thiomethyl)-N-methyl-*p*-toluidine, 13641-17-3; N-(*p*-*t*-butylphenylthiomethyl)-N-methylaniline, 13641-18-4; bis(N-methyl-*p*-toluidino)methane, 7137-82-8; α-chlorothioanisole, 13641-20-8; *p*-methylaminobenzyl phenyl sulfide, 13641-21-9; *p*-methylaminobenzyl *p'*-*t*-butylphenyl sulfide, 13641-22-0; *p'*-dimethylaminobenzyl-N-methyl-*p*-toluidine, 10509-65-6; *p*-methylaminobenzyl phenyl sulfone, 13641-24-2; *p*-aminobenzyl phenyl sulfone, 13640-67-0; *p*-dimethylaminobenzyl phenyl sulfone, 13640-68-1.

The Reactions of β-Aminoalkyl Hydrogen Sulfates. III. The Effect of Alkyl Substituents on the Rates of Cyclization of β-Aminoalkyl Sulfate Ions[1]

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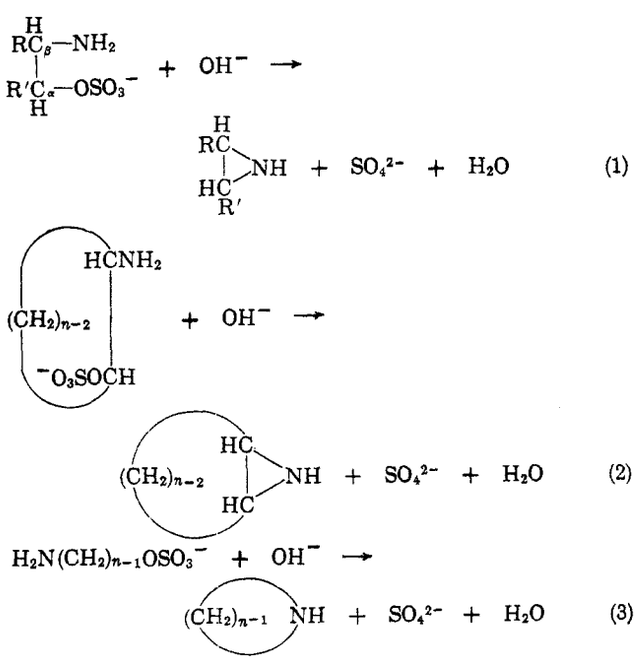
The cyclization of aminoalkyl sulfate ions to form aziridines has been studied at 75°. The rate constants and acidity constants have been determined for 20 alkyl- and aryl-substituted aminoalkyl sulfate ions. In the cyclization of β-aminoalkyl sulfate ions, alkyl substituents can be both rate enhancing and rate retarding, the over-all effect and its magnitude being dependent on the structure and position of the substituent. Rate retardation is ascribed to steric hindrance of the type found in SN2 reactions. Rate enhancement is probably partially due to stabilization of the three-membered ring by hyperconjugation. Any driving force from relief of compressive strain through ring formation is minor. Polar effects are not significant except where the substituent is aromatic, in which case it can be rate enhancing or rate retarding.

As part of our study of the reaction of β-aminoalkyl hydrogen sulfates with potassium ethyl xanthate,[3] we found it necessary to determine the rates for the cyclization of aminoalkyl sulfate ions to the corresponding aziridines (reactions 1, 2, and 3). These results



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are being reported because we believe that they disclose new information about the influence of alkyl substituents on the formation of three-membered rings. The specific rate constants for the cyclization, at 75°, of 20 aminoalkyl sulfate ions have been determined.

Experimental Section

The preparation of the aminoalkyl hydrogen sulfates and the techniques used to measure reaction rates and acidity constants (pK_a') have been reported.[3] Specific rate constants were determined graphically from log (reactant) against time plots and are the average of two to four runs.

Aziridines.—The aziridines were prepared by distilling a mixture of 0.05 mole of the aminoalkyl hydrogen sulfate and 25 ml of 50% aqueous potassium hydroxide solution and adding water periodically to the mixture until no further aziridine came over. The distillate was saturated with potassium hydroxide, and the organic layer was separated and dried over potassium hydroxide pellets. The aziridines were identified through published physical properties and their phenyl isothiocyanate addition products. Data for several new compounds[4] follows.

2-Isopropylaziridine was found to have a boiling point of 103–104° ($n^{25}D$ 1.4179).

Anal. Calcd for $C_5H_{11}N$: C, 70.55; H, 12.94; N, 16.45. Found: C, 70.38; H, 13.19; N, 16.41.

The N-phenylthiocarbamyl derivative has a melting point of 75.0–75.6°.

Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.39; H, 7.29; N, 12.40.

2-*t*-Butylaziridine has a boiling point of 111–112° ($n^{25}D$ 1.4229).

Anal. Calcd for $C_6H_{13}N$: C, 72.80; H, 13.12; N, 14.14. Found: C, 72.80; H, 13.17; N, 14.14.

The N-phenylthiocarbamyl derivative has a melting point of 86.0–86.3°.

Anal. Calcd for $C_{13}H_{18}N_2S$: C, 66.60; H, 7.69; N, 11.95. Found: C, 66.21; H, 7.79; N, 11.71.

Results

The specific rate constants for the cyclization reaction and the acidity constants of the aminoalkyl sulfate ions are summarized in Tables I, II, and III. In the concentration range studied (0.5–0.2 *M*), all cyclizations were first order with respect to aminoalkyl sulfate ion concentration and zero order with respect to sodium hydroxide concentration. Each run was followed for at least two half-lives or 72 hr, over which period none of the reactions deviated from first-order kinetics. In none of the examples studied was there

(1) (a) In part from the R. A. Bafford Ph.D. Thesis, University of Maryland, June 1960. (b) Presented at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, K077.

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(3) (a) C. S. Dewey and R. A. Bafford, *J. Org. Chem.*, **30**, 491 (1965). (b) C. S. Dewey and R. A. Bafford, *ibid.*, 495 (1965).

(4) Elemental analyses were carried out by Dr. Franz Kasler, University of Maryland, College Park, Md., and Galbraith Laboratories, Inc., Knoxville, Tenn.

TABLE I

RATE CONSTANTS FOR THE CYCLIZATION OF β-AMINOALKYL SULFATE IONS. DATA FOR REACTION 1

Substituent	Registry no.	pK_a'	$10^4\ k_\Delta$ (75°), min^{-1}	k_{rel}
None	13652-58-9	8.97 ± 0.01	4.80 ± 0.07	1.00
α-Methyl	13652-59-0	8.97 ± 0.02	9.45 ± 0.20	1.97
α-Ethyl	13699-62-2	9.09 ± 0.02	9.62 ± 0.12	2.01
α-Isopropyl	13652-60-3	9.18 ± 0.03	4.97 ± 0.14	1.03
α-*t*-Butyl	13652-61-4	9.46 ± 0.02	0.34	0.072
α-Phenyl	13652-62-5	8.58 ± 0.02	286 ± 4	59.2
α-Benzyl	13652-63-6	8.90 ± 0.01	2.38 ± 0.15	0.50
β-Methyl	13652-64-7	9.02 ± 0.01	31.0 ± 0.5	6.45
β-Ethyl	13652-65-8	9.02 ± 0.03	44.1 ± 0.1	9.21
β-Isopropyl	13699-63-3	9.23 ± 0.03	55.3 ± 0.8	11.51
β-Phenyl	13652-66-9	8.14 ± 0.03	5.87 ± 0.28	1.22
threo-α,β-Dimethyl	13652-67-0	9.11 ± 0.03	64.3 ± 0.1	13.4
erythro-α,β-Dimethyl	13652-67-0	9.11 ± 0.01	81.8 ± 0.02	17.0
β,β-Dimethyl	13652-69-2	9.06 ± 0.01	195 ± 3	40.5

TABLE II

RATE CONSTANTS FOR THE CYCLIZATION OF *trans*-2-AMINOCYCLOALKYL SULFATE IONS. DATA FOR REACTION 2

n	Registry no.	pK_a'	$10^4\ K_\Delta$ (75°), min^{-1}	k_{rel}
5	13699-64-4	8.89 ± 0.01	105 ± 1	22.0
6	13717-32-3	9.20 ± 0.01	11.4 ± 0.2	2.38
7	13652-70-5	9.33 ± 0.01	41.0 ± 0.5	8.54
8	13652-71-6	9.44 ± 0.02	13.1 ± 0.1	2.73

TABLE III

RATE CONSTANTS FOR THE CYCLIZATION OF ω-AMINOALKYL SULFATE IONS. DATA FOR REACTION 3

n	Registry no.	pK_a'	$10^4\ k_\Delta$ (75°, min^{-1})	k_{rel}
3	13652-58-9	8.97 ± 0.01	4.80 ± 0.07	1
4	13717-33-4	9.08 ± 0.03	0.39	0.08
5	13652-73-8	10.28 ± 0.03	2130[a]	443

[a] Extrapolated from data at 50.2° and 60.0°.

any evidence of a concerted reaction in which the attack of a hydroxide ion on the amino group is concerted with the approach of the nitrogen atom to the backside of the carbon–oxygen bond as suggested by Kashelikar and Fanta for the formation of *cis*-cyclooctenimine from *trans*-2-aminocyclooctyl sulfate ion.[5] In the preparation of cyclooctenimine by the described procedure, concurrent formation of cyclooctanone has been reported[5] and confirmed. Likewise, 2-phenylaziridine from 2-phenyl-2-aminoethyl sulfate ion contained 10% acetophenone. However, at 75°, where reaction rates were measured, these side reactions amounted to, at most, 5%. No byproducts were found in the remainder of the aziridine preparations.

Discussion

It has been widely observed that alkyl substituents facilitate the formation of small rings. Several theories have been proposed to explain this phenomenon and have been discussed by Eliel,[6a] Winstein and Grunwald,[6b] and Streitwieser.[6c] Briefly, these theories are (a) that spreading of the exocyclic bond angles results in a relief of compressive strain which thus assists ring formation,[6a] (b) that the bonds of three-membered rings possess some π-bond character, and alkyl substituents stabilize the ring by hyperconjugation much as alkyl groups stabilize the ethylenic linkage,[6b] and (c) that, since entropy changes are smaller for intramolecular displacements, polar effects are more important than steric effects, and, thus, alkyl substituents accelerate ring formation.[6c]

However, rate data has been published only on the formation of unsubstituted and methyl or phenyl substituted three-membered rings. The more extensive data in Table I indicates that some modification of present theories should be considered. It can be seen that β substituents are more rate enhancing than α substituents and, as the α substituent becomes more bulky, any rate enhancement disappears and instead there is rate retardation. This data is consistent with the premise that alkyl substituents can be both rate enhancing *and rate retarding* and that the latter is due to steric hindrance of the type found in classical SN2 reactions.[7] If the effect of alkyl groups were due to polar factors, then α substituents should be more rate enhancing than β substituents. Actually, as shown in Table I, α-methyl and α-ethyl groups double the rate while the corresponding β groups increase the rate six- and ninefold, respectively. If alkyl groups are rate enhancing because compressive strain is relieved by ring formation, then increasing the bulk of the alkyl groups should enhance the rate. This is not supported by the data.

In reality, these rate data are not inconsistent with those for β-aminoalkyl halides and β-haloalkoxides which have been published. It can be seen from Table IV that β-methyl groups are more rate enhancing than the α substituents.

Using a linear free-energy equation of the form[8]

$$\log \frac{k_\Delta}{k_{\Delta_0}} = r\alpha$$

where r is a constant for the reaction under study and

TABLE IV

RELATIVE RATES OF CYCLIZATION TO THREE-MEMBERED RINGS

Substituent	k_{rel} >Cβ(O⁻)–Cα(Cl)<	k_{rel} >Cβ(NH₂)–Cα(Cl)<
Hydrogen	1.0[a]	1.0[b]
α-Methyl	6.8	4
β-Methyl	26	30
β,β-Dimethyl	500	

[a] See ref 6b. [b] See ref 6a, p 117.

(5) D. Kashelikar and P. Fanta, *J. Am. Chem. Soc.*, **82**, 4927 (1960).

(6) (a) E. L. Eliel in "Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 112; (b) S. Winstein and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 828 (1948); (c) A. Streitweiser, Jr., *Chem. Rev.*, **56**, 718 (1956).

(7) An alternative explanation suggested by referee I was that since there will already be a large concentration of negative charge in the vicinity of the α-carbon atom in the transition state that the inductive effect of α-alkyl groups will not stabilize the transition state. However, the bulk of the literature on displacement reactions seems to support the hypothesis that in simple alkyl systems the α-carbon atom has a greater positive charge in the transition state than in the ground state and that stabilization of the positive charge by an electron-donating inductive effect would be rate accelerating. It must be admitted that there is very little data on the displacement reactions of alkyl sulfate anions where the leaving group carries a negative charge. A suitable test to separate inductive and steric factors would be to study the rate effects of *para*-substituted phenyl groups at the α-carbon atom.

(8) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p 158.

α is a structure constant for the alkyl substituent, then the relative rates for the di-substituted aminoalkyl sulfate ions can be predicted. The relative rate for the α,β-dimethyl compound would be 12.7 (1.97 $\times$ 6.45) and that for the β,β-dimethyl compound would be 41.6 (6.45 $\times$ 6.45). That there is reasonably good agreement with the experimental data (Table I, last three entries) may be fortuitous, since only three examples are available. The small difference in rate between the *threo* and *erythro*-dimethyl compounds can also be ascribed to a steric effect. In *cis*-2,3 dimethylaziridine, the two methyls are in an eclipsed position and ring closure will be slower than when the two methyls are *trans* to each other. This has also been shown in the formation of *cis*- and *trans*-stilbene oxides from the bromohydrins.[9]

The magnitude of the effect of two methyl substituents on the cyclization rate is consistent with the concept of rate acceleration due to stabilization of the three-membered ring by hyperconjugation with the hydrogen atoms of the methyl groups. If rate enhancement were due to relief of compressive strain, it seems unlikely that the rates of mono- and di-substituted aminoethyl sulfate ions could be correlated by a simple, linear, free-energy equation.

On the other hand, if rate enhancement were due solely to hyperconjugative stabilization of the ring by the methyl-hydrogen atoms, then replacement of methyl by an ethyl or isopropyl group at the β position should lead to a rate decline because of the decrease in the number of hydrogens available for hyperconjugation. Also, among amines, nucleophilicity can be correlated with base strength, deviations occurring in the direction of decreased nucleophilicity when the alkyl groups are branched. This effect is attributed to steric hindrance.[10] Since the base strengths of the amines having β-carbon substituents are about the same as those with equivalent α-carbon substituents (Table I) one might predict a decrease in reaction rate due to branching at the β-carbon atom. Clearly, this is not the case. At this time, we can offer no obvious explanation for the observation that branching of the β-alkyl substituent leads to a further, although rather small, increase in the cyclization rate.[11]

The relatively high rate for the α-phenyl compound is not surprising, since α-phenyl substituents are rate enhancing in both SN1 and SN2 reactions. The low rate for the β-phenyl compound was unexpected. In SN2 displacements, β-phenylethyl halides have about the same relative reactivity as *n*-propyl halides[12] but a phenyl substituent should stabilize the aziridines and therefore be rate enhancing. However, as indicated by the pK_a' value, the β-phenyl substituent reduces the basicity of the amino moiety. The low reaction rate is probably due to the reduced nucleophilicity of the amino moiety in 2-phenyl-2-aminoethyl sulfate ion.

The relative rates of formation of the azabicycloalkanes in Table II parallel those for the SN2 reactions of corresponding cycloalkyl halides. Facile displacements in cyclopentyl systems have been ascribed to a reduction in the number of carbon–hydrogen bond oppositions from ten to six in the transition state while the sluggishness of cyclohexyl systems is due to the engendering of two carbon–hydrogen bond oppositions in the transition state. It seems reasonable to assume that the same factors are operative in the formation of the azabicycloalkanes.

The relative rates of cyclization of the ω-aminoalkyl sulfate ions (Table III) are in agreement with those reported for the corresponding ω-aminoalkyl bromides.[13] The two major factors influencing rates in these compounds, distance of the amino group from the carbon atom it attacks and ring strain, have been adequately discussed elsewhere.[14]

Summary

In the cyclization of β-aminoalkyl sulfate ions, alkyl substituents can be both rate enhancing and rate retarding; the over-all effect and its magnitude being dependent on the structure and position of the alkyl substituent. Rate retardance can be best ascribed to steric hindrance of the type found in SN2 reactions. The cause of the rate enhancement is less clear; the most probable cause is stabilization of the three-membered ring by hyperconjugation. Any contribution from relief of compressive strain through ring formation is minor. Polar effects are not significant except where the substituents are aromatic in which case they can be both rate retarding and rate enhancing.

The phenyl group may stabilize the transition state by conjugation and be rate enhancing. However, if it reduces the basicity of the amino moiety, it is rate retarding.

A study of the influence of substituents on the nitrogen atom on the cyclization rate is in progress.

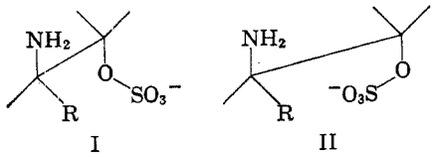
Registry No.—2-Isopropylaziridine, 13639-42-4; N-phenylthiocarbamyl derivative of 2-isopropylaziridine, 13639-43-5; 2-*t*-butylaziridine, 13639-44-6; N-phenylthiocarbamyl derivative of 2-*t*-butylaziridine, 13639-45-7.

Acknowledgment.—One of the authors (R. A. B.) wishes to express his gratitude to the management of Lucidol Division, Wallace & Tiernan Inc., for permission to continue this work at their Buffalo laboratory.

(9) See ref 6a, p 120.

(10) (a) P. A. Smith, "Open-Chain Organic Nitrogen Compounds," W. A. Benjamin, Inc., New York, N. Y., 1965, p 24; (b) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957); (c) G. S. Hammond and M. F. Hawthorne in "Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 196; (d) see ref 8, p 138.

(11) Referee II has suggested the possibility that increasing the bulk of the substituents on the β-carbon could orient the $-OSO_3^-$ group in a more favorable position for displacement, *i.e.*, favor conformation I over conformation II. Larger R groups would tend to hinder rotation around the



I II

oxygen–carbon bond and electrostatic repulsion between the NH_2 group and OSO_3^- group would be reduced for conformation I. We feel this is a reasonable explanation and we wish to express our appreciation for this comment.

(12) J. B. Conant, W. R. Kirner, and R. E. Hussey, *J. Am. Chem. Soc.*, **47**, 488 (1925).

(13) H. Freundlich and H. Kroepelin, *Z. Physik. Chem.* (Leipzig), **122**, 139 (1926).

(14) See ref 6a, p 115; ref 6c, p 677; ref 8, p 162.