Activation Parameters for Intramolecular Nucleophilic Substitution by Carbanions—the Insignificant Effect of Ring Strain on Cyclisation Rates

Fabio Benedetti and Charles J. M. Stirling*

Department of Chemistry, University College of North Wales, Bangor, Gwynedd LL57 2UW, U.K.

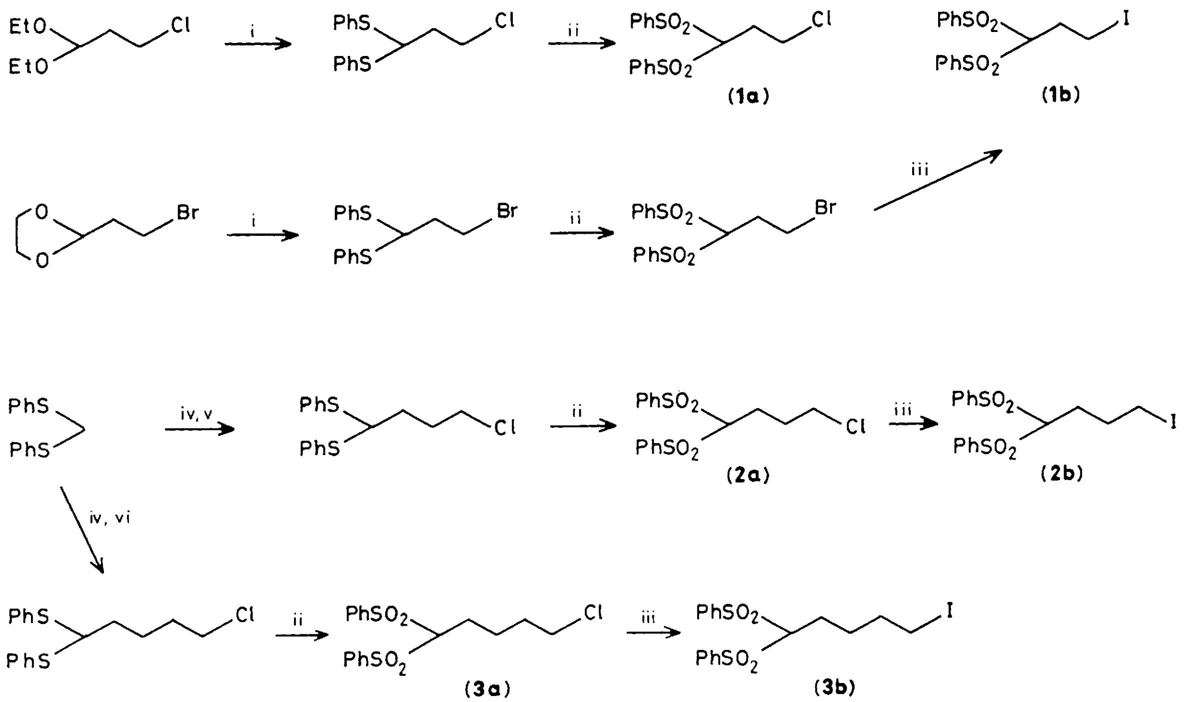
Activation parameters for the cyclisation of bis-sulphonyl-stabilised carbanions to bis-sulphonylcycloalkanes have been determined; cyclopropanes form nearly a million-fold faster than cyclobutanes and ring strain is a negligible factor in determining reactivity.

The effect of structure on intramolecular nucleophilic substitution has been studied systematically by several groups of workers for more than 50 years[1] but for carbocycle formation, however, few general conclusions have been reached about this important type of process. This is because activation parameters have not been determined for a series of different ring sizes. Consideration of ring size effects on intramolecular S_N2 processes has also been complicated by well-entrenched classical assumptions as to the factors which control such reactions.[2] We now present results for the system [equation (1)] which gives the first data defining clearly the factors which control formation of 3-, 4-, and 5-membered carbocycles:

$$(\mathrm{PhSO_2})_2\bar{\mathrm{C}}\text{–}[\mathrm{CH_2}]_n\mathrm{Z} \rightarrow (\mathrm{PhSO_2})_2\overline{\mathrm{C}[\mathrm{CH_2}]}\rceil_n + :\mathrm{Z}^- \qquad (1)$$

Substrates were obtained as shown in Scheme 1; rate constants and activation parameters are in Table 1. Reactions were followed by decrease in the concentration of the carbanion; reactions were of the first order in substrate and of zero order in base in all cases. Yields of carbocyclic bis-sulphone are in Table 1.

The bis-sulphones used are particularly suitable for assessment of the effect of transition state ring size on reactivity for intramolecular nucleophilic substitution. The pK_a of the bis-sulphone function (*ca.* 13) is sufficiently low to guarantee complete conversion into the carbanion in the base–solvent system (sodium ethoxide–ethanol) which has been employed. This is confirmed by the lack of dependence of rate constants on base concentration. The E_1 anion mechanism is thus



Scheme 1. i, PhSH, HCl; ii, m-$ClC_6H_4CO_3H$; iii, NaI, Me_2CO; iv, BuLi–tetrahydrofuran, −78 °C; v, $Br[CH_2]_3Cl$; vi, $Br[CH_2]_4Cl$.

Table 1. Cyclisation of bis-sulphonyl-stabilised carbanions.

Substrate	k_t $(s^{-1})^a$	$E_A{}^b$	$\Delta H^{\ddagger}{}_t{}^b$	$\Delta S^{\ddagger c}$	$\Delta G^{\ddagger}{}_t{}^b$	%Carbocycle isolated	Ring strain^b	$\Delta S^{c,d}$
(1a)	9.05×10^{-1}	88.2	85.7	+42	73	99	115	−29
	$(18.9)^e$							
(1b)	359							
(2a)	6.05×10^{-6}	93.7	91.2	−39	103	97	107	−43
	$(9.60 \times 10^{-5})^e$							
(2b)	4.05×10^{-3}							
(3a)	1.49×10^{-2}	70.8	68.3	−51	83	95	23	−55
	$(8.73 \times 10^{-2})^d$							
(3b)	3.58							

[a] In sodium ethoxide–ethanol, t = 25 °C. [b] kJ mol^{-1}, t = 25 °C. [c] J mol^{-1} K^{-1}. [d] Alkene → cycloalkane. [e] 40:60 v/v $EtOH$–H_2O.

followed and the results are free of assumptions involved in the calibration of pre-equilibrium formation of the reactive intermediate.[3] The effect of the leaving group on the nucleophilicity of the bis-stabilised carbanion has been neglected; were it to be taken into account, it would somewhat widen the large gap in reactivity between the systems giving 3- and 4-membered rings.

The results in Table 1 show the very large difference in cyclisation rates between 3- and 4-membered rings; attention has been called to this striking difference in earlier work[4] on ω-halogenoalkyl malonates but accurate data for the 3-ring system could not be obtained because of its high reactivity.

Enthalpies of activation show that strain in the ring to be formed has little effect on cyclisation rate constant. The Ruzicka hypothesis[2] is untenable on this point and the results suggest a low degree of ring formation in the cyclisation transition state. This result is in direct contrast to what is found for lactone formation; enthalpies of activation for 4- and especially 3-ring formation are very much higher than for 5-rings.[5]

Change of medium from ethanol to 60:40 v/v aqueous ethanol causes a roughly 10-fold acceleration. This suggests considerable separation of the leaving group in the transition state; the substantial chloride: iodide ratios for 3-, 4-, and 5-membered ring formation are consistent with this view, although high values of such ratios are also seen in intermolecular reactions of carbonyl-stabilised carbanions.[6]

It is remarkable that the enthalpy of activation for the formation of the 4-membered ring is *higher* than for the 3-membered ring. In a recent comparison of the much greater reactivity of 3- *vs.* 4-membered rings in eliminative fission,[7] 1,3-interactions in the 4-membered rings have been identified as the cause of differential reactivity. We suggest that the same factor inhibits ring *formation* even when the α,ω-carbon–carbon distance in the transition state is substantial.

In earlier attempts to account for high reactivity in formation of cyclopropanes in intramolecular nucleophilic substitution, conjugative interaction in the transition state between the three-membered ring and the carbanion-stabilising group was tentatively invoked. While both physico-chemical data[1] and calculations[8] support such a possibility, the interaction would have to be substantial even at modest extents of transition state ring formation.

Entropies of activation bear out the Ruzicka hypothesis in this respect. The difference between 4- and 5-ring systems is small; the activation entropy for the 3-ring system is the crucial factor in the rapid formation of cyclopropanes. An open transition state with considerable separation of the leaving group and little ring formation is indicated by the solvent effects, element effects, and activation enthalpy. For 3-ring formation, no orientation of the chain connecting nucleophile and electrophile is required. These factors are not interconnected but both contribute to the large positive value of $\Delta S^{\ddagger}$.

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