Intermolecular Methyl Transfer *vs.* the Endocyclic Reaction *via* an Eight-membered Cyclic Transition State

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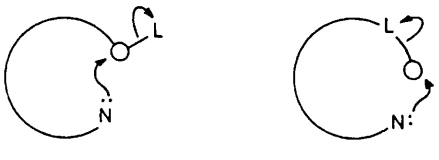
Summary Formation of the betaine (**5**) from methyl 4-(dimethylamino)butanesulphonate (**4**) proceeds by an intermolecular pathway and not by way of a cyclic eight-membered ring transition state; it is estimated that the effective concentration for the cyclic process is $<10^{-5}$ M.

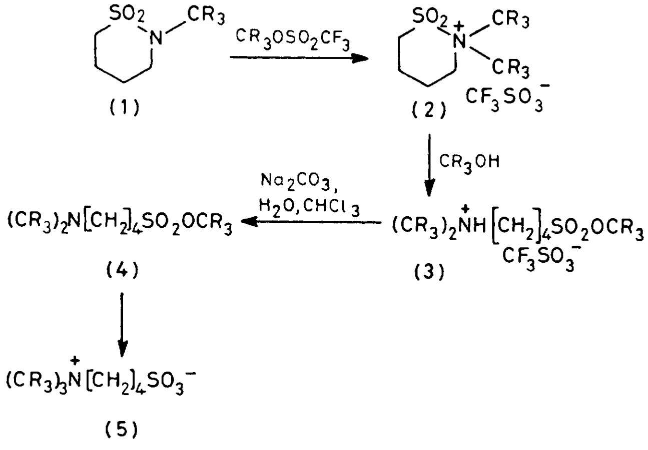
Whereas 'exocyclic'[1] S_N reactions forming the simplest versions of rings from three- to eighteen-membered and larger are known,[2] adequately described examples of 'endocyclic'[1] transfer of an sp^3 carbon are rare and involve strained or unusually constrained starting materials.†



Exocyclic Endocyclic

Cyclic modes of nucleophilic substitution

Eschenmoser and co-workers[1] studied two methyl transfer reactions which, if intramolecular, would have had to involve six-membered cyclic transition states. They found these to be intermolecular processes under their conditions, and pointed to the preference of tetrahedral carbon for backside attack in S_N2 reactions. Examination of molecular models suggest that whereas backside attack on carbon in a six-membered cyclic transition state would lead to severe bond angle distortions, such attack might be feasible in somewhat larger rings. We report our experiments on the transfer of the *O*-methyl group in (**4**) to the nitrogen atom to form (**5**), a reaction which, if intramolecular, would proceed by way of an eight-membered cyclic transition state.



Scheme 1. a, R = ^{1}H; b, R = ^{2}H

The aminoester (**4**) is obtained as shown in Scheme 1; compound (**1**) is prepared by a route parallel to one for the parent sultam,[3] and the conversion (**1**) → (**2**) → (**3**) is closely related to the first two steps in the preparation of '[3]betylates.'[4] On standing in aqueous solution (**4**) gives a mixture of (**5**) and the product of simple hydrolysis

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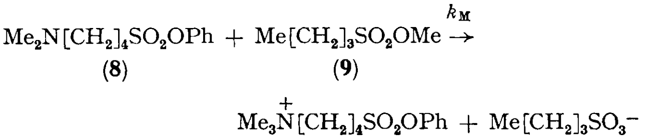
† *E.g.* the degenerate exchange of a C-9 alkyl group in an anthracene system between arylthio groups on C-1 and C-8 (J. C. Martin and R. J. Basalay, *J. Amer. Chem. Soc.*, 1973, **95**, 2572; T. R. Forbus, jun. and J. C. Martin, *ibid.*, 1979, **101**, 5057), and the cyclization of diethyl 4,5-epoxypentane-1,1-dicarboxylate to a substituted cyclopentanol (P. A. Cruickshank and M. Fishman, *J. Org. Chem.*, 1969, **34**, 4060). A report of endocyclic methyl transfer *via* a nine-membered cyclic transition state, does not, in our view, make its case; we can find, for example, no adequate evidence for the structure of the reaction product (R. Lok and J. K. Coward, *Bioorganic Chem.*, 1976, **5**, 169). Endocyclic transfer of a sulphur atom has recently been announced (K. K. Andersen, L. J. Yildiz, and B. T. Phillips, *Phosphorus and Sulfur*, 1979, **6**, 11).

($\mathrm{Me_2\overset{+}{N}H[CH_2]_4SO_3^-}$), but in an aprotic medium (*e.g.* chloroform) (**5**) is formed quantitatively. An equimolar mixture of (**4a**) and (**4b**), with an initial concentration of either 0·02 M or 2 × 10^{-4} M in $\mathrm{CHCl_3}$, gave a mixture shown by a mass spectrometric method‡ to consist of the nonadeuteriated [$^2\mathrm{H}_9$]-, hexadeuteriated [$^2\mathrm{H}_6$]-, trideuteriated [$^2\mathrm{H}_3$]-, and undeuteriated [$^2\mathrm{H}_0$]-betaine (**5**) in a 1 : 1 : 1 : 1 ratio, *i.e.* the reaction was completely intermolecular; control experiments showed the method to be easily capable of detecting 10% of any intramolecular reaction. Reaction of (**4a**) in $\mathrm{CDCl_3}$ (initial concentration 0·25 M) gave good second order kinetics to >80% reaction when followed by n.m.r.; $k_{\mathrm{obs}} = 2{\cdot}75 \times 10^{-3}\ \mathrm{l\ mol^{-1}\ s^{-1}}$ at 37 °C. Scheme 2 presents a likely kinetically bimolecular route from (**4**) to (**5**); from the steady state assumption we may obtain equation (1). Though the second and third

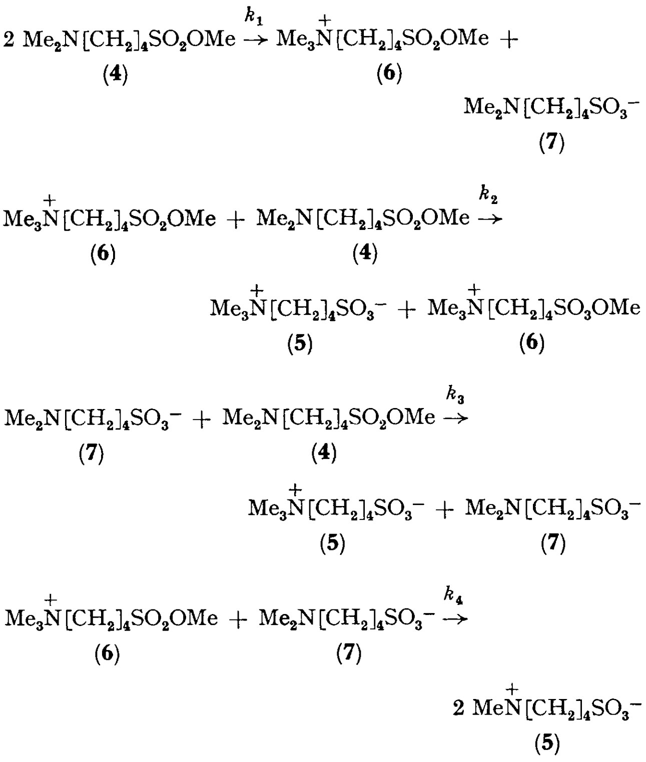
$$-\mathrm{d}[\mathbf{4}]/\mathrm{d}t = [2k_1 + (k_2 + k_3)\,(k_1/k_4)^{\frac{1}{2}}]\,[\mathbf{4}]^2 \qquad (1)$$

reactions in Scheme 2 are chain propagation steps, it is highly unlikely that they generate a greater proportion of the product (**5**) than the fourth step, since any (probably small) factor increasing k_2 or k_3 relative to k_1 would also tend to increase k_4 even more. The likelihood of any important contribution from chain processes may also be assessed by comparison with a model reaction, *e.g.* (**8**) + (**9**),



$$\underset{(\mathbf{8})}{\mathrm{Me_2N[CH_2]_4SO_2OPh}} + \underset{(\mathbf{9})}{\mathrm{Me[CH_2]_3SO_2OMe}} \xrightarrow{k_{\mathrm{M}}} \mathrm{Me_3\overset{+}{N}[CH_2]_4SO_2OPh} + \mathrm{Me[CH_2]_3SO_3^-}$$

since to the extent that this reaction is a suitable model for the first step in Scheme 2, k_1 should approximate k_{M}, the rate constant for the model process. In fact, we find $k_{\mathrm{M}} = 1{\cdot}37 \times 10^{-3}\ \mathrm{l\ mol^{-1}\ s^{-1}}$, *i.e.*, exactly $k_{\mathrm{obs}}/2$, or precisely what is required by equation (1) if there is no contribution at all from the second and third steps in Scheme 2.§



$$2\,\underset{(\mathbf{4})}{\mathrm{Me_2N[CH_2]_4SO_2OMe}} \xrightarrow{k_1} \underset{(\mathbf{6})}{\mathrm{Me_3\overset{+}{N}[CH_2]_4SO_2OMe}} + \underset{(\mathbf{7})}{\mathrm{Me_2N[CH_2]_4SO_3^-}}$$

$$\underset{(\mathbf{6})}{\mathrm{Me_3\overset{+}{N}[CH_2]_4SO_2OMe}} + \underset{(\mathbf{4})}{\mathrm{Me_2N[CH_2]_4SO_2OMe}} \xrightarrow{k_2} \underset{(\mathbf{5})}{\mathrm{Me_3\overset{+}{N}[CH_2]_4SO_3^-}} + \underset{(\mathbf{6})}{\mathrm{Me_3\overset{+}{N}[CH_2]_4SO_3OMe}}$$

$$\underset{(\mathbf{7})}{\mathrm{Me_2N[CH_2]_4SO_3^-}} + \underset{(\mathbf{4})}{\mathrm{Me_2N[CH_2]_4SO_2OMe}} \xrightarrow{k_3} \underset{(\mathbf{5})}{\mathrm{Me_3\overset{+}{N}[CH_2]_4SO_3^-}} + \underset{(\mathbf{7})}{\mathrm{Me_2N[CH_2]_4SO_3^-}}$$

$$\underset{(\mathbf{6})}{\mathrm{Me_3\overset{+}{N}[CH_2]_4SO_2OMe}} + \underset{(\mathbf{7})}{\mathrm{Me_2N[CH_2]_4SO_3^-}} \xrightarrow{k_4} 2\,\underset{(\mathbf{5})}{\mathrm{Me\overset{+}{N}[CH_2]_4SO_3^-}}$$

SCHEME 2

From the above it follows that failure to observe the endocyclic reaction arises not because the intermolecular reaction is inordinately fast but simply because the intramolecular reaction is slow. Since we observed <10% of endocyclic product from a reaction in which the initial concentration of (**4**) was 2 × 10^{-4} M, we may, by simple computer simulation, obtain a maximum value of 10^{-5} M for the effective concentration¶ for the endocylic reaction. Although any saturated eight-membered cyclic transition state is subject to the steric strain usual to such medium rings,[5] the fact that this effective concentration is less than 1/50 of that reported[2b] for analogous exocyclic reactions (lactonization of either 7-bromoheptanoate or 8-bromooctanoate anions) indicates that there is very likely additional strain associated with the endocyclic backside $S_{\mathrm{N}}2$-like reaction in a simple eight-membered cyclic system, or, in the terminology of Baldwin's Rules,[6] 8-*endo-tet* is probably 'disfavoured.'

This work was supported by the Natural Sciences and Engineering Research Council of Canada.

(*Received, 7th September* 1979; *Com.* 956.)

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‡ Thermolysis of (**5**) at 360 °C for 10 min gave trimethylamine (30% yield) which was isolated and analysed as the hydrochloride.

§ Though the very close agreement between k_{M} and $k_{\mathrm{obs}}/2$ may be regarded as fortuitous, it may well prove that the $k_2 + k_3$ term in equation (1) is insignificant and that $k_{\mathrm{obs}} = 2k_1$; this could arise, for example, if (**6**) and (**7**) simply reacted directly as the ion pair. Note that any contribution involving the (**6**) and (**7**) ion pair with (**4**) analogous to the second and third steps in Scheme 2, would lead to third order terms in the rate expression, contrary to observation.

¶ Effective concentration (or effective molarity) is defined as $k_{\mathrm{intra}}/k_{\mathrm{inter}}$, where the rate constants refer, respectively, to the (first order) intramolecular process and an appropriate (second order) intermolecular model reaction, see ref. 2a.

[1] L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, 1970, **53**, 2059.

[2] (a) See, for example, G. Illuminati, L. Mandolini, and B. Masci, *J. Amer. Chem. Soc.*, 1977, **99**, 6308; (b) C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *ibid.*, p. 2591, and references cited.

[3] B. Helferich, K. Geist, and H. Plümpe, *Annalen*, 1962, **651**, 17.

[4] J. F. King, S. M. Loosmore, J. D. Lock, and M. Aslam, *J. Amer. Chem. Soc.*, 1978, **100**, 1637.

[5] V. Prelog in 'Perspectives in Organic Chemistry,' ed. A. R. Todd, Interscience, New York, 1956, p. 96. For an estimate of the contributions to the 'total strain energies' of cycloalkanes of the component van der Waals, bending, torsional, and bond stretching energies, see N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, 1971, **93**, 1637.

[6] J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734.