Neighboring Group Effects in the β-Halo Amines. Synthesis and Solvolytic Reactivity of the *anti*-4-Substituted 2-Azaadamantyl System[1]

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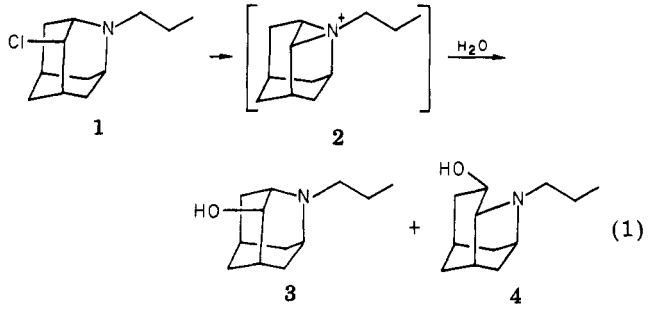
The syntheses of *anti*-4-chloro-2-*n*-propyl-2-azaadamantane (1) and 2-(2-chloroethyl)-2-azaadamantane (8) were carried out. When 1 was subjected to solvolysis in aqueous methanolic NaOH, a rate enhancement of ca. 2×10^6 was observed at 25 °C, compared to that for 2-chloroadamantane (23). The solvolytic rate of 1 is comparable to that of an aliphatic β-halo amine, and because of the absence of a kinetic rate component due to solvent assistance in the adamantyl system, the observed enhancement may represent the rate-limiting case for the substituted β-chloroethylamines. The solvolysis rate of 8 was 2.5-fold less than that of 1, despite an expected decrease in activation energy. The lower rate for 8 may be due to its larger negative entropy of activation compared to that of 1. Indirect evidence was found for the existence of aziridinium ion intermediates during solvolysis, but their direct observation remains to be accomplished.

The adamantane framework has been used on many occasions to investigate fundamental chemical relationships, particularly the processes encompassed by physical organic chemistry.[2] Many of these investigations have been based upon the parent carbocyclic system, which is now fairly well characterized. Fewer investigations have been performed on the various heteroadamantanes, and, correspondingly, less is known about these systems and the processes occurring therein. Of particular interest to us is the 2-azaadamantane system,[3] especially its 4-substituted derivatives, some of which we are investigating for their potential pharmacophoric actions. We believe that compounds of this class may also offer considerable insight into neighboring group solvolytic effects, and we report here some of the results of our investigations in this regard.

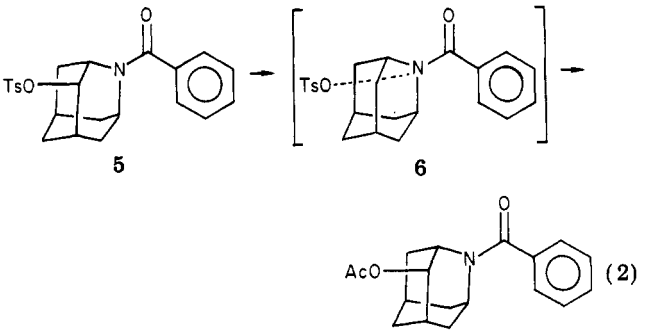
In an *anti*-4-substituted 2-azaadamantane such as 1, the relationship of the chlorine atom to the N is formally one of a conformationally defined β-halo amine. When exposed to solvolysis conditions, it may follow a typical β-halo amine decomposition pathway via a tetracyclic aziridinium ion 2 (eq 1). Nucleophilic solvent attack upon 2 would



1 2 3 4 (1)

result in the formation of tricyclic products 3 and possibly 4, depending on the nature of the solvolytic process. Moreover, if the nucleophilically assisted process 1 → 2 is indeed β-halo amine-like, a solvolytic rate enhancement for this step would be expected. Such an activation process has been used to advantage in the design of agents with selective cytotoxic[4] and other[5] pharmacophoric properties.

In fact, the *anti*-4-substituted 2-azaadamantyl system is known.[6,7] Staas and Spurlock[6] have reported the investigation of the solvolytic reactivity of *p*-toluenesulfonate 5, which was found to undergo acetolysis at a rate 4-fold slower than 2-adamantyl tosylate. They cited this rate retardation as evidence for neighboring group participation of the N (e.g., 6, eq 2), since the expected rate retardation



5 6 (2)

based upon purely inductive effects of the amide was 3–4 times greater than was actually observed. Unfortunately, this investigation was based upon a deactivated system (5), where the electron-donating influence of the nitrogen on solvolysis is not large, and interpretation is complicated by a large negative inductive effect due to the benzoyl function. Thus, the neighboring group effect in the parent tertiary amine is difficult to evaluate or predict on the basis of existing knowledge. A second point confounding this study was the inaccessibility of the 4-syn epimer of 5, in which only an inductive effect will operate. Thus, separation of any activating anchimeric influence from deactivating inductive influence in this manner was not possible. It would be instructive to examine the solvolytic behavior of the alkyl-substituted system rather than the acyl-substituted system, where positive anchimeric effects should be much more prominent.

That a nitrogen atom in an adamantyl framework may play an activating role in solvolysis is evidenced by the behavior of 1-chloro-2-methyl-2-azaadamantane (7).[8] Starewicz et al.,[9] reported a 700-fold rate increase for the ethanolysis of 7 (eq 3) compared to that for 1-chloroadamantane. An even greater increase (9000×) was ob-

(1) A preliminary account of this work was reported at the Second Chemical Congress of the North American Continent, Las Vegas, NV, Aug 24–29, 1980; Abstract ORGN 326.
(2) For a review of adamantane chemistry, see: Fort, R. C., Jr. "Adamantane, the Chemistry of Diamond Molecules"; Marcel Dekker: New York, 1976.
(3) Stetter, H.; Tacke, P.; Gartner, J. *Chem. Ber.* **1964**, *97*, 3480.
(4) For example, see: Price, C. C. In "Antineoplastic and Immunosuppressive Agents"; Sartorelli, A., Johns, D. G., Eds.; Springer-Verlag: New York, 1975; Part II, pp 1–5.
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(6) Staas, W. H.; Spurlock, L. A. *J. Org. Chem.* **1974**, *39*, 3822.
(7) Lessard, J.; Cote, R.; Mackiewicz, P.; Furstoss, R.; Waegell, B. *J. Org. Chem.* **1978**, *43*, 3750.
(8) Meyer, W. P.; Martin, J. C. *J. Am. Chem. Soc.* **1976**, *98*, 1231.
(9) Starewicz, P. M.; Hill, E. A.; Kovacic, P.; Gagneux, A. R. *J. Org. Chem.* **1979**, *44*, 3707.

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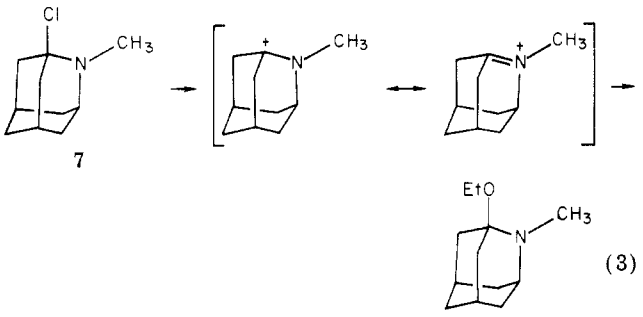

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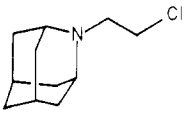
(3)

served for the *N*-demethylated parent compound. This anchimeric assistance occurred despite the unfavorable stereochemical relationship between the N electron pair and the developing p orbital. When the larger set of bridgehead-substituted β-halo amines was considered, an apparent positive relationship between solvolysis rate and ease of overlap between the N electron pair and the bridgehead empty p orbital was established.[9]

In light of the deactivation associated with **5** and the fact that **1** would not be expected to suffer from either the same deactivation or the unfavorable stereochemistry of **7**, we have investigated the solvolytic processes concerned with **1**, and we report here our results supporting considerable anchimeric assistance to its solvolysis.

Results

On the basis of earlier reports,[6] it was apparent that the 4-syn epimer of **1** would be accessible with difficulty, if at all. To provide some other basis for comparison, we chose to synthesize and study the corresponding "exocyclic" β-haloethylamine **8**. While the study of **8** would not allow



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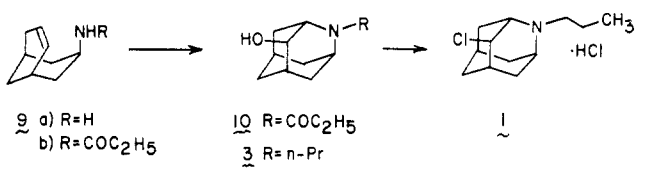
the separation of inductive deactivation and electron pair activation effects that the 4-syn epimer of **1** would, we believed that we could obtain some insight into the ease of activation of **1** by comparing its solvolytic behavior to that of **8** and to 2-chloro-adamantane. Both **1** and **8** should have very similar basicities.

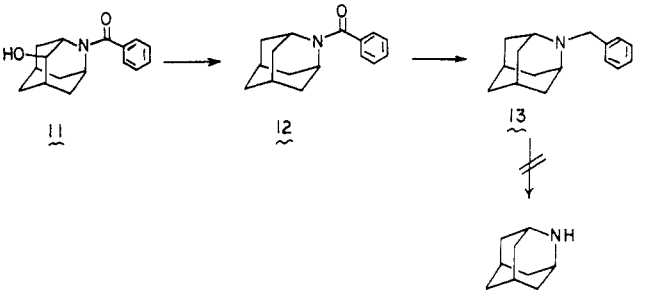
The synthesis of **1** was accomplished by starting from *endo*-bicyclo[3.3.1]non-6-en-3-ylamine (**9a**, Scheme I).[6] Treatment of **9a** with propionyl chloride in pyridine afforded propionamide **9b** which was subsequently oxidized with *m*-chloroperoxybenzoic acid to form 2-propionyl-2-azaadamantan-*anti*-4-ol (**10**) after workup. As previously reported,[6] the presumed intermediate epoxide was not isolable. Reduction of **10** with BH_3 produced amino alcohol **3**. ^{13}C NMR analysis of **3** confirmed its isomeric purity, which must be 4-anti on the basis of the direction of ring closure. No minor product peaks were present in the spectrum. Treatment of **3** with thionyl chloride completed the synthesis of **1**, isolated as the HCl salt.

The synthesis of **8** was more difficult than expected. Since **8** may be obtained from 2-azaadamantane by alkylation with ethylene oxide followed by treatment with thionyl chloride, our objective became the synthesis of 2-azaadamantane. With a supply of **9a** on hand, our first approach (Scheme II) used this intermediate, since much of the chemistry of this system had previously been worked out.[6] Benzamide **11**, prepared from **9a** by treatment first with benzoyl chloride followed by *m*-chloroperoxybenzoic acid,[6] was defunctionalized at the 4-position by oxidation with pyridinium chlorochromate,[10] and then reduction of

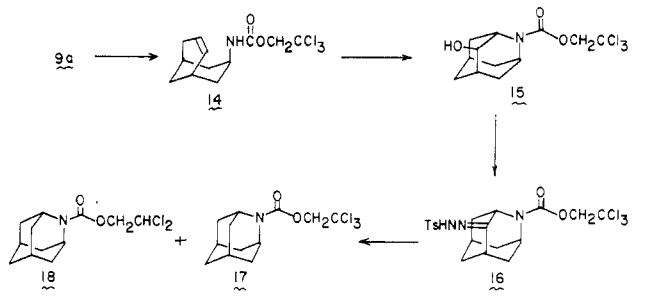
Scheme I



Scheme II



Scheme III



the corresponding *N*-tosylhydrazone with sodium cyanoborohydride.[11] The resulting benzamide **12** was further reduced with borane to 2-benzyl-2-azaadamantane (**13**). Hydrogenolytic debenzylation of **13** was uniformly unsuccessful, even at high pressures and temperatures. This result is particularly surprising in view of the ease with which the corresponding 4-hydroxy-2-benzyl-2-azaadamantane is debenzylated,[6] a result that we were able to duplicate. All attempts to saponify **12** to directly yield 2-azaadamantane were also unsuccessful, returning unchanged starting material even after treatment with aqueous ethanolic KOH at reflux for 1 week.

Because of the surprising unreactivity of **13**, we sought an alternative blocking group for the nitrogen atom that could later be removed by a method other than catalytic hydrogenolysis. The one that was chosen was the (2,2,2-trichloroethoxy)carbonyl function,[12] with which the transformations in Scheme II were repeated (Scheme III). Protection of **9a** by treatment with (2,2,2-trichloroethoxy)carbonyl chloride proceeded smoothly to give **14** which was subsequently epoxidized and closed to afford **15**. Oxidation as above and treatment with *p*-toluenesulfonohydrazide produced the expected toluenesulfonylhydrazone **16**. Reduction of **16** with sodium cyanoborohydride produced a mixture of the expected defunctionalized product **17** and, unexpectedly, its dichloro analogue **18** in a ratio of about 2.5:1 by NMR. Compound **18** was unreactive toward deblocking conditions (Zn in either acetic acid or methanol). The less nucleophilic reducing agent catecholborane[13] returned **16** unchanged,

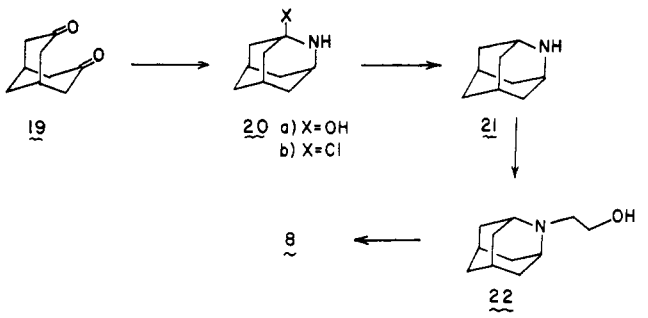
(10) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(11) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.
(12) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, 2555.
(13) Kabalka, G. W.; Baker, J. D., Jr.; Neal, G. W. *J. Org. Chem.* **1977**, *42*, 512.

Table I. Decomposition Rates in 20% Aqueous Methanol at pH 12

compd	temp, °C	10^3k,[a] s^{-1}	$t_{1/2}$, s	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1	15	4.08 (0.21)	170		
	20	4.80 (0.32)	144		
	25	7.33 (0.86)	95		
	25	8.60[b]	81	14.5	−19
	30	15.24 (0.10)	45		
8	20	2.11 (0.21)	329		
	25	2.91 (0.19)	238		
	25	3.00[b]	231	12.1	−30
	30	4.08 (0.26)	170		
	35	6.13 (1.00)	113		
23	25	4.73×10^{-6} [b]	4.07×10^4 [d]	25.6	−11
	90	0.0129 (0.0030)	902[c]		
	100	0.0352 (0.0076)	328[c]		
	110	0.0859 (0.0041)	134[c]		
24	10	1.64 (0.99)	422		
	20	4.55 (0.31)	152		
	25	7.38[b]	94	16.2	−14

[a] Numbers in parentheses represent 95% confidence limits for the slopes of the regression lines. [b] Rates based on the Arrhenius regression line formed by the measured data. [c] Half-life in minutes. [d] Half-life in hours.

Scheme IV



while borane accomplished the defunctionalization without concomitant reduction of the blocking group. However, the yield of **17** was disappointingly low (19%). Furthermore, when **17** was subjected to deblocking conditions (Zn in acetic acid or methanol), no 2-azaadamantane could be detected, and only low yields of **18** were isolable. Because of the unreactivity of **12** toward base hydrolysis conditions, similar attempts on **17** were not performed.

The anomalous unreactivities of the N-substituted 2-azaadamantanes caused us to seek a synthesis of **8** by modification of one of the published procedures (Scheme IV). Thus, bicyclo[3.3.1]nonane-3,7-dione (**19**) was synthesized from 1,3-dibromoadamantane[14] by the method of Gagneux and Meier.[15] Reductive amination of **19** to **20a** was accomplished in very low yield by using the published procedure.[3] However, the use of ammonium acetate and sodium cyanoborohydride produced **20a** in improved but still only fair yield (37%). Once formed, **20a** was easily converted to **20b** by using thionyl chloride. Dehalogenation of **20b** to 2-azaadamantane (**21**) was accomplished in good yield with $LiAlH_4$ in DME, after the published method[3] (H_2/Ni) met with a uniform lack of success. Formation of **8** was then easily effected by treatment of **21** with ethylene oxide followed by thionyl chloride. As was the case for **1**, **8** was isolated and stored as the HCl salt.

Product studies of **1** and **8** were performed in 20% aqueous CH_3OH at 25 °C. In the case of **8**, only **22** was recovered, as expected. However, **1** produced two apparent products. Unfortunately, the mixture of products was not separable by standard chromatographic methods, and the quantity of material available for study was too little to investigate in depth. The major product of the mixture (ca. 85%) was identified as **3** by comparison of its ^{13}C resonances to those of authentic **3**. The minor component of the mixture (ca. 15%) showed eight identifiable resonances that compared closely in chemical shifts to those of **3**, with the exception of the lowest field resonance at δ 78.7. Clearly the minor product was closely related to **3**, but based upon the information at hand, a firm assignment of its structure was not possible. Although one may assume that the minor product was 2-*n*-propyl-2-azaprotoadamantan-*anti*-4-ol (**4**), further work will be necessary before this can be confirmed. Other structures for the minor product are also possible (see Discussion).

Kinetic studies were undertaken on both **1** and **8** in 20% aqueous CH_3OH by following the appearance of Cl^- over time with a chloride ion selective electrode. For comparison, the rate of solvolysis of 2-chloroadamantane (**23**) was also determined in the same medium at higher temperatures and its rate then extrapolated to 25 °C. The results are shown in Table I. Each reaction was run in a medium 0.01 M in NaOH and carefully protected from atmospheric CO_2. The reaction was followed for 4–5 half-lives, over which time good first-order or pseudo-first-order kinetics were observed.

Discussion

Both the complete unreactivity of 2-benzyl-2-azaadamantane (**13**) to hydrogenolysis and the difficulty encountered in the removal of the (2,2,2-trichloroethoxy)carbonyl protecting group from **17** appear to be the result of limited access to a hindered, unreactive center. The striking difference in reactivity to hydrogenolysis between **13** and the corresponding 4-hydroxy analogue (which undergoes reduction at room temperature and atmospheric pressure[6]) may be due to either an inductive weakening of the benzylic C–N bond by OH or an anchoring effect on the catalyst surface, or a combination of both. That a mechanistically unrelated deblocking procedure (**17** → **21**) also failed may serve to discourage future synthetic approaches requiring the transformation of functional groups in this environment. In order to confirm that the lack of success lay in the substrate and not in the method, we subjected bicyclic amine **9a** to a blocking and deblocking operation (Zn in methanol) identical with that in Scheme III and recovered **9a** in excellent yield (85%). While the (2,2,2-trichlorethoxy)carbonyl group is stable to acid and base,[13] it appears to be somewhat sensitive to weakly nucleophilic reducing agents such as $NaBH_3CN$. Moreover, the

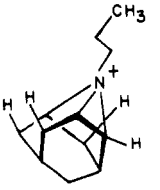
(14) Likhotvorik, I. R.; Dovgan, N. L.; Danilenko, G. I. *Zh. Org. Khim.* **1977**, *13*, 897.
(15) Gagneux, A. R.; Meier, R. *Tetrahedron Lett.* **1969**, 1365.

transformation that occurs (formation of a dichloro analogue such as **18**) inactivates the group to the deblocking reagents. The formation of this dichlorinated derivative may in fact be only a minor side reaction in the usual case where the substrate is more reactive and is observable here because of this system's special unreactivity. Further work will be necessary to elucidate this point.

By any measure, **1** shows unmistakably high solvolytic reactivity under the experimental conditions, which implies the operation of a very high degree of anchimeric assistance to ionization by the basic nitrogen atom. In order to obtain a quantitative measure of this large rate enhancement, we have compared the reaction rate of **1** to the extrapolated rate of the carbocyclic analogue 2-chloroadamantane (**23**) in the same medium. Strictly speaking, the comparison should be between **1** and 4-*n*-propyl-2-chloroadamantane, where the two functional groups have cis-diequatorial stereochemistry in the common cyclohexane ring. However, we have chosen to use **23** itself for comparison, due to synthetic difficulties associated with the former compound and to the likelihood that the differences in behavior between **23** and its 4-*n*-propyl analogue will be slight relative to the differences between **1** and **23**. This simplifying approach was analogous to that taken by Hammer et al.[16] in their study of the solvolytic reactivity of 3-chloro-1-ethylpiperidine. We have found a 1.8×10^6-fold rate enhancement for **1** vs. **23** at 25 °C. While many studies have been performed on the dynamics of β-halo amine solvolyses,[17] to our knowledge none have reported a rate enhancement of this magnitude. By comparison, Hammer et al.[16] reported a 5×10^3-fold rate enhancement at 80.5 °C in 80% aqueous ethanol, with respect to the rate for 2-chlorocyclohexane. While temperature and solvent differences between the two studies may account for a portion of the 364-fold difference in the magnitude of anchimeric assistance, other factors must also be operative.

Some insight into the causes of the large rate enhancement for **1** may be gained by an examination of both the characteristics of the substrates involved and the thermodynamic parameters associated with the reaction. On the basis of substrate considerations, the adamantane ring system represents a special case in many respects. Anchimeric activation of **1** is occurring at a site well-known for its limiting secondary solvolytic behavior, i.e., its reluctance to support a component of nucleophilic solvent assistance to ionization (k_s).[18,19] In fact, the large rate enhancement for **1** compared to **23** may be due to a combination of the activating effect of the N and the deactivating or limiting state of the carbocyclic analogue. Since careful studies have shown that the reduced solvolytic rates of secondary adamantyl substrates are due to the virtual absence of a k_s component,[18-21] one may expect that the reaction rate of **1** is essentially free of solvent (k_s) effects. Thus, its reaction rate may be composed solely of the unassisted solvolytic contribution (k_c), which is negligible, and one due to the anchimeric assistance of the neighboring nitrogen. The observed rate enhancement of 1.8×10^6 may then be considered to be the neighboring group component k_Δ or, perhaps more appropriately, k_n.[22] If this interpretation is valid, then the rate enhancement for **1** vs. **23** may represent the limiting case for anchimeric assistance in the β-halo amine series. To our knowledge, the rate enhancement for this substrate represents the greatest increase (relative to carbon) for a β-halo amine reported to date. One implication of these results is that in the less sterically hindered substrates (e.g., the acyclic alkylating drugs), solvent or medium nucleophilicity may play a role in the activation process. The separation of the rate expression for an anchimerically assisted substrate into component contributions due to solvent (k_s) and neighboring group (k_Δ) effects has been fully accomplished only for the 2-phenylethyl halides,[24] but the results reported here indicate to us that such a quantitative process may also be possible for the β-halo amines. However, a substantial amount of work remains before this question can be addressed.

On an absolute scale, the rate of activation of **1** is close to, if not slightly greater than the rate found for a typical β-halo amine such as *N,N*-diethyl-β-chloroethylamine **24** (Table I). Somewhat surprisingly, the "exocyclic" isomer **8** solvolyzed at a rate about 3-fold *slower* than that of **1** or **24** at 25 °C. Reference to the activation parameters for the reaction (Table I) provides a partial rationalization for the rate anomaly but simultaneously raises several questions. The difference between the enthalpies of activation of **1** and **8** (2.4 kcal/mol) is consistent with an expected higher strain energy for the transition state of **1**. It is noteworthy that the transition state of **1** is a reasonably stable species and appears to be comparable in stability to that of an aliphatic β-halo amine **24**. As expected, the enthalpies of activation of the β-halo amines are significantly lower than that of **23**, which derives no benefit from either solvent or anchimeric stabilization. Less explainable are the respective entropies of activation. It is unclear why **8** should possess such a highly negative $\Delta S^\ddagger$, but it apparently is this factor that accounts for the observed slower rate. While the added degrees of freedom of **8** will account for a portion of the decreased entropy of activation, other factors may also be operative. One of these may be solvent ordering. If an aziridinium ion transition state is formed in each case, each ion will interact with solvent molecules differently. The ease with which the aziridinium carbons (upon which considerable positive character resides[25]) can interact with solvent is much greater for the "exocyclic" intermediate **25** than the "endocyclic" intermediate **2**.



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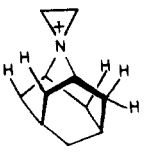

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(16) Hammer, C. F.; Heller, S. R.; Craig, J. H. *Tetrahedron* **1972**, *28*, 239.

(17) For example, see: (a) Cohen, B; Van Artsdalen, E. R.; Harris, J. M. *J. Am. Chem. Soc.* **1948**, *70*, 281. (b) Bartlett, P. D.; Ross, S. D.; Swain, C. G. *Ibid.* **1949**, *71*, 1415. (c) Levins, P. L.; Papanastassiou, Z. B. *Ibid.* **1965**, *87*, 826. (d) Knevel, A. M.; Kehr, P. F. *Anal. Chem.* **1972**, *44*, 1863. (e) Portmann, R. E.; Ganter, C. *Helv. Chim. Acta* **1973**, *56*, 1991.

(18) Fry, J. L.; Lancelot, C. J.; Lam, L. K. M.; Harris, J. M.; Bingham, R. C.; Raber, D. J.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1970**, *92*, 2538.

(19) Raber, D. J.; Harris, J. M.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 4821.

(20) Schleyer, P. v. R.; Fry, J. L.; Lam, L. K. M.; Lancelot, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 2542.

(21) Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7658.

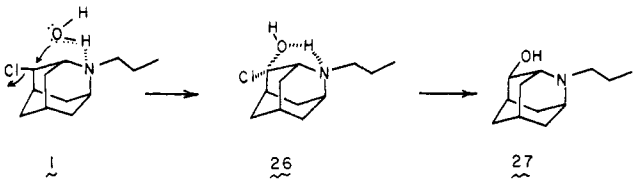
(22) The original neighboring group component was defined as k_Δ, in the context of neighboring aryl participation.[23] If one is dealing with activation by nonbonding electrons, it may be more appropriate to denote the activation process as a k_n process.

(23) (a) Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700. (b) Schleyer, P. v. R.; Fry, J. L.; Lam, L. K. M.; Lancelot, C. J. *Ibid.* **1970**, *92*, 2542.

(24) Schadt, F. L.; III; Lancelot, C. J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1978**, *100*, 228.

(25) Ruble, J. R.; Hite, G.; Soares, J. R. *Acta Crystallogr., Sect. B* **1976**, *32*, 136.

Scheme V



This interaction would produce a greater degree of solvent ordering for **25** than for **2**, with a concomitant decrease in $\Delta S^{\ddagger}$. An additional factor[26] that could contribute to the differences in rates is the degree of substitution at the sites of ionization. For **1**, the reaction path leading to the transition state (presumably **2**) will have a component of secondary ionic character, while the corresponding path for **8** leading to **25** will have a component of primary ionic character. The latter process could consequently be stabilized to a lesser degree. However, when one considers the behavior of **24**, this explanation appears to become less viable. This simple aliphatic system also generates its ionic center from a primary site, yet its activation parameters are about as expected relative to those of **1**, and no appreciable difference between the rates of **1** and **24** is observed.

One aspect of this study that deserves mention and further work is the precise nature and identity of the transition state for **1**. We presently have only indirect evidence in support of the existence of the tetracyclic aziridinium ion intermediate **2**. One can conceive of two potential solvolysis pathways for **1**. The more obvious one proceeds through **2**, affording a mixture of **3** and **4**, with **3** likely to predominate on thermodynamic grounds. A second process[26] that could operate in an aqueous medium is one where a water molecule strongly hydrogen bonded to the basic nitrogen is "guided" by it toward the backside of the developing positively charged 4-carbon to produce an intermediate such as **26** (redrawn for clarity). This process would result in the 4-*syn*-hydroxy product **27** (Scheme V). On the basis of the reluctance of the adamantyl bridge position to undergo nucleophilic attack[18,19] and the present product study of **1**, we currently favor the former interpretation. Clearly the major product of solvolysis of **1** is the *anti*-4-hydroxy product **3**. On this basis alone one may conclude that solvent attack proceeds predominantly from the anti direction with retention of configuration about C-4. This fact supports but does not prove the existence of **2**. It also does not refute the existence of **26**, for the processes could operate competitively. Either the isolation and characterization of **2** or the identification of the minor product of solvolysis will provide the necessary information to differentiate between these possible pathways. We have been handicapped by our inability to purify the small amount of minor solvolytic product resulting from **1**, and thus we have undertaken the synthesis and study of the intermediate **2**. Its characterization and solvolytic behavior will be the subject of a future report.

Experimental Section

Melting points were obtained on a Thomas-Hoover Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on either a Beckman Acculab 3 or a Beckman 620MX spectrometer. Proton NMR spectra were obtained on a Hitachi Perkin-Elmer R24B spectrometer, with chemical shifts reported relative to Me_4Si. ^{13}C spectra were run on either a Bruker WP-60 or a Bruker WH-270 spectrometer, again by using Me_4Si as an internal standard. Mass spectra were obtained on an AEI MS902 instrument. Microanalyses were performed by Baron Consulting Co. or MHW Laboratories. All solvents and reagents were of reagent purity and were used without further purification unless otherwise noted.

***endo*-Bicyclo[3.3.1]non-6-en-3-ylamine (9a)** was prepared by modification of the method of Staas and Spurlock[6] and by starting from 2-adamantanone (Aldrich).

***N*-(*endo*-Bicyclo[3.3.1]non-6-en-3-yl)propionamide (9b).** To a 6.291-g (45.9 mmol) quantity of **9b** in 25 mL of C_6H_6 and 4.0 g of dry pyridine was added dropwise 4.53 g (49 mmol) of propionyl chloride at 0 °C. The mixture was stirred for 1 h and then stored at 5 °C overnight. The product was dumped into ice–H_2O and extracted three times with Et_2O. The extracts were washed with 10% HCl, twice with H_2O, and 5% $NaHCO_3$ and then dried over $MgSO_4$. Evaporation of solvent afforded 8.43 g (95%) of pale yellow oil that showed no tendency to solidify: IR (neat) 3400, 3300, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (3 H, t, CH_3), 1.5–2.6 (12 H, m), 4.3 (1 H, br s, NCH), 6.0 (2 H, m, CH=CH), 6.8 (1 H, br s, NH); mass spectrum, for M^+, *m/e* 193.1467 (calcd for $C_{12}H_{19}NO$ *m/e* 193.1466).

2-Propionyl-2-azaadamantan-*anti*-4-ol (10). To 8.657 g (42.5 mmol) of 85% MCPBA in 100 mL of CH_2Cl_2 was slowly added 8.209 g (42.5 mmol) of **9b** in 100 mL of CH_2Cl_2. The temperature was maintained at <25 °C during addition. After 36 h excess peracid was removed by washing several times with 10% $NaHSO_3$ and then 5% $NaHCO_3$. Drying over $MgSO_4$ and evaporation of solvent produced 6.963 g (78%) of **10** as a pale yellow oil: IR (neat) 3300, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3 H, t, CH_3), 1.3–2.7 (12 H, m), 3.8 (2 H, m, CHN), 4.63 (1 H, m, CHOH), 6.4 (1 H, s, OH); mass spectrum, for M^+, *m/e* 209.1409 (calcd for $C_{12}H_{19}NO_2$ *m/e* 209.1416).

2-*n*-Propyl-2-azaadamantan-*anti*-4-ol (3). A 6.800-g (32.5 mmol) quantity of **3** in 50 mL of dry THF was treated with 67 mL of 1 M BH_3 in THF (Aldrich) under N_2. The solution was heated to reflux for 3 h. Excess BH_3 was destroyed by addition of 6 N HCl and heating, which drove off the THF. The aqueous solution was cooled, made strongly basic with solid NaOH, and extracted with Et_2O. The extracts were dried over Na_2SO_4 and evaporated to afford a pale yellow oil which was distilled (bp 110–115 °C (0.1 mm)] to yield 5.597 g (88%) of **3**: IR (neat) 3397, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, t, CH_3), 4.06 (1 H, m, CHOH), 2.6–2.8 (4 H, m, CHN, CH_2N), 1.3–2.1 (12 H, m); ^{13}C NMR δ 12.0 (CH_3), 21.4 (C10), 25.2 (C7), 26.8 (C9), 30.8 (C6), 31.8 (C8), 33.9 (C5), 34.1 (CH_2Me), 50.4 (NCH_2), 54.5 (Cl), 56.1 (C3), 69.5 (C4); mass spectrum, for M^+, *m/e* 195.1619 (calcd for $C_{12}H_{21}NO$ *m/e* 195.1624).

***anti*-4-Chloro-2-azaadamantane (1).** A 505-mg (2.59 mmol) portion of **3** and 10 mL of freshly distilled $SOCl_2$ were combined and heated to reflux for 2.5 h. The residual $SOCl_2$ was removed in vacuo to afford a pale yellow solid. Trituration with dry Et_2O afforded 567 mg (88%) of **1**·HCl. Recrystallization from CH_2Cl_2–C_6H_6 afforded white crystals: mp 242–243 °C; IR (Nujol) 2500, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (3 H, t, CH_3), 1.5–3.2 (16 H, m), 5.25 (1 H, br s, CHCl).

Anal. Calcd for $C_{12}H_{21}NCl_2$: C, 57.60; H, 8.46; N, 5.60. Found: C, 57.44; H, 8.67; N, 5.80.

2-Benzoyl-2-azaadamantan-*anti*-4-ol (11) was synthesized from **9a** by the method of Staas and Spurlock.[6]

2-Benzoyl-2-azaadamantane (12). To a suspension of 426 mg (16.5 mmol) of pyridinium chlorochromate in 24 mL of CH_2Cl_2 was added 705 mg (2.74 mmol) of **10** in 12 mL of CH_2Cl_2. The mixt. was stirred for 30 min and then diluted with anhydrous Et_2O. The supernatant was decanted and the residue triturated with Et_2O. The combined extracts were washed with 5% aqueous NaOH until the color disappeared, then with 5% HCl, and finally with H_2O. Drying over $MgSO_4$ and evaporation of solvent afforded 677 mg (97%) of a colorless oil that was not further purified. The product was combined with 590 mg (3.09 mmol) of *p*-toluenesulfonohydrazide in absolute ethanol and heated for 5 min. The resulting *p*-toluenesulfonylhydrazone was combined with 350 mg (1.84 mmol) of *p*-toluenesulfonic acid monohydrate in 12 mL of ethanol. A 816-mg (12.3 mmol) portion of $NaBH_3CN$ was added and the mixture heated to reflux for 1 h, after which time a second

(26) We thank one of the referees for this suggestion.
(27) Hoek, W.; Strating, J.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1045.

identical portion of $NaBH_3CN$ was added. After being stirred at reflux overnight, the mixture was diluted with 30 mL of H_2O and extracted with C_6H_6. The combined extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, and evaporated to give 560 mg (88%) of **12** as a pale yellow oil that resisted crystallization: IR (neat) 3050, 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.6 (12 H, m), 3.9 (1 H, br s, CHN), 7.35 (5 H, s, C_6H_5).

2-Benzyl-2-azaadamantane (13). A 488-mg (2.04 mmol) quantity of **12** in 10 mL of dry THF was treated with 5.7 mL of 1 M BH_3 in THF. The mixture was heated to reflux for 3 h, cooled, and then treated dropwise with 2.5 mL of 6 N HCl. When H_2 evolution ceased, the solution was heated to remove THF, cooled, made strongly basic with solid NaOH, saturated with NaCl, and extracted with $CHCl_3$. The combined extracts were washed with H_2O, dried over $MgSO_4$, and evaporated to yield 432 mg (94%) of **13** as a pale yellow oil: bp 120–130 °C (0.6 mm); HCl salt, mp 193–194.5 °C; NMR ($CDCl_3$) δ 1.30–4.0 (15 H, m) 4.3–4.6 (2 H, br d, CH_2), 7.1–8.1 (5 H, m, C_6H_5).

Anal. Calcd for $C_{16}H_{22}NCl$: C, 68.19, H, 8.58; N, 4.97. Found: C, 68.05; H, 8.50; N, 5.12.

***N*-[(2,2,2-Trichloroethoxy)carbonyl]-*endo*-bicyclo[3.3.1]non-6-en-3-ylamine (14).** To a solution of 4.350 g (31.8 mmol) of **9a** in 50 mL of dry C_6H_6 and 2.5 mL of pyridine was added dropwise 7.007 g (31.8 mmol) of (2,2,2-trichloroethoxy)-carbonyl chloride with stirring. After 21 h another 50 mL of C_6H_6 was added. The solution was washed with 0.5 N HCl, dried over $MgSO_4$, and evaporated to yield 10.4 g (100%) of yellow solid that was shown to be a mixture of **14** and trichloroethyl carbonate. The mixture (10.4 g) was stirred with 8 g of KOH in 160 mL of MeOH and 12 g of $KHCO_3$ in 80 mL of H_2O for 15 h. The MeOH was evaporated and the aqueous residue extracted with CH_2Cl_2. The combined extracts were washed with 0.5 N HCl and H_2O, dried over $MgSO_4$, and evaporated to afford crude **14**. Recrystallization from MeOH–H_2O produced 6.575 g (67%) of **14**: mp 91–94 °C; IR (KBr) 3390, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.5 (10 H, m), 4.05 (1 H, m, CHNH), 4.75 (2 H, s, OCH_2), 6.05 (2 H, m, CHCH).

[2-(2,2,2-Trichloroethoxy)carbonyl]-2-azaadamantan-*anti*-4-ol (15). A solution of 2.705 g (8.70 mmol) of **14** in 20 mL of CH_2Cl_2 was added dropwise to 1.770 g (8.70 mmol) of MCPBA in 20 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for 2 days at room temperature, and then 40 mL of additional CH_2Cl_2 was added. The solution was washed with 10% $NaHSO_3$, 10% $NaHCO_3$, and H_2O, dried over $MgSO_4$, and evaporated to yield 2.694 g (94%) of **15** as a thick oil that resisted all crystallization attempts: IR (neat) 3410, 1685 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.5 (10 H, m), 3.93 (1 H, m, CHOH), 4.30 (3 H, m, CHN,OH), 4.80 (2 H, s, CH_2).

2-[(2,2,2-Trichloroethoxy)carbonyl]-2-azaadamantan-4-one *p*-Toluenesulfonylhydrazone (16). A 2.694-g (8.24 mmol) quantity of **15** was treated with 10.860 g (49.4 mmol) of pyridinium chlorochromate in 70 mL of CH_2Cl_2 in a manner identical with that for **12** to produce 2.492 g (93%) of a thick oil that was used without further purification (IR 1695 cm^{-1}). The product was combined with 1.712 g (9.2 mmol) of *p*-toluenesulfonohydrazide in 50 mL of absolute EtOH and heated to reflux for 24 h. The mixture was reduced in volume and cooled to 0 °C to precipitate crude **16**. Recrystallization from EtOH produced 1.781 g (47%) of **16** as a powdery solid: mp 156–158 °C; IR (KBr) 3120, 1695, 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.2 (10 H, m), 2.45 (3 H, s, CH_3), 4.4 (2 H, m, CHN), 4.8 (2 H, s, OCH_2), 7.2–7.9 (4 H, m, C_6H_4), (NH not assignable).

2-[(2,2,2-Trichloroethoxy)carbonyl]-2-azaadamantane (17). Method A. A solution of 300 mg (0.609 mmol) of **16**, 153 mg (2.43 mmol) of $NaBH_3CN$, and 30 mg of *p*-toluenesulfonic acid monohydrate in 30 mL of absolute EtOH was heated to reflux for 4 h. An additional 111 mg (1.77 mmol) of $NaBH_3CN$ and 30 mg of acid were added, and the reaction was continued for 18 h. The mixture was evaporated, and 25 mL of H_2O was added. The mixture was extracted with C_6H_6, and the combined extracts were dried over $MgSO_4$ and then evaporated to give 151 mg of crude **17**, contaminated with ca. 27% **18**. The two products were inseparable by standard techniques: IR (neat) 1689, 1420, 1123 cm^{-1}; NMR ($CDCl_3$) δ 1.45–2.59 (12 H, m), 4.35 (2 H, m), 4.43 (d, J = 6.5 Hz, OCH_2 of **18**), 4.78 (s, OCH_2 of **17**), 5.9 (t, J = 6.5 Hz, $CHCl_2$ of **18**).

Method B. A 100-mg (0.203 mmol) portion of **16** in 20 mL of dry THF was treated at room temperature with 0.30 mL (0.30 mmol) of 1 M BH_3 in THF. After 15 min an additional 0.30 mL of 1 M BH_3 was added. After 13 h, H_2O was added and the THF removed by distillation. Heating at reflux was continued for 12 h. The mixture was cooled, then extracted with C_6H_6. The combined extracts were dried over $MgSO_4$ and evaporated to produce 49 mg of a colorless oil. The product was chromatographed on silica gel, eluting with C_6H_6–EtOH–NH_3 (50:1:1). The second component solidified on being allowed to stand and was recrystallized from aqueous MeOH to give 13 mg (20%) of **17**: mp 69–71 °C; IR (Nujol) 1689, 1421, 1123 cm^{-1}; NMR ($CDCl_3$) δ 1.35–2.35 (12 H, m), 4.35 (2 H, m), 4.80 (2 H, s); mass spectrum, for M^+, m/e 311.0240 (calcd for $C_{12}H_{16}NO_2Cl_3$ m/e 311.0249).

Attempted Synthesis of 2-Azaadamantane from 17. A 0.518-g quantity of Zn powder was added in small portions to a solution of 0.371 g (1.19 mmol) of **17** in 15 mL of absolute EtOH. The solution was heated at reflux for 7 h and then stirred at room temperature for an additional 13 h. The mixture was filtered, acidified with 10 mL of 1 N HCl, and evaporated to dryness. The residue was dissolved in H_2O, made strongly basic with 10% aqueous NaOH, and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and evaporated to produce 25 mg (7.5%) of **18**. No other product could be isolated, either from the alkaline solution or from the Zn residue.

1,3-Dibromoadamantane was prepared by the method of Likhotvorik et al.,[14] in 61% yield after recrystallization from MeOH.

Bicyclo[3.3.1]nonane-3,7-dione (19) was prepared from 1,3-dibromoadamantane as outlined by Gagneaux and Meier;[15] mp 251–256 °C (lit.[15] mp 254–256 °C).

2-Azaadamantan-1-ol (20a). To a solution of 3.0 g (20 mmol) of **19** and 15.4 g (0.199 mol) of ammonium acetate in 90 mL of MeOH was added 0.868 g (13.8 mmol) of $NaBH_3CN$. The solution was stirred at room temperature for 8 days, made acidic by dropwise addition of 12 N HCl, and evaporated in vacuo. The residue was taken up in 2 N HCl and then extracted with CH_2Cl_2. The aqueous layer was made basic with solid NaOH and then extracted again with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated to yield 1.1 g (37%) of **20a** after recrystallization from hexane; mp 254–257 °C (lit.[3] mp 277–278 °C).

1-Chloro-2-azaadamantane (20b). To 1.159 g (7.575 mmol) of **20a** at 0 °C was added dropwise 12.5 mL of freshly distilled $SOCl_2$ over 30 min. The solution was heated to reflux for 1 h, and then the excess $SOCl_2$ was removed by distillation. The solution was cooled, after which 65 mL of CH_2Cl_2 was added, followed by 130 mL of H_2O. The two-phase mixture was rapidly stirred at 0 °C for 30 min. A 50% aqueous NaOH solution was added dropwise until the aqueous phase became strongly basic. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined yellow extracts were treated with Norite, filtered, dried over Na_2SO_4, and evaporated to give 1.20 g (93%) of **20b** [mp 90–94 °C (lit.[9] mp 97–98 °C)] which was not further purified.

2-Azaadamantane (21). A solution of 1.495 g (8.717 mmol) of **20b** in dry dimethoxyethane (DME) was added dropwise to a suspension of 0.536 g (14.1 mmol) of $LiAlH_4$ in dimethoxyethane. The mixture was heated at reflux for 2 days. The excess DME was then distilled off and the residue suspended in ether. After the sequential addition of 0.54 mL of H_2O, 1.6 mL of 15% NaOH, and 0.54 mL of H_2O, the suspension was filtered and the filter cake washed with hot THF. The combined extracts were evaporated to produce 1.26 g of a brown solid. The solid was taken up in 50 mL of CH_2Cl_2 and extracted with 2 N HCl. The combined aqueous extracts were made strongly basic with solid NaOH and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated to produce a tan solid. Sublimation at 85 °C (5 mm) resulted in 0.551 (46%) of **21** as a white solid: mp 224–227 °C (lit.[3] mp 265.5–268.5 °C); NMR ($CDCl_3$) δ 1.5–2.2 (12 H, m), 2.45–2.75 (1 H, br s, exch), 2.90–3.25 (2 H, br s).

2-(2-Hydroxyethyl)-2-azaadamantane (22). To a solution of 0.551 g (4.02 mmol) of **21** in anhydrous MeOH at 0 °C was added 0.200 g (4.5 mmol) of ethylene oxide. The ice bath was removed, and the solution was stirred at room temperature for

24 h. An additional 0.200 g of ethylene oxide was added and the solution stirred at room temperature for an additional 24 h. The solvent was then evaporated to produce a brown oil. Trituration with anhydrous Et_2O gave 0.625 g (86%) of **22** as a tan solid which was not further purified: mp 45–48 °C; IR (neat) 3370 cm^{-1}; NMR ($CDCl_3$) δ 1.35–2.30 (12 H, m), 2.65–3.05 (4 H, m), 3.45 (2 H, t, J = 5 Hz); mass spectrum, for M^+, m/e 181.1462 (calcd for $C_{11}H_{19}NO$ m/e 181.1467.

2-(2-Chloroethyl)-2-azaadamantane (8). A 5.187-g (43.6 mmol) quantity of $SOCl_2$ was added dropwise to 350 mg (1.90 mmol) of **22** with stirring at 0 °C. After the addition was complete, the ice bath was removed, and the solution was brought to reflux for 2.5 h. Excess $SOCl_2$ was then distilled off, leaving a brown residue which solidified upon standing. The solid was washed with several portions of anhydrous ether and then dried under reduced pressure to produce 231 mg (61%) of **8**·HCl after recrystallization from CH_2Cl_2–C_6H_6: mp 232–233 °C dec; IR (Nujol) 2560, 2485, 1100 cm^{-1}; NMR ($CDCl_3$) δ 1.50–3.15 (13 H, m), 3.35–3.82 (4 H, m), 4.19 (2 H, t, J = 5.5 Hz).

Anal. Calcd for $C_{11}H_{18}NCl$·HCl: C, 55.94; H, 8.11; N, 5.93. Found: C, 55.74; H, 7.92; N, 6.12.

2-Chloroadamantane (23). A 1.00-g (6.58 mmol) portion of 2-adamantanol (Aldrich) was treated with 5.0 mL of freshly distilled $SOCl_2$. The mixture was stirred at reflux for 3 h. The excess $SOCl_2$ was removed by heating under a stream of N_2. Residual $SOCl_2$ was destroyed by addition of ca. 2 mL of dry MeOH. Evaporation of solvent produced 1.073 g (95.7%) of crude **23**, which was recrystallized from MeOH; mp 183–185 °C (lit.[27] mp 186–188 °C).

Solvolysis Product Studies. An approximately 1.0 mM solution of the substrate was prepared by dissolving it in a solution of 480 mL of 0.02 M NaOH and 120 mL of MeOH. The reaction vessel was flushed with N_2 and stirred at a constant temperature (25 °C) for a minimum of 8 half-lives. After evaporation of the MeOH in vacuo, the basic aqueous layer was saturated with NaCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to produce the mixture of products.

Kinetic studies were performed by following the liberation of Cl^- with an Orion 94-17 chloride ion electrode and an Orion 90-02 double-junction reference electrode connected to an Orion 701A ion analyzer. A typical procedure for the β-halo amines follows. Into a jacketed titration cup maintained at 20.00 (±0.01) °C were placed 6.2 mL of 0.010 N NaOH, 1.50 mL of MeOH, and 0.20 mL of 5.0 M $NaNO_3$ (ionic strength adjustor). The stirred solution and electrodes were allowed to equilibrate, after which time a 0.100-mL aliquot of the halo amine in dry MeOH was added at t = 0. The rate of reaction of the test compound was followed by plotting ln ($Cl_\infty - Cl_t$) vs. time. All reactions showed good first-order kinetic behavior through 3–4 half-lives when fitted by using linear least-squares regression techniques on a Hewlett-Packard HP41C calculator. Each rate value is based on 10–15 points per run. Most rates represent averages of three determinations. Arrhenius values were determined from a plot of (log k) vs. $1/T$ for each reaction.

The kinetic study of **23** was run in an identical manner, except that modifications were made to accommodate the required higher temperatures. Thus, 1.6-mL aliquots of a 5.0 mM solution of **23** in absolute MeOH were added to breakseal ampules, each containing 6.4 mL of 0.02 M NaOH that was also 3.2×10^{-4} M in NaCl. The ampules were sealed and immersed in an isothermal bath. At appropriate intervals, an ampule was withdrawn, cooled in ice–H_2O, and opened, and the contents were assayed as above. After the initial Cl^- present was corrected for, the rates were determined as above.

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Registry No. 1, 79191-36-9; 1·HCl, 79254-04-9; 3, 79191-37-0; 8, 79191-38-1; 8·HCl, 14578-33-7; 9a, 53092-72-1; 9b, 79191-39-2; 10, 79191-40-5; 11, 40810-53-5; 12, 3015-16-5; 13, 79191-41-6; 13·HCl, 79191-42-7; 14, 79191-43-8; 15, 79191-44-9; 16, 79191-45-0; 17, 79191-46-1; 18, 79191-47-2; 19, 770-15-0; 20a, 3015-19-8; 20b, 3632-95-9; 21, 768-41-2; 22, 14578-32-6; 23, 7346-41-0; 24, 100-35-6; 1,3-dibromoadamantane, 876-53-9; 2-adamantanol, 700-57-2.

Differentiation of Nucleophilic and General Base Catalysis in the Hydrolysis of *N*-Acetylbenzotriazole Using the Proton Inventory Technique[1]

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The hydrolysis of *N*-acetylbenzotriazole is catalyzed by acetate and imidazole by two different modes as shown by the proton inventory technique. Acetate acts as a general base catalyst to abstract a proton from the attacking water molecule. The unexpected upward curvature in the proton inventory plot can be attributed to a reactant-state isotopic fractionation factor contribution from acetate ion. The proton inventory for imidazole catalysis exhibits downward curvature and is shown to be consistent with a nucleophilic catalysis role for imidazole. The intermediate, 1-acetylimidazole, then undergoes rate-determining water-catalyzed hydrolysis via the expected mechanism.

Introduction

The neutral, water-catalyzed hydrolysis of esters, amides, and carbonates has, in many instances, been shown to involve a transition-state structure in which one water molecule acts as a base to abstract a proton from the attacking water molecule.[2-5] For the general-base-catalyzed reactions the general base (e.g., imidazole) acts to abstract a proton from the attacking water molecule.[6-9] The two

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