Nucleophilic Substitution with Inversion of Configuration at the Nucleophile

Clayton H. Heathcock,* Thomas W. von Geldern, Carlito B. Lebrilla, and Wilhelm F. Maier*

Department of Chemistry, University of California, Berkeley, California 94720

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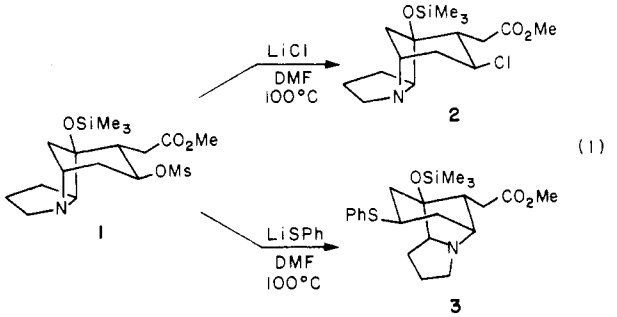
Treatment of the tricyclic amino alcohol methanesulfonate **1** with lithium chloride in dimethylformamide gives only the tricyclic chloro amine **2**, while similar treatment of **1** with sodium thiophenoxide in DMF produces solely the rearranged skeleton **3**. Analogous skeletal rearrangement is seen in the reaction of alcohol **4** with phosphorus oxychloride and in the pyrolysis of the (thiocarbonyl)imidazolide **6**. It is proposed that all of these reactions proceed through a tetracyclic azetidinium ion, B, and that thioether **3**, chloride **5**, and compound **7** are products of kinetic control, while chloride **2** is the product of thermodynamic control (Schemes I and II). It is unusual that chloro amine **5**, which is forced to undergo S_N2 reaction *with net inversion of configuration at nitrogen*, is substantially more reactive than its isomer **2**, in which the substitution occurs with retention of configuration at the nucleophilic center. Several theoretical calculations have been carried out in order to assess the importance of possible stereoelectronic and steric effects. The marked preference of azetidinium ion B to react at C-4 rather than at C-2 can be nicely explained by steric effects; there is no indication of stereoelectronic control in the reactions of B.

In connection with a total synthesis of the *Securinega* alkaloid norsecurinine[1] we treated the tricyclic methanesulfonate **1**[2] with lithium chloride in hot dimethylformamide (DMF). The product of this reaction, obtained in 87% yield, is chloride **2**, in which nucleophilic substitution has occurred with retention of configuration (eq 1).

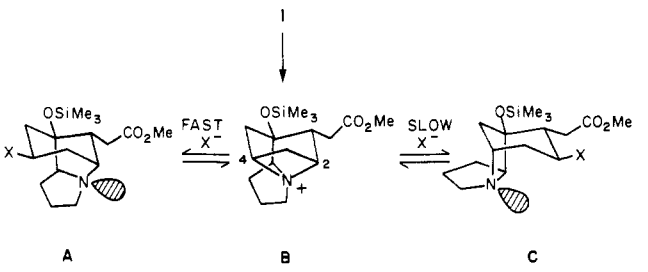


(1)

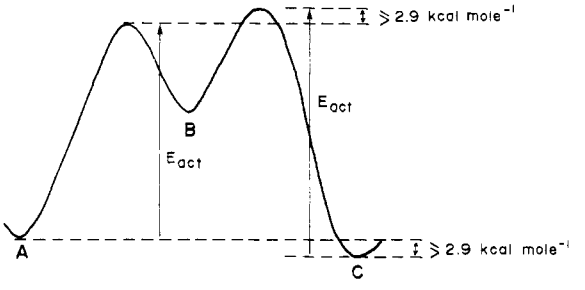
Careful analysis of the crude reaction mixture by ^1H NMR spectroscopy reveals no other isomers of **2**; it is estimated that the isomeric purity is >98:2. However, when methanesulfonate **1** is treated with sodium thiophenoxide in DMF under similar conditions, rearranged sulfide **3** is obtained in 80% yield as the sole identifiable product (eq 1). Again, a careful search for a minor isomer allows us to assign an isomeric purity of >98:2.

The most rational explanation for this divergent behavior is summarized in Scheme I. We propose that methanesulfonate **1** reacts via the azetidinium ion B, which can react with nucleophiles either at C-2 or at C-4. Reaction at C-2 gives a product (C) of unrearranged skeleton, whereas reaction at C-4 gives the rearranged product A. Furthermore, we propose that A is the kinetic and C the thermodynamic reaction product. The reaction with thiophenoxide ion shows that reaction B → A is faster than reaction B → C by a considerable amount; a ratio >98:2 at 100 °C corresponds to a difference in activation energies of at least 2.9 kcal mol^{-1} (Scheme II). Since thiophenoxide itself is not a good leaving group, structure A is essentially the sole product under these conditions. We suppose that the same kinetic preference for formation of structure A

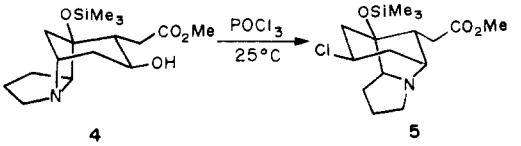
Scheme I



Scheme II



is seen when the nucleophile is chloride ion. However, in this case, the reaction if freely reversible and we do not see the initial product (A, X = Cl). Instead, thermodynamic control prevails, and the more stable isomer (C) is obtained. Indeed, when chloride formation is carried out under mild conditions (treatment of alcohol **4** with phosphorus oxychloride in dichloromethane, 25 °C), the rearranged chloride **5** is the sole reaction product (eq 2).



(2)

Again, the observed isomeric purity of >98:2 requires a difference in activation energies of at least 2.3 kcal mol^{-1} under the conditions of the reaction.

A third example of the foregoing skeletal rearrangement was encountered in the pyrolysis of the imidazolylthiocarboxylate **6**; the sole isolated product is the rearranged isomer **7** (eq 3). It is assumed that reaction occurs by heterolysis to give azetidinium ion B and the imidazolyl-

(1) Iketubosin, G. O.; Mathieson, D. W. *J. Pharm. Pharmacol.* **1963**, *15*, 810; *Chem. Abstr.* **1964**, *60*, 4370*d*.

(2) Details of the synthesis and proof of stereostructure of **1**, **4**, and **6** (single-crystal X-ray analysis of **4**) will be reported separately, in connection with the total synthesis of norsecurinine.

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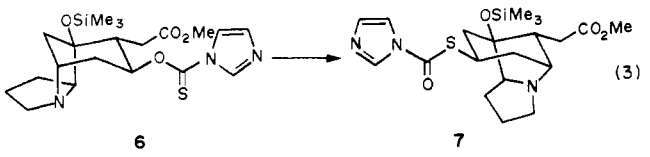
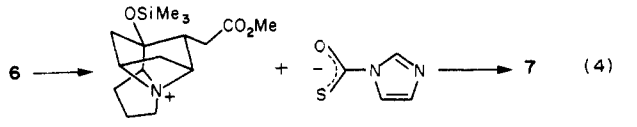


6 7 (3)

monothiocarboxylate 8; recombination occurs with the sulfur atom of the ambident anion virtually exclusively at C-4 of B (eq 4).



6 B 8 7 (4)

Schemes I and II contain two salient features, one a thermodynamic one and the other a kinetic one. First, in the formation of chloride **2** under equilibrating conditions (DMF, 100 °C), careful ^1H NMR and ^{13}C NMR analysis of the crude product does not reveal as much as 2% of the isomeric chloride **5**. Thus, the difference in energy between the isomeric skeletons of **2** and **5** must be at least 2.9 kcal mol^{-1}. It is not difficult to accept such a difference in stability. We start with the assumption that the 1-azabicyclo[3.3.0]octane moiety strongly prefers the "cis" conformation.[3] In the case of isomer **5**, this places the trimethylene bridge of the pyrrolidine ring endo to the three-carbon bridge of the bicyclo[3.2.1]octane ring system. In isomer **2**, the trimethylene bridge is oriented away from this side of the molecule.

What is not quite so obvious is why there should be such a bias for attack at C-4, rather than at C-2, of the intermediate azetidinium ion (see Scheme II). Furthermore, Scheme II also requires that azetidinium ion B form much more rapidly from chloro amine A than from the isomeric chloro amine C (a difference of activation energies of at least 5.8 kcal mol^{-1} at 100 °C) even though the nitrogen lone pair in A is directed *away* from the electrophilic center while that in C is oriented toward the electrophilic center. Thus, in the isomeric reactions of A → B and C → B, the reaction that proceeds with overall *inversion of configuration at the attacking nucleophile* is substantially more rapid (by at least 2×10^3 at 100 °C) than the reaction that proceeds with retention of configuration at this atom.

Of course, relief of strain is part of the reason for the enhanced reactivity of structure A. However, at least 2.9 kcal mol^{-1} of the difference in activation energy (the difference in the energies of the two transition states) must be due to some other factor. Because of the novelty of these observations, we have carried out a qualitative theoretical investigation of the S_N2 transition state, from the viewpoint of the stereochemistry at the nucleophilic center.

One possible reason for the difference in reactivity at C-2 and C-4 in azetidinium ion B is that reaction at C-2 is disfavored by the adjacent appendage at C-3. However, we do not think that the steric retardation from a trans substituent would be of sufficient magnitude to account for the high stereoselectivity seen in eq 1–3.

A second explanation that we considered is that there is a stereoelectronic preference for reaction at C-4. Consider the two ring-closure reactions depicted in Scheme III, which model the reactions C → B and A → B, respectively. In the first case, the nitrogen lone pair orbital attacks the rear of the C–Cl bond and reaction occurs with retention of configuration at nitrogen. This mode of approach has the advantage that the lone pair electron density is initially near the electrophilic center. However, the optimum geometry for the S_N2 transition state is linear; that is, the angle described by the entering nucleophile, the reacting nucleus, and the leaving group should be 180°.[4] In Scheme IIIa, the symmetry axes of the nitrogen lone pair orbital and the C–Cl bond make an angle of approximately 140°. It might be expected that some of this distortion would remain in the transition state. In the second mode of formation of the azetidinium ion (Scheme IIIb), the symmetry axes of the nitrogen lone pair and C–Cl bond are colinear and can remain nearly so throughout the course of ring closure. Thus, whatever strain is associated with deforming the S_N2 transition state from its ideal linear geometry is not associated with this reaction. The importance of a colinear arrangement of nucleophile, reaction center, and leaving group has been demonstrated experimentally by Eschenmoser[4a] and Stork[4b] and forms a part of the basis of "Baldwin's Rules" for ring formation.[4c]

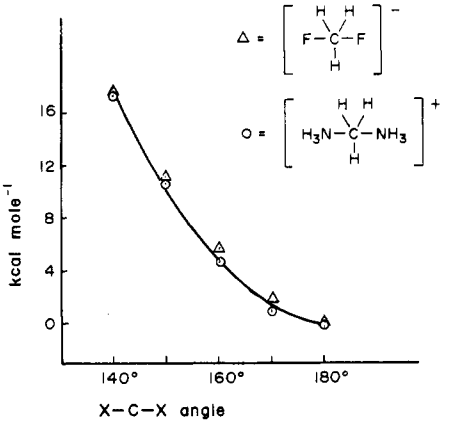
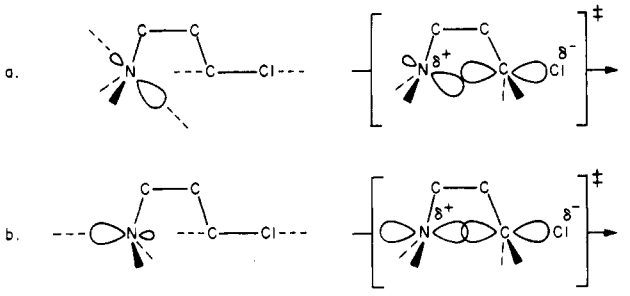


Figure 1. Effect of angle deformation on the energy of S_N2 transition states.

Scheme III



To examine this hypothesis in our system, we carried out theoretical calculations. Quantum mechanical calculations are known to reproduce S_N2 reactions reliably.[5] The combination of ab initio methods with Monte Carlo calculations has even reproduced solution data with remarkable accuracy.[6] For economic reasons, we have utilized the semiempirical MNDO program,[7] which has al-

(3) In bicyclo[3.3.0]octane itself, the cis form is known to be more stable than the trans form by approximately 6 kcal mol^{-1}: Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637. For pyrrolizidine, it has been suggested that the cis form may be only 2 kcal mol^{-1} more stable than the trans form: Kozina, M. P.; Timofeeva, L. P.; Gal'chenko, G. L.; Skvortsov, I. M.; Antipova, I. V. *Zh. Obshch. Khim.* **1981**, *51*, 451.

(4) (a) Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059. (b) Stork, G.; Cama L. D.; Coulson, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(5) Wolfe, S.; Mitchell, D. J.; Schlegel, H. B. *J. Am. Chem. Soc.* **1981**, *103*, 7692, 7694.

(6) Chandrasekhar, J.; Smith, S. F.; Jorgenson, W. L. *J. Am. Chem. Soc.* **1984**, *106*, 3048.

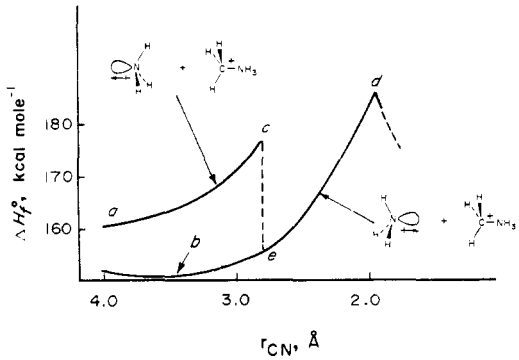
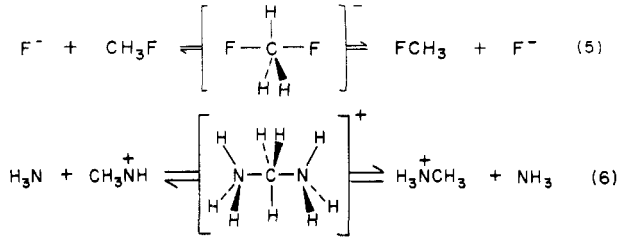


Figure 2. Reaction paths for nucleophilic substitution of ammonia on methylammonium ion.

ready been used successfully for the investigation of substitution reactions and related processes.[8] We first evaluated the energetic cost of bending the relevant S_N2 transition structures from linearity. Calculations were performed with the MOPAC[9] program. Transition-state structures were optimized with a gradient optimization method and are characterized by a single negative eigenvalue in the force matrix. The systems studied were fluoride ion plus methyl fluoride (eq 5) and ammonia plus methylammonium ion (eq 6). [These reactions were



chosen because they are symmetrical and because the net charge on the reacting system remains constant throughout.] The results are plotted in Figure 1. Note that eq 5 and 6 give similar curves, suggesting that they are reasonable models for the mixed system, $[FCH_3NH_3]$, which is difficult to evaluate because of the charge difference between the ground states and the transition state. The bending constant is relatively soft for deformations of ±10°, but it increases markedly beyond that point. For deformations of 20° and 30°, the calculated strain energy is about 5 and 10 kcal mol^{-1}, respectively.

To examine the behavior of an amine nucleophile as it approaches the electrophilic carbon in a nucleophilic substitution process, we calculated reaction potentials for the approach of ammonia to the rear of the C–N bond in methylammonium ion with the ammonia lone pair oriented in the direction of the electrophile and with the lone pair oriented away from the electrophile. The results of this study are summarized in Figure 2. When the nitrogen lone pair is oriented in the direction of the electrophile, there is a smooth increase in energy as the molecules are brought together, resulting in the symmetrical transition state (points b → d in Figure 2). Energetically, the computed activation enthalpy is on the order of 34 kcal mol^{-1} (with r_{CN} = 3.6 Å (b) the energy is 151.1 kcal mol^{-1}; for the transition state optimized with D_{3h} symmetry the energy is 185.2 kcal mol^{-1} and r_{CN} is 1.96 Å).

For the other orientation (point a in Figure 2), there is an energetic price even at relatively large r_{CN}; the computed energy with r_{CN} = 4.0 Å is 160.6 kcal mol^{-1}. This difference in energy of approximately 10 kcal mol^{-1}, relative to the first case, is presumably due to the difference between the favorable and unfavorable dipole interactions in the two orientations. As the C–N distance is shortened in the latter orientation, the energy increases until r_{CN} = 2.8 Å, at which point the ammonia molecule undergoes abrupt inversion. The energy of the system just prior to inversion (point c in Figure 2) is calculated to be 175.8 kcal mol^{-1}, *approximately 10 kcal mol^{-1} below the activation barrier for the substitution process.* Inversion converts the system to the "normal" substitution reaction path (point e in Figure 2); from this point the two reactions follow identical paths to the common transition structure d.

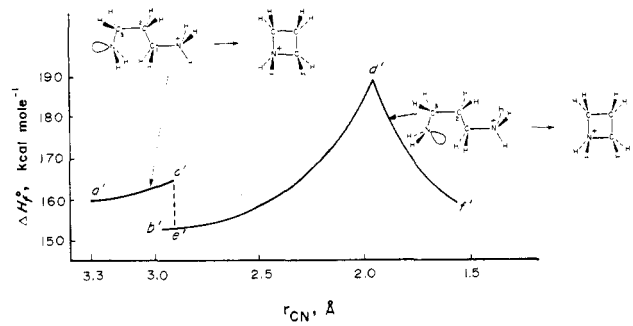


Figure 3. Cyclization of monoprotonated propane-1,3-diamine.

The foregoing evaluation gives no information on the question of a possible stereoelectronic bias for nucleophilic substitution reactions of amines, since both orientations chosen for study have the C_3 axis of the ammonia molecule and the C–N leaving group bond colinear. However, it does reveal a perfectly reasonable mechanism for nucleophilic substitution with net inversion at the nucleophilic center—one in which the amine approaches the electrophilic center in the wrong orientation and then undergoes inversion before any substantial bonding has occurred. In the case evaluated, the inversion is probably triggered by an exacerbation of the aforementioned unfavorable dipole interaction and also by the fact that the hydrogens of the attacking NH_3 and the CH_3 group begin to come into van der Waals contact at about 3 Å.

However, the questions posed in Scheme III still remain. In such a case, is the S_N2 transition-state structure distorted from linearity in one case and not in the other? To address this issue, we calculated reaction potentials for cyclization of (3-aminopropyl)ammonium ion, starting in the two analogous orientations. The results of this evaluation are summarized in Figure 3. The structures in this study were all optimized without symmetry, for various values of r_{CN}. The general shape of the diagram is the same as shown in Figure 2. However, there are some differences. Because the nucleophilic nitrogen and electrophilic carbon are in the same molecule, they can only be 3.3 Å apart in the conformation having N–C–C–C syn coplanar. When ring closure begins with the nitrogen lone pair oriented toward C-1 (point b′, r_{CN} = 2.89 Å, 153.1 kcal mol^{-1}) the energy of the system undergoes a smooth increase until it reaches the transition structure (point d′, r_{CN} = 1.96 Å, 187.8 kcal mol^{-1}). If one starts with the nitrogen-inverted conformation (point a′) r_{CN} = 3.06 Å and the calculated energy is 161.6 kcal mol^{-1}. The longer C–N distance and the higher energy of this starting conformation probably reflect both the unfavorable dipole–dipole interaction and nonbonded H–H repulsion. As r_{CN} is decreased, abrupt inversion occurs at a distance of about 2.8 Å (c′ → e′). The transition structure for this inversion was located by gra-

(7) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.
(8) Carrion, F.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1983**, *106*, 3531.
(9) Stewart, J. J. P., QCPE, no. 455.

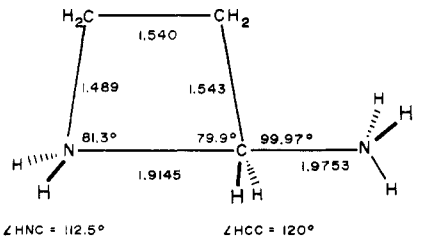
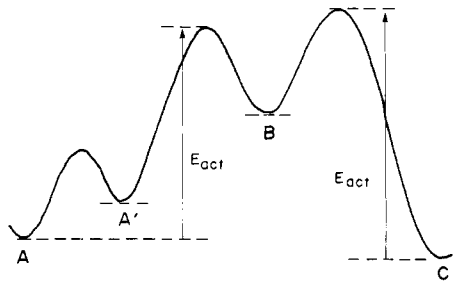


Figure 4. Calculated transition-state structure for the cyclization of monoprotonated propane-1,3-diamine.

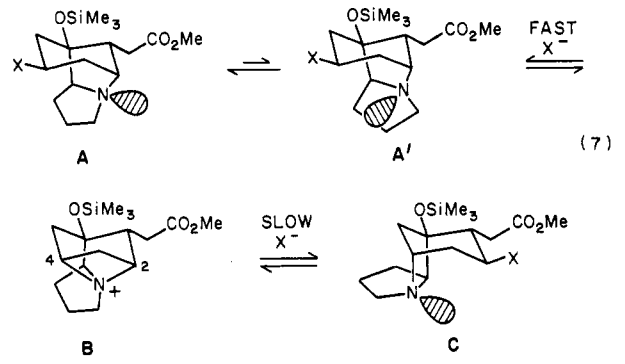
Scheme IV



dient optimization at 2.86 Å; the energy was found to be 163.8 kcal mol^{-1}. From this point, the normal reaction path is followed, leading to the common transition state (point d′).

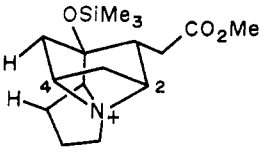
The structure of the computed transition state for the cyclization of monoprotonated propane-1,3-diamine is of some interest. As shown in Figure 4, the N–C–N angle is exactly 180°. The carbon undergoing substitution is planar, but the nucleophile–leaving group axis is *not* perpendicular to this plane. Instead, the C-2,C-1,N angles are approximately 100° and 80°. One may imagine that, as the attacking nitrogen begins its approach to the rear of C-1, it undergoes partial inversion to bring its lone pair orbital more into alignment with the axis of the C-1, leaving group bond. As the leaving group departs, C-1 flattens and the leaving group follows a path that maintains the N,C-1,N angle of 180°.

The net result of these calculations is that there is no evidence for a stereoelectronic bias as the reason for the C-4/C-2 reactivity in azetidinium ion B. Instead, we are led to a slight reformulation of Scheme I, shown below in eq 7.



The energetics of this process are depicted in Scheme IV. The only difference between Schemes II and IV is the insertion of the *trans*-1-azabicyclo[3.3.0]octane conformer A′ between A and B. Since A′ is expected to be about 6 kcal mol^{-1} less stable than A (the normal nitrogen inversion barrier), the conversion of A to A′ represents an unobservable equilibrium prior to actual ring closure to B. In particular, these theoretical investigations indicate that it should not matter how an amine nucleophile attacks an electrophilic center. If it approaches with its lone pair already oriented in the direction of the electrophilic center, then there is obviously no problem. If it approaches with its lone pair oriented in the wrong direction, the energy of the system will increase markedly at first, as a result of the unfavorable dipole–dipole interaction and of van der Waals interaction. However, inversion will occur at a relatively long C–N distance, and at an energy well below that of the transition state for the substitution.

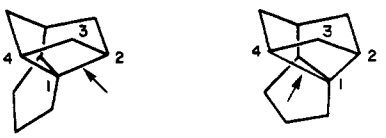
However, this still leaves us with no satisfying explanation for the difference in reactivity of the azetidinium ion at C-2 and C-4; that is, we have still not accounted for the difference in absolute energy of the two transition states leading from B to A′ and C. Since the answer does not seem to lie in the stereoelectronics of the two processes, we examined simple steric effects. Close examination of a molecular model of azetidinium ion B shows that there is a serious nonbonded interaction between the two hydrogens indicated in the following structure. As the C-2,N



B

bond is lengthened, these two hydrogens are at first forced to come closer together; only upon bond breakage do they eventually move farther apart. However, as the C-4,N bond is lengthened, the two hydrogens in question immediately move apart from one another.

To investigate this possibility in a more quantitative manner, we carried out force-field calculations with the Allinger MM2 program.[10] To mimic the two transition states, we calculated the optimized energy for tetracyclo-[5.3.1.0^{1,4}]undecane, first with the C-1,C-2 bond and then with the C-1,C-4 bond fixed at 1.96 Å (structures D and E, respectively). The relative energies of the lowest energy



D E

conformations of these two transition-state models were found to be 0 and 8 kcal mol^{-1}, respectively!

In summary, we have found that a number of derivatives of the basic structure C undergo nucleophilic substitution by way of the tetracyclic azetidinium ion B. The same intermediate may be reached with greater ease from tricyclic amines of the isomeric structure A, presumably by prior inversion to intermediates of type A′. The azetidinium ion B shows a remarkable preference to react with nucleophiles to give (initially) product A′, rather than C. The difference in activation energies for the two reactions, which is at least 2.9 kcal mol^{-1} and may be as much as 8 kcal mol^{-1}, appears to be steric, rather than stereoelectronic, in origin.

Experimental Section

General Methods. Tetrahydrofuran (THF) was distilled from sodium benzophenone immediately prior to use. Dimethylformamide (DMF) was distilled from CaH_2 at reduced pressure; dichloromethane and toluene were taken from freshly opened bottles

(10) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Allinger, N. L., QCPE, no. 395.

and stored over 4A molecular sieves. Methanesulfonyl chloride was distilled from P_2O_5 at reduced pressure; triethylamine was distilled from CaH_2. Infrared (IR) spectra were determined as dilute $CHCl_3$ solutions. ^1H NMR spectra were determined as $CDCl_3$ solutions at 200, 250, or 300 MHz. ^{13}C NMR were measured in $CDCl_3$ at 62.98 MHz. Significant ^1H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constant(s) in hertz. Mass spectral data are tabulated as m/z (intensity expressed as percent of total ion current). ASI (amine solvent no. 1) refers to a mixture of 95% CH_2Cl_2/4.5% methanol/0.5% ammonia; ASII is a 1:1 mixture of ASI and CH_2Cl_2.

(1*RS*,2*SR*,7*SR*,9*SR*,10*RS*)-6-Aza-10-(carbomethoxymethyl)-9-[(methylsulfonyl)oxy]-1-[(trimethylsilyl)oxy]tricyclo[5.3.1.0^{2,6}]undecane (1). To a solution of 50 mg (0.15 mmol, 1.0 equiv) of alcohol **4** in 3 mL of CH_2Cl_2 were added 0.106 mL (77 mg, 0.76 mmol) of triethylamine and 53 mg (0.46 mmol, 3.0 equiv) of methanesulfonyl chloride. The mixture was stirred overnight at room temperature, 3 mL of distilled water was added, and the mixture was extracted 3 times with CH_2Cl_2. The combined organic layers were dried (K_2CO_3), filtered through a pad of Celite, and concentrated with a rotary evaporator. The crude product was chromatographed on 3 g of silica gel, using ASII as eluant, to give 55.5 mg (90%) of a white solid. Recrystallization from acetone gave white crystals, mp 126–129 °C: IR 1725, 1360, 1170, 970, 930, 845 cm^{-1}; ^1H NMR δ 0.17 (s, 9 H), 1.42–1.90 (m, 6 H), 2.14 (dd, 1 H, J = 7, 11), 2.35–2.63 (m, 5 H), 2.87 (dd, 1 H, J = 5, 17), 3.03 (s, 3 H), 3.08 (br t, 1 H, J = 9), 3.29 (br t, 1 H, J = 8), 3.70 (s, 3 H), 4.67 (dt, 1 H, J = 8, 10); ^{13}C NMR δ 1.8 (3 C), 26.0, 29.1, 32.8, 38.0, 38.5, 39.3, 49.4, 51.5, 57.1, 59.3, 67.6, 82.8, 173.4. Anal. Calcd for $C_{17}H_{31}NO_6SSi$: C, 50.34; H, 7.70; N, 3.45. Found: C, 50.19; H, 7.63; N, 3.37.

(1*RS*,2*SR*,7*RS*,9*SR*,10*SR*)-6-Aza-10-(carbomethoxymethyl)-9-chloro-1-[(trimethylsilyl)oxy]tricyclo[5.3.1.0^{2,6}]undecane (2). A solution of 25.7 mg (0.063 mmol) of mesylate **1** and 13 mg (0.32 mmol, 5.0 equiv) of LiCl in 1 mL of DMF was heated overnight at 80 °C. The reaction mixture was cooled to room temperature, 3 mL of distilled water was added, and the mixture was extracted 3 times with CH_2Cl_2. The combined organic layers were dried (K_2CO_3), filtered through Celite, and concentrated with a rotary evaporator. Chromatography on 2 g of silica gel, using ASII as eluant, gave 19.1 mg (87%) of a colorless oil, which crystallized upon standing to form waxy white leaves, mp 62–64 °C: IR 1725, 1250, 1165, 845 cm^{-1}; ^1H NMR δ 0.16 (s, 9 H), 1.42–1.75 (m, 4 H), 1.84 (m, 1 H), 2.02 (m, 1 H), 2.13 (dd, 1 H, J = 7, 11), 2.24–2.74 (m, 3 H), 2.61 (dt, 1 H, J = 5, 10), 2.80 (dd, 1 H, J = 5, 17), 2.94–3.08 (m, 2 H), 3.26 (br t, 1 H, J = 9), 3.69 (s, 3 H), 3.80 (dt, 1 H, J = 6, 10); mass spectrum, m/z 345 (0.56), 272 (1.77), 240 (2.00), 196 (2.27), 167 (5.01), 96 (3.34), 73 (7.73), 70 (9.97). Anal. Calcd for $C_{16}H_{28}NO_3SiCl$: C, 55.56; H, 8.16; N, 4.05. Found: C, 55.65; H, 8.12; N, 3.87.

(1*RS*,2*SR*,7*RS*,9*RS*,11*SR*)-6-Aza-11-(carbomethoxymethyl)-9-(phenylthio)-1-[(trimethylsilyl)oxy]tricyclo[5.3.1.0^{2,6}]undecane (3). To a mixture of 80 mg of sodium hydride (50% oil dispersion; 1.56 mmol) in 5 mL of distilled dimethylformamide (DMF) was added 170 mg (1.56 mmol) of thiophenol. The solution was stirred for 30 min, and then a solution of 420 mg (1.04 mmol) of mesylate **1** in 5 mL of DMF was added. The mixture was heated to 80 °C for 2.5 h and then was allowed to cool to room temperature. A 1:1 mixture of distilled water and saturated aqueous $NaHCO_3$ was added, and the mixture was extracted 3 times with 3-mL portions of $CHCl_3$. The combined organic layers were dried (K_2CO_3), filtered through a pad of Celite, and concentrated by using first a rotary evaporator and then a vacuum pump. The crude product was chromatographed on 7 g of silica gel, using ASII as eluant, to give 350 mg (80%) of a yellowish oil: IR 1725, 1435, 1250, 1150, 915, 840 cm^{-1}; ^1H NMR δ 1.24–2.70 (m, 12 H), 2.78 (dd, 1 H, J = 8, 20), 3.19 (br d, 1 H, J = 4), 3.33 (tt, 1 H, J = 8, 16), 3.54 (dd, 1 H, J = 8, 10), 3.66 (s, 3 H), 7.25–7.50 (m, 5 H); ^{13}C NMR δ 2.0 (3 C), 23.0, 29.5, 32.1, 34.0, 38.8, 43.5, 44.4, 51.2, 55.9, 58.2, 68.9, 77.9, 127.2, 128.7 (2 C), 132.5 (2 C), 133.8, 173.8. Anal. Calcd for $C_{22}H_{33}NO_3SSi$: C, 62.97; H, 7.93; N, 3.34. Found: C, 63.08; H, 8.02; N, 3.27.

(1*RS*,2*SR*,7*RS*,9*RS*,11*RS*)-6-Aza-11-(carbomethoxymethyl)-9-chloro-1-[(trimethylsilyl)oxy]tricyclo[5.3.1.0^{2,6}]undecane (5). To a solution of 20 mg (0.061 mmol) of alcohol **4** in 1 mL of CH_2Cl_2 was added 50 mg (0.49 mmol, 8 equiv) of triethylamine and 30 mg (0.33 mmol, 5.3 equiv) of phosphorus oxychloride. After the mixture was stirred for 12 h at 25 °C, reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted 3 times with CH_2Cl_2; the extracts were dried (K_2CO_3), filtered through Celite, and concentrated with a rotary evaporator. The crude product was chromatographed on 4 g of silica gel, using ASII as eluant, to give 7.3 mg (35%) of a colorless oil: IR 1730, 1440, 1160, 1060, 915, 885, 845 cm^{-1}; ^1H NMR δ 0.11 (s, 9 H), 1.62 (dq, 1 H, J = 7, 12), 1.71 (dt, 1 H, J = 4, 11), 1.80 (d, 1 H, J = 12), 2.0–2.3 (m, 2 H), 2.10 (t, 1 H, J = 12), 2.4–2.8 (m, 6 H), 2.81 (dd, 1 H, J = 3, 16), 3.17 (d, 1 H, J = 2), 3.53 (dd, 1 H, J = 7, 10), 3.68 (s, 3H), 4.14 (tt, 1 H, J = 7, 10); mass spectrum, m/z 345 (0.36), 310 (1.38), 203 (7.55), 142 (7.96), 96 (7.83), 73 (4.99), 70 (2.41). Anal. Calcd for $C_{16}H_{28}NO_3SiCl$: C, 55.56; H, 8.16; N, 4.05. Found: C, 55.63; H, 8.06; N, 4.12.

Compound 6. A solution of alcohol **4** (100 mg, 0.31 mmol) and (thiocarbonyl)diimidazole (109 mg, 0.6 mmol, 2.0 equiv) in 0.6 mL of THF was stirred at 25 °C for 4 h. The solvent was removed under reduced pressure, and the residue was chromatographed on 8 g of silica gel, using ASII as eluant. The thiocarbamate (133 mg, 100%) was isolated as a yellowish oil: IR 1735, 1530, 1390, 1340, 1290, 935 cm^{-1}; ^1H NMR δ 1.32 (dt, 1 H, J = 2, 10), 1.50 (d, 1 H, J = 10), 1.4–1.90 (m, 4 H), 2.91 (t, 1 H, J = 7), 2.25 (m, 1 H), 2.42 (dt, 1 H, J = 5, 10), 2.55 (m, 1 H), 2.77 (m, 1 H), 2.91 (dd, 1 H, J = 3, 18), 3.06 (br t, 1 H, J = 4), 3.10 (t, 1 H, J = 8), 3.29 (br t, 1 H, J = 7), 3.44 (s, 3 H), 5.57 (dt, 1 H, J = 6, 10), 7.00 (s, 1 H), 7.60 (s, 1 H), 8.31 (s, 1 H); HRMS calcd for $C_{20}H_{31}N_3O_4SSi$ 437.1804, obsd 437.1789.

Compound 7. A solution of 15.0 mg (0.034 mmol) of thiocarbamate **6** in 3 mL of toluene was heated at 90 °C for 12 h. After cooling to room temperature, the solvents were removed under reduced pressure and the residue was chromatographed on 4 g of silica gel, using ASII as eluant. Compound **7** was isolated as a light yellowish oil (11.2 mg, 75%): IR 1730, 1440, 1255, 1160, 915, 885, 845 cm^{-1}; ^1H NMR δ 0.11 (s, 9 H), 1.60–1.82 (m, 3 H), 1.99–2.27 (m, 2 H), 2.34 (dt, 1 H, J = 12, 6), 2.44–2.66 (m, 4 H), 2.71–2.92 (m, 3 H), 3.28 (br s, 1 H), 3.65 (m, 1 H), 3.72 (s, 3 H), 4.40 (tt, 1 H, J = 5, 10), 7.02 (s, 1 H), 7.11 (s, 1 H), 7.57 (s, 1 H); HRMS calcd for $C_{20}H_{31}N_3O_4SSi$ 437.1804, obsd 437.1784.

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