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The Mechanism of Epoxide Reactions. IV.[1] The Reactions of Benzylamine with a Series of *m*- and *p*-Substituted Styrene Oxides in Ethanol[2]

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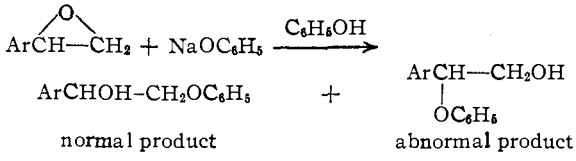
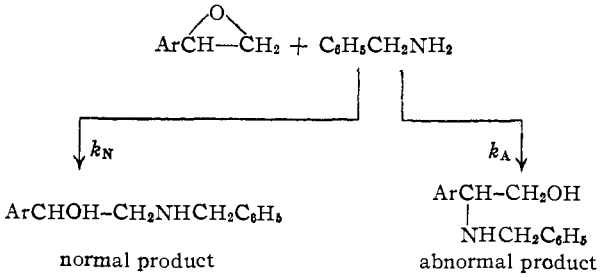
Rate constants at three temperatures have been determined for the first reactions of benzylamine with *m*-chloro-, *m*-methoxy-, *m*-methyl-, *m*-trifluoromethyl- and 3,4-dimethylstyrene oxide in ethanol. Product analyses have been carried out by infrared spectroscopy and the results have been used to separate the measured rate constants into rate constants for the normal (attack at CH_2) and the abnormal (attack at CH) reactions. An analysis of the results, together with those previously determined for styrene oxide and its *p*-bromo and *p*-methyl derivatives, shows that the Hammett reaction constant ρ for the normal reaction ($\rho = +0.87$ at 40°) is of opposite sign to that for the abnormal reaction ($\rho = -1.15$ at 40°). Both reactions show second-order kinetics and the results are interpreted in terms of a bimolecular mechanism in which bond breaking is the dominant factor, the positive ρ for the normal reaction being due to the special geometry of the system.

Introduction

Although the direction of ring opening in the reactions of unsymmetrical epoxides with nucleophiles has been determined in a large number of cases by analysis of the products,[3] such determinations have not been accompanied by kinetic studies and the results cannot therefore be unambiguously interpreted. For example, it is known that, in the reactions of substituted styrene oxides with sodium phenoxide in aqueous phenol, the presence of an



electron-withdrawing group in the benzene ring increases the proportion of normal product.[4] This is capable of interpretation in several different ways: the presence of the electron-withdrawing group may increase the rate of normal attack or decrease that of abnormal attack or both, or it may increase or decrease both rates differentially. In order to discover which of these alternatives is correct, we have studied the reactions of a number of *m*- and *p*-substituted styrene oxides with benzylamine in ethanol. The reactions may be represented as shown and we have measured the over-all rate



constants by following the decrease in the concentration of benzylamine (determined spectrophotometrically as its anil with salicylaldehyde) and also the ratios of products (by comparison of the infrared spectrum of the product with that of each pure isomer, synthesized unambiguously). The over-all rate constants have been divided in the ratio of the products to give the rate constants for normal (k_N) and for abnormal (k_A) attack. This is justifiable, since we have shown that the ratio of products is not influenced by the initial ratio of benzylamine to styrene oxide and therefore that the normal and abnormal reactions are of the same kinetic order. The over-all reactions all obey the second-order rate equation and, for *m*-chlorostyrene oxide and 3,4-dimethylstyrene oxide, the reactions have been shown to be first order with respect to oxide and first order with respect to amine. There can be no doubt, therefore, that both the normal and the abnormal reactions are bimolecular processes.

The complication due to further reaction of the initial products with styrene oxide (to give products which are tertiary amines[5]) has been minimized in the present study by the use of a fourfold excess of benzylamine over styrene oxide. Under these conditions the second reaction is insignificant for at least the first 50% of the first reaction and, for the reaction of styrene oxide at 59.6°, it has been shown[6] that the rate constant obtained by determinations of benzylamine alone and application of the simple second-order rate equation is identical with that obtained by the more precise treatment used previously.[5] The occurrence of the second reaction will also disturb the ratio of normal to abnormal products of the first reaction, insofar as these products undergo further reaction with epoxide at different rates. However, this disturbance cannot be significant, since the experimentally found ratio of normal to abnormal product of the first reaction is independent of the initial ratio of reactants and is the same whether it is measured at the end of the over-all reaction or at an earlier stage.

Experimental

Materials.—Ethanol was dried by Lund and Bjerrum's method:[7] the water content was determined by Karl Fischer titration to a conductimetric end-point and adjusted to 0.20% w./w. by addition of distilled water. Benzylamine was dried (NaOH, and then Na) and fractionated through a 60 × 1.5 cm. column packed with Fenske helices and the middle fraction collected. b.p. 185° (768 mm.). $n^{25}D$ 1.5392. The styrene oxides were prepared in all cases from the appropriate phenacyl bromide by the method of Fuchs and Vander-

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(3) R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

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Werf[8,9] and were distilled *in vacuo* to constant refractive index.

***m*-Chlorostyrene Oxide.**—*m*-Nitroacetophenone, prepared by nitration of acetophenone,[10] was converted into *m*-chloroacetophenone.[11]

To a cooled, stirred solution of *m*-chloroacetophenone (29 g.) in glacial acetic acid (100 ml.) was added dropwise bromine (10 ml.) in glacial acetic acid (15 ml.) over a period of 10–15 min. The mixture was evacuated on the water-pump to remove dissolved hydrogen bromide and then poured into ice-water (2 l.). The crystalline precipitate was filtered, washed with water and dried. Crystallization from absolute ethanol below 35° gave *m*-chlorophenacyl bromide, m.p. 39.5–40° (44 g.).

Anal. Calcd. for C_8H_6BrClO: C, 41.2; H, 2.7; silver halide, 141.8. Found: C, 41.5; H. 2.7; silver halide, 142.8.

The oxide was prepared from the phenacyl bromide in 80% yield and had b.p. 60° (0.1 mm.), $n^{19}D$ 1.5511, $n^{24}D$ 1.5490.

Anal. Calcd. for C_8H_7ClO: C, 62.2; H, 4.6; Cl, 22.9. Found: C, 62.2; H, 4.8; Cl, 23.0.

***m*-Methoxystyrene Oxide.**—*m*-Methoxyacetophenone, prepared from *m*-methoxybenzoyl chloride by the method of Gilman and Nelson for the *p*-methyl compound.[12] was brominated and converted into the oxide.[9]

***m*-Methylstyrene Oxide.**—*m*-Methylacetophenone, prepared from *m* toluic acid by the method of Gilman and Nelson,[12] was brominated to yield *m*-methylphenacyl bromide, b.p. 92° (0.1 mm.). This was a colorless oil which rapidly became greenish-black on standing in a sealed tube and which was readily hydrolyzed to *m*-methylphenacyl alcohol by atmospheric moisture. Conversion of freshly prepared *m*-methylphenacyl bromide gave *m*-methylstyrene oxide, b.p. 40° (0.1 mm.), $n^{18}D$ 1.5292.

Anal. Calcd. for $C_9H_{10}O$: C, 80.6; H, 7.5. Found: C, 80.6; H, 7.7.

***m*-Trifluoromethylstyrene Oxide.**—*m*-Bromobenzotrifluoride, prepared from *m*-aminobenzotrifluoride by a Sandmeyer reaction, was converted into *m*-trifluoromethylacetophenone by the method of Corse, *et al.*[13] This was brominated by the method used for the preparation of *m*-chlorophenacyl bromide, except that the oil obtained on pouring into ice-water was taken up in ether, washed with water, dried, the ether removed and the residue crystallized from ethanol to give *m*-trifluoromethylphenacyl bromide, m.p. 22°.

Anal. Calcd. for $C_9H_6BrF_3O$: C, 40.5; H, 2.3. Found: C, 40.8; H, 2.3.

Conversion in the usual way gave *m*-trifluoromethylstyrene oxide, b.p. 40° (0.1 mm.), $n^{20}D$ 1.4610.

Anal. Calcd. for $C_9H_7F_3O$: C, 57.4; H, 3.8. Found: C, 57.0; H, 4.0.

3,4-Dimethylstyrene Oxide.—Bromination in acetic acid of 4-acetyl-1,2-xylene (from Friedel–Crafts acetylation of *o*-xylene in CS_2 [14]) gave 3,4-dimethylphenacyl bromide, m.p. 63°.

Anal. Calcd. for $C_{10}H_{11}BrO$: C, 52.9; H, 4.9; Br, 35.2. Found: C. 53.2; H, 4.9; Br, 35.9.

This was converted into 3,4-dimethylstyrene oxide, b.p 60° (0.1 mm.), $n^{15}D$ 1.5368.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.0; H, 8.2. Found: C, 80.7; H, 8.3.

Syntheses of Products.—The normal isomers were synthesized in each case from the appropriate phenacyl bromide. A solution of the phenacyl bromide in dioxane was allowed to react with two equivalents of benzylamine, the benzylamine hydrobromide removed by filtration, and the resulting solution of amino-ketone reduced with aqueous ethanolic $NaBH_4$ to give the normal isomer in above 50% over-all yield.

$$ArCOCH_2Br \longrightarrow ArCOCH_2NHCH_2C_6H_5 \longrightarrow ArCH(OH)CH_2NHCH_2C_6H_5$$

The abnormal isomers were synthesized by the route

$$ArCHO \xrightarrow{HCN} ArCH(OH)CN \xrightarrow{H^+} ArCH(OH)COOH \xrightarrow{SOCl_2} ArCHClCOCl \xrightarrow{CH_3OH} ArCHClCOOCH_3 \xrightarrow{C_6H_5CH_2NH_2} ArCHCOOCH_3 \quad (NHCH_2C_6H_5) \xrightarrow{LiAlH_4} ArCHCH_2OH \quad (NHCH_2C_6H_5)$$

Ar = *m*-ClC_6H_4: normal isomer, **2-benzylamino-1-*m*-chlorophenylethanol**, m.p. 85.5–87°. *Anal.* Calcd. for $C_{15}H_{16}ClNO$: C, 68.7; H, 6.2; N, 5.4; Cl, 13.6. Found: C, 69.0; H, 6.3; N, 5.6; Cl, 13.3.

Abnormal Isomer, 2-Benzylamino-2-*m*-chlorophenylethanol.—*m*-Chloromandelic acid, prepared from *m*-chlorobenzaldehyde,[15] was converted by the method used for the *p*-methyl compound[16] into methyl α-chloro-*m*-chlorophenylacetate, b.p. 94° (0.5 mm.), 80° (0.1 mm.), $n^{18}D$ 1.5420.

Anal. Calcd. for $C_9H_8Cl_2O_2$: C, 49.4; H, 3.7; Cl, 32.4. Found: C, 49.2; H, 3.8; Cl, 32.6.

This ester was converted by the above route into the abnormal isomer, b.p. 180–200° (4×10^{-4} mm.), $n^{13}D$ 1.5940, which crystallized on standing and had m.p. 69°.

Anal. Calcd. for $C_{15}H_{16}ClNO$: C, 68.7; H, 6.2; N, 5.4; Cl, 13.6. Found: C, 69.0; H, 6.4; N, 5.3; Cl, 13.3.

The product was accompanied by a small amount of material of m.p. 112–113°, which was shown by infrared analysis to contain a carbonyl group.

Anal. Found: C, 69.5; H, 5.9; N, 5.4; Cl, 13.2.

Ar = *m*-$CH_3OC_6H_4$: normal isomer, **2-benzylamino-1-*m*-methoxyphenylethanol**, m.p. 89.5–90.5°. *Anal.* Calcd. for $C_{16}H_{19}NO_2$: C, 74.7; H, 7.4; N, 5.5. Found: C, 74.6; H, 7.6; N, 5.3.

Abnormal Isomer, 2-Benzylamino-2-*m*-methoxyphenylethanol.—*m*-Methoxybenzaldehyde[17] was converted into its cyanohydrin, which was hydrolyzed[15] to *m*-methoxymandelic acid. The acid failed to crystallize or to form a crystalline S-benzylthiouronium salt or *p*-nitrobenzyl ester, but it did form a crystalline *p*-bromophenacyl ester, m.p. 114–115°.

Anal. Calcd. for $C_{17}H_{15}BrO_5$: C, 53.8; H, 4.0; Br, 21.1. Found: C, 53.8; H, 4.2; Br, 21.0.

Thionyl chloride (70 ml.) was added dropwise with cooling to *m*-methoxymandelic acid (67 g.) containing a few drops of pyridine and the mixture was allowed to stand at room temperature for 0.5 hr. and then heated on a steam-bath for 1 hr. Excess of thionyl chloride was removed *in vacuo* and the residue added to methanol (500 ml.). After 2 hr. the mixture was diluted with water (1 l.), extracted with ether and the extract washed with $NaHCO_3$ solution and dried (Na_2SO_4). Removal of the ether gave methyl α-chloro-*m*-methoxyphenylacetate, b.p. 112–3° (0.5 mm.), $n^{18}D$ 1.5339.

Anal. Calcd. for $C_{10}H_{11}ClO_3$: C, 56.4; H. 5.2; Cl, 16.5. Found: C, 56.6; H, 5.4; Cl, 15.9.

This was converted into the abnormal isomer, b.p. 140° (4×10^{-4} mm.).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.7: H, 7.4; N, 5.5. Found: C, 75.9; H, 7.8; N, 5.4.

Further distillation of the product resulted in a worse analysis (Found: C, 77.0; H, 7.6; N, 5.5) and it appears that distillation causes slow decomposition to a compound of higher carbon content. The same is true for the other abnormal isomers, but the analyses are affected only when the product cannot be finally purified by crystallization.

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Ar = *m*-$CH_3C_6H_4$: normal isomer, **2-benzylamino-1-*m*-tolylethanol**, m.p. 102°. *Anal.* Calcd. for $C_{16}H_{19}NO$: C, 79.6; H, 7.9; N, 5.8. Found: C, 79.6; H, 7.8; N, 5.9.

Abnormal Isomer, 2-Benzylamino-2-*m*-tolylethanol.—*m*-Tolualdehyde, obtained from *m*-xylene by the Etard reaction,[18] was converted into *m*-methylmandelic acid. This was converted, by the method used for *m*-methoxymandelic acid, into methyl α-chloro-*m*-tolylacetate, b.p. 80° (0.1 mm.), $n^{21}D$ 1.5246.

Anal. Calcd. for $C_{10}H_{11}ClO_2$: C, 60.4; H, 5.6; Cl, 17.9. Found: C, 60.5; H, 5.8; Cl, 17.8.

The ester was allowed to react with benzylamine in diisopropyl ether and, after filtration from benzylamine hydrochloride, the resulting solution of methyl α-benzylamino-*m*-tolyacetate was reduced with lithium aluminum hydride in diethyl ether to give the abnormal isomer, b.p. 140° (10^{-4} mm.), $n^{20}D$ 1.5748.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.6; H, 7.9; N, 5.8. Found: C, 80.9; H, 7.8; N, 6.3.

During the working-up a second product was isolated which differed from the abnormal isomer in forming a hydrochloride insoluble in water. This hydrochloride was crystallized from a mixture of ethanol and ether and had m.p. 200°. It is believed to be the hydrochloride of N-benzyl-α-benzylamino-*m*-tolyacetamide.

Anal. Calcd. for $C_{23}H_{25}ClN_2O$: C, 72.3; H, 6.7; N, 7.4. Found: C, 71.8; H, 6.6; N, 7.4.

Ar = *m*-$CF_3C_6H_4$: normal isomer, **2-benzylamino-1-*m*-trifluoromethylphenylethanol**, m.p. 79.5–80°. *Anal.* Calcd. for $C_{16}H_{16}F_3NO$: C, 65.1; H, 5.5; N,4.8. Found: C, 65.3; H, 5.7; N, 5.0.

Abnormal Isomer, 2-Benzylamino-2-*m*-trifluoromethylphenylethanol.—*m*-Trifluoromethylacetophenone was converted into *m*-trifluoromethylphenylacetic acid by a modified Willgerodt reaction.[13] Bromination of trifluoromethylphenylacetyl chloride in thionyl chloride and treatment of the product with methanol gave methyl α-bromo-*m*-trifluoromethylphenylacetate, b.p. 72° (0.1 mm.). Although fractional distillation produced no further purification, gas chromatography showed that this bromo-ester was contaminated with another compound, presumably unbrominated ester, and the analytical figures were compatible with this interpretation.

Anal. Calcd. for $C_{10}H_8BrF_3O_2$: C, 40.4; H, 2.7. Calcd. for $C_{10}H_9F_3O_2$: C, 55.0; H, 4.2. Found: C, 43.7; H, 3.4.

The crude material was converted into the abnormal isomer, m.p. 95–95.5° (from light petroleum (b.p. 40–60°)).

Anal. Calcd. for $C_{16}H_{16}F_3NO$: C, 65.1; H. 5.5; N, 4.8. Found: C, 65.2; H, 5.3; N, 5.2.

Ar = 3,4-$(CH_3)_2C_6H_3$: normal isomer, **2-benzylamino-1-(3,4-dimethylphenyl)-ethanol**, m.p. 113–114°. *Anal.* Calcd. for $C_{17}H_{21}NO$: C, 80.0; H, 8.3; N, 5.5. Found: C, 80.1; H, 8.4; N, 5.5.

Abnormal Isomer, 2-Benzylamino-2-(3,4-dimethylphenyl)-ethanol.—3,4-Dimethylbenzaldehyde, prepared from 4-chloromethyl-1,2-xylene by a Sommelet reaction,[19] was converted into 3,4-dimethylmandelic acid, m.p. 130–134° (lit.[20] 135°), and thence into methyl α-chloro-3,4-dimethylphenylacetate, b.p. 94° (0.5 mm.), $n^{12}D$ 1.5328.

Anal. Calcd. for $C_{11}H_{13}ClO_2$: C, 62.1: H, 6.2: Cl, 16.7. Found: C, 62.4; H, 6.2; Cl, 16.7.

This was converted into the abnormal isomer, b.p. 170–180° (4×10^{-4} mm.), $n^{15}D$ 1.5730.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 80.0; H, 8.3; N, 5.5. Found: C, 81.1; H, 8.2; N, 5.6.

On long standing (5 months) the product crystallized and had m.p. 50–51° (from light petroleum (b.p. 40–60°)) Found: C, 80.0; H, 8.0; N, 5.7.

Method.—The reactions were followed by measuring the rate of decrease of benzylamine concentration by a spectrophotometric method.[1] It was found that, by employing a molar ratio of amine to oxide of not less than 4, the further reaction between oxide and primary product could be discounted and the course of 50–60% of the reaction followed. All the runs were carried out in duplicate and all gave good second-order rate constants.

For the product analyses, the reaction between the oxide and benzylamine in ethanol, carried out under the same conditions as in the kinetic experiments, was allowed to go to completion and the total secondary amine product was isolated by distillation. Infrared spectra of the products and of known mixtures of normal and abnormal isomers (all at the same total concentration) as solutions in chloroform were determined on a Unicam SP 100 double-beam infrared spectrophotometer. In every case the ratio of appropriate peak heights was found to be a continuous function of the isomer ratio.

Results

Table I lists the measured rate constants (k), the measured proportions of normal and abnormal isomer, and the rate constants for normal (k_N) and abnormal (k_A) attack. The Arrhenius parameters and heats and entropies of activation, together with the rate constants interpolated to 40°, are collected in Table II. The measured rate constants for the over-all reaction are all accurate to ±3% or better, as shown by the agreement between duplicate determinations. The error in the determinations of product ratios is difficult to assess exactly, but it appears to vary from about ±1% for the *p*-methyl compounds to about ±5% for the *m*-trifluoromethyl compounds (*i.e.*, in the latter case, x% of one isomer is really between $(x + 5)$% and $(x - 5)$%. On this basis we estimate that the rate constants for all the normal reactions and for the abnormal reactions of the *m*-methoxy, *m*-methyl, *p*-methyl and 3,4-dimethyl compounds are accurate to ±10% or better. For the abnormal reactions of styrene oxide and its *p*-bromo and *m*-chloro derivatives, the rate constants are accurate to only about ±20% and, for the abnormal reaction of *m*-trifluoromethylstyrene oxide, the rate constant can be quoted to only about ±40%. These uncertainties

TABLE I

ISOMER PROPORTIONS AND MEASURED RATE CONSTANTS, $10^5 k$ (L. MOLE^{-1} SEC.$^{-1}$)

Substituent	Temp., °C.	k	% normal	% abnormal	k_N	k_A
3,4-Dimethyl	20.10	1.41	19	81	0.27	1.14
	40.65	7.45	19	81	1.42	6.03
	59.60	25.3	24	76	6.1	19.2
p-Methyl[1]	25.85	2.20	45	55	0.99	1.21
	35.20	4.47	45	55	2.01	2.46
	49.00	11.5	45	55	5.2	6.3
m-Methyl	20.00	1.09	39	61	0.43	0.66
	40.50	4.87	49	51	2.39	2.48
	59.60	19.9	62.5	37.5	12.4	7.5
H[5]	20.00	1.39	83	17	1.15	0.24
	40.50	6.40	78	22	4.99	1.41
	59.68	25.3	73	27	18.5	6.8
m-Methoxy	20.10	1.77	68	32	1.20	0.57
	50.00	16.0	66	34	10.6	5.4
	59.60	24.8	61	39	15.1	9.7
p-Bromo[1]	20.10	2.59	85	15	2.20	0.39
	35.30	6.45	82	18	5.29	1.16
	49.20	14.7	79	21	11.6	3.1
m-Chloro	40.65	8.54	92	8	7.86	0.68
	50.70	15.2	88	12	13.4	1.8
	59.60	28.0	86	14	24.1	3.9
m-Trifluoromethyl	20.00	1.57	89	11	1.40	0.17
	40.50	5.83	89	11	5.19	0.64
	59.60	21.8	89	11	19.4	2.4

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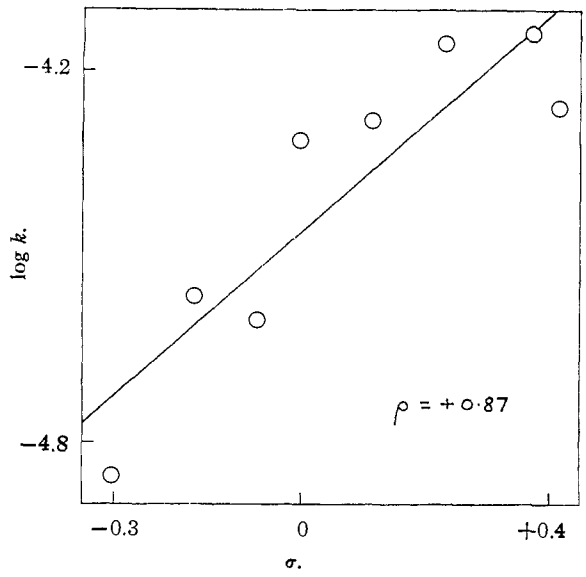


Fig. 1.—Hammett $\rho\sigma$ plot for the normal reactions.

of ±10%, ±20% and ±40% in the rate constants correspond to uncertainties in E and $\Delta H^{\ddagger}$ of ±0.9, ±1.8 and ±3.4 kcal. mole^{-1}, in log A of ±0.6, ±1.2 and ±2.2 units, and in $\Delta S^{\ddagger}$ of ±2.7, ±5.5 and ±10 units, respectively.

TABLE II

RATE CONSTANTS INTERPOLATED TO 40°, ARRHENIUS PARAMETERS AND HEATS AND ENTROPIES OF ACTIVATION

k and A in l. mole^{-1} sec.$^{-1}$, E and $\Delta H^{\ddagger}$ in kcal. mole^{-1}, $\Delta S^{\ddagger}$ in cal. mole^{-1} deg.$^{-1}$

Substituent	$10^5 k$	E	log$_{10}$ A	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
	Normal reactions				
3,4-Dimethyl	1.41	15.5	6.0	14.9	−33.2
p-Methyl	2.74	13.7	5.0	13.1	−37.6
m-Methyl	2.51	16.5	6.9	15.9	−29.0
H	4.90	13.5	5.1	12.9	−37.3
m-Methoxy	5.26	12.8	4.6	12.2	−39.6
p-Bromo	7.00	10.7	3.3	10.1	−45.5
m-Chloro	7.28	12.4	4.5	11.8	−40.0
m-Trifluoromethyl	5.50	12.8	4.7	12.2	−39.0
	Abnormal reactions				
3,4-Dimethyl	5.50	14.2	5.6	13.6	−35.0
p-Methyl	3.37	13.7	5.1	13.1	−37.3
m-Methyl	2.40	11.8	3.6	11.2	−44.1
H	1.38	16.2	6.5	15.6	−30.9
m-Methoxy	2.69	14.3	5.4	13.7	−35.9
p-Bromo	1.66	13.4	4.6	12.8	−39.6
m-Chloro	0.66	18.9	7.8	18.3	−24.9
m-Trifluoromethyl	0.69	12.9	3.8	12.3	−43.2

In spite of the above uncertainties, it is clear from Table II that the rate of the normal reaction is increased by electron-withdrawing substituents and decreased by electron-releasing substituents, *i.e.*, the reaction has a positive value of the Hammett reaction constant ρ. Conversely, the rate of the abnormal reaction is decreased by electron-withdrawing substituents and increased by electron-releasing substituents, and this reaction therefore has a negative ρ. Plots of log k against σ for the normal and abnormal reactions are shown in Figs. 1 and 2, respectively. The slopes of the best

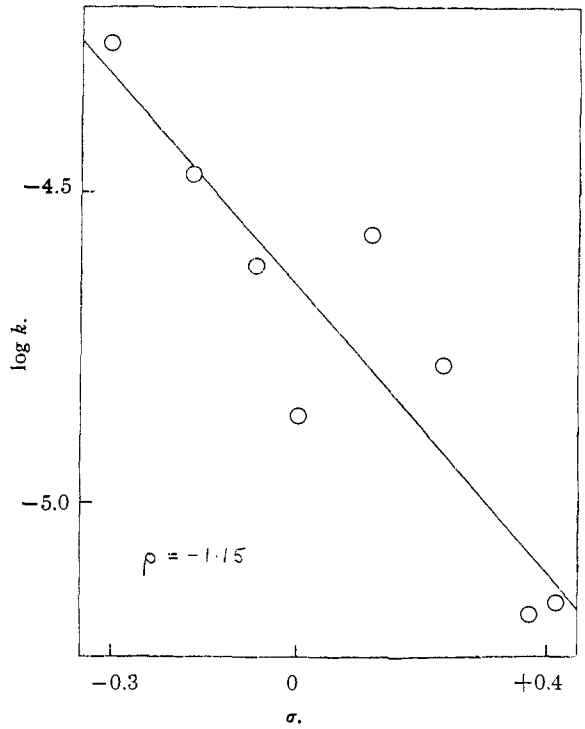
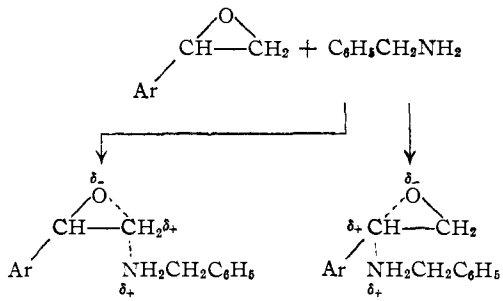


Fig. 2 —Hammett $\rho\sigma$ plot for the abnormal reactions.

straight lines have been found by the least-squares method and give values of $\rho = +0.87$ for the normal reaction and $\rho = -1.15$ for the abnormal reaction. The values of σ used in these plots have been taken from Jaffé's review.[21] As might be expected, the use of the purely inductive constants σ_I for the normal reaction and of σ^+ constants for the abnormal reaction give rather better straight lines, but the differences are slight and the differences in ρ are negligible.

While the plots shown in Figs. 1 and 2 are by no means good straight lines, there can be no doubt that ρ is positive for the normal reaction and negative for the abnormal reaction, and we believe that this is unique for reactions involving the attack of a reagent at either of two positions in the same compound. Since both reactions involve the opening of the highly strained three-membered ring, a process which should not require much help from the reagent, it would be expected that bond breaking would have progressed further than bond making in the formation of both transition states. This implies that the two partial bonds in each transition state would be together less than a full single bond and that the attacked carbon atom is more positive than in the initial state (see diagram). Such a situation usually results in a negative value of ρ, since the increased positive charge on the attacked carbon atom in the transition state is stabilized by electron-releasing substituents and destabilized by electron-withdrawing substituents. This is the case for the abnormal reactions and we believe that the negative ρ found for these reactions correctly reflects a process in which bond breaking is dominant. Of the three charges shown in the transition state for the abnormal reactions,

(21) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).



transition state for normal reaction — transition state for abnormal reaction

the one on carbon is nearer than the other two to the substituent group and, to a first approximation, only the interaction between this charge and the substituent group need be considered.

On the other hand, two of the three charges on the transition state for the normal reactions (those on oxygen and carbon) are almost exactly equidistant from the substituent group and are nearer than the charge on nitrogen. To a first approximation, therefore, only the interactions between the substituent group and these two charges need be considered. Since the three charges must add up to zero, the positive charge on carbon must be smaller than the negative charge on oxygen. Consequently, an electron-withdrawing group will stabilize the negative charge on oxygen more than it will de-stabilize the positive charge on carbon and the reaction will have a positive ρ. The same conclusion can be reached from a consideration of the structure of the epoxide itself, where a substituent group, since it is almost exactly equidistant from both ends of the O–CH_2 bond, will have no effect on the ease of breaking of this bond. The only remaining effect of the substituent will be on the ease of approach of the nucleophile and this will necessarily result in a positive ρ.

The unusual situation of a nucleophilic displacement reaction, in which bond breaking is dominant, having a positive ρ should also occur in reactions involving the attack of a nucleophile at the primary carbon atom of monosubstituted ethyleneimines and ethylene sulfides and in certain ring-opening reactions of larger-ring compounds.

In view of the limited accuracy, the variations in the Arrhenius parameters and the heats and entropies of activation are not large enough to justify any detailed comment. The energies of activation all fall within the range 13.6 ± 2.9 kcal. $mole^{-1}$ and the values of $\log_{10} A$ within the range 5.1 ± 1.8, except for the abnormal reaction of the *m*-chloro compound and the values of E and $\log_{10} A$ for this reaction are among the least accurate of all the values. The low values of the entropy of activation are what would be expected for a reaction in which two neutral molecules form a charged transition state in a hydrogen-bonding solvent and the general similarity of energies and entropies of activation for both the normal and the abnormal reactions supports the conclusion that both reactions take place by similar mechanisms, in spite of the reversal of sign of ρ.

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Mechanisms of Nucleophilic Displacement in Aqueous Dimethyl Sulfoxide Solutions

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Sodium thiosulfate and α-chlorotoluene react in dimethyl sulfoxide (DMSO)–acetonitrile–water mixtures predominantly by a "normal" mechanism in which DMSO acts only as a solvent. Studies of substituent effects, salt effects, activation energies and the stereochemistry of the 2-bromoöctane–thiocyanate reaction all support this mechanism. Evidence is presented for a second mechanism in which DMSO slowly reacts with α-chlorotoluene to give a highly reactive intermediate which is rapidly attacked by thiosulfate. The over-all reaction is first order in α-chlorotoluene and thiosulfate; the rate increases markedly with increasing DMSO concentration in the solvent mixture.

The remarkable acceleration of a variety of reactions by the solvent dimethyl sulfoxide (DMSO) has been reported during the last few years. Thus, the elimination reaction of arylsulfonate esters to give olefins,[2] base-catalyzed proton abstraction from carbon,[3] the alkylation of sodiomalonic esters with alkyl halides,[4] the displacement of halide by cyanide, azide, thiocyanate and halide ions,[5] and the thiosulfate-α-chlorotoluene reaction[6] are reported qualitatively or quantitatively to react at greatly enhanced rates when DMSO is a component of the solvent. The last three of these reactions are bimolecular, nucleophilic displacements on carbon—a type which appears to be widely, but not universally, speeded by DMSO.

In the present work an effort has been made to study the mechanism or mechanisms of the α-chlorotoluene–thiosulfate reaction in aqueous DMSO by a consideration of the kinetics, and by a comparison of the activation energy, substituent effect and ionic strength effect with those in other solvent mixtures of similar dielectric constant.[6]

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