

466. *The Mechanism of Epoxide Reactions. Part VIII.¹ The Effect of Solvent Variation on the Reaction of Benzylamine with 1,2-Epoxyethylbenzene*

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Overall rate constants for the first reactions of 1,2-epoxyethylbenzene with benzylamine have been determined in a series of six protic solvents and in six aprotic solvents by a spectrophotometric method. Product analyses have been carried out by infrared spectroscopy, and Arrhenius parameters calculated in several cases. The effects of protic and aprotic solvents on the reaction are discussed in terms of the Glasstone and Hiromi equations and the semiempirical Brownstein equation. The much greater rates of reaction in protic than in aprotic solvents are attributed to the specific electrophilic assistance to ring cleavage exerted by protic solvents.

PREVIOUS Papers in this Series have reported the effect of substituent variation on the reactions at the normal and the abnormal positions of unsymmetrical epoxides under both neutral¹⁻⁵ and acidic^{1,4} conditions. In the present study, the rate and position of attack on 1,2-epoxyethylbenzene by benzylamine have been examined in a series of protic solvents and in a number of aprotic solvents. Benzylamine and 1,2-epoxyethylbenzene were chosen as reactants, since they yield appreciable amounts of both the normal and the abnormal products,² and the reaction between these species may be readily analysed.² As the reaction involves the formation of a charged transition state from initially neutral reactants, it should be favoured by strongly solvating solvents.⁶ The solvating power of a medium has often been directly related to its dielectric constant,⁷ and, thus, the emphasis of the investigation was placed on solvents of high dielectric constant.

Very few investigations of the effect of solvents on epoxide ring-cleavage reactions have been made, and only in a single case⁵ have kinetic measurements been coupled with

¹ Part VII, J. K. Addy and R. E. Parker, *J.*, 1965, 644.

² J. K. Addy, R. M. Laird, and R. E. Parker, *J.*, 1961, 1708.

³ R. M. Laird and R. E. Parker, *J. Amer. Chem. Soc.*, 1961, **83**, 4277.

⁴ J. K. Addy and R. E. Parker, *J.*, 1963, 915.

⁵ R. M. Laird and R. E. Parker, *J.*, 1963, 6065.

⁶ C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953, p. 345.

⁷ (a) S. Glasstone, K. J. Laidler, and H. Eyring, "Theory of Rate Processes," 1st edn., McGraw-Hill, New York and London, 1941, p. 419; (b) K. Hiromi, *Bull. Chem. Soc., Japan*, 1960, **33**, 1251.

product analyses. Knorr⁸ and Krassuski⁹ were the first to suggest that a protic solvent was necessary for reaction to occur, and the failure of diethylamine to attack ethylene oxide in the absence of a solvent has been noted.¹⁰ Guss and Williams¹¹ isolated the products of the reaction of phenol with 1,2-epoxyethylbenzene, and observed that the ratio of isomeric products varied with the solvent employed and with the temperature. In ethanol, the normal/abnormal product ratio was 43/57, while in the more polar methanol it was 31/69, and an increase of temperature from 22 to 74° for the reaction in methanol increased the proportion of the normal product by 12%. However, the absence of kinetic measurements makes the interpretation of these results difficult, since the observed variations may have been due to changes in the rates either of the normal reactions, or of the abnormal reactions, or both. Recently,⁵ the rates of normal and of abnormal attack on substituted 1,2-epoxyethylbenzenes by benzylamine have been compared in methanol and in ethanol. In the former solvent, the reaction was less selective as between normal and abnormal attack, and was faster at both positions. These results can be explained in terms of the acidity difference between the two solvents, the more acidic methanol exerting greater electrophilic assistance to ring-cleavage through hydrogen bonding to the epoxide oxygen and thus favouring a faster and less-selective reaction.

In the present investigation, a four-fold excess of benzylamine over 1,2-epoxyethylbenzene was used (in order to minimise further reaction of the product with the epoxide), and the reaction was followed by determination of the primary amine, as described in Part III.² Product analyses were carried out, as before,² by comparing the infrared spectrum of the reaction product with that of the normal isomer and of the abnormal isomer. The considerable reactivity of both epoxides and amines made an examination for solvolysis imperative. Epoxides are known to react with secondary amines¹² and sulphoxides,¹³ and with aliphatic alcohols under forcing conditions.¹⁴ However, a previous investigation¹⁵ showed that no reaction occurred between 1,2-epoxyethylbenzene and ethanol in the presence of 2-methylpiperidine, under conditions similar to those used in the present work. Benzylamine, being a weaker base than 2-methylpiperidine, is less likely to favour formation of alkoxide ions (which would attack the epoxide), and solvolysis by monohydric alcohols was assumed to be insignificant in the present case.

EXPERIMENTAL

Materials.—After preliminary purification, each solvent was fractionated through a 50 × 1.5 cm. column packed with Fenske helices, and the middle portion of the distillate collected. The boiling points and refractive indices of methanol, n-propanol, n-butanol, butan-2-ol, and 1,1-dimethylethanol, methyl cyanide, benzene, nitrobenzene, fluorobenzene, ethyl acetate, and dioxan agreed with those recorded in the literature (Beilstein's "Handbuch"). The water content of each solvent was determined by Karl Fischer titration¹⁶ and adjusted to 0.20% w/w for each alcohol by the addition of distilled water. The aprotic solvents were dried as completely as possible.

Methanol, propanol, and butanol were dried by the method of Lund and Bjerrum,¹⁷ and, after distillation from the desiccant, were fractionated. Butan-2-ol and 1,1-dimethylethanol were purified essentially as described¹⁸ for n-butanol. 2-Methylbutan-2-ol was dried over successive portions of sodium sulphate and freshly prepared calcium oxide, and was then distilled from the desiccant and fractionated under reduced pressure. It had b. p. 75°/254 mm.,

⁸ L. Knorr, *Ber.*, 1899, **32**, 729.

⁹ K. Krassuski, *J. prakt. Chem.*, 1927, **115**, 315.

¹⁰ W. H. Horne and R. L. Shriner, *J. Amer. Chem. Soc.*, 1932, **54**, 2925.

¹¹ C. O. Guss and H. R. Williams, *J. Org. Chem.*, 1951, **16**, 1809.

¹² W. S. Emerson, *J. Amer. Chem. Soc.*, 1945, **67**, 516.

¹³ E. S. Narracott, *Brit. Plastics*, 1953, **26**, 120.

¹⁴ W. Reeve and I. Christoffel, *J. Amer. Chem. Soc.*, 1950, **72**, 1480; A. Kaelin, *Helv. Chim. Acta*, 1947, **30**, 2132.

¹⁵ N. B. Chapman, N. S. Isaacs, and R. E. Parker, *J.*, 1959, 1925.

¹⁶ K. Fischer, *Angew. Chem.*, 1935, **48**, 394.

¹⁷ H. Lund and J. Bjerrum, *Ber.*, 1931, **64**, 210.

¹⁸ C. P. Smyth and W. N. Stoops, *J. Amer. Chem. Soc.*, 1929, **51**, 3312.

and n_D^{18} 1.4063 (lit.,¹⁹ b. p. 101.6°/755 mm., n_D^{20} 1.4052). Dioxan was purified as previously described,²⁰ and contained 0.01% w/w of water. 1,2-Dimethoxyethane and bis-2-methoxyethyl ether were purified as described by Vogel.²¹ The former had b. p. 85°/768 mm., n_D^{25} 1.3767 (lit.,²² b. p. 84°/755 mm., n_D^{20} 1.3779) and contained 0.005% w/w of water, and the latter had b. p. 163°/767 mm., n_D^{25} 1.4062 (lit.,²² b. p. 161°/754 mm., n_D^{20} 1.4053) and contained 0.004% w/w of water. Di-isopropylamine was purified as previously described²³ for ethylenediamine. It had b. p. 85°/763 mm., n_D^{25} 1.3894 (lit.,²⁴ b. p. 84°), and contained 0.008% w/w of water. Nitrobenzene was dried (P_2O_5), and fractionated under nitrogen at reduced pressure. It contained 0.01% w/w of water. Fluorobenzene was dried $[Mg(ClO_4)_2]$, and fractionated. It contained 0.01% w/w of water. Methyl cyanide was purified as previously described.²⁵ It contained 0.004% w/w of water. Benzene was purified by the method of Weissberger,²⁶ and contained 0.003% w/w of water. Tetrahydrothiophen 1,1-dioxide (from Whiffen and Sons, I.t.d.) was fractionated twice at 3 mm. pressure under nitrogen. It had b. p. 126°/3 mm., n_D^{25} 1.4814 (lit.,²⁷ b. p. 115°/3mm.), and contained 0.006% w/w of water. Dimethyl sulphoxide was dried (freshly prepared CaO), and fractionated at reduced pressure under nitrogen. It had b. p. 60°/1.5 mm., n_D^{25} 1.4773 (lit.,²⁸ b. p. 87°/23 mm., n_D^{25} 1.4771), and contained 0.003% w/w of water.

Ethylene glycol was dried (Na_2SO_4 and then CaO) and, after distillation from the latter, was fractionated at reduced pressure under nitrogen. It had b. p. 94.5°/11 mm., $n_D^{17.5}$ 1.4324 (lit.,²⁹ b. p. 197°/760 mm., n_D^{25} 1.43055). Ethyl acetate was purified essentially as described³⁰ for isopropyl acetate. Trimethyl phosphate was dried $[Mg(ClO_4)_2]$, and fractionated under nitrogen at reduced pressure. It had b. p. 85.5°/17 mm., n_D^{25} 1.3951 (lit.,³¹ b. p. 79°/12 mm.). 1,2-(Carbonyldioxy)ethane (ethylene carbonate) was crystallised to constant m. p. 36° (lit.,³² m. p. 36.4°) from light petroleum.

Benzylamine, 1,2-epoxyethylbenzene, and salicylaldehyde were purified as described in Part III.²

Calcium oxide. Precipitated calcium carbonate was heated to 900° for 8 hr., then allowed to cool *in vacuo*, and used immediately.

Rate Measurements.—The reactions were carried out in the same way as those described in Part III,² and, at appropriate intervals, aliquots were withdrawn, quenched, and analysed as described previously.³ When di-isopropylamine was used as solvent, the usual analytical procedure was ineffective, since di-isopropylamine forms a complex with salicylaldehyde, which absorbs in the same region as the benzylamine-salicylaldehyde anil. However, the addition of 1% of glacial acetic acid to the normal quenching solution completely suppressed the reaction of the secondary amine with salicylaldehyde without affecting the formation of the benzylamine anil.³³ The volatility and chemical reactivity of di-isopropylamine made it necessary to carry out kinetic runs in this solvent in sealed tubes. When tetrahydrothiophen 1,1-dioxide was used as solvent, kinetic runs were conducted under dry nitrogen, since this solvent reacted slowly at thermostat temperature with atmospheric oxygen.

Examination for Solvolysis.—(a) Standard solutions of benzylamine (ca. 0.5M) were prepared at thermostat temperature (59.6°) in each of the following solvents: 1,2-dimethoxyethane; bis-2-methoxyethyl ether; dioxan; di-isopropylamine; benzene; fluorobenzene; nitrobenzene; ethyl acetate; trimethyl phosphate; 1,2-(carbonyldioxy)ethane; dimethyl sulphoxide; tetrahydrothiophen 1,1-dioxide; methyl cyanide; and ethylene glycol. During 3 days, portions were withdrawn from each of the solutions and analysed as in normal kinetic runs.

¹⁹ J. F. Norris and R. Reuter, *J. Amer. Chem. Soc.*, 1927, **49**, 2624.

²⁰ E. A. S. Cavell, N. B. Chapman, and M. D. Johnson, *J.*, 1960, 1413.

²¹ A. I. Vogel, *J.*, 1948, 616.

²² H. Böhme and W. Schürhoff, *Chem. Ber.*, 1951, **84**, 28.

²³ J. T. Clarke and E. R. Blout, *J. Polymer Sci.*, 1946, **1**, 419.

²⁴ A. Skita and F. Keil, *Ber.*, 1928, **61**, 1452.

²⁵ P. Walden and E. J. Birr, *Z. phys. Chem.*, 1929, **144**, 269.

²⁶ A. Weissberger, "Techniques of Organic Chemistry, Vol. VIII, Organic Solvents," 2nd edn., Interscience, New York and London, 1955, p. 317.

²⁷ S. F. Birch and D. T. McAllan, *J.*, 1951, 2556.

²⁸ H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Amer. Chem. Soc.*, 1960, **82**, 2895.

²⁹ C. P. Smyth and W. S. Walls, *J. Amer. Chem. Soc.*, 1931, **53**, 2115.

³⁰ C. J. Haggerty and J. F. Weiler, *J. Amer. Chem. Soc.*, 1929, **51**, 1623.

³¹ C. Neuberg and K. P. Jacobsohn, *Biochem. Z.*, 1928, **199**, 498.

³² R. P. Seward and E. C. Vieira, *J. Phys. Chem.*, 1958, **62**, 127.

³³ A. J. Milun, *Analyt. Chem.*, 1957, **29**, 1502.

The experiments involving 1,2-(carbonyldioxy)ethane, ethyl acetate, and trimethyl phosphate showed appreciable decreases in benzylamine concentration, and these solvents were rejected. The experiments involving the remaining eleven solvents showed no measurable decrease (*i.e.*, less than 1% in 3 days) in benzylamine concentration.

(b) An approximately molar solution of 1,2-epoxyethylbenzene was prepared in each of the eleven solvents which were indifferent to benzylamine in the above experiments. A vapour-phase chromatogram of each of the freshly prepared solutions was run on a column of silicone resin supported on Celite. After the solutions had been maintained at 60° for three days, chromatograms were again recorded, under identical conditions to those used initially. Comparison of the two sets of chromatograms revealed no differences in the ratios of the peak heights and no additional peaks appeared, except in the case of ethylene glycol, with which the epoxide peak disappeared, and was replaced by a very strongly retained component; this solvent was rejected.

Product Analysis.—The infrared spectra of (a) the reaction product, (b) the normal product, (c) the abnormal product, and (d) several synthetic mixtures of the normal and abnormal products were recorded as previously described.² All the measurements were made on 5–7% w/v chloroform solutions on a Unicam S.P. 100 double-beam spectrophotometer, and equal overall concentrations were used within each series of analyses.

RESULTS

The reaction between 1,2-epoxyethylbenzene and benzylamine at 59.6° was carried out at three different sets of initial concentrations in *n*-propanol, dimethyl sulphoxide, and methyl cyanide, and, by application of the Van't Hoff method³⁴ of determining reaction orders, was shown to be of the first order with respect both to the epoxide and to the amine in all three solvents. Since all the other cases examined obeyed the second-order rate law, they were assumed also to be second-order reactions, first-order in each reactant. The measured overall rate constants (*k*) were divided into their normal (*k_N*) and abnormal (*k_A*) components by the

TABLE I
Measured rate constants, proportions of normal and abnormal isomers, and rate constants for the normal and abnormal reactions of 1,2-epoxyethylbenzene with benzylamine (*k*, *k_N*, and *k_A*, in l. mole⁻¹ sec.⁻¹)

Solvent	Temp.	10 ⁷ <i>k</i>	Normal		10 ⁷ <i>k_N</i>	10 ⁷ <i>k_A</i>
			product (%)	Abnormal product (%)		
Methanol	20.4°	173	59.5	40.5	103	70
	40.7	980	62.5	37.5	612	368
	59.6	3910	64	36	2500	1410
Ethanol ³⁵	20.0	139	83	17	115	24
	40.5	640	78	22	499	141
	59.6	2530	73	27	1850	680
<i>n</i> -Propanol	59.6	2280	74	26	1690	590
<i>n</i> -Butanol	20.1	125	72	28	90.0	35.0
	40.5	610	72	28	439	171
	59.6	1950	72	28	1400	550
Butan-2-ol	59.6	1530	74	26	1132	398
1,1-Dimethylethanol	29.5	100	78	22	78.0	22.0
	40.5	194	77	23	149	45.0
	59.6	605	75	25	454	151
2-Methylbutan-2-ol	20.1	37.6	76	24	28.6	9.0
	40.8	134	75.5	24.5	101	33.0
	59.6	352	75	25	264	88.0
Dimethyl sulphoxide	59.6	119	87	13	102	17.0
Tetrahydrothiophen 1,1-dioxide	59.6	44.5	100	0	44.5	0.0
Methyl cyanide	40.7	3.35	86	14	2.88	0.47
	49.8	8.49	85	15	7.22	1.27
	59.6	18.5	83	17	15.4	3.1
Nitrobenzene	59.6	13.5	80	20	10.8	2.7
Bis-2-methoxyethyl ether	59.6	6.0	92	8	5.5	0.5
Di-isopropylamine	59.6	3	—	—	—	—
1,2-Dimethoxyethane	59.6	<0.1	—	—	—	—
Benzene	59.6	<0.1	—	—	—	—
Fluorobenzene	59.6	<0.1	—	—	—	—

³⁴ See, *e.g.*, K. J. Laidler, "Chemical Kinetics," McGraw-Hill, New York, 1950, p. 14.

method previously described,³ and the values obtained, together with the isomer proportions, are collected in Table 1.

Table 2 records the values of the normal and abnormal rate constants interpolated to 40°, the Arrhenius parameters, and the entropies of activation (for those reactions studied at more than one temperature). Duplicate determinations showed that the error in the measured rate constants was less than ±3%. The error in the rate constants, introduced by the determinations of product ratio, varies inversely with the proportion of the relevant isomer in the product mixture, and, since the abnormal isomers are invariably present in minor amount, the abnormal rate constants are subject to the greatest errors. Thus we estimate that the rate constants for the normal reactions are accurate to better than ±6%, while the abnormal rate constants vary in accuracy from ±10% or better for the reaction in protic solvents and nitrobenzene, to ±15% or better for the reactions in methyl cyanide and dimethyl sulphoxide, and ±20% or better for the reaction in bis-2-methoxyethyl ether.

DISCUSSION

The Reaction in Protic Solvents.—The relative rate constants in Table 3 show that the rates of both normal and abnormal reactions decrease as the alcohol solvent molecules

TABLE 2

Rate constants interpolated to 40°, Arrhenius parameters, and entropies of activation for the normal and abnormal reactions of 1,2-epoxyethylbenzene with benzylamine (k_N , k_A , and A in l. mole⁻¹ sec.⁻¹; E in kcal. mole⁻¹; ΔS^* in cal. mole⁻¹ deg.⁻¹)

Solvent	Normal reactions				Abnormal reactions			
	10 ⁷ k_N	E	log A	− ΔS^*	10 ⁷ k_A	E	log A	− ΔS^*
Methanol	582	15.9	6.9	29	358	14.8	5.9	34
Ethanol ³⁵	490	13.5	5.1	37	138	16.2	6.5	31
n-Butanol	417	13.5	5.0	38	162	13.5	6.7	39
1,1-Dimethylethanol	150	11.6	3.3	46	45.0	12.7	3.5	43
2-Methylbutan-2-ol ...	98.4	10.9	2.6	49	32.0	11.0	2.2	51
Methyl cyanide	2.81	18.6	6.5	31	0.45	21.0	7.3	27

TABLE 3

Rate constants relative to those in ethanol for the normal and abnormal reactions of 1,2-epoxyethylbenzene with benzylamine at 59.6°, and dielectric constants (accurate to ±0.1, unless otherwise stated)

Solvent	Relative rate constant		Dielectric constant (static value at 60°)
	Normal reaction	Abnormal reaction	
Methanol	140	200	26.5 ³⁶
Ethanol ³⁵	100	100	19.6 ³⁷
n-Propanol	91	87	15.9 ³⁸
n-Butanol	76	81	13.4 ³⁸
Butan-2-ol	61	59	12.4 ³⁹
1,1-Dimethylethanol	25	22	7.7 ⁴⁰
2-Methylbutan-2-ol	14	13	4.5 ⁴¹
Dimethyl sulphoxide	5.5	2.5	38.1 ± 0.6 ⁴²
Tetrahydrothiophen 1,1-dioxide ...	2.4	0.0	39.8 ± 0.6 ⁴³
Methyl cyanide	0.84	0.46	31.0 ± 0.5 ⁴⁴
Nitrobenzene	0.58	0.40	28.3 ⁴⁵
Bis-2-methoxyethyl ether.....	0.3	0.07	5.4 ²²

³⁵ N. S. Isaacs and R. E. Parker, *J.*, 1960, 3497.

³⁶ P. S. Albright and L. J. Gosting, *J. Amer. Chem. Soc.*, 1946, 68, 1061.

³⁷ R. J. W. Le Fèvre, *Trans. Faraday Soc.*, 1938, 34, 1127.

³⁸ A. R. Von Hippel, "Dielectric Materials and Applications," The Technology Press of M.I.T. and John Wiley and Sons, New York, 1954, p. 362.

³⁹ R. G. Larson and H. Hunt, *J. Phys. Chem.*, 1939, 43, 417.

⁴⁰ W. S. Muney and J. F. Coetzee, *J. Phys. Chem.*, 1962, 66, 89.

⁴¹ A. N. Shidlovskaya and Ya. K. Syrkin, *Zhur. fiz. Khim.*, 1948, 22, 913.

⁴² H. L. Schläfer and W. Schaffernicht, *Angew. Chem.*, 1960, 72, 618.

⁴³ B. D. Coleman and R. M. Fuoss, *J. Amer. Chem. Soc.*, 1955, 77, 5472.

⁴⁴ G. L. Lewis and C. P. Smyth, *J. Chem. Phys.*, 1939, 7, 1085.

⁴⁵ "Handbook of Chemistry and Physics," 44th edn., Chemical Rubber Publishing Co., Cleveland, Ohio, 1962.

become larger and increasingly branched. The constancy of the normal/abnormal rate ratios is striking (Table 1), $73.5 \pm 1.5\%$ of the reaction at 59.6° occurring at the normal position in every case except one (methanol), and this invariance strongly suggests a similarity between the normal and abnormal reaction mechanisms. The invariant rate ratios may be rationalised in terms of the mode of interaction of the solvents with the reactants in the transition state. The principal interaction almost certainly occurs by hydrogen bonding of the hydroxyl group of the solvent molecule to the epoxide oxygen atom, thus facilitating heterolysis of the carbon-oxygen bonds of the epoxide ring. Variation of the solvent will affect the magnitude of this interaction and hence the rate of reaction, but not the product ratio. The latter will be determined by electronic and steric effects at the site of bond formation, and these effects should not be markedly solvent-dependent, since benzylamine is probably not strongly solvated by protic solvents. The only exception to the regular pattern is provided by methanol, in which only 62% of the reaction takes place at the normal position. Guss and Williams¹¹ have observed a similar effect in the reaction of phenol with 1,2-epoxyethylbenzene in this solvent (see Introduction).

The dependence of rate on the dielectric constant of the medium is marked, and is not unexpected in such a homologous series. This dependence suggests that either the Hiromi^{7b} or Glasstone^{7a} theories may apply to this series of reactions. The former relation predicts that the logarithm of the rate constant of a reaction will be inversely proportional to the dielectric constant of the reaction medium, while the latter relationship predicts that the logarithm of the rate constant will be proportional to $(D - 1)/(2D + 1)$, where D is the dielectric constant of the medium. In Table 4 are listed the correlation coefficients

TABLE 4

Correlation coefficients for the variation of some theoretical and empirical parameters with the logarithms of the rate constants for the reaction of 1,2-epoxyethylbenzene with benzylamine at 59.6°

Parameter	Protic solvents		Aprotic solvents	
	Normal reaction	Abnormal reaction	Normal reaction	Abnormal reaction
$(D - 1)/(2D + 1)$	0.97	0.94	0.77	0.88
$1/D$	0.97	0.94	0.90	0.96
S	0.97	1.00	—	—
Z	0.98	1.00	—	—

obtained by application of these theoretical equations to the data from Tables 1 and 3. The high coefficients demonstrate the strongly linear relationships that exist in each of the eight cases examined, and suggest that electrostatic effects dominate the rate changes in this series of solvents. However, to adopt such a simple picture would be to ignore the structure of the solvent and the question of solvent-solvent and solvent-solute interactions. These interactions are considered below, and it is only necessary to recall here that both $1/D$ and $(D-1)/(2D+1)$ are often almost linearly related to other solvent properties. That the abnormal reactions show worse agreement with theory than do the normal reactions, is almost certainly due to the very high abnormal rate in methanol, which causes the corresponding point to lie well clear of the expected curve. It is interesting to note that, in protic solvents, the rate constants correlate equally well with the Glasstone and the Hiromi parameters over the short range of dielectric constants examined.

Also listed in Table 4 are the correlation coefficients obtained by application of the semiempirical Brownstein⁴⁶ equation and the Z values of Kosower.⁴⁷ The Brownstein linear free-energy equation is:

$$\log k - \log k_{\text{EtOH}} = SR,$$

where k is the rate constant for reaction in a particular solvent, k_{EtOH} is the rate constant

⁴⁶ S. Brownstein, *Canad. J. Chem.*, 1960, **38**, 1590.

⁴⁷ E. M. Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3253.

for the same reaction in ethanol, R is a measure of the susceptibility of the reaction to solvent effects, and S is a characteristic of the solvent. The Kosower treatment is essentially similar, $\log k$ being proportional to Z , which is again a characteristic of the solvent. Indeed, Brownstein's treatment is a development of Kosower's. Correlation coefficients for the normal reactions are of similar magnitude to those obtained by use of the dielectric parameters, while the coefficients for the abnormal reactions show marked improvements and are higher than those for the normal reactions. Construction of the appropriate curves of S or Z against $\log k$ reveals that this improvement is due principally to the good fit of the data for the reaction in methanol to the curves, although the use of a smaller number of points (S and Z values being available for only five of the alcohols) may have enhanced the correlations.

These results suggest that the solvent methanol exerts some specific effect on the abnormal reaction that is not simply electrostatic in origin. The same effect must also facilitate photo-induced charge-transfer reactions, since the S and Z values are obtained from such spectral sources. The explanation of this specific effect of methanol may be that its methyl group differs from the alkyl groups of the higher alcohols in having no β -carbon atom, and this may give the methanol molecule a sufficient steric advantage to enable it to solvate the developing positive charge on the nitrogen atom of benzylamine in the transition state for the abnormal reaction.

A quantitative measure of the susceptibility of the reaction to change of solvent may be obtained by application of the Brownstein equation to the measured rate constants. Values of R of 4.0 and 4.3 were obtained for the normal and abnormal reactions, respectively, and these illustrate the similar susceptibilities of the two reactions to solvent changes and thus argue for the similarity of the normal and abnormal reaction mechanisms. These values are in reasonable accord with the figure of 4.3 calculated by Brownstein⁴⁶ for a typical bimolecular reaction, that of aniline with phenacyl bromide in a series of alcohols.⁴⁸ In contrast, the R values for unimolecular reactions, which are generally more susceptible to solvent effects, are considerably larger; values of 35.9 and 25.4 have been calculated for the hydrolyses of *t*-butyl chloride and trityl fluoride, respectively.⁴⁶

Both the energies and entropies of activation for the reactions of 1,2-epoxyethylbenzene with benzylamine in protic solvents increase steadily from 2-methylbutan-2-ol to methanol (Table 2), but, since the rates also increase from the former to the latter, the entropy changes outweigh the energy changes. The direction of the changes in activation energy is reasonable, since the more-polar alcohols are highly organised in the initial state of the reaction and the necessary increase in solvation required to form the transition state can only be accomplished at the expense of some reorganisation of the solvent structure. The less-polar solvents are less organised in the initial state and the breakdown of the solvent structure is an energetically easier prelude to solvation of the transition state. Activation energies are higher for the abnormal than for the normal reactions, with the exception of the reactions in methanol. Since the formation of the transition state for the abnormal reaction involves more steric compression than does the formation of the corresponding state for the normal reaction, the differences in activation energy are again generally in the expected direction. The activation energy for the abnormal reaction in methanol is slightly lower than that for the normal reaction, and this accounts to some extent for the unusually fast abnormal reaction that has already been mentioned. The steady fall in the magnitude of the entropies of activation from the reactions in methanol to those in 2-methylbutan-2-ol could indicate that the transition states are becoming conformationally more restricted or that the initial states are becoming conformationally less restricted. As has been mentioned above, this entropy effect is dominant in determining the rates, and such entropy-controlled solvent effects are uncommon.

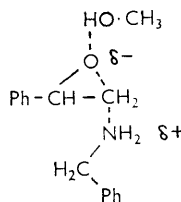
It seems probable that a considerable number of polymerically hydrogen-bonded methanol molecules participate in the proton-transfer stage of the reaction in methanol,

⁴⁸ H. E. Cox, *J.*, 1921, **119**, 142.

by simple bond-rearrangement. A single methanol molecule acting as a Lewis acid is probably hydrogen bonded to the epoxide oxygen (Figure 1), by analogy with the protonated state of this oxygen in the presence of a strong acid. In contrast, the amino-group of the benzylamine molecule in the transition state may be solvated by the lone-pair on the methanol oxygen atom, the methanol here acting as a Lewis base. Solvation of the transition state by 2-methylbutan-2-ol probably differs in that the large hydrocarbon residues of the solvent molecules interfere sterically with each other and with the reactants, with the result that fewer, but more carefully oriented, solvent molecules participate in the transition state. Here, too, the solvent is less restricted in the initial state (because of less-extensive hydrogen bonding) than in the case of methanol, and the decrease in entropy on formation of the transition state is therefore greater.

The Reaction in Aprotic Solvents.—Perhaps the most significant fact concerning the reaction of 1,2-epoxyethylbenzene with benzylamine in aprotic solvents is that it occurs at all. Several earlier workers^{8,9,49} failed to observe epoxide ring-cleavage in the absence of a protic solvent, although this was probably due to insensitive analytical methods or

FIGURE 1. Transition state for normal reaction of 1,2-epoxyethylbenzene with benzylamine in methanol: electrophilic by solvent assistance to bond-breaking



failure to select suitable solvents, or both. In aprotic, as in protic, solvents, rates of the normal and abnormal reactions increase with an increase in the dielectric constant of the medium. The rate constants in Table 1 also demonstrate the considerable variation in the proportions of normal and abnormal attack in different aprotic solvents. It is apparent that protic solvents exert a specific effect on the reactions, since the rates in these solvents are much faster than the corresponding rates in aprotic solvents of higher dielectric constant (Table 3). This specific catalysis is, of course, due to the ability of the protic solvent to hydrogen bond to the epoxide oxygen and thereby electrophilically to assist ring-fission.

Coefficients correlating the logarithms of the observed rate constants with the Glasstone and Hiromi parameters are recorded in Table 4. The rates of reaction in bis-2-methoxyethyl ether were not included in the calculations (for reasons which are explained later) and, since no reaction occurred at the abnormal position in tetrahydrothiophen 1,1-dioxide, only three rate constants were left from which to determine the correlation coefficients for the abnormal reactions. Because the statistical probability of obtaining a good correlation between two independent populations is quite high when a sample of size three is taken, the coefficients obtained for the abnormal reactions must be treated with reserve. Those for the normal reactions indicate good linear correlations with both parameters, the correlation with $1/D$, however, being significantly better than that obtained with the Glasstone factor. That the agreement with theory is not as good as was found for the series of alcohols, is hardly surprising, since each aprotic solvent contains a different functional group.

Dimethyl sulphoxide. The reaction proceeds more than twice as fast in dimethyl sulphoxide as in tetrahydrothiophen 1,1-dioxide (Tables 1 and 3), in spite of the slightly lower dielectric constant of the former solvent. Similar anomalies have been noted before with dimethyl sulphoxide,^{28,50} although A. J. Parker gives an order of solvating power of

⁴⁹ N. S. Isaacs, Ph.D. Thesis, Southampton University, 1958.

⁵⁰ C. D. Ritchie and E. S. Lewis, *J. Amer. Chem. Soc.*, 1962, **84**, 591; R. G. Pearson, H. B. Gray, and F. Basolo, *ibid.*, 1960, **82**, 787.

aprotic solvents which is the same as the order of rates found here.⁵¹ Cram *et al.*⁵² have shown that the rate of proton abstraction from a saturated carbon atom by alkoxide ion is enhanced by a factor of 10^9 when dimethyl sulphoxide replaces methanol as solvent, and the high proton affinity of dimethyl sulphoxide which this implies may be operating in the present case by helping to remove a proton from the benzylamine in the transition state (Figure 2). The affinity of dimethyl sulphoxide for amines has recently been demonstrated cryoscopically.⁵³

Nitrobenzene and tetrahydrothiophen 1,1-dioxide. It has been suggested that the sulphur atom in dimethyl sulphoxide is sp^3 -hybridised and participates in a $d\pi$ -molecular orbital which extends over the sulphur-oxygen bond and reduces its ionic character.⁵⁴ Nitrobenzene also has a delocalised molecular orbital over the nitro-group, which reduces the polarity of the nitrogen-oxygen bond.⁵⁵ Partial relocation of negative charge occurs, as in dimethyl sulphoxide, but to a smaller extent, because nitrogen is more electronegative than sulphur and because the negative charge is distributed between two oxygens. The solvent effect of nitrobenzene is probably exerted through the interaction of the oxygen atoms of the nitro-group with the amino-protons of benzylamine.

Tetrahydrothiophen 1,1-dioxide is less solvating than dimethyl sulphoxide because, as in the nitro-group of nitrobenzene, the electron density of the delocalised molecular orbital over the sulphone group is partially relocated over two oxygen atoms. That tetrahydrothiophen 1,1-dioxide is more solvating than nitrobenzene, is probably a consequence of the electronegativity of nitrogen being higher than that of sulphur.

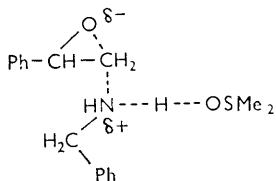


FIGURE 2. Transition state for normal reaction of 1,2-epoxyethylbenzene with benzylamine in dimethyl sulphoxide: nucleophilic assistance by solvent to bond forming

Methyl cyanide. The ability of methyl cyanide to sustain the reaction is presumably due to the developing positive charge on the nitrogen atom of the benzylamine molecule in the transition state being stabilised by interaction with the negative end of the carbon-nitrogen dipole of the cyanide group. The high energies of activation obtained in this solvent, compared with those in the series of protic solvents, are indicative of the inability of methyl cyanide to solvate the transition state as strongly as do protic solvents, no doubt because of its inability to form hydrogen bonds with the epoxide oxygen. The entropies of activation compare closely with the values obtained for the reactions in methanol, and indicate that these two solvents impose similar steric limitations on the reactions.

Bis-2-methoxyethyl ether. The way in which this solvent facilitates the reaction is not easy to understand, for, although its low dielectric constant is qualitatively compatible with the low rate observed, the plot of $\log k$ against $1/D$ for the other aprotic solvents is a straight line which does not pass near the value for β -methoxyethyl ether. The position of the latter point relative to the line indicates a considerably greater rate than would be predicted. Catalysis by adventitious hydroxylic impurities seems, at first, to be the obvious explanation, but the normal/abnormal product ratio for bis-2-methoxyethyl ether at 59.6° was 92/8, which contrasts with the corresponding value for most alcohols of about 73/27. Bis-2-methoxyethyl ether could solvate the positive charge that develops on the amino-group of benzylamine during the reaction, and the conformations that the molecule

⁵¹ A. J. Parker, *Quart. Rev.*, 1962, **16**, 163.

⁵² D. J. Cram, B. Rickborn, and G. R. Knox, *J. Amer. Chem. Soc.*, 1960, **82**, 6412.

⁵³ J. Kenttämä and J. J. Lindberg, *Suomen Kem.*, 1961, **34**, 117.

⁵⁴ J. R. Van Wazer, "Phosphorus and its Compounds," Interscience, New York, 1958, pp. 42 and 43.

⁵⁵ W. J. Orville-Thomas, *Chem. Rev.*, 1957, **57**, 1179.

might adopt in order to do this are depicted in Figure 3. Conformations (I), (II), (III), and (IV) are common to bis-2-methoxyethyl ether and 1,2-dimethoxyethane,⁵⁶ and, since no reaction was detected in the latter solvent, these conformations are probably unimportant. Conformations (V) and (VI) for bis-2-methoxyethyl ether have no analogy in 1,2-dimethoxyethane. Conformation (V) might be important, since it would be capable of solvating the large benzylamine amino-group. On the other hand, conformation (VI) would be the most favourable of the two for solvating a small positive charge such as an amino-group proton in the transition state.

Other aprotic solvents. The reaction was examined in di-isopropylamine, since it was thought that this solvent might electrophilically assist ring-cleavage by hydrogen bonding to the epoxide oxygen, as do protic solvents, but the very small rate constant obtained indicates that assistance of this type is unimportant. No reaction was observed in either

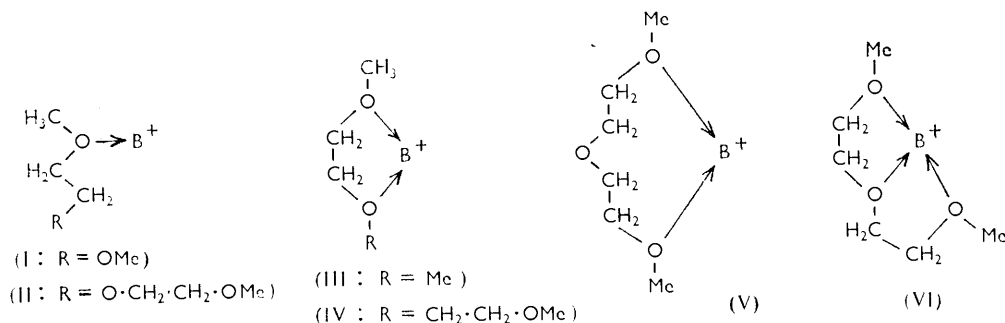


FIGURE 3. Conformations of 1,2-dimethoxyethane and bis-2-methoxyethyl that permit solvation of a positive charge (B⁺)

benzene or fluorobenzene. For benzene, this is in accord with its very low dielectric constant and zero dipole moment. Fluorobenzene, however, has a dipole moment comparable with that of ethanol,⁴⁵ and might be expected to solvate a positive charge, especially in view of the well-known ability of fluorine to form hydrogen bonds. Its failure to promote the reaction may be due to attenuation of the negative charge on fluorine by conjugation with the benzene ring. The reaction in dioxan was very slow and the rate constants obtained were not reproducible, perhaps a consequence of the strong affinity of this solvent for water.

The considerable differences in the proportions of normal and abnormal attack in the series of aprotic solvents may be attributable to steric factors. Approximate measurements, on Stuart models, of the distance (*d*) between the centre of the dipolar group and the centre of the hydrocarbon residue, for each solvent molecule, indicate that, as this distance decreases, the proportion of abnormal isomer formed also decreases (Table 5).

TABLE 5

Proportions of abnormal isomer formed by reaction of 1,2-epoxyethylbenzene with benzylamine in aprotic solvents at 59.6°, and corresponding values of *d*

Solvent	Abnormal product (%)	<i>d</i> (Å)
Nitrobenzene	20	3.55
Methyl cyanide	17	2.65
Dimethyl sulphoxide	13	2.2
Bis-2-methoxyethyl ether	8	(1.5)
Tetrahydrothiophen 1,1-dioxide	0	0.5

If *d* is large, the dipolar part of the solvent molecule is considerably removed from the inert hydrocarbon residue, and such a situation might be expected to lower steric hindrance to abnormal attack, since nucleophile and solvent molecules are probably associated

⁵⁶ H. D. Zook and T. J. Russo, *J. Amer. Chem. Soc.*, 1960, **82**, 1258.

closely in the transition state. The linear relationship that exists between d and the percentage of abnormal product is demonstrated in Table 5. It is difficult to measure the value of d for bis-2-methoxyethyl ether, because the geometry of this molecule does not provide for a precise centre of the hydrocarbon residue. The value in Table 5 is the average of the distances measured on conformations (V) and (VI).

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