[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

The Lithium Aluminum Hydride Reduction of *p*-Substituted Stilbene Oxides

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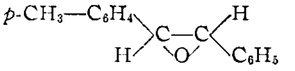
As part of a study of the effect of electronic factors on the direction of S_N2 ring opening in unsymmetrical epoxides where steric factors are largely eliminated, the reduction of *trans-p*-methylstilbene oxide and *trans-p*-chlorostilbene oxide with lithium aluminum hydride was investigated. *trans-p*-Methylstilbene oxide gave approximately 60% of *p*-methylbenzylphenylcarbinol and 40% of benzyl-*p*-tolylcarbinol, whereas *trans-p*-chlorostilbene oxide gave 60% of benzyl-*p*-chlorophenylcarbinol and 40% of *p*-chlorobenzylphenylcarbinol. These results indicate that an electron-releasing group favors attack by the nucleophilic aluminum hydride ion at the α-carbon atom, an electron-withdrawing group, at the β-carbon atom. The substituent effect noted is particularly interesting because it is the reverse of that which has come to be regarded as normal for typical S_N2 reactions. Such a negative substituent effect is interpreted as consistent with broad concepts of epoxide ring opening, based on the absolute reaction rate theory, and on resonance theory.

Introduction

The fact that there are in unsymmetrically substituted epoxides two non-equivalent reactive carbon centers which are attacked essentially irreversibly in S_N2 displacement renders the epoxides ideal compounds for a study of the factors which influence the relative rates of such displacements. For a given reaction, the relative rates of attack at the two carbon atoms may, in effect, be measured simply by a determination of the ratio in which the two possible isomeric products are formed. The importance of electronic factors in governing the direction of ring opening has long been recognized, and more recently the influence of such steric factors as the degree of ring substitution,[1] the size of the substituent on the ring,[2] the size of the attacking group,[3] and the configuration of the epoxide[4] has been pointed out. In a majority of the cases thus far studied, however, it is difficult to differentiate between electronic and steric effects.

The present work was designed to provide a clear-cut study of electronic effects on the direction of ring opening where the epoxide carbon atoms are essentially sterically equivalent. The compounds chosen were the *trans-p*-substituted stilbene oxides, specifically *trans-p*-methylstilbene oxide (I), which is unsymmetrically substituted with the electron-releasing methyl group, and *trans-p*-chlorostilbene oxide (II), in which the over-all effect of the substituent, the chlorine atom, is that of electron withdrawal. These stilbene oxides, as well as *trans-p*-nitrostilbene oxide, proved remarkably unreactive toward many of the usual bases such as sodium hydroxide and sodium methoxide,[5] but did react facilely with lithium aluminum hydride. Reaction of the hydride with epoxides has been shown to proceed by the typical S_N2 mechanism[4b,c,d,6] and this reagent had the further advantage that the composition of the mixture of isomeric 1,2-diarylethanol reduction products obtained with each epoxide could be determined with a high degree of accuracy. Lithium aluminum hydride could not, of course, be used to study the direction of ring opening in *trans-p*-nitrostilbene oxide, which, from other standpoints, would logically have been included in the present study.



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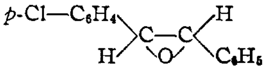

II

Experimental[7]

Synthesis of *p*-Nitrostilbene Oxide.—*p*-Nitrostilbene oxide, m.p. 126.0–127.0° (reported[8] 125–126°), was prepared according to the method of Bergmann and Hervey.[8] Attempted methanolysis with 0.015 *M* sodium methoxide in methanol for 5 days led only to recovery of the epoxide. Simple hydrolytic ring opening could not be effected in dilute potassium hydroxide solution; refluxing for 12 hours with 15% potassium hydroxide solution led to partial breakdown of the *p*-nitrostilbene oxide with evolution of ammonia and formation of benzaldehyde.

Synthesis of *trans-p*-Methylstilbene Oxide and Its Reduction Products.—*trans-p*-Methylstilbene oxide, m.p. 60.8–61.9° (reported[9] 59–60°), was prepared in good yield by the perbenzoic acid oxidation of *trans-p*-methylstilbene.[9] The melting point of *trans-p*-methylstilbene oxide was depressed by the isomeric ketones, *p*-methylbenzyl phenyl ketone, m.p. 96.3–97.5° (reported[10] 94°), and benzyl *p*-tolyl ketone, m.p. 109.6–111.1° (reported[9] 107.5°), prepared by Oppenhauer oxidation of the corresponding carbinols.

Benzyl-*p*-tolylcarbinol, m.p. 66.8–68.2° (reported[11] 68°), was synthesized by the reaction of *p*-methylbenzaldehyde[12] with benzylmagnesium chloride or by the reaction of phenylacetaldehyde with *p*-tolylmagnesium bromide.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.9; H, 7.6. Found: C, 84.9; H, 7.2.

p-Methylbenzylphenylcarbinol, m.p. 44.6–46.2°, obtained in low yield, together with *sym-p,p'*-ditolylethane and some *p*-methylbenzyl phenyl ketone,[13] by reaction of

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[1] (a) S. Winstein and R. B. Henderson in "Heterocyclic Compounds," Vol. I, ed. by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 32; (b) E. E. van Tamelen, G. Van Zyl and G. D. Zuidema, THIS JOURNAL, **72**, 488 (1950).

[2] R. M. Adams and C. A. VanderWerf, *ibid.*, **72**, 4368 (1950).

[3] R. R. Russell and C. A. VanderWerf, *ibid.*, **69**, 11 (1947); R. Fuchs and C. A. VanderWerf, *ibid.*, **74**, 5917 (1952).

[4] (a) E. Fourneau and G. Benoit, *Bull. soc. chim. France*, **12**, 985 (1945); (b) A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949); (c) J. Pataki, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 5375 (1951); (d) P. A. Plattner, H. Heusser and M. Feurer, *Helv. Chim. Acta*, **32**, 587 (1949); (e) D. A. Prins, THIS JOURNAL, **70**, 3955 (1938).

[5] This fact was noted previously by (a) J. Read and I. G. M. Campbell, *J. Chem. Soc.*, 2377, 2674 (1930); *Nature*, **125**, 16 (1930); (b) J. Böeseken and G. Elsen, *Rec. trav. chim.*, **47**, 694 (1928); (c) W. E. Steinmetz, Ph.D. Thesis, Iowa Univ., 1949.

[6] (a) L. W. Trevoy and W. G. Brown, THIS JOURNAL, **71**, 1675 (1949); (b) P. J. Leroux and H. J. Lucas, *ibid.*, **73**, 41 (1951).

[7] All melting points are corrected, boiling points are uncorrected. Analyses by the Clark Microanalytical Laboratories, Urbana, Illinois.

[8] E. Bergmann and J. Hervey, *Ber.*, **62B**, 893 (1929).

[9] M. Tiffeneau and J. Levy, *Bull. soc. chim. France*, **49**, 1738 (1931).

[10] H. Strassman, *Ber.*, **22**, 1229 (1889).

[11] P. Weill and F. Kayser, *Bull. soc. chim. France*, [5] **3**, 841 (1936).

[12] Obtained by the procedure of H. B. Hass and M. L. Bender, THIS JOURNAL, **71**, 1767 (1949). Commercial samples were highly contaminated with the *o*-isomer. *p*-Methylbenzaldehyde was obtained also by the lithium aluminum hydride reduction of *p*-toluic acid, along with *p*-methylbenzyl alcohol and a small amount of di-*p*-xylyl ether, b.p. 171.4° (12 mm.), m.p. 63.0–64.0° [J. Zeltner and B. Tarassov, *Ber.*, **43**, 991 (1910), reported b.p. 310–311° (755 mm.), m.p. 61.5–62.5°].

[13] Oxidation of the carbinol formed in Grignard reactions was observed previously by J. Marshall, *J. Chem. Soc.*, **107**, 509 (1915).

benzaldehyde with *p*-methylbenzylmagnesium bromide,[14] was obtained in better yield (66.1%) by the addition of styrene oxide to *p*-tolyllithium.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.9; H, 7.6. Found: C, 84.7; H, 7.3.

Phenylurethan, m.p. 98.6–100.2°.

Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.7; H, 6.4. Found: C, 80.0; H, 6.4.

Synthesis of *trans-p*-Chlorostilbene Oxide and Its Reduction Products.—*trans-p*-Chlorostilbene oxide, m.p. 100.4–101.5°, was prepared in 96.5% yield by perbenzoic acid oxidation of *trans-p*-chlorostilbene, m.p. 129.6–130.2° (reported[15] 127°). The melting point of *trans-p*-chlorostilbene oxide was depressed by the isomeric ketones, benzyl *p*-chlorophenyl ketone, m.p. 106.4–107.4° (reported[16] 107.5°), and *p*-chlorobenzyl phenyl ketone, m.p. 136.5–137.6° (reported[16] 138°), prepared by Oppenhauer oxidation of the corresponding carbinols.

The attempted condensation of *p*-chlorobenzaldehyde with benzyl chloride failed to give the epoxide. With sodium methoxide in ether, there was obtained a colorless chlorine-containing compound, m.p. 64.0–64.5°, which analyzed correctly for the chlorohydrin of *p*-chlorostilbene. When sodium ethoxide was used as the condensing agent in *n*-butyl ether, *p*-chlorobenzoic acid was isolated in 67% yield. From the attempted condensation of benzaldehyde with *p*-chlorobenzyl chloride by means of potassium carbonate in methanol, *p*-chlorobenzaldehyde was isolated.

Benzyl-*p*-chlorophenylcarbinol, b.p. 213° (20 mm.), m.p. 52.5–53.6°, was synthesized by reaction of *p*-chlorobenzaldehyde with benzylmagnesium chloride.

Anal. Calcd. for $C_{14}H_{13}ClO$: C, 72.3; H, 5.6. Found: C, 72.3; H, 5.5.

The phenylurethan was prepared as follows: A mixture of 50.0 g. (0.215 mole) of benzyl-*p*-chlorophenylcarbinol and 25 ml. (27.5 g., 0.231 mole) of phenyl isocyanate was heated on a steam-bath for 1 hour. The product was triturated with ligroin, b.p. 30–60°, dissolved in carbon tetrachloride, and filtered. After evaporation of the solvent, there was obtained 55.0 g. (72.5%) of the urethan, m.p. 114.6–115.6° after recrystallization from ligroin, b.p. 60–90°.

Anal. Calcd. for $C_{21}H_{18}ClNO_2$: C, 71.7; H, 5.2. Found: C, 72.0; H, 5.2.

The refractive index bands of the phenylurethan determined with a Fisher–Jelly Refractometer at 140° were as follows: red, 1.550–1.555; green, 1.555–1.563; violet, 1.563–1.570.

p-**Chlorobenzylphenylcarbinol**, m.p. 55.0–56.5°, was prepared in 67.0% yield from benzaldehyde and *p*-chlorobenzylmagnesium chloride.

Anal. Calcd. for $C_{14}H_{13}ClO$: C, 72.3; H, 5.6; Cl, 15.2. Found: C, 72.3; H, 5.6; Cl, 14.9.

The phenylurethan, m.p. 130.4–132.0°, was prepared in 88.2% yield as described for the isomer.

Anal. Calcd. for $C_{21}H_{18}ClNO_2$: C, 71.7; H, 5.2. Found: C, 71.8; H, 5.0.

The refractive index bands were identical with those of the isomer.

Lithium Aluminum Hydride Reductions. *trans-p*-Methylstilbene Oxide.—To 300 ml. of an ether solution containing 0.156 mole (0.0180 g. per ml.) of lithium aluminum hydride, analyzed by a modification of the gasometric procedure of Field and Grunwald,[17] there was added dropwise with stirring a solution of 65.7 g. (0.313 mole) of *trans-p*-methylstilbene oxide dissolved in 500 ml. of ether. The reaction mixture was stirred at room temperature for 12 hours and was then hydrolyzed with water and saturated ammonium chloride solution. The ether layer was separated and the aqueous solution extracted with fresh solvent. The combined ether solutions were washed with saturated sodium bicarbonate solution, dried over Drierite and concentrated under vacuum on a steam-bath. The residual oil weighed 59.0 g. The aqueous portion was acidified carefully with cold dilute hydrochloric acid and extracted with ether and treated as before. An additional 2.6 g. of oil was recovered, bringing the total to 61.6 g. (93.9%).

***trans-p*-Chlorostilbene Oxide.**—The above procedure was employed except that cold dilute acetic acid was used as the hydrolyzing medium. Addition of methanol to the residual oil gave 30.7% of unchanged epoxide and 65.0% of a mixture of *p*-chlorobenzylphenylcarbinol and benzyl-*p*-chlorophenylcarbinol.

Conversion of Unknown Mixture from Reduction of *p*-Chlorostilbene Oxide to Phenylurethans for Thermal Analysis.—To 6.0 g. (0.026 mole) of the reduction products of *p*-chlorostilbene oxide, there was added 3.0 ml. (3.3 g., 0.028 mole) of phenyl isocyanate. The reaction mixture was warmed on a steam-bath for an hour. The product was triturated with ligroin, b.p. 30–60°, dissolved in carbon tetrachloride and filtered. Removal of the solvent and trituration with ligroin gave 4.6 g. (50.5%) of the mixture of urethans, which was analyzed without further treatment.

Anal. Calcd. for $C_{21}H_{18}ClNO_2$: C, 71.7; H, 5.2; Cl, 10.1; N, 4.0. Found: C, 71.4, 71.7; H, 4.9, 5.0; Cl, 10.1, 9.8; N, 4.3, 4.2.

Cryoscopic Analysis.—The mixture formed by reduction of *p*-methylstilbene oxide with lithium aluminum hydride was analyzed for benzyl-*p*-tolylcarbinol and *p*-methylbenzylphenylcarbinol by a modification, applicable to cases involving formation of solid solutions, of the Bureau of Standards' cryoscopic method.[18]

Samples.—Benzyl-*p*-tolycarbinol, m.p. 67.31°, and *p*-methylbenzylphenylcarbinol, m.p. 45.64°, were redistilled and crystallized from ligroin, b.p. 30–60°, until constant melting points were attained. The samples analyzed correctly for carbon and hydrogen to within ±0.05%. The oil from the reduction was used without further purification. The test mixture was prepared from analytically pure *trans-p*-methylstilbene oxide and the pure carbinols.

Apparatus and Melting Points.—A modified Beckman cell with a platinum resistance thermometer and a Mueller bridge was used. At least three melting points were taken on any given sample. The average deviation did not exceed ±0.04° and the maximum deviation, ±0.07°, except that, for one sample which was not stirred, an average deviation of ±0.09° for six determinations was obtained.

Apparent Cryoscopic Constant of Benzyl-*p*-tolylcarbinol (A) and *p*-Methylbenzylphenylcarbinol (B).—A melting point–composition curve was constructed from the melting points of pure A and three mixtures with A as solvent and B as solute. The apparent cryoscopic constant was calculated for several concentrations through use of the equation $K'_f = \Delta t/m$. The variation of K'_f for compound A with concentration was then plotted (Fig. 1). The same procedure was followed for compound B. The approximate K'_f for each unknown mixture and test mixture could then be determined.

Analysis of Unknown Mixture.—It was found that the oil obtained on reduction of *trans-p*-methylstilbene oxide contained 28.1 ± 3.1% of benzyl-*p*-tolylcarbinol (Table I, 1, 2)

TABLE I

MELTING POINT–COMPOSITION DATA FOR MIXTURES OF BENZYL-*p*-TOLYLCARBINOL (A) AND *p*-METHYLBENZYLPHENYLCARBINOL (B)

Sample no.	Wt. of A, g.	Wt. of B, g.	Wt. of mixture, g.	M.p. depression, °C.	Appar. cryoscopic constant, K'_f	A, %	B, %
1[a]	7.637		0.3866	1.13	6.65	25.0	
2[a]	7.637		.4991	1.34	6.76	31.1	
3[a]		8.735	.2990	0.67	7.25		39.0
4[a]		8.076	.4930	1.08	7.40		45.0
5[b]	4.167		.1941	1.12	6.64	22.7	
6[c]		7.653	.3880	0.96	7.31		44.1

[a] Unknown mixture obtained by the reduction of *p*-methylstilbene oxide. [b] Test mixture containing 25.6% of A, 49.7% of B and 24.7% of *p*-methylstilbene oxide. [c] Test mixture containing 26.0% of A, 49.0% of B and 25.0% of *p*-methylstilbene oxide.

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[14] *p*-Methylbenzyl bromide was prepared by the method of E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **91**, 1687 (1907).

[15] F. Bergmann, A. Weizman and D. Shapiro, *J. Org. Chem.*, **9**, 408 (1944).

[16] S. S. Jenkins and E. M. Richardson, THIS JOURNAL, **55**, 1618 (1933).

[17] L. Field and F. A. Grunwald, *J. Org. Chem.*, **16**, 946 (1951).

[18] A. J. Streiff and F. D. Rossini, *J. Research Natl. Bur. Standards*, **32**, 185 (1944).

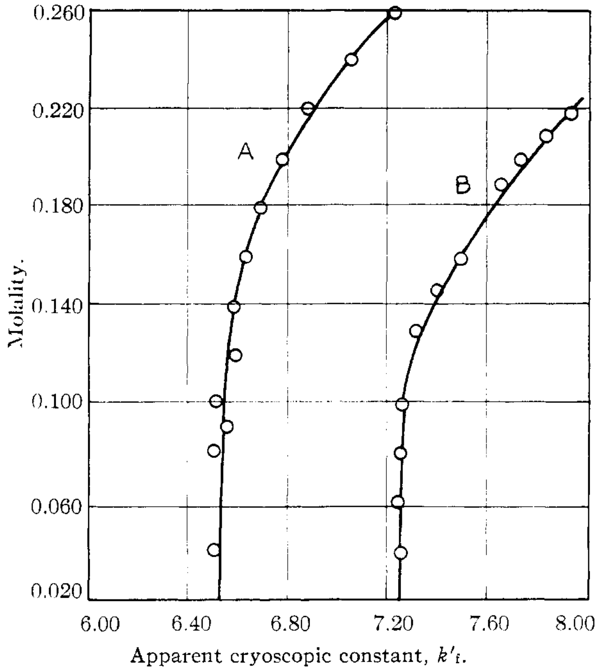

Fig. 1.—Variation of apparent cryoscopic constant of benzyl-*p*-tolylcarbinol (A) and of *p*-methylbenzylphenylcarbinol (B) with concentration.

and 42.0 ± 3.0% of *p*-methylbenzylphenylcarbinol (Table I, 3, 4). The average molecular weight of the oil was found to be 218, suggesting that the third component was unchanged epoxide.

Analysis of Test Mixtures.—The accuracy of the method was checked by analysis of a synthetic mixture of approximately the same composition as the unknown mixture. The mixture which contained 25.6% of benzyl-*p*-tolylcarbinol (A) analyzed for 22.7% (Table I, 5) and the mixture which contained 49.0% of *p*-methylbenzylphenylcarbinol (B) analyzed for 44.1% (Table I, 6).

Thermal Analysis.—The mixture of benzyl-*p*-chlorophenylcarbinol and *p*-chlorobenzylphenylcarbinol formed as the product of the lithium aluminum hydride reduction of *trans*-*p*-chlorostilbene oxide was converted to an analytically pure unknown mixture of the isomeric urethans whose composition was then determined by the melting point–composition method.

Samples.—The phenylurethans of benzyl-*p*-chlorophenylcarbinol (C) and of *p*-chlorobenzylphenylcarbinol (D) were prepared and purified as described previously. All samples were analyzed for carbon and hydrogen.

Apparatus and Melting Points.—Time–temperature curves were taken in a modified Beckman cell with a copper-constantan thermocouple and a Micromax recording potentiometer. Melting points were reproducible to within ±1.0°.

Phase Diagram.—Nine samples of pure C and D with compositions which ranged from 0 to 100% of C were prepared and analyzed thermally. The phase diagram was typical of solid solution formation with a minimum at 77.5° and a composition of 57.5% of C (Fig. 2).

Analysis of Unknown Mixture.—The unknown mixture of phenylurethans was found to contain 60.9 ± 3.0% of C and 39.1 ± 3.0% of D. It was assumed that the carbinols from which the urethans were derived were present in the reduction products of *p*-chlorostilbene oxide in the same ratio.

Analysis of Test Mixture.—As a check on the accuracy of the method, a synthetic mixture of 61.4% of benzyl-*p*-chlorophenylcarbinol and 38.6% of *p*-chlorobenzylphenylcarbinol was prepared. The mixture of carbinols was converted to the phenylurethans in 56% yield by the procedure described for the mixture of carbinols obtained in the reduction of *trans*-*p*-chlorostilbene oxide. The thermal analysis showed 64.4% of C, an error of 3.0%.

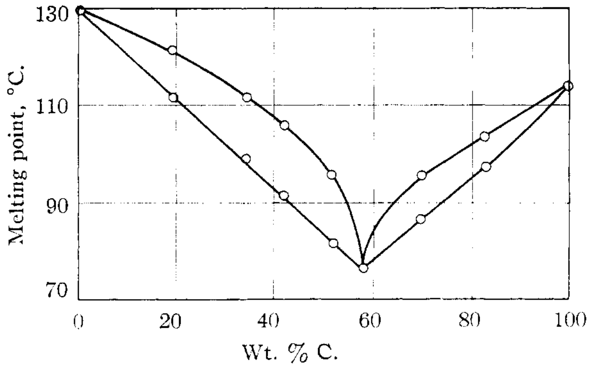

Fig. 2.—Phase diagram of the phenylurethans of benzyl-*p*-chlorophenylcarbinol (C) and of *p*-chlorobenzylphenylcarbinol (D).

Results and Discussion

Although perbenzoic acid is in general an effective reagent for the conversion of olefins to the corresponding epoxides, Weisenborn and Taub[19] have noted several examples in which the major products were aldehydes or ketones. In order that the product of the reaction of perbenzoic acid with *trans*-*p*-methylstilbene might be clearly established as *trans*-*p*-methylstilbene oxide, the previously reported isomeric ketones, benzyl *p*-tolyl ketone and *p*-methylbenzyl phenyl ketone, were synthesized; the non-identity of the three isomers was easily shown. The physical properties of the ketones were markedly different from those of the perbenzoic acid–*trans*-*p*-methylstilbene reaction product, and only the latter gave a positive qualitative test for the epoxide linkage.[20] The formation of α,β-diarylethanol isomers in the lithium aluminum hydride reduction is further confirmation of the epoxide function. The epoxide structure of the product formed from reaction of perbenzoic acid and *trans*-*p*-chlorostilbene was established unequivocally in a similar manner.

The assignment of the *trans* configuration to the *p*-methylstilbene oxide, m.p. 60.8–61.9°, and to the *p*-chlorostilbene oxide, m.p. 100.4–101.5°, obtained from the corresponding *trans*-olefins, is based upon the observation that the reaction of olefins with perbenzoic acid proceeds by *cis* addition of oxygen.[21]

Attack of *p*-tolyllithium on styrene oxide occurred almost entirely at the primary carbon atom[22] to give good yields of *p*-methylbenzylphenylcarbinol. The direction of ring opening in this reaction is probably dictated mainly by the steric factors since Cathcart[23] found that the α-carbon atom of 3,4-dihydronaphthalene-1,2-epoxide, which is sterically less hindered than the secondary carbon atom in styrene, is attacked preferentially by the phenyl group.

Formation of *p*-chlorobenzaldehyde in the attempted synthesis of *p*-chlorostilbene oxide by the

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[19] F. L. Weisenborn and D. Taub, THIS JOURNAL, **74**, 1329 (1952).

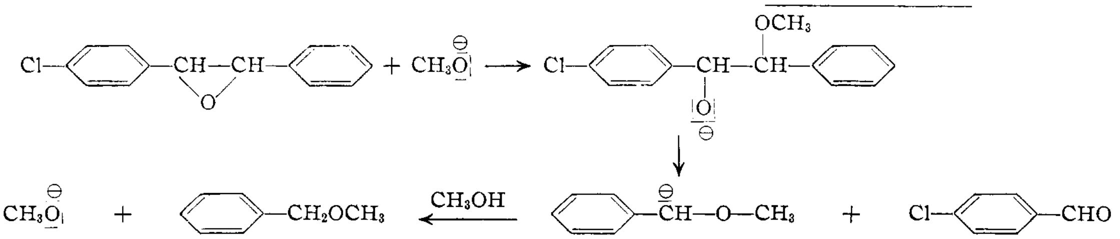
[20] R. Fuchs, R. C. Waters and C. A. VanderWerf, *Anal. Chem.*, **24**, 1514 (1952).

[21] D. Swern, THIS JOURNAL, **70**, 1235 (1948); G. Braun, *ibid.*, **51**, 228 (1929).

[22] Phenyllithium also attacks the primary carbon atom of styrene oxide; *cf.* S. J. Cristol, J. R. Douglass and J. S. Meek, *ibid.*, **73**, 816 (1951).

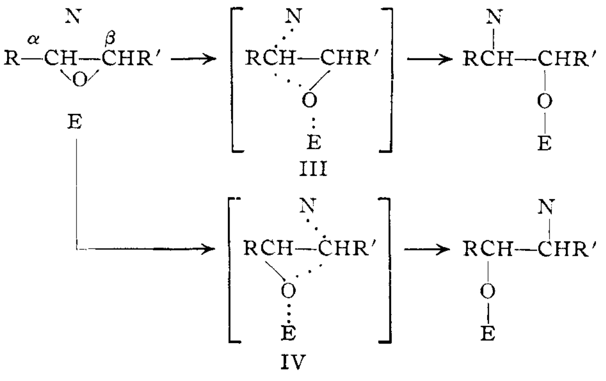
[23] J. A. Cathcart, Ph.D. Thesis, Ohio State University, 1941.

condensation of *p*-chlorobenzyl chloride with benzaldehyde in the presence of potassium carbonate in methanol is interesting. Bergmann and Hervey[8] isolated the methyl ether of *p*-nitrobenzyl alcohol in the attempted condensation of *p*-nitrobenzaldehyde with benzyl chloride under the same conditions. The first step in these reactions may be the formation of the stilbene oxides followed by cleavage of the carbon–carbon bond as illustrated.



The stilbene oxides studied proved quite remarkably unreactive in acid- and base-catalyzed hydrolysis and in base-catalyzed methanolysis, as did *p*-nitrostilbene oxide. *p*-Chlorostilbene oxide and *p*-methylstilbene oxide were likewise unreactive toward the common basic reagents, but yielded to the attack of lithium aluminum hydride. The reduced reactivity of stilbene epoxides, in general, was previously observed for stilbene oxide,[5b] *p*-nitro- and *p*-methoxystilbene oxides[5c] and *o,o'*- and *p,p'*-dimethoxystilbene oxides.[5a] Read and Campbell[5a] felt that "the extraordinary stability of these well defined crystalline oxides is in keeping with the views of Thorpe and Ingold on the effect of substituents in relieving the strain inherent in small ring compounds." It is possible that the epoxide ring in stilbene oxides is considerably stabilized through resonance interaction of the ring with the two phenyl groups, much as the reactivity of the double bond in stilbene is reduced through resonance.[24] Experiments designed to explore this problem further are in progress in our Laboratories.

The diverse and often seemingly contradictory facts concerning the effect of substituents on the direction and kinetics of ethylene oxide ring opening can be rationalized in terms of the absolute reaction rate theory,[25] especially as extended by Winstein, Grunwald and Jones[26] in their significant discussion of driving forces in solvolysis. According to the theory, apart from entropy considerations, there are three major factors affecting the energy required for the change from the initial to the transition state, which must be considered in epoxide displacement reactions: (1) the approach of the nucleophilic reagent, (2) the ionic splitting of the carbon–oxygen bonds, and (3) the approach of an electrophilic reagent (solvent or acid catalyst). On this basis, the mechanism of displacement reactions on epoxides is pictured as follows, where N is the attacking nucleophilic reagent and E is the approaching electrophilic molecule or ion (below)



Electron-withdrawing substituents facilitate factor (1) (bond-making), but hinder factor (2) (bond-breaking) and factor (3) (coördination of the epoxide oxygen with an electrophilic reagent). Electron-releasing substituents, on the other hand, hinder factor (1) and facilitate factors (2) and (3). The net effect of a substituent in a given reaction on the energy of activation and on the direction of ring opening will then depend upon the relative importance, in the transition state, of factor (1) relative to factors (2) and (3).

If factor (1) is the more important, that is, if in the transition state bond-making has progressed to a greater extent than bond-breaking, then an electron withdrawing substituent causes a decrease in the energy of activation and hence an increase in rate of reaction. This may be termed a positive substituent effect ($\rho = +$). In such cases, if R has greater *electron-withdrawing* power than R', and if the two positions are sterically equivalent, then the approach of the nucleophilic reagent will be facilitated to a greater degree at the α-carbon than at the β-carbon; in other words, transition state III will be favored.

On the other hand, if factors (2) and (3) are the more important, that is, if in the transition state bond-breaking has progressed to a greater extent than bond-making, then electron-releasing substituents cause an increase in the rate of reaction. This

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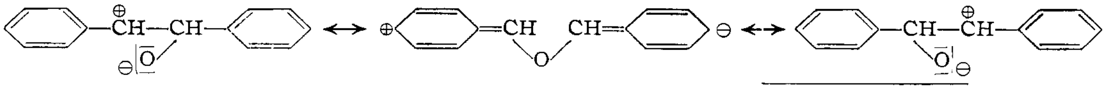
[24] The remarkable resemblance of epoxides and olefins in their chemical reactions and physical–chemical properties has been noted previously by P. V. Zimakov, *Acta Physicochim. U.R.S.S.*, **21**, 401 (1946), and by A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949). The π-bond character of the epoxides has been attributed by Walsh and by M. T. Rogers [THIS JOURNAL, **69**, 2544 (1947)] to the fact that the electrons are more loosely held due to the ring strain. Some of the structures contributing to resonance in the stilbene oxide molecule are (*cf.* Rogers)



[25] (a) C. N. Hinshelwood, K. J. Laidler and E. W. Timm, *J. Chem. Soc.*, 848 (1938); (b) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., New York, N. Y., 1950, pp. 137–143.

[26] S. Winstein, E. Grunwald and H. W. Jones, THIS JOURNAL, **73**, 2700 (1951).

may be referred to as a negative substituent effect (ρ = —). Here, if the *electron-release* of R is greater than that of R′, attack at the α-carbon is once more favored and transition state III is the preferred route.

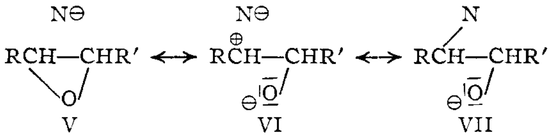
A positive substituent effect seems to be most likely under typical S_N2 conditions. Ideally, it may be expected in the reactions of epoxides (a) with negatively charged nucleophilic reagents in which the negative charge is highly localized and (b) in the absence of any acid catalyst or solvent capable of coördinating with the epoxide oxygen atom. Kinetic data for such ideal cases are lacking. Under conditions somewhat less than ideal, a positive substituent effect has, however, been observed in the reactions of the aliphatic epoxides such as propylene oxide, glycidol and epichlorohydrin, with water,[27] with aqueous sodium chloride[27] and with sodium alloxide in allyl alcohol.[28]

The tendency for a negative substituent effect to be operative should be enhanced with a shift toward typical S_N1 conditions. A negative substituent effect may be expected in the reactions of epoxides (a) with relatively weak bases, either uncharged or highly polarizable so that the negative charge can be broadly diffused in the transition state, (b) in the presence of a strong acid catalyst or a strongly solvating solvent, (c) especially if an unsaturated group, such as vinyl or phenyl, which is capable of aiding the ionization of the carbon–oxygen bond by virtue of its ability to stabilize a positive charge on the carbon, is substituted on the epoxide ring.

Study of epoxide reactions suggests that the epoxides have a certain predisposition to show a negative substituent effect; that is, the negative substituent effect is exhibited under less favorable conditions than are required in the familiar displacement reaction of other types of compounds. This fact may no doubt be attributed to the inherent strain in the epoxide ring, which provides a certain driving force for strain-relieving ionic splitting of a C–O bond. A negative substituent effect has been observed for a number of reactions in which either two or all of the above conditions obtain, *i.e.*, in the acid-catalyzed reactions of the aliphatic epoxides with water,[27] with hydrochloric acid[27] and with allyl alcohol[28] and in the reactions of *p*-substituted styrene oxides with sodium phenoxide in the presence of excess phenol.[29] In the last-mentioned case, the base employed (phenoxide ion) permits extensive diffusion of the negative charge in the transition state, and phenol, itself, can function as the acid catalyst. It is also interesting, in this connection, that for propylene oxide the substituent effect is less positive in the reaction with the uncharged methyl alcohol than with the negatively charged methoxide ion.[30] Significant, too, is the fact that in the reaction of ethylene and propylene oxides with *p*-substituted phenoxides,[31] the substituent effect shifts from positive to negative as the acidity of the substituted phenol increases and the basicity of the ion decreases.

The substituent effect noted in the reduction of the *p*-substituted stilbene oxides is of particular interest. *trans-p*-Methylstilbene oxide gave approximately 60% of *p*-methylbenzylphenylcarbinol and 40% of benzyl-*p*-tolylcarbinol, whereas *trans-p*-chlorostilbene oxide gave 60% of benzyl-*p*-chlorophenylcarbinol and 40% of *p*-chlorobenzylphenylcarbinol. These results conform to a negative substituent effect and indicate that the reduction of *p*-substituted stilbene oxides with lithium aluminum hydride falls in that class of displacement reaction in which the bond-breaking effect (2) and the acid catalysis factor (3) are more important, in the transition state, than the bond-making factor (1). With (a) the complex aluminum hydride ion, which can give rise to a rather diffuse transition state, as the attacking base, with (b) the possibility of acid catalysis by lithium ion; and with (c) the phenyl groups as substituents, all three of the factors favorable to a negative substituent effect are met, at least to an extent. The relative importance of each of these factors in bringing about a negative substituent effect cannot be assessed at the present time. Further studies designed to provide evidence on this question are in progress in our laboratories.

The negative substituent effect for the *p*-substituted stilbene oxide–lithium aluminum hydride reaction may also be explained by application of resonance concepts. The transition state for typical S_N2 displacements on epoxides may be considered as a resonance hybrid of the following principal contributing structures



In the typical case, structure VI, which carries a positive charge on the carbon atom being attacked, is relatively unstable, because of its high charge separation, and makes only a minor contribution to the transition state. Even so, this structure is perhaps more important in the case of epoxides, because of the inherent ring strain, than it is for displacement reactions of non-cyclic compounds. Now, however, if the high charge separation of structure VI is decreased by coördination of an acid, such as lithium ion, at the oxygen and by diffusion of the negative charge on N$^-$, as it is over the whole aluminum hydride ion in our reaction, then structures of the type of VI, showing neither the incoming base nor the epoxide oxygen atom bonded to one of the carbon atoms, assume much greater importance in the transition state, particularly if the positive charge on the carbon can also be widely diffused. If R is a phenyl group, this is accomplished through resonance interaction of the benzene ring with the adjacent carbon atom[32]

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(27) N. Brönsted, M. Kilpatrick and M. Kilpatrick, THIS JOURNAL, **51**, 428 (1929).

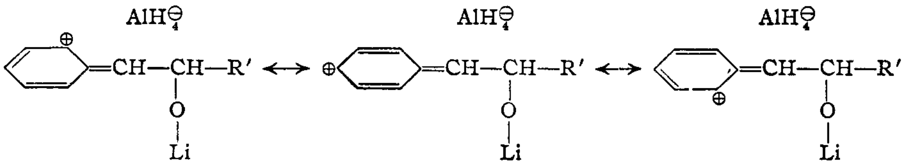
(28) D. Swern, G. N. Billen and H. B. Knight, *ibid.*, **71**, 1152 (1949).

(29) C. O. Guss, *J. Org. Chem.*, **17**, 678 (1952); THIS JOURNAL, **71**, 3460 (1949); *ibid.*, **74**, 2561 (1952).

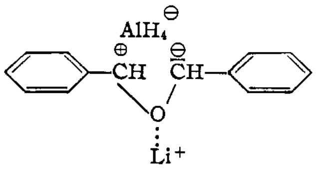
(30) H. C. Chitwood and B. T. Freure, *ibid.*, **68**, 680 (1946).

(31) D. R. Boyd and E. R. Marle, *J. Chem. Soc.*, **105**, 2117 (1914); *ibid.*, **115**, 1239 (1919).

(32) Attention has already been called [C. A. VanderWerf, R. Y. Heisler and W. E. McEwen, THIS JOURNAL, **76**, 1231 (1954)] to the role played by unsaturated groups, such as phenyl and vinyl, in promoting attack at the secondary carbon atom in mono-substituted ethylene oxides. This may likewise be explained by resonance interaction between the unsaturated group and the positively charged epoxide carbon atom in the transition state.



If R′ is also a phenyl group, a whole series of resonance structures of the type of VIII


VIII

involving no bond between the epoxide carbon atoms, in which the positive and negative charges are diffused over the two phenyl groups, respectively, may also make an important contribution to the transition state. As a result of all these possibilities, it appears that for the reaction of stilbene oxides with lithium aluminum hydride the most important contribution to the transition state may well be made by a whole group of resonance structures in which a positive charge is diffused over the carbon atom being attacked and the phenyl group attached to it. Now, the effect of a *p*-substituent, which should introduce no steric complication, on the direction of ring opening may perhaps be determined simply on the basis of its stabilization or de-stabilization of the positive charge. An electron-donating group, which would tend to stabilize the positive charge, would promote attack at the carbon to which it is attached, whereas an electron-withdrawing group would have exactly the opposite effect. This is, of course, an example of the negative substituent effect.

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LAWRENCE, KANSAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

Direction of Ring Opening in the Reduction of *p*-Substituted Styrene Oxides with Lithium Borohydride

BY RICHARD FUCHS[1] AND CALVIN A. VANDERWERF

RECEIVED JULY 15, 1953

Reduction of *p*-substituted styrene oxides with lithium borohydride in ether solution has been studied in continuation of our evaluation of electronic effects on the direction of S_N2 ring opening of unsymmetrical epoxides. Percentage of secondary attack by the borohydride was found to range from less than 16% when the *p*-substituent was the electron-withdrawing -Br to more than 95% when it was the electron releasing $-OCH_3$ group. The $-NO_2$ compound, with 62% of secondary attack, is an exception to this order, which otherwise is the reverse of that considered normal for S_N2 reactions. The experimental results are rationalized in terms of Swain's treatment of the substituent effect on the transition state for nucleophilic displacements.

Introduction

It has been fairly generally assumed that the electronic effect of an electron-releasing substituent on the direction of S_N2 ring opening in ethylene oxides is to favor attack at the primary carbon atom; conversely, an electron-withdrawing group is assumed to favor attack at the secondary carbon atom. Experimental tests of this assumption have, in most cases, been clouded by the possible interplay of steric factors. Recent studies by Guss[2] on the effect of *p*-substituents on the reported unimolecular ring opening of styrene oxides by sodium phenoxide in excess phenol suggest the desirability of a study on the same series of styrene oxides in an S_N2 reaction. Guss found that the percentage of secondary attack for the reaction with sodium phenoxide increased in the *p*-substituent order $-NO_2 < -H < -OCH_3$. This order, which corresponds to a negative rho in the Hammett equation, also has been observed for the rates of solvolysis of the *p*-substituted benzyl chlorides.[3] The opposite substituent effect was noted[3] for the S_N2 reaction of the benzyl chlorides with iodide ion in acetone, and it has been commonly inferred[4] for the styrene oxide series under S_N2 conditions.

The lithium borohydride reduction is a particularly favorable case for study of the direction of ring opening in *p*-substituted styrene oxides because a change in the ratio of the isomeric alcohols produced can be followed in either direction from the 1:3 primary to secondary alcohol ratio obtained in the case of styrene oxide itself. The products are all known and the composition of the mixture of isomers can be determined by means of fractional distillation, from melting point curves or from infrared absorption.

Results

The relative percentages of secondary alcohols, formed by attack at the primary carbon atom, and of primary alcohols, formed by attack at the sec-

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[1] The authors wish to acknowledge their appreciation to the University of Kansas for a fellowship to one of us under which a large part of this work was performed.

[2] (a) C. O. Guss, THIS JOURNAL, **71**, 3460 (1949); (b) *ibid.*, **74**, 2561 (1952); (c) C. O. Guss and H. Mautner, *J. Org. Chem.*, **16**, 887 (1951).

[3] G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935).

[4] See, for example, S. J. Cristol and R. F. Helmreich, THIS JOURNAL, **74**, 4083 (1952).