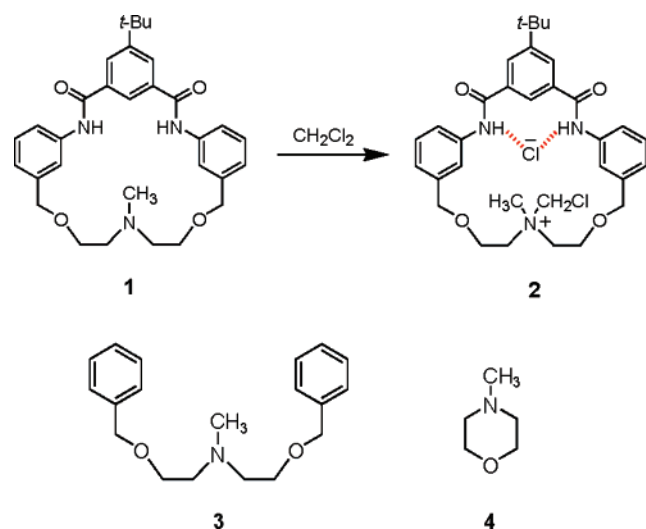
Rapid Fixation of Methylene Chloride by a Macrocyclic Amine

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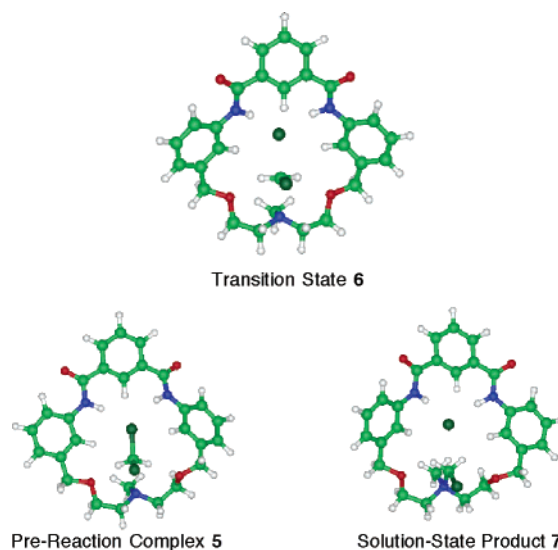
Methylene chloride is a volatile but relatively inert organic liquid that is used extensively as a solvent in small and large scale synthesis and extraction processes.¹ In addition, it is employed industrially as a paint stripper, degreaser, and blowing agent for foam production. It is known that amines can be alkylated by methylene chloride, but the reaction is very slow with half-lives of many weeks to several months.² Here, we report that the simple macrocyclic amine **1** attacks methylene chloride with unprecedented high reactivity to give the quaternary ammonium salt **2**.



Initially, we studied the reaction using methylene chloride as the solvent. The reaction exhibits pseudo-first-order kinetics, and the reaction half-life at 298 K is 2.0 min. The reaction half-life for acyclic amine **3** under identical conditions was determined to be 80 000 min, which is similar to the half-life of 180 000 min reported for **4**.^{2a} Thus, macrocyclic amine **1** reacts with methylene chloride approximately 50 000 times faster than structurally related tertiary amines. The structure of product **2** was elucidated using a range of spectroscopic methods, including X-ray crystallography (see below). There is no evidence for subsequent N-alkylation by a second equivalent of **1**, and the reverse reaction of **2** back to **1** does not occur readily at room temperature.

Detailed calculations using DFT and second-order Møller–Plesset perturbation theory favor the reaction mechanism that is illustrated in Chart 1.³ The methylene chloride associates with the macrocycle to form prereaction complex **5** with one of its chlorine atoms weakly hydrogen bonded to the macrocyclic NH's and its

Chart 1. Calculated Solution-State Structures for the Reaction of **1** with Methylene Chloride³



two CH residues interacting with the macrocyclic ether oxygens.⁴ The macrocyclic nitrogen attacks the methylene chloride with a classic S_N2 trajectory, and the reaction passes through transition state **6**. Although the carbon–chlorine bond breaks, the chloride leaving group does not separate from the newly formed cationic macrocycle, such that the product **2** is a tightly associated ion-pair (its calculated solution-state conformation is shown as structure **7**).

This mechanistic picture is consistent with the following experimental evidence. The X-ray crystal structure of the starting amine **1** (see Supporting Information) shows a macrocyclic conformation that is very similar to that depicted in the calculated complex, **5**, with the ring nitrogen well positioned to attack the electrophilic carbon of a methylene chloride molecule that binds to the macrocyclic cavity. The X-ray structure of ion-pair **2** (Figure 1) has the N–CH₃ group pointing into the macrocycle, which leads to a circular arrangement of two partially positive NH residues and six CH residues around the chloride anion (solid-state distances (Å): N···Cl 3.29, 3.32; aromatic C···Cl 3.36, 3.64, 3.74; N–CH₃···Cl 3.26). This solid-state conformation differs slightly from the calculated, solution-state conformation, **7**, and it appears that the difference is due to crystal packing forces.⁵ In any case, the macrocyclic ammonium cation in **2** has a very strong affinity for its counteranion.⁶

The reaction of **1** (a tertiary amine) with methylene chloride (an alkyl halide) is an example of the Menshutkin reaction.⁷ In contrast to the normal Menshutkin reaction,^{7,8} the alkylation of **1** is greatly inhibited by polar solvents. For example, the presence of a few

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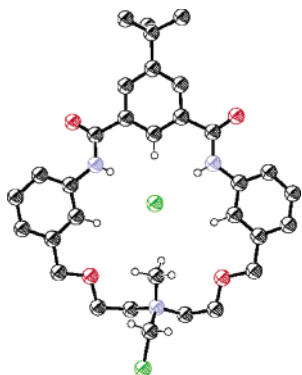


Figure 1. X-ray structure of quaternary ammonium chloride **2**.

percent of methanol or DMSO is sufficient to completely shut down the reaction. It appears that these polar additives associate with **1** and inhibit the formation of prereaction complex **5**.⁹ When methylene chloride is the solvent and the concentration of **1** is above 0.5 mM, the kinetic measurements are complicated by two factors that arise in the later part of the reaction: precipitation of the ion-pair product **2** and product inhibition (i.e., the product **2** associates with **1** and inhibits its reaction with methylene chloride). However, when the concentration of **1** is below 0.5 mM, the reaction exhibits ideal pseudo-first-order kinetics (determined by HPLC), and at 298 K, the derived second-order rate constant is $1.8 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$. Repeating the measurement in CD_2Cl_2 leads to a value of $k_{\text{H}}/k_{\text{D}} = 0.75$.¹⁰ Macrocycle **1** does not react with chloroform, and so CDCl_3 is a useful solvent for kinetic studies using ^1H NMR. The reaction rate of **1** with a large excess of methylene chloride in CDCl_3 has a first-order dependence on the concentration of both reactants and a second-order rate constant of $1.0 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ at 298 K, essentially the same as when the solvent is methylene chloride.^{11,12}

The enhanced reactivity of macrocycle **1** with methylene chloride has potentially useful applications. For example, it is well documented that breathing air that is contaminated with methylene chloride can lead to serious health problems. Indeed, the US EPA currently classifies methylene chloride as a probable human carcinogen (group B2), and exposure to methylene chloride is regulated by OSHA.¹³ The reaction described here converts methylene chloride, a volatile organic compound, into a nonvolatile salt. It may be possible to incorporate this fixation process into a sensing method that can detect contaminated air in the workplace. Finally, we note that studies are underway to determine if macrocycle **1** reacts rapidly with other types of alkyl halides, and preliminary results favor the affirmative.

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Supporting Information Available: Structural and kinetic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Bekkevold, S.; Svortøl, I.; Høiland, H.; Songstad, J. *Acta Chem. Scand. B* **1983**, *37*, 935–945. (b) Kost, D.; Aviram, K. *J. Am. Chem. Soc.* **1986**, *108*, 2006–2013.
- (2) (a) Nevstad, G. O.; Songstad, J. *Acta Chem. Scand. B* **1984**, *38*, 469–477. (b) Almarzoqi, B.; George, A. V.; Isaacs, N. S. *Tetrahedron* **1986**, *42*, 601–607. (c) Wright, D. A.; Wulff, C. A. *J. Org. Chem.* **1970**, *35*, 4252.
- (3) The calculations were conducted in the following manner. Initial guesses for the geometries were obtained by full optimization using the PM3 semiempirical Hamiltonian. Geometries were reoptimized at the HF/LanL2DZ and PBEPBE/LanL2DZ levels of theory. Frequency calculations at the same levels indicated that the stationary points are minima for the prereaction complex **5** and product **7**, and a first-order saddle point for the transition state structure **6**. To determine the minimum energy reaction path, intrinsic reaction coordinate calculations were performed using an established second-order method (Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523–5527). Single point calculations were carried out at the MP2/LanL2DZ//HF/LanL2DZ and MP2/LanL2DZ//PBEPBE/LanL2DZ levels of theory in order to compute heats of reactions and barriers in the gas phase and in solution. The energetics in solution were computed by the polarizable continuum model (Cancès, E.; Menucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3041), and a dielectric constant of 8.93 was used for CH_2Cl_2 . The energies relative to the sum of **1** plus methylene chloride are: **5** (−8.4 kcal/mol), **6** (−2.1 kcal/mol), and **7** (−38.0 kcal/mol).
- (4) Ab initio molecular dynamics calculations of the degenerate $\text{S}_{\text{N}}2$ reaction of chloride anion with methylene chloride indicate that the nucleophile interacts with the two CH residues and forms a prereaction complex. Pagliai, M.; Raugei, S.; Cardini, G.; Schettino, V. *Phys. Chem. Chem. Phys.* **2001**, *3*, 4870–4873.
- (5) Ion-pair **2** crystallizes as a cofacial dimer in the solid state (see Supporting Information). However, calculations indicate that an unaggregated version of this conformation in solution is 2–3 kcal/mol less stable than conformation **7**.
- (6) The association constant for ion-pair **2** in DMSO is 2270 M^{-1} at 298 K, (determined by NMR dilution experiments), which is substantially higher than the expected value for a quaternary ammonium chloride in DMSO. See, for example: Savedoff, L. G. *J. Am. Chem. Soc.* **1966**, *88*, 664–667.
- (7) (a) Menshutkin, N. *Z. Phys. Chem.* **1890**, *6*, 41–57. (b) 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.
- (8) Swain, C. G.; Eddy, R. W. *J. Am. Chem. Soc.* **1948**, *70*, 2989–2994.
- (9) The rapid reaction of macrocycle **1** with methylene chloride prohibits direct measurement of the association constant for complex **5**. However, it is very likely to be lower than the association constant for DMSO binding to **1**, which was determined by NMR titration experiments to be 150 M^{-1} in CDCl_3 at 298 K.
- (10) More studies are needed before the meaning of this kinetic isotope effect can be properly evaluated. However, it is worth noting at this point that the Menshutkin reaction typically exhibits an inverse secondary KIE. See, for example: Leffek, K. T.; Matheson, A. F. *Can. J. Chem.* **1972**, *50*, 982–985.
- (11) The reaction rate in CDCl_3 was determined by measuring the disappearance of **1** relative to an internal standard of TMS. The rate is sensitive to the age and purity of the CDCl_3 . It is important to pretreat the CDCl_3 with alumina and eliminate any residual HCl that otherwise inhibits the nucleophilicity of **1**.
- (12) The reaction mechanism in Chart 1 involves a prereaction complex which implies a kinetic picture that is more complicated than the pseudo-first-order model that is applied in this paper. However, the approximation is valid because the observed pseudo-first-order rate constant, k_1 , is linearly dependent on the concentration of excess methylene chloride. For a detailed discussion of a related N-alkylation system that also exhibits simplified kinetics, see: Heemstra, J. M.; Moore, J. S. *J. Org. Chem.* **2004**, *69*, 9234–9237.
- (13) This information can be found on the Internet at <http://www.epa.gov> and <http://www.osha.gov>.

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