(10) C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Am. Chem. Soc.*, **90**, 1958 (1968).
(11) D. G. Lee and M. H. Sadar, *J. Am. Chem. Soc.*, **96**, 2862 (1974).
(12) Log $I = 0.43(-H_0) - 3.48$.
(13) K. Yates and R. A. McClelland, *Prog. Phys. Org. Chem.*, **11**, 323 (1974).
(14) J. N. Anderson, Ph.D. Thesis, University of Pittsburgh, 1974.
(15) K. Yates and R. A. McClelland, *Can. J. Chem.*, **52**, 1098 (1974).
(16) N. P. Librovich, P. I. Valov, and M. I. Vinnik, *Russ. J. Phys. Chem. (Engl. Transl.)*, **41**, 1206 (1967).
(17) Both isopropyl acetate and *p*-nitrobenzyl acetate show such a break around 80% H_2SO_4. However, the calculations at these acidities are based on f_S values obtained on extrapolation over a considerable range of acidity and are therefore not as reliable.
(18) (a) This study again shows the powerful stabilizing effect of a cyclopropyl group adjacent to a carbonium ion center, even stronger than the corresponding effect of a phenyl group.[20b] (b) D. G. Garratt, A. Modro, K. Oyama, G. H. S. Schmid, T. T. Tidwell, and K. Yates, *J. Am. Chem. Soc.*, **96**, 5295 (1974), and references therein.
(19) This is the ρ value based on the A_{Ac}-2 hydrolysis of the other benzyl acetates of this study and also agrees with a literature value for hydrolysis in aqueous acetone.[19b] (b) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).
(20) The failure of the "*r*" treatment for *p*-methoxybenzyl acetate lies in the substantially negative "*r*" value for A_{Al}-1 hydrolysis in dilute acids (−9 for *t*-BuOAc). Even in a region of relatively small contribution of this mechanism, it therefore has an overriding effect on the value of the slope in the "*r*" plot.
(21) D. C. Lee and R. Cameron, *J. Am. Chem. Soc.*, **93**, 4724 (1971).
(22) An alternative way of looking at this is in terms of the acidity of the $^+$O–H bond. The $^+$O–H bond in the tetrahedral intermediate is considerably more acidic than that of a protonated alcohol and thus is capable of forming stronger hydrogen bonds with water.
(23) (a) For example, in Kurz's calculations of transition state pK_a(‡) values[23b] for SN2 reactions, even in the extreme cases in which he assumes a fully product-like or reagent-like transition state, the additional molecule that is present has a significant influence. (b) J. L. Kurz, *Acc. Chem. Res.*, **5**, 1 (1972).
(24) D. P. N. Satchell, *J. Chem. Soc.*, 3911 (1956).
(25) V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, 3609 (1955).
(26) See, for example: R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds", Elsevier, Amsterdam, 1965, pp 140, 237, 242.
(27) (a) It has been suggested[27b] that, in certain cases, the phenolic hydrogen is being removed during the electrophilic attack, with the resultant formation of a neutral quinoid intermediate. (b) P. B. D. de la Mare, A. Singh, T. G. Tillett, and M. Zeltner, *J. Chem. Soc. B*, 1122 (1971).

Transition State Structure for Peracid Epoxidation. Secondary Deuterium Isotope Effects

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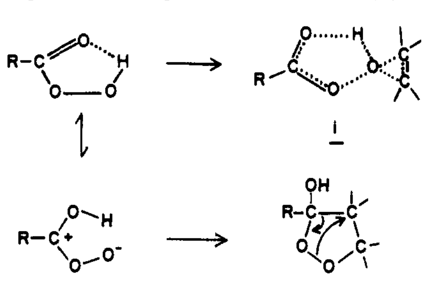
Abstract: Kinetic deuterium isotope effects have been measured for the epoxidation of *p*-phenylstyrene (**3**) and three deuterated derivatives (α-*d* (**4**); β,β-d_2 (**5**); α,β,β-d_3 (**6**)) with *m*-chloroperbenzoic acid in 1,2-dichloroethane at 0°. The isotope effects (k_H/k_D) observed for **4**, **5**, and **6** are 0.99, 0.82, and 0.82, respectively; for *p*-nitrostyrene and its α-*d* analog k_H/k_D at 25° was 0.98. The peracid isotope effect for epoxidation of **3** with *m*-$ClC_6H_4COOOH(D)$ at 0° was $k_H/k_D = 1.17$. These data suggest that in the transition state for epoxidation there is substantial C_β-O bond formation, but negligible change in the bonding or hybridization at C_α of the olefin. Epoxidation mechanisms suggested previously cannot accommodate these findings, thus an alternate transition state structure has been proposed. It is characterized by (1) sp^2 geometry and partial positive charge at C_α of the olefin, (2) extensive C_β-O bond formation but with retention of some π bonding between C_α and C_β, (3) a nearly equal amount of partial negative charge on the peracid carboxylate, and (4) little change in the bonding of the peracid proton.

The epoxidation of olefins by peracids is a familiar and synthetically useful reaction. As summarized in recent reviews,[1] numerous mechanistic studies of this reaction have centered around two proposed mechanisms. The first of these was proposed by Bartlett[2] and involves the symmetrical transfer of an oxygen atom to the olefin from the internally hydrogen bonded peracid monomer (**1**). Kwart and Hoffman[3] later proposed a 1,3-dipolar addition mechanism involving a 1,2-dioxolane intermediate (**2**). Recent arguments based on Hammett correlations and solvent effect studies[4] support the former mechanism more readily than the latter.



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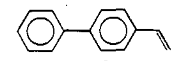
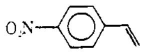
Peracid epoxidation has also been proposed[5,6] as a possible "model" reaction for certain enzymatic epoxidations, probably because both reactions are stereospecific and appear to involve an attack on the olefin by an electrophilic reagent. In our attempts to elucidate the nature of the attacking species in the enzymatic epoxidation, we sought to extend, and if possible to quantitate, the similarity of enzymatic, peracid, and other types of epoxidations by means of Hammett correlations and kinetic deuterium isotope effects. While there have been several Hammett[7-9] studies of peracid epoxidation, this reaction had not been previously studied by kinetic isotope effect methods. We therefore undertook such a study and have found that neither of the two mechanisms mentioned above can adequately accommodate our results. Rather, our data suggest that the transition state for peracid epoxidation has an open chain structure with a large degree of charge separation as shown in Figure 1.

Experimental Section

***p*-Phenylstyrene (3) and *p*-Phenylstyrene-α-*d* (4).** 4-Acetylbiphenyl (Aldrich) was purified by column chromatography and reduced with $LiAlH_4$ (or $LiAlD_4$) in ether to give 4-(1-hydroxyethyl)biphenyl in 88% yield: mp 95-96° (lit.[10] 97°). Dehydration of this alcohol by heating for several hours in DMSO with small amounts of $KHSO_4$ and hydroquinone at 190° under nitrogen, followed by dilution with water, extraction with hexane, and chromatography of the hexane extract on active silica gel, gave an 82%

Table I. Rates and Isotope Effects for Epoxidation of Styrenes with *m*-Chloroperbenzoic Acid[a]

Substrate (m*M*)	Peracid (m*M*)	Runs	Temp, °C	$10^3k'$, min^{-1}	k_H/k_D
					
h_3 (5.34)[b]	H (42.7)	5	0	2.51 ± 0.04	
α-*d*	H	5		2.54 ± 0.02	0.99
β,β-d_2	H	5		3.07 ± 0.08	0.82
α,β,β-d_3	H	2		3.114, 3.043	0.82
h_3 (5.35)[b]	90% D (44.8)	3	0	2.06 ± 0.04[d]	1.15[e]
h_3	H	3		2.35 ± 0.01[d]	
					
h_3 (8.12)[c]	H (81)	3	25	1.15 ± 0.02	
α-*d*	H	3		1.18 ± 0.01	0.98

[a] All reactions were run in 1,2-dichloroethane which had been distilled from P_2O_5. Observed rates are expressed as the slope of a plot of ln $[\text{olefin}]_0/[\text{olefin}]_t$ vs. *t*, with $k' = k_2[\text{peracid}]$. [b] Also contained 6.56 m*M* biphenyl as internal standard for GLC. [c] Also contained 5.94 m*M* diphenylmethane as internal standard for GLC. [d] These rates seem low but are reproducible. This is attributed to constant but trace amounts of H_2O or D_2O remaining after drying the exchanged solutions with Na_2SO_4 (see Experimental Section). [e] Extrapolates to 1.17 for fully deuterated peracid.

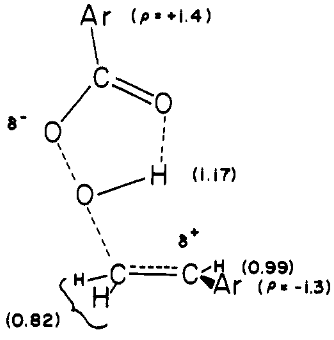


Figure 1. Transition-state structure for epoxidation of arylethylenes with substituted perbenzoic acids. Numbers in parentheses refer to observed isotope effects (k_H/k_D) or to Hammett parameters.

yield of the olefin: mp 119° (lit.[10] 119°); NMR (CCl_4) δ 5.2 (dd, *J* = 10, 2 Hz, 1 H; broad s in **4**), 5.7 (dd, *J* = 17, 2 Hz, 1 H; broad s in **4**), 6.7 (dd, *J* = 17, 10 Hz, 1 H; absent in **4**), 7.4 (m, 9 H); ir (CCl_4) 3070-3020, 2230 (**4** only), 1640 (1620 in **4**), 1610, 1495, 990 (weak in **4**), 905, 840, 695 cm^{-1}.

***p*-Phenylstyrene-β,β-d_2 (5) and *p*-Phenylstyrene-α,β,β-d_3 (6).** 4-Acetylbiphenyl was exchanged three successive times by refluxing 1 g of the ketone in 30 ml of glyme containing 2 ml of D_2O and 100 mg of $NaOCH_3$ for 2 days under nitrogen. NMR showed complete exchange of the $COCH_3$ group. This material was reduced with $LiAlH_4$ or $LiAlD_4$ and dehydrated in hot DMSO as described above to yield the desired styrenes: mp 118.5°; NMR (CCl_4) δ 6.7 (broad s, 1 H; absent in **6**), 7.4 (m, 9 H); ir (CCl_4) 3070-3020, 2330, 2260 (**6** only), 2220, 1610, 1495, 960 (**5** only), 935 (only), 905, 840, and 690 cm^{-1}.

***m*-Chloroperbenzoic Acid-*O-d*.** Aldrich *m*-chloroperbenzoic acid, found by iodometric titration to be 75% peracid, was used without further purification. For the kinetic runs with deuterated peracid, a solution of 1.28 g of peracid in 50 ml of 1,2-dichloroethane was divided into two equal portions. Each was shaken with either 2 ml of H_2O or D_2O for 10 min, centrifuged, decanted, dried with anhydrous Na_2SO_4, and diluted to 50.0 ml with dichloroethane. After two such exchanges, aliquots of the protio and deuterio peracids were titrated and found to be 55.6 and 56.0 m*M*, respectively. NMR integration indicated 90 atom % D in the deuterio peracid.

***p*-Nitrostyrene (7) and *p*-Nitrostyrene-α-*d* (8).** *p*-Nitroacetophenone was reduced with either $LiAlH_4$ or $LiAlD_4$ in ether at room temperature for 30 min to give the nitro alcohol in 85-90% yield. The alcohols were dehydrated by heating with an equal weight of polyphosphoric acid in a sublimation apparatus maintained at 90-120° and 10-30 Torr.[11] *p*-Nitrostyrene was collected on the cold finger and purified by chromatography on silica gel in 35% yield based on starting alcohol: mp 21-21.5° (lit.[12] 29°); NMR (CCl_4) δ 5.4 (d, 1 H, *J* = 11 Hz; broad s in **8**), 5.9 (d, 1 H, *J* = 18 Hz; t in **8**, *J* = 3 Hz), 6.8 (dd, 1 H, *J* = 18, 11 Hz; absent in **8**), 7.5 (d, 2 H, *J* = 9 Hz), 8.1 (d, 2 H, *J* = 9 Hz); ir (CCl_4) 3080 (w), 1605, 1520, 1345, 1100, 985 (absent in **8**), 920, 855, 755, 695 cm^{-1}.

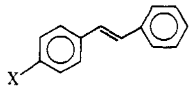
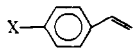
Kinetic Runs. Reactions were run in 25 × 125 mm screw-cap culture tubes which had been modified by fusing a small glass test tube (13 × 30 mm) half-way up the inside wall of the large tube. In the main chamber of this vessel were placed the peracid and internal standard (see Table I) in 9.0 ml of 1,2-dichloroethane, and 1.0 ml of a dichloroethane solution of the olefin was placed in the small inner reservoir. The charged reaction vessels were then capped and immersed in a constant temperature bath for 2 hr. Reactions were started by removing a tube, inverting and shaking it, and returning it to the bath. Thirty seconds later, and at 20-min intervals thereafter, 1.0-ml aliquots were removed and quenched with 0.1 ml of 2*M* $Na_2S_2O_3$ followed by 0.05 ml of 2 *M* Na_2CO_3; double the amount of quenchers were used for the nitrostyrene reactions. After shaking and centrifuging, the dichloroethane layer was analyzed for olefin by GLC on 3% SE30 at 120° with electronic integration of the olefin and internal standard peaks. Initial rates were obtained by a least-squares fit of 6-9 data points per run, representing the consumption of ≤35% of the olefin.

Results and Discussion

By the measurement of secondary kinetic deuterium isotope effects, one can derive information about the hybridization changes occurring at an isotopically substituted carbon atom as a set of reactants pass from their ground states to the transition state complex.[13] These effects are related to the change in vibrational energy of C-H vs. C-D out-of-plane bending modes. Because the potential energy curve for a H-C (sp^2) bond is a relatively shallow parabola the zero-point energies of the C-H and C-D reactants are relatively close. However, the potential curve for a H-C (sp^3) bond is a relatively steeper parabola so that the zero-point energy of a C-D bond is substantially less than that of a C-H bond. Therefore the energy of activation for an $sp^2 \rightarrow sp^3$ change in hybridization is *lower* for the deuterated material, and the kinetic isotope effect is *inverse* ($k_D > k_H$).

In the case of olefin epoxidation, two sp^2 carbons become more sp^3-like in the oxirane product. However, the isotope effect data in Table I show a clear distinction between the α and β carbons of the olefin in the transition state; only the β carbon has undergone a change in its hybridization from sp^2 toward sp^3 ($k_H/k_D = 0.82$), while the α carbon remains essentially sp^2 ($k_H/k_D \simeq 1$). This implies that in the transition state there is substantial C_β-O bond formation but negligible C_α-O bond formation. The small primary peracid isotope effect indicates that the peracid hydrogen remains hydrogen bonded, or at least is not being transferred in the transition state. This is consistent with (1) the failure of added acids to catalyze the reaction[7] and (2) the inhibi-

Table II. Substituent Effects in Peracid Epoxidation of Olefins

Peracid	Olefin	Correlation with	ρ	Ref
p-X-$C_6H_4CO_3H$	*trans*-Stilbene	σ	+1.39	*a*
$C_6H_5CO_3H$		$\sigma + 0.63\Delta\sigma^+$	−1.09	*a*
$C_6H_5CO_3H$		$\sigma + 0.48\Delta\sigma^+$	−1.30	9
$C_6H_5CO_3H$	p-X-$C_6H_4C{\equiv}CH$	σ^+	−1.40	8

[a] Calculated from data of ref 7.

tory effects of basic solvents which disrupt the internally hydrogen-bonded structure of the peracid monomer.[4] In contrast, for an "in flight" proton such as in the Bartlett mechanism, a primary isotope effect of ~2 could have been expected.[13] Since our results cannot be accommodated by either the Bartlett mechanism or the Kwart and Hoffman mechanism, they necessitate the consideration of an alternative transition state structure for peracid epoxidation. Figure 1 shows a transition state structure which would be consistent with our isotope effect data, as well as all previously reported characterizations of peracid epoxidation, including kinetic studies, stereospecificity, Hammett correlations, and solvent effect studies.[1,4]

Several solvent effect studies of peracid epoxidation indicate that the greatest reaction rates are obtained in solvents of high polarity and low basicity.[1,4] In this respect chloroform, dichloromethane, and 1,2-dichloroethane are exceptionally good solvents. Table II summarizes the results of several Hammett studies of peracid epoxidation reactions. For the olefinic substrates the negative value of ρ, together with the importance of σ^+ contributions to the correlations, indicates the accumulation of a partial positive charge on the olefin-derived portion of the transition state. The positive sign and nearly equal magnitude of the ρ value for the peracids indicate the accumulation of a comparable amount of partial negative charge on the peracid-derived portion of the transition state. The observed dependence of the reaction rate on solvent polarity also supports the postulated separation of charge in the transition state.

Since only *one* C–O bond of the oxirane product is formed in the transition state, the observed stereospecificity of peracid epoxidations must be attributed to the rate of ring closure being considerably faster than rotation about the C–C bond axis. This in turn can be attributed either to retention of a small amount of π bond character in the transition state (i.e., C_β not fully sp^3), or to a weak interaction of the oxygen lone pairs with the partially positive p orbital on the α carbon. If the latter mechanism were operative, destabilization of the positive charge at C_α would "tighten up" the C_α–O interaction in the transition state to approach **1**. This in turn would lead to changes in the hybridization at C_α and give rise to a measurable inverse isotope effect. Such an effect has been observed by Wilkins and Regulski[11] for the bromination of α-deuterio-para-substituted styrenes. Since p-nitrostyrene did not give rise to an observable α-carbon isotope effect for epoxidation, we conclude that in the transition state some fractional π bonding is retained between C_α and C_β. Only a small fraction of a π bond is required to explain the observed stereospecificity.

Finally, the question may be raised, how much does the choice of an unsymmetrically substituted olefin have to do with the inequality of the secondary isotope effects? The relative rates[7] of epoxidation of stilbene, 4-methoxystilbene, and 4,4′-dimethoxystilbene (83:20:4.3) indicate that each methoxy group causes the same increase in rate (ca. fourfold). This would be expected statistically since peracid attack at either olefinic carbon (in stilbene or dimethoxystilbene) could give rise to a structure like that of Figure 1, and suggests that all three stilbenes are epoxidized via the same mechanism, regardless of their substitution pattern. The substitution of ethylene with alkyl groups is well known to increase the rate of attack of electrophiles at the double bond. For example, 2-methyl-2-butene is epoxidized by peracetic acid ten times faster[14] than *cis*-2-butene, despite greater steric hindrance, because the tertiary center in the former is better able to support carbonium ion character. Since p-nitrostyrene is epoxidized by m-chloroperbenzoic acid 13× *slower* than p-phenylstyrene, and still no secondary isotope effect is seen upon deuteration at $C\alpha$, we conclude that the mechanism of Figure 1 is not simply a consequence of the choice of an unsymmetrically substituted olefin.

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References and Notes

(1) (a) D. I. Metelitsa, *Russ. Chem. Rev.* (*Engl. Transl.*), 41, 807 (1972); (b) J. B. Lee and B. C. Uff, *Q. Rev., Chem. Soc.*, 21, 431 (1967); (c) D. Swern in "Organic Peroxides", Vol. II, D. Swern, Ed., Wiley-Interscience, New York, N.Y., 1971, pp 355–533.

(2) P. C. Bartlett, *Rec. Chem. Prog.*, **18**, 111 (1957).

(3) H. Kwart and D. M. Hoffman, *J. Org. Chem.*, **31**, 419 (1966).

(4) H. Kropf and M. R. Yazdanbachsch, *Tetrahedron*, **30**, 3455 (1974).

(5) V. Ullrich and H. Staudinger, *Handb. Exp. Pharmacol.*, **28**, 251 (1972).

(6) D. M. Jerina and J. W. Daly in "Oxidases and Related Redox Systems", Vol. 1, T. E. King, H. Mason, and M. Morrison, Ed., University Park Press, Baltimore, Md., 1973, p 143.

(7) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).

(8) Y. Ogata, Y. Sawaki, and H. Inoue, *J. Org. Chem.*, **38**, 1044 (1973).

(9) Y. Ishii and Y. Inamoto, *Kogyo Kagaku Zasshi*, **63**, 765 (1960).

(10) W. F. Huber et al., *J. Am. Chem. Soc.*, **68**, 1109 (1946).

(11) C. L. Wilkins and T. W. Regulski, *J. Am. Chem. Soc.*, **94**, 6016 (1972).

(12) W. Saunders and R. Williams, *J. Am. Chem. Soc.*, **79**, 3712 (1957).

(13) C. J. Collins and N. S. Bowman, "Isotope Effects in Chemical Reactions", Van Nostrand-Reinhold, New York, N.Y., 1970.

(14) D. Swern, *J. Am. Chem. Soc.*, **69**, 1692 (1947).