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SOLVENT SELECTIVITY AND STEREOSELECTIVITY OF THE SOLVOLYSIS OF 1-PHENYLCYCLOHEXENE OXIDE IN WATER-ETHANOL MIXTURES

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Abstract—The title reaction has been examined in solvent mixtures ranging from pure ethanol to pure water and the product compositions have been determined. Selectivity for attack by ethanol increases in the x_{H_2O} range from 0 to 0.83, the variation being higher for the *syn* than for the *anti* adducts. *Syn* stereoselectivity increases with increasing water mole fraction, more for the ethanol than for the water adducts. The usual irregularities are observed at high x_{H_2O}. The data are in accordance with an elaboration of a previously proposed mechanistic scheme.

Previous work from this Institute has provided proofs for the fact that in the acid-catalysed solvolysis of aryl substituted oxiranes the transition state leading to *syn* adducts has a higher degree of development of positive charge on carbon than the one going to *trans* adducts[1] and that entropic factors favor *syn* addition, enthalpic ones *anti* addition.[2] Evidence was also obtained indicating that changes in stereoselectivity between hydrolysis and ethanolysis are due mostly to changes in the enthalpy of activation.[2]

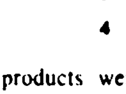
We have now sought more information on the detailed mechanism of these reactions in a study of the variations in stereoselectivity and in solvent selectivity of the solvolysis of 1-phenylcyclohexene oxide **1** in a wide range of $EtOH-H_2O$ mixtures. Competition in the attack by different nucleophiles has received much attention as a mechanistic probe for solvolytic displacement reactions, mainly on the basis of the principle by which selectivity should be proportional to the stability of the intermediate,[3] a hypothesis that is often supported by good experimental correlations, but suffers from several exceptions and from an insufficient theoretical motivation.[4] While most of available experimental data have used N_3^- as the competing nucleophile, mixtures of alcohols and water have been initially employed by Hammett[5] and by Ingold,[6] and recently J. M. Harris *et al.*[7] have used these solvent mixtures to investigate stability-selectivity relationships in the solvolysis of several tosylates and chlorides, and found good correlations between reactivity and selectivity. Since the azide ion could not be used in the acid-catalysed epoxide solvolysis we therefore chose the $EtOH-H_2O$ system in the presence of H_2SO_4, because of the wide variations in polarity that are possible for this solvent mixture.

RESULTS AND DISCUSSION

The data obtained in the solvolytic experiments are summarized in the Table and analysed in Figs. 1–4. In all cases (except for the pure solvents) the reaction products consisted of mixtures of the diols **2** and **3** and hydroxy ethers **4** and **5** which were analysed by GLC. The reactions were entirely regiospecific in the case of EtOH (and presumably also of H_2O),[1] involving exclusive attack on the tertiary benzylic carbon. The products were completely stable under the reaction conditions. The only side products were small amounts of 2-phenylcyclohexanone and of 1-phenylcyclopentane-1-carbaldehyde: a maximum of 4% in pure ethanol, much less in water-rich mixtures.

Table 1. Molar ratios of products in the acid-catalyzed solvolysis of **1** in $EtOH-H_2O$ mixtures

H_2O:EtOH (v/v)	x_{H_2O}	**5**	**4**	**3**	**2**
100:0	1.000	—	—	62.6	37.4
95:5	0.984	1.1	0.5	60.8	37.6
90:10	0.967	2.5	1.0	60.4	36.1
80:20	0.929	5.7	2.2	53.3	38.8
70:30	0.883	10.0	4.6	50.4	35.0
60:40	0.830	14.8	7.5	44.8	32.9
50:50	0.765	18.2	11.1	39.8	30.9
40:60	0.684	20.6	14.1	35.1	30.2
23.55:76.45	0.500	25.8	25.0	24.2	25.0
10:90	0.263	29.7	40.4	13.5	16.4
5:95	0.146	31.6	50.5	8.1	9.8
0:100	0.000	32.5	67.5	—	—



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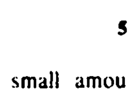

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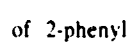

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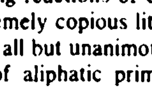

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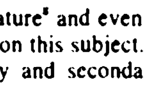

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The interpretation of the mechanism of acid-catalysed ring opening reactions of epoxides has been the subject of an extremely copious literature[8] and even very recent papers are all but unanimous on this subject. Whereas in the case of aliphatic primary and secondary epoxides there is some agreement on the fact that they open by an A-2[9,10] or "borderline A-2" mechanism,[11] the situation is less clear for tertiary and aryl-substituted ones, since evidence from stereochemistry, regiochemistry, entropy and volume of activation often provide conflicting evidence that has been interpreted in favor of A-1, A-2 or intermediate mechanisms.[9-16] An alternative mechanistic scheme involving ion pair intermediates has recently been proposed,[17] in accordance with the present trend in the interpretation of nucleophilic displacements by the unified treatment first proposed by Winstein that does away with the traditional S_N1-S_N2 dichotomy and considers equilibria between several types of ionic intermediates.[5-8] Acid-catalysed epoxide solvolysis is a peculiar type of displacement since it involves a preliminary proton transfer from an oxonium ion to the oxirane oxygen, and the leaving group is neutral and remains covalently bound in close vicinity to the reaction site. A tentative representation of the solvolysis of an aryloxirane that is an extension of our previous proposals[1,2] is given in Scheme 1.†

An S_N2-type reaction on the unprotonated epoxide is certainly not competitive in our case, since it should be very much slower and exhibit the opposite regioselectivity. Branching of the two paths, leading respectively to the *anti* and *syn* adducts, presumably occurs after the proton transfer stage, that is from an intermediate, tentatively depicted as **7**, in which the C–O bond has broken, but a strong electrostatic interaction still exists between carbon and leaving oxygen. This intermediate cannot be equated to the intimate ion pair of the Winstein scheme, since the OH group and one or more solvent molecules should efficiently separate ion from counter-ion. It can rather be related to the "ion-dipole pair" proposed by Sneen *et al.*[19] to account for the mechanism of nucleophilic substitution into sulphonium ions. Intermediate **7** can then undergo a nucleophilic attack by a solvent molecule that must take place mainly from the back, because of the strong shielding at the front, to give the *anti* adduct.

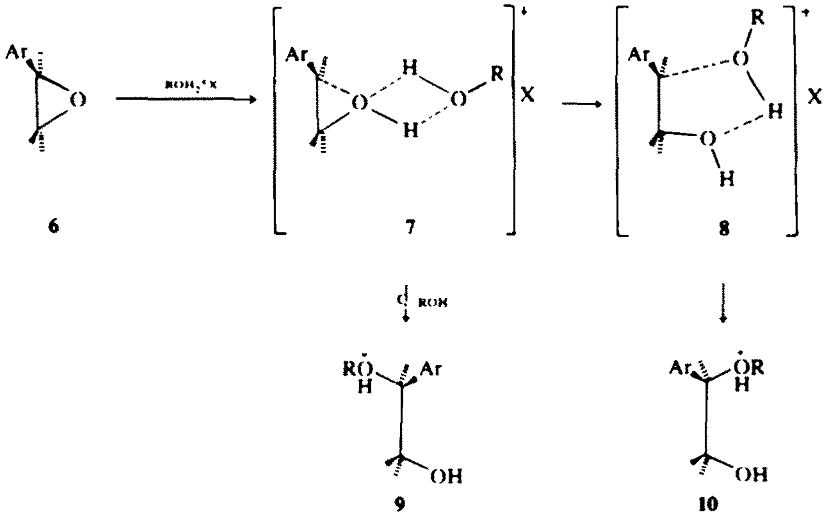
Alternatively, rearrangement in the solvation shell can lead from **7** to an intermediate such as **8**, which is equivalent to the solvent separated ion pair of the Winstein scheme, but is particularly stabilized by hydrogen bonding. It should preferentially collapse to the *syn* adduct because of its highly favourable geometry.[20] The potential energy profile should therefore have a shape such as that indicated in Fig. 5 (no quantitative significance is implied) and the *anti*/*syn* ratio is determined by the difference in the transition states T_a and T_s.

The solvent selectivity of the reaction under discussion should on the other hand depend on the distribution of EtOH and H_2O in these intermediates: the presence of four variables (*syn* and *anti* attack by H_2O and EtOH) makes it very difficult to rigorously interpret the data, but the observed trends can be reconciled with the proposed mechanistic scheme.

Figure 1 shows the change in overall selectivity with an increasing water content. Selectivity is defined as usual by eqn (1), where the ratios of the rate constants

$$\text{Selectivity} = \log\frac{k_E}{k_W} - \log\frac{[\text{ROEt}][\text{H}_2\text{O}]}{[\text{ROH}][\text{EtOH}]} \qquad (1)$$

relative to ethanolysis (k_E) and to hydrolysis (k_W) are deduced from the molar ratios of hydroxy ethers to diols, divided by the molar ratios of EtOH to H_2O in the solvent mixture. The selectivity increases up to $x_{H_2O} = 0.83$, with the result that in this range the richer the solution is in H_2O the higher is the preference for attack by EtOH. It may also be observed that selectivity is almost exactly 0 for $x_{H_2O} = 0.50$, that is when an equal number of molecules of the two solvents is present, but this may be pure coincidence.



Scheme

This behaviour indicates a composition of the solvation shell in the transition states that is different from that of the bulk solvent. Such a "solvent sorting" effect has been invoked by Hyne[21] as an explanation for the anomalous variations of activation energies with solvent composition in the solvolysis of benzyl chloride in H_2O-rich H_2O/EtOH mixtures, but Harris *et al.*[7], and Arnett[22] provided evidence against it in other cases. It must be stressed however that only very few data are available in the literature on the variation of selectivity with mixed

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† In order to avoid unnecessary complication of the Scheme we are using simplified general formulae that should be valid for any aryl-substituted epoxide. The conformational situation of **1**, which can exist in two non-equivalent half-chair conformers with a low interconversion barrier, is of no particular importance for the present discussion, since on the basis of the Curtin–Hammett principle the ground state conformation should not be relevant. This is consistent with preliminary experiments on the solvent selectivity in the solvolysis of styrene oxide that gives a curve that is very similar to that depicted in Fig. 1.

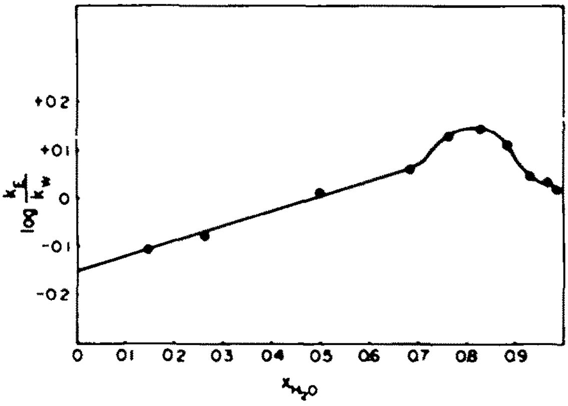

Fig. 1. Overall solvent selectivity.

solvent composition, most of the data having been based either on kinetic measurements only, without product analysis, or taken at only one solvent composition. The fact that the more polar solvent can better exert its solvating properties in a medium of low polarity explains why, at $x_{H_2O} < 0.5$, the ratios of diols to hydroxy ethers are higher than those of H_2O to EtOH in the solvent. Furthermore, in excess EtOH the doubly hydrogen bonded water molecule, $\underset{H}{O}(H\cdots OEt)_2$, has the enhanced nucleophilic properties.[23] At $x_{H_2O} > 0.5$ the increased polarity of the solvent favors the more polar intermediate **8** in which there should be a preference for solvation by EtOH, a better and more easily polarized nucleophile than H_2O,[24] thus leading to a higher percentage of ethanolysis than could be expected from the solvent composition.

The fact that at $x_{H_2O} > 0.83$ selectivity decreases again is not surprising since, in the presence of a large excess of water molecules, the alcohol molecules will be solvated by water both on hydrogen and oxygen, thus decreasing their nucleophilic character. It is also well known that at high x_{H_2O} in H_2O–alcohol mixtures anomalous effects in physical and chemical properties occur, this being usually attributed to structure formation in the solvent.[22,23]

Figure 2 shows the solvent selectivity data for *syn* ($\log k_{EC}/k_{WC}$) and *anti* opening ($\log k_{ET}/k_{WT}$). The reaction proceeding through intermediate **8** shows the higher variation in selectivity with increasing polarity which should correspond to increasing stability of the intermediate, in accordance with the stability-selectivity principle.

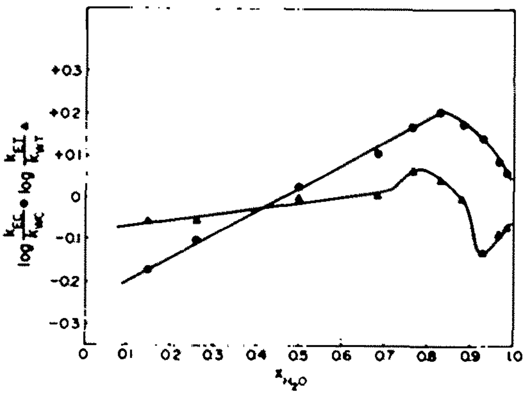

Fig. 2. Selectivity for *syn* and *anti* adducts.

Figure 3 analyses the data from the point of view of stereoselectivity, showing the variation of the logarithm of the ratios of total *cis* to total *trans* adducts with solvent composition. The higher preference for *anti* attack in pure EtOH with respect to pure H_2O is in good agreement with the fact that the contribution of the less polar intermediate **7**, leading to the *trans* adduct, must be more important in the low polarity solvent. There is a monotonous variation of the stereoselectivity in going from pure EtOH to pure H_2O, except for some small irregularities in the high x_{H_2O} region. Figure 4, in which the stereoselectivities for the hydroxyethers and for the diols are plotted separately, shows a much more pronounced variation for the former than for the latter. Again, the more easily polarized EtOH molecule is more

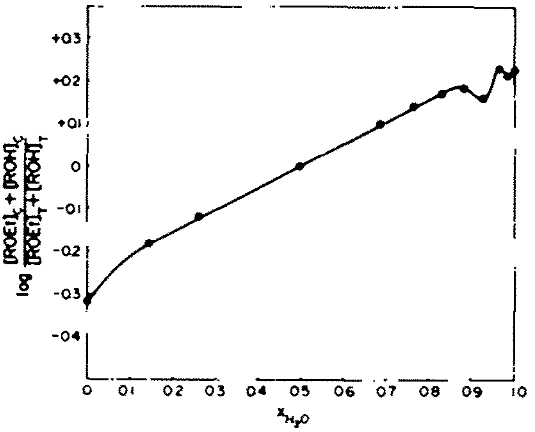

Fig. 3. Overall stereoselectivity.

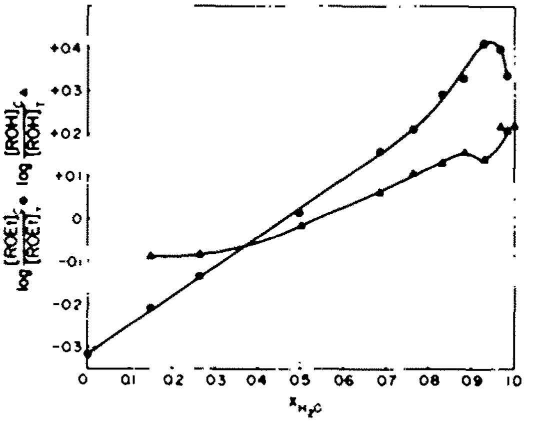

Fig. 4. Stereoselectivity for the hydroxy ethers and diols.

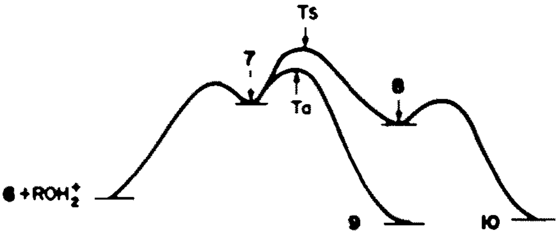

Fig. 5. Potential energy profile for the reaction of epoxide 1.

sensitive to solvent polarity variation and consequently to the balance between intermediates **7** and **8**.

In conclusion, although the present set of data cannot be taken by themselves as proof of the mechanism outlined in the Scheme, they are not in disagreement with it. Work is now in progress on the solvolysis of simpler epoxides where solvent selectivity can be investigated separately from stereoselectivity.

EXPERIMENTAL

GLC analyses were run on a Carlo Erba Fractovap GV apparatus with a flame ionization detector, using a dual column system with glass columns. The relative percentages of compounds **2**, **3**, **4** and **5** were determined using columns packed with 10% diethyleneglycol succinate on 80–100 mesh silanized Chromosorb W (2.5 mm × 1.5 m); temperature program: low isotherm 130° (7 min), high isotherm 170° (increase 6°/min), evaporator and detectors 200°, nitrogen flow 30 ml/min. Order of increasing retention times: $4 < 5 < 3 < 2$.

The values given in Table 1 were the average of at least three measurements done on at least two different runs for each point. The accuracy is ± 1%, except for the values relating to the hydroxy ethers in the $> 90\%$ H_2O mixtures where the error could be greater.

1-Phenylcyclohexene oxide **1**,[25] 1-phenyl-*r*-1,*trans*-2-cyclohexanediol **2**,[26] 1-phenyl-*r*-1, *cis*-2-cyclohexanediol **3**,[25] 2-phenyl-*trans*-2-ethoxy-*r*-2-cyclohexanol **4**,[27] 2-phenyl-*cis*-2-ethoxy-*r*-1-cyclohexanol **5**,[27] 1-phenyl-*trans*-2-ethoxy-*r*-1-cyclohexanol **11**,[27] 2-phenylcyclohexanone[28] and 1-phenylcyclopentane-1-carbaldehyde[28] were prepared as previously described.

Reactions of 1-phenylcyclohexene oxide **1** *with sulfuric acid in ethanol–water mixtures*. The reactions were carried out in the following way: a suspension (water or water-rich mixtures) or solution (ethanol or ethanol rich-mixtures) of **1** (0.100 g) in 0.2 N H_2SO_4 in the chosen solvent mixture (10 ml) (see Table 1) was stirred for 2 h at 25°, quenched with $NaHCO_3$ and satd $NaHCO_3$ and extracted with ether. Evaporation (rotary evaporator) of the washed (H_2O) and dried ($MgSO_4$) ether extracts gave (except for pure solvents) mixtures of the diols, **2** and **3**, and hydroxy ethers, **4** and **5**, which were analysed by GLC (see Table 1). The reactions were completely regiospecific in the case of EtOH; no trace of the isomeric hydroxy ether **11** was detected.[27] Compounds **2–5** were completely stable when kept 24 h under the reaction conditions and their overall yields were almost quantitative. The only side products were 2-phenylcyclohexanone and 1-phenylcyclopentane-1-carbaldehyde, a maximum of 4% in pure ethanol, much less in water-rich mixtures.

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