Reactivities of 2,3-Dialkylaziridinium Salts with Thiosulfate[1]

Albert T. Bottini,* Lynn R. Sousa, and Barry F. Dowden

Department of Chemistry, University of California, Davis, California 95616

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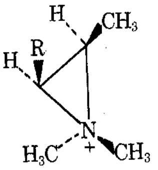
Rate constants and thermodynamic parameters were determined for reactions in water of thiosulfate with *cis*- and *trans*-1,1,2-trimethyl-3-alkylaziridinium iodides and *trans*-1-alkyl-2,3-dimethylaziridinium iodides, wherein the alkyl group is methyl, ethyl, isopropyl, or *tert*-butyl. The observed reactivities are interpreted as resulting from a combination of steric hindrance and steric acceleration.

Studies of the formation and reactions of aziridinium ions seem particularly well suited for assessing the role of steric effects on reactivity. We describe here our determination of the reactivities of the aziridinium ions **1a–d**, **2a–d**, and **3a–d** with thiosulfate in water.



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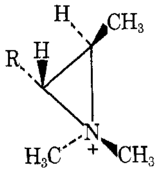

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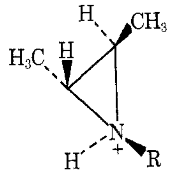

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a, R = CH_3; **b**, R = C_2H_5; **c**, R = *i*-C_3H_7; **d**, R = *t*-C_4H_9

Previous study[2a,b] of reactions of aziridinium ions, including 2-methyl- and 2,2-dimethylaziridinium ions, with thiosulfate and other strong nucleophiles has established that these reactions occur by the SN2 mechanism with negligible competition from pathways involving carbonium ions. We therefore proceeded with reasonable assurance that reactions of **1**–**3** with thiosulfate would also be clean second-order reactions. It should also be noted here that rate constants for iodide ion catalyzed equilibration of several *N*-deuteriomethylaziridinium ions analogous to **1** and **2** are related linearly to rate constants for reactions of **1** and **2** with thiosulfate.[2b,c]

We expected that increase of the bulk of the alkyl groups on the aziridinium ring would result in a decrease in reactivity because of increased steric hindrance to attack by thiosulfate. We also expected that such increase of bulk might, for certain compounds, result in a perceptible enhancement of rate reflecting a relief of nonbonded interactions in the transition state for the ring-opening reaction. Our results bore out these expectations.

The methods used for determination of the kinetics of the reactions of the aziridinium ions with thiosulfate were patterned after those described by others.[2a] Prior to making kinetic runs, the iodides of the aziridinium ions **1a–d** and **2a–d** were characterized by means of elemental analysis and nmr spectroscopy. Aziridinium compounds of **3a–d** were not isolated but were generated *in situ*. Three of the products were characterized by elemental analysis.

The second-order rate constants and activation parameters for the reactions of the aziridinium ions with thiosulfate are summarized in Table I.

Several noteworthy features of the data are (1) the reactivity in the **1a–d** and **2a–d** series decreases as the size of the 3-alkyl group increases; (2) for these two series, the cis isomer is the more reactive, and the cis/trans reactivity ratio increases as the size of the 3-alkyl group increases; and (3) for the **3a–d** series, the reactivity order is **3d** > **3a** > **3b** > **3c**.

For both the *cis*- and *trans*-1,2-dimethyl-3-alkylaziridinium ions (**1** and **2**), the reactivity decreases by a factor of 1.9 when the 3-alkyl group is changed from methyl to ethyl. This is near the statistical factor of 2, which would be expected if all the ring opening took place by attack of thiosulfate on a ring carbon bearing methyl. Replacement of the ethyl group of an isopropyl or *tert*-butyl group slows the rate of ring opening by factors of 9.6 or 9.9, respectively, in the case of the cis isomers and 21.6 or 37, respectively, in the case of the trans isomers. The net rate-retarding effect can be ascribed to increased steric hindrance to attack at C_2 by the larger alkyl groups at C_3. It is noteworthy that replacement of ethyl by isopropyl has a greater effect on rate than replacement of isopropyl by *tert*-butyl, although the difference in effective size is normally greater for *tert*-butyl and isopropyl than for isopropyl and ethyl.[8] This greater than expected reactivity of the *tert*-butyl ions requires that some factor other than steric hindrance is playing a role in their reactivity, and this factor is certainly steric acceleration of reactivity.[9]

This is seen more clearly by comparing the relative reactivities of the cis and trans isomers. The cis/trans reactivity ratio of 3.4–3.5 for both the 1,2,3-trimethyl and the 1,2-dimethyl-3-ethyl ions can be ascribed to steric acceleration being greater for the cis compounds, which undergo greater relief of steric crowding as the ring opens. As the size of the 3-alkyl group increases to isopropyl and *tert*-butyl, this difference in reactivity becomes amplified, and the cis/trans reactivity ratio increases to 7.7 and 13.

Perhaps the effect of steric acceleration of reactivity is seen most clearly from comparison of the reactivities of the 1-alkyl-*trans*-2,3-dimethylaziridinium ions (**3a–d**). The rate of ring opening drops by nearly a factor of 2 as the size of the 1-alkyl group is increased from methyl to ethyl to isopropyl. Then increase in size from isopropyl to *tert*-butyl, which should result in a continued decrease in rate if steric hindrance were the only effect, results in a steric acceleration of rate by a factor of 7.2.

Experimental Section

Boiling points and melting points are uncorrected. Nmr spectra were obtained at 60 MHz with a Varian Associates HR-60 system equipped with electronic integrator and base-line stabilizer. Resonance frequencies in nmr spectra were determined using the sideband technique with a Packard CD-200 audiooscillator. Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif.

***cis*- and *trans*-1,1,2-Trimethyl-3-alkylaziridinium Iodides (1a–d and 2a–d).** The procedure described for the conversion of *cis*-1,2-dimethyl-3-isopropylaziridine to *cis*-1,1,2-trimethyl-3-isopropylaziridinium iodide[3a] was found to be satisfactory for the preparation of the other 1,1,2,3-tetraalkylaziridinium iodides from the corresponding aziridines[3b] in over 90% yield. The aziridinium compounds were characterized by means of their decomposition points, nmr spectra, and elemental analysis, which are summarized in Table II, as well as by their reactivities with thiosulfate.

***trans*-1-Alkyl-2,3-dimethylaziridinium compounds** were prepared *in situ* from the corresponding aziridines.[4] *trans*-1-Methyl,[3,5] 1-ethyl-,[6] and 1-isopropyl-2,3-dimethylaziridine[5] have been described, *trans*-1-*tert*-Butyl-2,3-dimethylaziridine, bp 120–121°, $n^{24}D$ 1.4176, was prepared from *trans*-2,3-dimethyloxirane by the method described for preparation of other 1,2,3-trialkylaziridines.

Anal. Calcd for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.17; H, 13.46; N, 10.53.

Table I
Rate Constants and Activation Parameters for Reactions of Aziridinium Salts with Thiosulfate

	$10^5 k_2$, M^{-1} sec^{-1} at				ΔF^*, 30.24°,	ΔH^*, 30.24°,	$-\Delta S^*$, 30.24°,
Compd	20.00°	30.24°	39.84°	50.16°	kcal/mol	kcal/mol	cal deg^{-1} mol^{-1}
1a	119	316	868		21.2	17.6	12.0
2a	31.1	91.2	238		22.0	18.0	13.2
1b	56.1	167	493		21.6	19.5	7.0
2b	17.4	48.7	153		22.4	19.2	10.4
1c		17.3	52.2	135	23.0	19.7	10.8
2c		2.25	6.58	19.0	24.2	19.1	17.0
1d		16.8	49.7	134	23.0	19.8	10.5
2d		1.29	3.95	11.1	24.6	20.4	13.7
3a		30.8	95.3	239	22.6	19.5	10.4
3b		23.8			22.8		
3c		16.7			23.0		
3d		121	336	893	21.8	18.9	9.6

Table II
Decomposition Points and Principal Nmr Resonance Frequencies of *cis*- and *trans*-1,1,2-Trimethyl-3-alkylaziridinium Iodides

	Mp, °C,[a]	Resonance frequencies, ppm[b]				
Compd	dec	NCH$_3$		CCH$_3$		
1a[c]	178	1.57	1.83	3.17		
2a[d]	155	1.65		3.03		
1b[e]	138	1.56	1.78	3.11[f]	3.47[g]	
2b[h]	116	1.63[i]		3.05[f]	3.50[j]	
1c[k]	144[l]	1.52	1.70	3.16[f]	3.49[m]	3.61[m]
2c[k]	147[l]	1.42	1.48	3.00[f,f']	3.51[m]	3.58[m]
1d[n]	181	1.52[o]	1.57	2.97[f,f'']	3.40	
2d[p]	194	1.47[q]	1.62	3.05[f]	3.45	

[a] The temperature listed is the high temperature of the 2–5° range over which decomposition was noted when the sample was heated in an open capillary at *ca.* 1°/min within 10° of the decomposition range. [b] Spectra were taken of 10% solutions in deuterium oxide at 30–35°, and resonance frequencies are reported in parts per million upfield from the band due to residual water. [c] *Anal.* Calcd for $C_6H_{14}IN$: C, 31.73; H, 6.21. Found: C, 31.37; H, 6.15. [d] *Anal.* Found: C, 31.68; H, 6.24. [e] *Anal.* Calcd for $C_7H_{16}IN$: C, 34.87; H, 6.69. Found: C, 33.09, 36.26; H, 6.58, 6.61. [f] Resonance due to C_2 CH_3; $J \cong 5.4$ Hz. [f'] $J = 6.2$ Hz. [f''] $J = 5.8$ Hz. [g] Triplet, $J \cong 7.0$ Hz; center of the methylene resonance at 2.85 ppm. [h] *Anal.* Found: C, 34.26; 34.22; H, 6.44, 6.56; I, 52.22. [i] A chemical shift (<1 Hz) between the *N*-methyl resonances is discernible. [j] Triplet, $J \cong 7.0$ Hz; center of the methylene resonance at 2.80 ppm. [k] See ref 1. [l] The decomposition range is 166.5–170° when the sample is heated at *ca.* 5°/min (see ref 1). [m] Doublet, $J \cong 7.0$ ppm. [n] *Anal.* Calcd for $C_9H_{20}IN$: C, 40.16; H, 7.49; I, 47.15. Found: C, 39.99; H, 7.27. [o] C_2 H and C_3 H resonances at 1.25 and 1.68 ppm, respectively; $J_{cis} = 9.6$ Hz. [p] Found: C, 40.39; H, 7.43; I, 47.20. [q] C_2 H and C_3 H resonance at 1.22 and 1.70 ppm, respectively; $J_{trans} = 8.5$ Hz.

Reactions of the aziridinium compounds with thiosulfate were carried out in acetate-buffered aqueous solutions with concentrations chosen so that the initial ionic strength was unity. The initial concentrations for reactions of **1a-d** and **2a-d** were 0.15 *M* **1** or **2**, 0.15 *M* sodium thiosulfate, 0.40 *M* sodium acetate, and 0.50 *M* acetic acid. For reactions of **3a-d,** initial concentrations were 0.15 *M* imine, 0.15 *M* perchloric acid, 0.15 *M* sodium thiosulfate, 0.40 *M* sodium acetate, and 0.50 *M* acetic acid. During the course of each reaction, eight or nine 2.0-ml samples were withdrawn, *the last sample being taken after the reaction* was 60–75% complete. Each sample was quenched immediately with 50 ml of water, and the amount of unreacted thiosulfate was determined by titration with a standardized potassium iodide-iodine solution. An aliquot from each run was taken 4–8 min after the reaction was begun, sealed in an ampoule, and heated at 60° in an oil bath for at least 1 week, and the amount of unreacted thiosulfate, which ranged from 2 to 8% of the original thiosulfate, was determined.

The rate constant for each run was taken as the least-squares slope of the plot of the reciprocal of the sodium thiosulfate concentration *vs.* time. In all cases, good linear plots were obtained to at least 60–75% reaction. Each run was repeated at least once; rate constants from duplicate runs agreed to within 2%. Rate constants and activation parameters for reactions of the aziridinium compounds with thiosulfate are summarized in Table I.

Formation of white, crystalline precipitates, presumed to be thiosulfates, was noted during the reactions with **1c**,[7a] **1d**,[7b] **2c**,[7c] **2d**, and **3d**.

Registry No. **1a** iodide, 43177-74-8; **1b** iodide, 43177-75-9; **1c** iodide, 932-24-1; **1c** thiosulfate, 43177-77-1; **1d** iodide, 43177-78-2; **1d** thiosulfate, 43177-79-3; **2a** iodide, 872-43-5; **2b** iodide, 43177-81-7; **2c** iodide, 1003-93-6; **2c** thiosulfate, 43177-83-9; **2d** iodide, 43177-84-0; **3a** iodide, 43177-85-1; **3b** iodide, 43177-86-2; **3c** iodide, 43177-87-3; **3d** iodide, 43177-88-4; sodium thiosulfate, 10124-57-9; *trans*-1-*tert*-butyl-2,3-dimethylaziridine, 6125-02-6; *trans*-2,3-dimethyloxirane, 21490-63-1.

References and Notes

(1) Structure Activity Relationships of Ethylenimines. IX. Previous paper in the series: A. T. Bottini, V. Dev, B. F. Dowden, and A. J. Gandolfi, *J. Med. Chem.*, **12**, 332 (1969). Supported by Grant CA-05528 from the National Cancer Institute of the Public Health Service.

(2) (a) J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lowes, *J. Amer. Chem. Soc.*, **80**, 3458 (1958); (b) A. T. Bottini, B. F. Dowden, and L. Sousa, *ibid.*, **87**, 3249 (1965); (c) A. T. Bottini, A. G. Bellettini, and B. F. Dowden, manuscript in preparation.

(3) (a) A. T. Bottini and R. L. Van Etten, *J. Org. Chem.*, **30**, 575 (1965); (b) *ibid.*, **30**, 2994 (1965).

(4) *cis*- and *trans*-1,2-dimethyl-3-*tert*-butylaziridinium perchlorate, mp 160° dec and 188° dec, respectively, are described in the Ph.D. Dissertation of R. L. Van Etten, University of California, Davis, 1965.

(5) G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, *J. Org. Chem.*, **30**, 666 (1965).

(6) R. Ghirardelli and H. J. Lucas, *J. Amer. Chem. Soc.*, **79**, 734 (1957).

(7) (a) Mp 215–218°. *Anal.* Calcd for $C_8H_{19}NO_3S_2$: C, 39.81; H, 7.93. Found: C, 39.86; H, 8.07. (b) Mp 204–206°. *Anal.* Calcd for $C_9H_{21}NO_3S_2$: C, 42.36; H, 8.28. Found: C, 42.18; H, 8.00. (c) Mp 229–231°. *Anal.* Found: C, 39.75; H, 7.87.

(8) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 440–441.

(9) A referee pointed out the possibility that reactions of the 3-*tert*-butyl salts **1d** and **2d** might have an S$_N$1 component wherein the carbon bearing the *tert*-butyl group ionizes with methyl participation. This seems very unlikely because the diastereomeric *trans*-1-deuteriomethyl-1,2-dimethyl-3-*tert*-butylaziridinium ions are cleanly equilibrated by iodide ion in methanol–water.[2b,c]