The Base-catalysed Cyclisation of ω-Epoxy 1,1-Bis-sulphones. Reactivity and Selectivity as a Function of Ring Size

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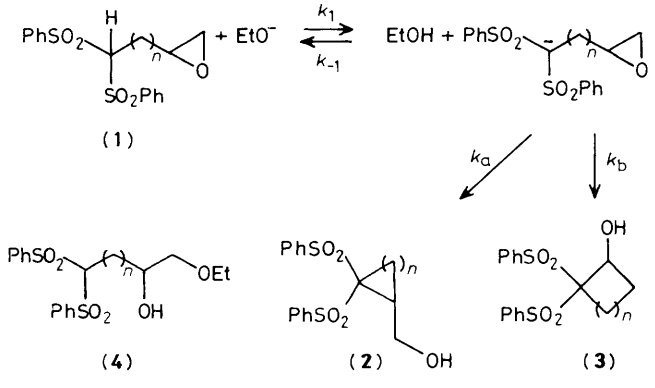
Cyclisation of terminal epoxy bis-sulphones can occur in two different modes; rates of ring closure for three- to seven-membered rings span over three orders of magnitude.

Intramolecular ring opening of epoxides by carbanions is a well established method for the synthesis of functionalized cycloalkanes, particularly for three- to six-membered rings.[1] However the reactivity as a function of ring size has never been quantitatively investigated, as it has been, for example, in the intramolecular S_N2 displacement of halides by carbon nucleophiles.[2,3]

In this communication we report on the base-catalysed cyclisation of epoxy bis-sulphones to give three- to seven-membered cyclic alcohols (Scheme 1). Nucleophilic attack by carbanions, which are generated by dissolving the bis-sulphones (**1**) in 20 equiv. of a 0.1 M solution of sodium ethoxide in ethanol, can take place at the nearest, more substituted position on the oxirane ring (pathway a) or at the other ring carbon (pathway b), to give, after protonation, hydroxymethylcycloalkanes (**2**) and cycloalkanols (**3**). Attack by the competing external nucleophile, ethoxide ion, affords hydroxy ethers (**4**).

Substrates were obtained as shown in Scheme 2; we have chosen bis-sulphonyl carbanions for this study for their stability in the medium and because the acidity of the precursors (**1**) ensures that the pre-equilibrium (Scheme 1) lies well on the carbanion side.[2] This allows rate constants k for the cyclisation step to be measured directly from the rate of disappearance of the carbanions; accordingly reaction rates were not dependent on the base concentration.

The results collected in Table 1 show that the mode of attack varies with the substrate. Thus (**1a**) gives exclusively the cyclopropane (**2a**) (pathway a), while pathway b is preferred in the case of (**1b**) and (**1d**). The butyl oxirane (**1c**) is the only substrate in this series which yields two alcohols, (**2c**) and (**3c**) in a ratio of 6 : 1. Cyclisation of (**1a**) and (**1b**), by analogy with the situation found in mono-sulphones,[4] does not lead to cyclobutanes and this is consistent with the reactivity commonly observed in intramolecular displacements.[5] The preference for the formation of a seven- rather than a six-membered ring from (**1d**) is, on the contrary, unusual and seems to be peculiar to this system.



Scheme 1

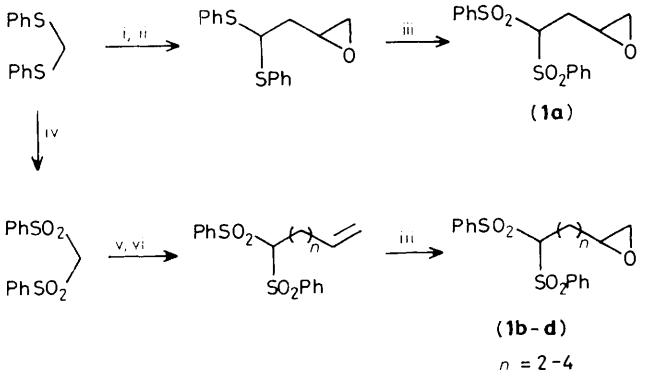
Regioselectivity in the ring opening of this series of terminal epoxides cannot thus be generalised as in non-terminal epoxides, where, with equal degree of substitution at the electrophilic carbons,[6] cyclisation always leads to the small ring, or in intermolecular reactions where attack at the less substituted position prevails.[7]

Examination of the rate constants (Table 1) allows some quantitative considerations on the ease of ring closure for different ring sizes. In pathway a the five-membered derivative (**2c**) is formed faster than the corresponding cyclopropane (**2a**); this result is surprising because it is a well known feature of intramolecular S_N2 displacement that, when the nucleophile is a carbanion, cyclopropanes are cyclised faster than cyclopentanes. As far as we know, this is the first example in which a reverse order of reactivity is observed. This is undoubtedly a special case: in the transition state, the partially-opened oxirane ring and the partially-closed carbocycle are arranged in a spirotype structure around the penta-co-ordinated electrophilic carbon. In the cyclisation of (**1a**) both rings are three-membered, a situation which is particularly demanding energetically: spiropentane, for example, is about 10 kcal mol^{-1}† more strained than two isolated

Table 1. Ring closure of epoxy bis-sulphones.

Epoxide	n	Alcohol	Ring size	Pathway	% Yield	k/s^{-1} [a]
(**1a**)	1	(**2a**)	3	a	92	1.44×10^{-2}
(**1b**)	2	(**3b**)	5	b	68[b]	1.13×10^{-4}
(**1c**)	3	(**2c**)	5	a	77	4.04×10^{-2}
		(**3c**)	6	b	14	7.13×10^{-3}
(**1d**)	4	(**3d**)	7	b	45[c]	2.71×10^{-5}

[a] 25 °C, in sodium ethoxide–ethanol. [b] Remainder is (**4b**). [c] Remainder is (**4d**).



Scheme 2. *Reagents:* i, Bu^{n}Li, tetrahydrofuran, −78 °C; ii, epibromohydrin; iii, *m*-$ClC_6H_4CO_3H$; iv, $MeCO_2H$; v NaH, *N*,*N*-dimethylformamide, 75 °C; vi, $Br[CH_2]_{n+1}CH{=}CH_2$.

† 1 kcal = 4.184 kJ.

cyclopropane rings. It is probably this very high strain energy, partially reflected in the transition state leading to (**2a**), which makes ring closure slower in spite of the favourable entropy associated with the cyclisation of the shorter chain.

The rate constants for pathway b show a trend which again is different from the usual pattern of reactivity in intramolecular displacements, where rates invariably decrease on going from five-membered to larger rings. Here, on the contrary, the highest rate corresponds to the formation of the six-membered compound (**3c**): closure of the corresponding cyclopentanol (**3b**) is approximately 65 times slower. As the number of methylene groups in the side chain decreases from three to two it becomes more difficult for the internal nucleophile to attain the correct alignment with the C–O bond of the epoxide. A similar pattern of reactivity is also observed in intramolecular addition to double bonds, both nucleophilic[8] and free radical,[9] where cyclisation to a five-membered ring is not favoured when it involves attack at the far end of the double bond.

Finally the comparison between the rates of formation of products (**3b**) and (**2c**), which have the same ring size and, presumably, are of similar strain energy, deserves a comment. Although cyclisation to (**2c**) involves attack at a more substituted carbon, it is 400 times faster than formation of (**3b**). This large difference in rates confirms that formation of five-membered rings by ring opening of epoxides is facile only in the mode corresponding to pathway a.

We thank the CNR for generous financial support and Professor C. J. M. Stirling for stimulating discussions.

Received, 29th September 1986; Com. 1381

References

1 J. Gorzynski Smith, *Synthesis*, 1984, 629; A. S. Rao, S. K. Paknikar, and J. G. Kirtane, *Tetrahedron*, 1983, **39**, 2323.
2 F. Benedetti and C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.*, 1983, 1374; *J. Chem. Soc., Perkin Trans. 2*, 1986, 605.
3 M. A. Casadei, C. Galli, and L. Mandolini, *J. Am. Chem. Soc.*, 1984, **106**, 1051.
4 J. M. Decesare, B. Corbel, T. Durst, and J. F. Blount, *Can. J. Chem.*, 1981, **59**, 1415.
5 C. J. M. Stirling, *Tetrahedron*, 1985, **41**, 1613.
6 G. Stork, L. D. Cama, and D. R. Coulson, *J. Am. Chem. Soc.*, 1974, **96**, 5268; G. Stork and J. F. Cohen, *ibid.*, 1974, **96**, 5270.
7 J. Fuhrhop and G. Penzlin, 'Organic Synthesis,' Verlag Chemie, Weinheim 1983, p. 41.
8 J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, 1977, **42**, 3846.
9 A. L. J. Beckwith, *Tetrahedron*, 1981, **37**, 3073.