°C, cooled to 0 °C, and quenched with water (0.17 mL), 15% NaOH (0.17 mL), and water (0.51 mL). The aluminum salts were removed by filtration and rinsed with ether (2 × 20 mL). The combined filtrate afforded the crude product which was redissolved in benzene (10 mL) and washed 3 times with 1 M HCl. The benzene layer residue was dissolved in a minimum quantity of CH_2Cl_2 and ether was added to afford a precipitate of 11 (402 mg, 60% yield), spectroscopically and chromatographically identical with an independently prepared sample:[25] mp 108–110 °C (lit. mp 110–111 °C,[14] 125 °C[25]); ^{1}H NMR ($CDCl_3$) δ 2.70 (4 H, m), 3.98 (2 H, m), 4.17 (2 H, d), 4.75 (2 H, d), 7.27 (10 H, s);[25] ^{13}C NMR ($CDCl_3$) δ 159.5, 137.4, 128.8, 128.3, 127.7, 61.4, 46.5, 37.5.

The aluminum salts were further extracted 3 times with CH_2Cl_2 to afford the starting material (140 mg, 19% recovery) which could be recrystallized from hot chloroform and recycled.

(3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]-imidazole (12). The combined HCl phase was basified with NaOH and extracted 3 times with CH_2Cl_2. The organic phase was dried and evaporated to afford overreduced product 12 (90 mg, 14% yield): mp 48–50 °C; mass spectrum, m/e (relative intensity) 310.1512 (12, M^+; calcd m/e 310.1506), 309 (47), 219 (4), 91 (100); ^{1}H NMR ($CDCl_3$) δ 2.55 (4 H, m), 3.02 (1 H, d, J = 5 Hz), 3.42 (2 H, m), 3.64 (4 H, s), 3.94 (1 H, d, J = 5 Hz), 7.25 (10 H, s); ^{13}C NMR ($CDCl_3$) δ 37.69 (t), 58.00 (t), 72.03 (d), 77.91 (t), 127.23 (d), 128.22 (d), 129.04 (d), 138.11 (s).

(3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]-imidazole 5,5-Dioxide (13). Reduction of 4 in CH_2Cl_2 with Dibah (460 mol %) in toluene for 14 h, followed by quenching with HCl, afforded crude product which was purified by chromatography on silica gel eluted with CH_2Cl_2–EtOAc (95:5) to afford the product as a white solid (35 mg, 62% yield): mp 107–111 °C; IR (KBr) 3000 cm^{-1}; mass spectrum, m/e (relative intensity) 342.1398 (4, M^+; calcd m/e 342.1404), 341 (16), 251 (13), 146 (23), 91 (100); ^{1}H NMR ($CDCl_3$) δ 2.81 (4 H, m), 3.19 (1 H, d, J = 5 Hz), 3.45 (2 H, m), 3.64 (4 H, AB quartet), 3.99 (1 H, d, J = 5 Hz), 7.26 (10 H, s); ^{13}C NMR ($CDCl_3$) δ 55.36 (t), 57.46 (t), 62.27 (d), 76.54 (t), 127.76 (d), 128.55 (d), 128.89 (d), 137.29 (s).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research, to the National Institutes of Health for support of this research under Biomedical Research Support Grant 5 S07 RR07067, and to the National Science Foundation for Grant CHE 8114412 which enabled the purchase of the Nicolet NMR spectrometer.

Ozonolysis of Styrene and *p*-Nitrostyrene. Secondary Deuterium Isotope Effects

Hyung-Soo Choi and Robert L. Kuczkowski*

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

Received August 8, 1984

It is widely accepted that the initial attack of ozone at a sterically unhindered alkene proceeds via a concerted 1,3-dipolar cycloaddition.[1] The recent observation of an inverse kinetic secondary isotope effect (KSIE, $k_H/k_D \approx 0.88$) for the reaction between O_3 and $CH_3CD{=}CH_2$ or $CH_3C{=}CHD$ lent support to this picture and indicated that both carbon atoms at the double bond are significantly perturbed in the transition state.[2]

Table I. Kinetic Secondary Isotope Effect for the Addition of Ozone to Styrene and *p*-Nitrostyrene in CCl_4 at 25 °C

mixture	runs	k_H/k_D[a]
styrene-d_0/styrene-α-d_1	7	0.93 ± 0.02
styrene-d_0/styrene-β-d_2	7	0.93 ± 0.02
p-nitrostyrene-d_0/*p*-nitrostyrene-α-d_1	4	0.91 ± 0.04
p-nitrostyrene-d_0/*p*-nitrostyrene-β-d_2	4	0.94 ± 0.01

[a] Per deuterium basis.

There have been several previous deuterium KSIE studies of addition reactions to styrene resulting in normal, inverse, or negligible isotope effects at C_α and C_β depending on the reaction system (polymerization,[3] (2 + 2) cycloaddition,[4] epoxidation,[5] acid-catalyzed hydration,[6] electrophilic addition of halogens,[7] addition of methyl radical,[8] or oxidation by chromyl chloride[9]). A particularly curious result was the inverse isotope effect observed at C_β and the normal effect at C_α for the concerted (2 + 2) cycloaddition between styrene and diphenylketene.[4] Oxidation reactions of styrene derivatives with *m*-chloroperbenzoic acid,[5a] chromyl chloride,[9] and cytochrome P-450 rat liver microsomes[5b] also show different KSIE at C_α and C_β. In the first two systems there is a 9–12% inverse KSIE at C_β and a negligible effect at C_α. In the third system, there is a 7% inverse effect at C_α and negligible effect at C_β. Since styrene derivatives have proven to be a sensitive probe of the transition state in cycloaddition and oxidation reactions, we decided to investigate the addition of ozone to deuterated styrene. We were interested to learn if different KSIE would be seen at C_α and C_β as in other styrene cyclizations or if the same inverse KSIE would be found as in the ozonolysis of propene.[2]

The reaction of ozone with styrene and other phenyl-substituted alkenes has already been the subject of considerable investigation.[10] For example, kinetic measurements on ring-substituted styrenes have shown that the ozone attack is electrophilic in nature.[10a,b] Styrene and *p*-nitrostyrene were chosen for this KSIE investigation. The substituted styrene was selected in order to make a direct comparison with the *m*-chloroperbenzoic acid epoxidation study[5a] where it also was a substrate.

Results and Discussion

Ozonolysis was carried out in CCl_4 using a 1:1 mixture of $PhCH{=}CH_2/PhCD{=}CH_2$ or $PhCH{=}CH_2/PhCH{=}CD_2$ to evaluate the corresponding secondary deuterium isotope effects. Analogous mixtures of *p*-nitrostyrenes were also ozonized. These competition reaction were run to 30% completion. The reaction mixture was then analyzed by 360-MHz ^{1}H NMR spectroscopy, which provides a well-resolved spectrum for quantitative analysis of each species remaining in the solution. The resultant values for k_H/k_D

---

(1) See the following for reviews on this subject: (a) Bailey, P. S. "Ozonation in Organic Chemistry"; Academic Press: New York, 1978; Vol 1. (b) Kuczkowski, R. L. "1,3-Dipolar Cycloaddition of Ozone and Carbonyl Oxides"; Padwa, A. W., Ed.; Wiley: New York, 1984.

(2) Choe, J.-I.; Srinivasan, M.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 4703.

(3) (a) Pryor, W. A.; Henderson, R. W.; Patsiga, R. A.; Carroll, N. *J. Am. Chem. Soc.* **1966**, *88*, 1199. (b) Henderson, R. W.; Pryor, W. A. *Int. J. Chem. Kinet.* **1972**, *4*, 325.

(4) (a) Baldwin, J. E.; Kapecki, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4874. (b) Collins, C. J.; Benjamin, B. M.; Kabalka, G. W. *J. Am. Chem. Soc.* **1978**, *100*, 2570.

(5) (a) Hanzlik, R. P.; Shearer, G. O. *J. Am. Chem. Soc.* **1975**, *97*, 5231. (b) Hanzlik, R. P.; Shearer, G. O. *Biochem. Pharmacol.* **1978**, *27*, 1441.

(6) Schubert, W. M.; Lamm, B. *J. Am. Chem. Soc.* **1966**, *88*, 120.

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

(8) Field, M.; Stefani, A. P.; Szwarc, M. *J. Am. Chem. Soc.* **1972**, *84*, 4451.

(9) Freeman, F.; Yamachika, N. J. *J. Am. Chem. Soc.* **1972**, *94*, 1214.

(10) (a) Whitworth, A. J.; Ayoub, R.; Rousseau, Y.; Fliszâr, S. *J. Am. Chem. Soc.* **1969**, *91*, 7128. (b) Klutsch, G.; Fliszâr, S. *Can. J. Chem.* **1972**, *50*, 2841. (c) Fliszâr, S.; Carles, J. *J. Am. Soc.* **1969**, *91*, 2637. (d) Fliszâr, S.; Granger, M. *J. Am. Chem. Soc.* **1969**, *91*, 3330. (e) Bailey, P. S.; Lane, A. G. *J. Am. Chem. Soc.* **1967**, *89*, 4473. (f) Bailey, P. S.; Ward, J. W.; Hornish, R. E.; Potts IV, F. E. *Adv. Chem. Ser.* **1972**, *112*, 1. (g) Criegee, R.; Korber, H. *Adv. Chem. Ser.* **1972**, *112*, 22.

0022-3263/85/1950-0901$01.50/0

are summarized in Table I.

The results for styrene and *p*-nitrostyrene show that a similar inverse KSIE occurs at either carbon atom. The data are not precise enough to distinguish a substituent effect on the isotope effect arising from the NO_2 moiety although the reactivity toward ozone decreases by a factor of about 4–6[10a,b] in *p*-nitrostyrene.

The KSIE for the styrenes (Table I) can be compared to the values (per deuterium at 25 °C) obtained for ozone addition in solution to C_2D_4 (0.94 ± 0.02),[11] $CH_3CD{=}CH_2$ (0.88 ± 0.05),[2] $CH_3CH{=}CHD$ (0.88 ± 0.07),[2] and stilbene-d_2 (0.93).[12] It is apparent that for these systems the cycloaddition of ozone to the double bond significantly affects the carbon atoms in the transition state. This is consistent with other evidence that the addition of ozone is stereospecific and concerted[1] and that an inverse KSIE is usually associated with a transition state involving transformation of an sp^2 carbon to sp^3 hybridization.[13]

As a follow up study, the epoxidation of styrene by *m*-chloroperbenzoic acid was also investigated. The purpose was to compare our method, which employed an NMR assay of competition reactions between d_0 and d_x species, against the epoxidation results of Hanzlik and Shearer[5a] who measured the absolute reaction rates of d_0 and d_x *p*-phenylstyrene and *p*-nitrostyrene. Reactions of $PhCH{=}CH_2/PhCD{=}CH_2$ with the acid were followed by NMR spectroscopy. The results of six runs gave k_H/k_D = 0.99 ± 0.04, which is consistent with the α-d_1 results of Hanzlik and Shearer (0.98–0.99). Furthermore, we confirmed the expected high stereospecificity (>99%) for the epoxidation process by control experiments using either *cis*- or *trans*-styrene-β-d_1.[14] The stereospecificity of the peracid epoxidation reaction and the paradoxical absence of a KSIE at C_α have been discussed elsewhere.[5a]

Experimental Section

^1H NMR spectra were obtained with a Brüker WM-360 spectrometer. A Welsbach Model T-408 ozonator was employed.

Materials. Styrene (Aldrich) was freshly purified by column chromatography (silica gel, 40–140 mesh) before ozonolysis. Deuterated styrenes were prepared from acetophenone (Aldrich) by modified literature procedures.[5a,15]

Styrene-α-d_1. Acetophenone (3 g in 5 mL of ether) was added dropwise to $LiAlD_4$ (0.5 g in 10 mL of ether) at a rate producing gentle boiling. After 1 h of refluxing, water was added followed by 12 mL of 10% HCl. The ether layer was separated and distilled. The secondary phenethyl alcohol was dehydrated[5a] by heating with hydroquinone (10% of the alcohol by mass) and a small amount of $KHSO_4$ in 10 mL of Me_2SO at 190 °C for 4 h. Water was added to the Me_2SO solution before extracting the styrene with hexane. This was followed by chromatography of the hexane extract on silica gel. The styrene was 100% deuterated at C_α on the basis of the absence of H_α in the ^1H NMR. NMR ($CDCl_3$) δ 5.23 (d, 1 H), 5.73 (dt, 1 H), 7.33 (m, 5 H).

Styrene-β,β-d_2. Acetophenone (3 g) was refluxed with D_2O (4 mL) and a small amount of Bu_4NBr and $NaOCH_3$ (1 g) in benzene (10 mL) for 6 h. This procedure was repeated 3 times. The deuterated acetophenone was obtained by distillation under reduced pressure (at 73 °C, 6 mm). It was reduced with $LiAlH_4$, and the product was dehydrated. The styrene was >97% deuterated at C_β on the basis of ^1H NMR. NMR ($CDCl_3$) δ 6.69 (s, 1 H), 7.32 (m, 5 H).

***p*-Nitrobenzaldehyde-α-d_1.** *p*-Nitrobenzyl-α,α-d_2 alcohol was prepared by the reaction of methyl *p*-nitrobenzoate with lithium aluminum deuteride. It was treated with pyridinium chlorochromate[16] in dry CH_2Cl_2, and the product mixture was washed with ether several times. The ether solution was filtered through Florisil and distilled.

***p*-Nitrostyrene-α-d_1.** *n*-Butyllithium (1.55 M in hexane), 0.01 mol, was added to 0.01 mol of methyltriphenylphosphonium bromide in THF continuously over a 5-min period under an inert atmosphere. After stirring for 30 min at room temperature, 0.011 mol of *p*-nitrobenzaldehyde-α-d_1 in THF was added dropwise. After 4 h a saturated NaCl solution was added. This solution was extracted with ether. The ether and THF solutions were combined and reduced in volume. The product was obtained by chromatography through a silica gel column using an ethyl-acetate–hexane (3:97) mixture. The ^1H NMR spectrum showed >99.9% deuteration at C_α. ^1H NMR ($CDCl_3$) δ 5.50 (1 H), 5.92 (1 H), 7.52–7.54 (2 H), 8.17–8.20 (2 H).

***p*-Nitrostyrene-β,β-d_2.** The procedure for the α-d_1 derivative was employed. Unlabeled benzaldehyde was used and (methyl-d_3)-triphenylphosphonium bromide (Aldrich) was substituted for the Wittig reagent. p-$NO_2C_6H_4CH{=}CHD$ was produced in minor amounts (8.8%). ^1H NMR (in $CDCl_3$) δ 6.78 (s, 1 H), 7.54 (d, 2 H), 8.19 (d, 2 H).

Ozonolysis and Kinetic Procedure. The 1:1 mixtures of the d_0 and d_x styrenes were prepared by weighing followed by dilution to 0.1 M with CCl_4. The solutions were ozonized at room temperature to 30% on the basis of ozone uptake. Reaction aliquots were added to $CDCl_3$ and analyzed by ^1H NMR. The non-phenyl proton resonances in the starting materials and ozonides[10d,g] are well resolved and the amounts of the four species needed to calculate the KSIE from eq 1 were obtained by integration. The

$$k_H/k_D = \left(\ln \frac{[\text{styrene-}d_0]}{[\text{styrene-}d_0]_0} \Bigg/ \ln \frac{[\text{styrene-}d_n]}{[\text{styrene-}d_n]_0} \right)^{1/n} \qquad (1)$$

results in Table I were obtained by assuming that the styrene was converted quantitatively to the ozonide. Actual ozonide yields were estimated to be 70–80% but calculations showed that correction for this affects k_H/k_D less than 0.2% and could be neglected.

This procedure might lead to errors arising from secondary isotope effects in side reactions or in the conversion to the final ozonide adversely affecting the deuterium content in the products. This was cross-checked for styrene by determining the amounts of styrene before reaction from weight and NMR and after reaction on the basis of O_3 uptake and the NMR of the unreacted styrene. The results of seven runs were identical with those in Table I.

Epoxidation of Styrene. A 1:1 mixture of styrene and styrene-α-d_1 (1 mmol of each in 1 mL of CCl_4) was added to 0.6 mmol of *m*-chloroperoxybenzoic acid in 9 mL of CCl_4. After 40 min the reaction was complete and benzoic acid was separated at −20 °C. The ^1H NMR spectra were obtained in $CDCl_3$ and k_H/k_D was estimated with eq 1. When stereolabeled *cis*-styrene-β-d_1 or *trans*-styrene-β-d_1 was epoxidized with excess *m*-chloroperoxybenzoic acid, the NMR of the epoxide indicated less than 1% loss of stereochemistry.

Acknowledgment. The work was supported by Grant CHE-8303615 from the National Science Foundation. We are grateful to Dr. Helmut Keul for advice on numerous procedural and synthetic matters as well as providing the stereolabeled styrene materials. Dr. Yoshihito Watanabe and Prof. J. Groves provided helpful suggestions on the synthesis of the deuterated *p*-nitrostyrene species.

Registry No. Styrene, 100-42-5; *p*-nitrostyrene, 100-13-0; styrene-α-*d*, 1193-80-2; styrene-β,β-d_2, 934-80-5; *p*-nitrobenzaldehyde-α-*d*, 94781-50-7; *p*-nitrostyrene-α-*d*, 57204-41-8; *p*-nitrostyrene-β,β-d_2, 94781-51-8; acetophenone, 98-86-2; *p*-nitrobenzyl-α,α-d_2 alcohol, 73908-63-1; methyl *p*-nitrobenzoate, 619-50-1; methyltriphenylphosphonium bromide, 1779-49-3; benzaldehyde, 100-52-7; (methyl-d_3)triphenylphosphonium bromide, 1787-44-6; p-$NO_2C_6H_4CH{=}CHD$, 94781-52-9; D_2, 7782-39-0.

---

(11) Fong, G. D.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 4763.

(12) Denney, D. B.; Tunkel, N. *Chem. Ind.* (*London*) **1959**, 1383.

(13) See the following for a summary of pertinent references: Choe, J.-I.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 4839.

(14) *cis*-Styrene-β-d_1 and *trans*-styrene-β-d_1 were obtained from Dr. Helmut Keul, University of Michigan, Ann Arbor, MI.

(15) Fanghänel, E. "Organikum"; VEB Deutscher Verlag der Wissenshaften: Berlin, 1967; p 481.

(16) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647.