External Activation of Epoxides by Polarising Groups borne by the Nucleophile

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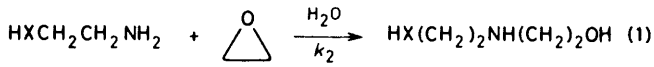
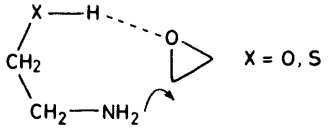
There is much current interest in the chemistry of epoxides which are activated as electrophiles, but almost without exception, systems studied thus far involve internal activation by hydroxy-groups. Herein a new mode of external activation is pointed out, whereby increased susceptibility to nucleophilic attack occurs by interaction of the epoxide with polarising groups such as OH and SH borne by primary amine nucleophiles. Rate data for the reactions of a number of 2-substituted ethylamines with methyloxiran in tetrahydrofuran, ethanol, and water show that while a 2-mercapto-group may increase rates 10—25 fold, a 2-hydroxy-group only appears to be effective in aprotic solvents. Determined values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are discussed, and interpreted as providing evidence for the operation of an intramolecular concerted-like activation process. In drawing a biological analogy, particularly with regard to the physiological action of toxic epoxides, these results draw attention to the possible need to consider alternative modes of *in vitro* action.

A GOOD deal of attention has recently been directed towards the chemistry of ' activated ' epoxides, where ring opening is facilitated by, for example, the presence of an appropriately situated hydroxy-group [1,3,4a,c,d] or chelated transition-metal ion.[2] The reasons for this current scrutiny are interestingly diverse. From a biological viewpoint, it has been suggested that enhanced activity of epoxides towards nucleophiles may, in some cases, parallel an increase in toxicity towards living systems.[2a,3] For example, a number of benzopyrenoid diol epoxides are known to be extremely potent carcinogens,[3] whose physiological (mutagenic) activity may be due to their reaction as electrophiles with nucleophilic groups present on vital macromolecules. In other cases, it appears that the damaging effects of some hydroxy-epoxides can be turned to advantage, since it has also been reported that certain of these compounds possess anti-tumour [4] and antibiotic [4b] properties. Reactions of activated epoxides are also interesting from mechanistic [5] and synthetic † standpoints, ‡ because of the facility of neighbouring hydrogen-bonding groups in directing regio- and stereo-specific ring cleavages.

Thus far however, attention has been focussed almost entirely on reactions in which the epoxide bears the activating group, and in which activation may be described as internal. We have, however, pointed out the existence of an alternative mode of *external* activation,[7] where enhanced epoxide reactivity is achieved by the similar interaction of epoxide oxygen with a suitable grouping borne *externally by the nucleophile*. Specifically, we observed that the reaction of certain epoxides with primary amines [equation (1)] is markedly accelerated by the presence of activating groups such as hydroxy, and in particular, thiol, on C-2 of the amine §, and suggested that the nature of the activation may involve a lowering of relative transition-state energy by intramolecular hydrogen-bonding between the β-grouping and epoxide oxygen, as shown in the species (1).





(1)

We have now carefully investigated the reactions of a number of 2-substituted ethylamines with methyloxiran (propylene oxide), and below present kinetically determined evidence, including thermodynamic parameters for these reactions which strongly support our earlier suggestions. The potential biological implications of this form of activation for *in vitro* processes are also noted.

EXPERIMENTAL

Materials.—Following purification, all solvents and liquid reagents described below were stored over 3A molecular sieves.[8]

' Super-dry ' ethanol was prepared from commercial 99.9% grade material by the magnesium alkoxide method[9a] (final H_2O content, *ca.* 50 p.p.m. by Karl Fischer analysis). Commercial grade tetrahydrofuran was purified by de-

† The classic case of the use of an activated epoxide in synthesis must surely be attributed to the Darzens Ester Condensation, wherein free glycidic acids formed as intermediates undergo spontaneous regiospecific decarboxylation.

‡ A pertinent example is provided by the synthesis of cyclopent-2-enecarbaldehydes from α-hydroxycyclohexene oxides.[6a] The regiospecificity of this very useful reaction appears to rely on the directing properties of the hydroxy-group. Other synthetically useful regio-orientational effects by similarly located hydroxy-groups have also been noted.[6b]

§ It should be pointed out that our earlier product studies [7] have unambiguously demonstrated that reactions of 2-aminoethanethiol with epoxides under neutral conditions proceed as formulated in equation (1), *i.e.* the amine group functions as the nucleophile.

peroxidation with cuprous chloride, distillation, mechanical stirring overnight with calcium hydride, and final fractionation (b.p. 66—67 °C). Methyloxiran (Koch-Light, 99%) and 2-methoxyethylamine (Tokyo-Kasei, >99%) were used as received except for sieve-drying. Commercial grade 2-aminoethanol was treated by drying overnight with KOH pellets followed by fractional distillation (b.p. 55—56 °C at 5 mmHg). 2-Aminoethanethiol was purified by vacuum sublimation [9b] (50—60 °C at *ca.* 0—1 mmHg), and methyl 2-aminoethyl sulphide was prepared by alkylation of the thiol as detailed elsewhere.[7] Stock solutions of ethylamine (1.0—4.3M), prepared by passage of the dried gas (3A molecular sieve) into rigorously dried solvent, were standardised by acid titration and diluted accordingly.

Techniques.—Reaction rates were determined by dilatometry, since in contrast to the volumetric methods conventionally used for following amine-epoxide reactions,[10] dilatometry requires only small samples, and allows continuous monitoring of the reaction with minimal possibility for sample contamination and introduction of sampling errors. Such features are ideal for the generally slow reactions encountered in this study.

Dilatometers were constructed from 2-mm precision bore capillary joined to a 25-ml reaction bulb equipped with a magnetic follower. Requisite volumes of solutions of amine and epoxide were syringed directly into the dilatometer, which, after degassing, was sealed *in vacuo*. The dilatometer was then immediately immersed in a thermostat bath ($\pm 10^{-2}$ °C) and the meniscus height monitored with a cathetometer ($\pm 10^{-3}$ cm) to complete conversion. The reproducibility of duplicate runs was within 1%.

Calculation of Reaction Rate.—Rates were determined by assuming the linearity of the contraction–conversion relationship for these reactions. The validity of this assumption was confirmed for several cases by an independent g.l.c. calibration (see Figure 1). (Varian Aerograph Series

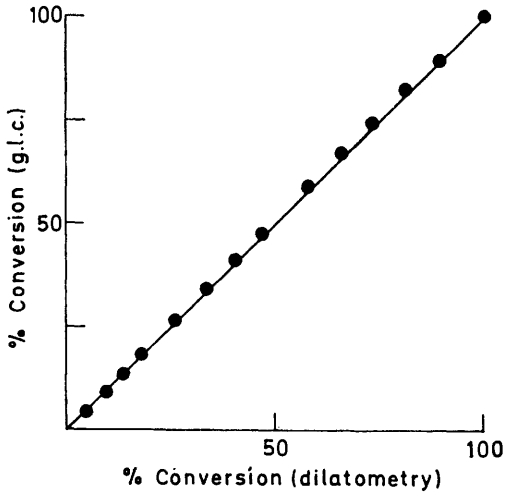


FIGURE 1 Correlation of conversion determination by g.l.c. and dilatometric methods

1800 Instrument, column: 10 ft × 0.25 in packed with 15% Carbowax 20 M operated at 50 °C.)

Since the products of these reactions contain a secondary amino-grouping [see equation (1)], consecutive reactions between the amino-alcohols and epoxide are possible. These secondary processes were minimised by using the amine in excess. In this context, although a ten-fold excess of amine was used initially for all runs, later experiments showed that in ethanol solvent, the pseudo-first-order rate constants remained invariable down to a two-fold excess. Second-order rate constants (k_2) were derived from the pseudo-first-order plots (see Figure 2) according

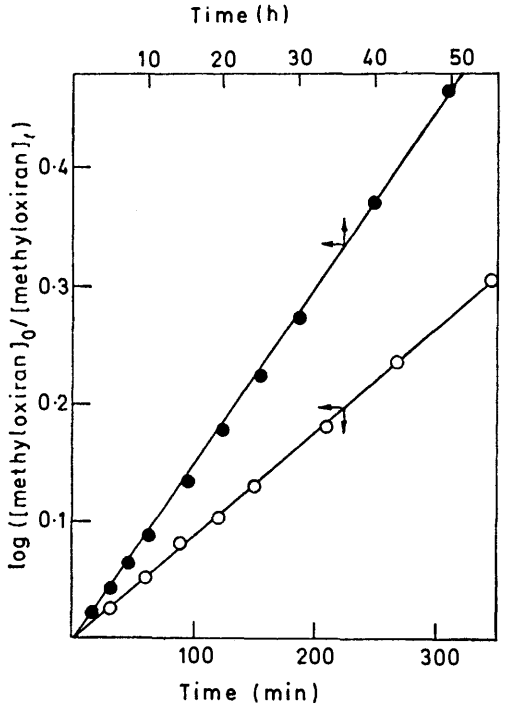


FIGURE 2 Pseudo-first-order plots for the 2-aminoethanol–methyloxiran reaction: ● solvent = THF; [amine] = 2.0 mol dm^{-3}, [epoxide] = 0.20 mol dm^{-3}; t = 30.0 °C; ○ solvent = ethanol; [amine] = 0.50 mol dm^{-3}; [epoxide] = 0.25 mol dm^{-3}; t = 30.0 °C

to the relationship $k_2 = k_{obs.}/[\text{Amine}]_0$ where $k_{obs.}$ is the pseudo-first-order rate constant and $[\text{Amine}]_0$ is the initial amine concentration. Activation parameters were determined from appropriate Arrhenius plots by a least-square analysis.

RESULTS AND DISCUSSION

The results obtained in ethanol, THF, and water solvents are summarised in Tables 1, 2, and 3 respectively. From Table 1, it is apparent from the rate constants that a thiol grouping on C-2 of the amine (Run 1) enhances the reaction rate by a factor of about 10 relative to the other ethylamines; that this effect is directly connected with the weakly acidic nature of the thiol grouping is demonstrated by the loss of activity for the methylthio-compound (Run 2).

The mechanism of this activation might reasonably involve either an intramolecular process, as represented by (1), or a more entropically advantaged intermolecular alternative. An intermolecular pathway already seemed less likely from our earlier observations that no activation was observed unless the polarising group and nucleophile were part of the same molecule.[7] Moreover, as has been argued in other cases,[11] an intermolecular

activation process should lead to product mixtures resulting from nucleophilic competition by the solvent. Therefore, the production of only an amino-alcohol from the reactions reported here may be taken as a further indication of intramolecular activation. Definitive evidence is obtained from the values of the activation parameters for Run 1. Compared with Runs 2, 3, and 4, Run 1 shows large decreases in $\Delta S^{\ddagger}$, as well as $\Delta H^{\ddagger}$. By external hydrogen bonding, we examined the reactions summarised in Table 2 in THF.

As can be seen, besides reducing relative reaction rates by a factor of 10^2, the substitution of THF as solvent also reveals the same pattern as that observable in Table 1. Specifically, the 2-hydroxy-group causes significant rate increases (*ca.* 40-fold) compared with ethylamine (see Runs 5 and 7) and this effect is completely lost on *O*-methylation (Runs 5 and 6), which results in a 100-fold rate decrease. In addition, the consistent decrease in enthalpy and entropy of reaction for Run 5 as against 6 and 7 again suggests the importance of (1) as the mode of activation. It is interesting to note that the magnitude of the external activation effects observed here is of similar order to other comparable results obtained for internal activation.[1a]

TABLE 1

Rate constants and activation parameters for the reaction of β-substituted amines with methyloxiran in ethanol

Run	Amine	Second-order rate constant $k_2 \times 10^5$/mol dm^{-3} s^{-1} 20 °C	25 °C	30 °C	35 °C	E_a / kJ mol^{-1}	$\Delta H^{\ddagger}$ / kJ mol^{-1}	$\Delta S^{\ddagger}$ / J K^{-1}
1	$HSCH_2CH_2NH_2$	35.7	42.7	51.7	59.4	25.9 ± 1.0	23.4 ± 1.0	−231.0 ± 3.3
2	$MeSCH_2CH_2NH_2$	2.93	4.43	6.22	9.22	56.9 ± 1.3	54.4 ± 1.3	−146.0 ± 4.2
3	$HOCH_2CH_2NH_2$	3.08	4.33	6.55	8.61	53.1 ± 2.5	52.7 ± 2.5	−160.7 ± 8.8
4	$CH_3CH_2NH_2$	3.97	5.45	8.16	10.7	51.0 ± 2.5	48.5 ± 2.5	−164.8 ± 8.4

Solvent = ethanol; $[epoxide]_0 = 0.25$ mol dm^{-3}; $[amine]_0 = 0.50$ mol dm^{-3}.

While it might be contended that a highly ordered transition state cannot be assumed from the entropy data because of unknown contributions arising from the solvent, the singularly low value of $\Delta H^{\ddagger}$ indicates little change in bond energies between reactants and activated complex in this case. In other words, it seems likely that activation occurs by a mechanism which can be described as concerted, in the sense that hydrogen bonding beginning at one pair of termini is accompanied by the inception of nucleophilic attack at the other, and this gives rise to an early transition state [12] in which the epoxide ring remains as yet unbreached. Taken together, the sum of the available evidence strongly implicates the importance of a transition state such as (1).

Importantly, a 2-hydroxy-grouping shows no activating effect whatever in ethanol. However, when the well-known reluctance of thiol-groups to form hydrogen bonds is contrasted with the behaviour of hydroxy-groups this result is not altogether surprising, and an analogy is found in the results of a recent kinetic study of the activating influence of a *syn*-hydroxy-grouping in the epoxides of aromatic tetrahydro-diols. Here, Bruice and his co-workers [1a] found that activation towards nucleophilic attack was only displayed in aqueous organic solvents, and diminished rapidly in importance with increasing concentrations of water.

In order to determine whether hydroxy-groups might show an activating effect in the absence of interference

TABLE 2

Rate constants and activation parameters for the reaction of β-substituted amines with methyloxiran in THF

Run	Amine	Second-order rate constants $k_2 \times 10^7$/mol dm^{-3} s^{-1} 30 °C	35 °C	40 °C	45 °C	E_a / kJ mol^{-1}	$\Delta H^{\ddagger}$ / kJ mol^{-1}	$\Delta S^{\ddagger}$ / J K^{-1}
5	$HOCH_2CH_2NH_2$	29.6	44.8	61.0	84.0	55.2 ± 2.1	52.7 ± 2.1	−177.8 ± 6.7
6	$MeOCH_2CH_2NH_2$	0.35	0.56	0.86	1.41	73.2 ± 2.1	70.7 ± 2.1	−154.0 ± 7.1
7	$CH_3CH_2NH_2$	0.78	1.13	1.78	2.85	69.5 ± 3.3	66.9 ± 3.3	−161.9 ± 11.3

Solvent = THF; $[epoxide]_0 = 0.20$ mol dm^{-3}; $[amine]_0 = 2.0$ mol dm^{-3}.

processes. For example, 2-aminoethanethiol in water reacts 2.6×10^5 times faster than ethylamine in THF, and 7×10^3 times more rapidly than 2-aminoethanol in the same solvent. Furthermore, an examination of the

TABLE 3

Comparison of second-order rate constants in ethanol, THF, and water at 30 °C

Amine	$k_2 \times 10^5$/mol dm^{-3} s^{-1} THF	Ethanol	Water
$HOCH_2CH_2NH_2$	0.296	6.55	80.3
$HSCH_2CH_2NH_2$		51.7	2 040
$CH_3CH_2NH_2$	0.0078	8.16	

respective rate increases in changing from ethanol to water shows that while 2-aminoethanol exhibits a 12-fold enhancement, the amino-thiol shows a 39-fold increase. To rephrase, it is apparent that, relative to the other amines, the activating effect of thio-groups is even more

pronounced in water than in organic solvents. While this particular result may be reasonably explained in terms of differential hydrogen-bonding effects by the solvent, the well documented [14] and quite general phenomenon of the facility of water in causing dramatic increases in the rates of epoxide–amine reactions still, in our opinion, awaits a convincing explanation.

In conclusion, although epoxide activation by interaction with external hydroxy-groups is demonstrably present in non-hydrogen-bonding solvents, its importance in the physiological medium must be deemed questionable. On the other hand, activation by external thio-groups, still apparent in water, raises new biochemical possibilities. The selective alkylation of cellular nucleophiles, *e.g.* in enzymes, by external electrophiles has been correlated with antitumour and cytotoxic activity, as well as some aspects of chemoprophylaxis.[14] It is customary to assume,[14,15] not unreasonably, that substrates containing thiol groups react as thiolates, and reactivity towards thiol-containing reagents is routinely used as a measure of potential mode of biological action.[15] However, the results presented above suggest that, at least for epoxides, alkylation at *other* nucleophilic centres, assisted by the activating effect of neighbouring thiol moieties ought to be considered as an alternative mode of *in vitro* reaction.*

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* It is of interest to note that the mutual biological reactivity of such systems has already been implicated, *inter alia*, by a suggestion that proteins containing thiol and amino-groups in close proximity may bind biologically important carbonyl groups through the formation of thiazolidine-like linkages.[16]

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