Lewis, and A. Weissberger, Ed., Interscience, New York, N.Y., 1961, pp 343–388.
(13) (a) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 619; (b) see also L. S Levitt and H. F. Widing in "Progress in Physical Organic Chemistry", Vol. 12, R. W. Taft, Ed., Wiley, New York, N.Y., 1976, p 119.
(14) (a) See R. Fellows and R. Luft, *J. Am. Chem. Soc.*, **95**, 5593 (1973), and references cited therein; (b) see also S. H. Unger and C. Hansch in ref 13b, p 91; (c) C. K. Hancock, E. A. Meyers, and B. J. Yager, *J. Am. Chem. Soc.*, **83**, 4211 (1961).
(15) S. W. Benson in "Thermochemical Kinetics", Wiley, New York, N.Y., 1968, pp 25, 179.
(16) E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 3817 (1973).
(17) C. R. Johnson and G. A. Duka, *J. Am. Chem. Soc.*, **95**, 7777 (1973).
(18) H. Dürr, *Chem. Ber.*, **103**, 369 (1970).
(19) R. B. Reinarz and G. T. Fonken, *Tetrahedron Lett.*, 441 (1974).
(20) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).
(21) W. J. Ball and S. R. Landor, *J. Chem. Soc.*, 2298 (1962).
(22) H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).
(23) R. E. Kent and S. M. McElvain, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 490.

Synthesis of Epoxides with Electronegative Substituents. Photometric Substrates for Epoxide Hydrase

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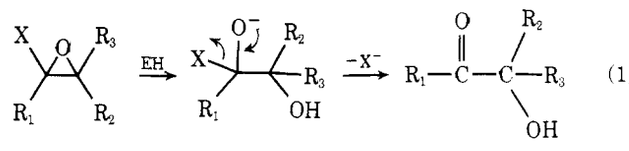
The synthesis of styrene oxides bearing potential leaving groups as α substituents was attempted via peracid epoxidation of the corresponding olefins. Such epoxides were sought as potential photometric substrates for epoxide hydrase. Peracid epoxidations of α-chloro-, α-trimethylsilyloxy-, α-ethoxy-, or α-bromostyrene, as well as α-bromo- or α-(*tert*-butyl)dimethylsilyloxy-*p*-nitrostyrene, lead only to oxidized rearranged products; their epoxides could not be detected among the reaction products. Peracid epoxidation of α-acetoxystyrene and α-methoxy-*p*-nitrostyrene did lead to mixtures containing the desired epoxides, as judged by their NMR spectra, but attempts to isolate these epoxides were unsuccessful due to their great reactivity in the presence of acids or protic solvents. However, using similar methods we were able to synthesize, purify, and characterize the epoxides of α-acetoxy-, α-trifluoroethoxy-, and α-fluoro-*p*-nitrostyrene (**4d, 4h,** and **4i,** respectively). The half-lives of these oxides (0.25 mM) in 0.1 M phosphate buffer (pH 8.00) were 35, 0.4, and 0.4 min, respectively, and each was cleanly hydrated to α-hydroxy-*p*-nitroacetophenone. The hydration of **4d** (which could be monitored conveniently at 310 nm) was accelerated 11-fold by solubilized liver microsomal epoxide hydrase; this compound was not significantly affected by microsomal esterases. The effects of α substituents on the reactivity of styrene oxides and the mechanisms of their rearrangements are discussed. A mechanism involving a halonium ion–enol π complex is proposed to account for the fact that chloro- and bromooxiranes readily undergo proton-catalyzed halogen migrations, whereas fluorooxirane **4i** was much less reactive and reacted only with loss of fluoride ion.

The recognition of epoxides as cytotoxic, carcinogenic, and mutagenic metabolites of arenes and olefins has over the past few years stimulated considerable interest in both the enzymatic and nonenzymatic reactivity of this class of compounds.[1-3] The enzyme epoxide hydrase is thought to play a protective role in vivo by converting chemically reactive epoxides to relatively nontoxic diols. The relatively broad substrate specificity of epoxide hydrase has led to the development of numerous chromatographic and radiometric assays for this enzyme.[4] Unfortunately these assays do not lend themselves readily to mechanistic studies of the enzyme, because they are rather tedious and often tend to be less precise than one would like. A photometric assay for epoxide hydrase which could provide continuous data rather than data points would be greatly preferred. Since the oxirane ring itself is not a chromophore which can be observed spectrally in the presence of protein, it thus becomes necessary to consider substrates whose enzymatic hydration can be chemically coupled to the unmasking of a suitable chromophore. In contemplating this problem we came upon the idea that a styrene oxide with a suitable leaving group at the α position should, upon enzymatic hydration, generate an aromatic ketone chromophore as shown below (eq 1). Our reasoning was based on the fact that 1,1-disubstituted epoxides are relatively good substrates for epoxide hydrase[5] and that their enzymatic hydration involves exclusive ($\geq$97%) cleavage of the O–CH_2 bond by a nucleophilic mechanism.[6]

Epoxides bearing good leaving groups directly on the oxirane ring are known to be very unstable and highly prone to rearrangement or hydrolysis.[7] Thus it was apparent from the outset that synthesis of epoxides suitable for enzymatic use according to eq 1 would require a delicate compromise between the electronic (and possibly steric) properties of the aryl group R_1 and the leaving group X. In this paper we report the synthesis and characterization of three such epoxides, one of which is suitable for photometric assay of epoxide hydrase. We also report the attempted syntheses of several related epoxides and discuss the effects of the substituents on the relative reactivity of epoxides of this type.



(1)

Results and Discussion

In designing a photometric substrate for a particular enzyme a number of factors must be taken into consideration. For example, the enzyme catalyzed reaction must generate, at a wavelength not subject to interference by other chromophores in the system, a large enough difference in absorption to give the desired sensitivity. If chromophore generation is to depend on the occurrence of nonenzymatic steps subsequent to the initial enzymatic event, then the former must be considerably faster than the latter. In addition, the substrate should be chemically stable under the assay conditions, so that nonenzymatic background rates are negligible. Finally, the compound should be a good substrate, conforming to the

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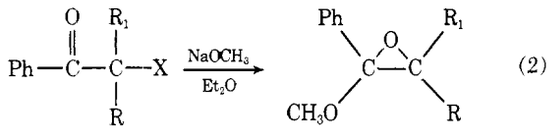
general pattern of structure–activity relationships established for the enzyme.

For the specific case of microsomal epoxide hydrase (EH) we reasoned that if a suitable leaving group X were substituted on the oxirane ring the diol formed by hydration would undergo spontaneous and rapid loss of HX (eq 1) to generate a carbonyl group, which, depending on R_1, might have absorption characteristics suitable for a sensitive photometric assay. A number of tri- or tetrasubstituted chloro- and methoxy oxiranes have been synthesized by various groups,[7-10] but unfortunately epoxide hydrase is extremely selective for mono-, 1,1-di-, or *cis*-1,2-disubstituted epoxides. Since styrene oxide is an efficiently hydrated prototype substrate used in numerous chromatographic and radiometric assays[4] for EH, α-monosubstituted styrene oxides appeared to a logical choice for development as photometric substrates.

In contrast to the numerous syntheses of highly substituted chloro- and methoxyoxiranes, simple styrene oxides bearing an electronegative substituent at the α position are virtually unknown. Our attempts to prepare α-methoxystyrene oxide by analogy (eq 2c) to Stevens' synthesis of α-methoxy-β-substituted styrene oxides (eq 2a,b) were uniformly unsuccessful. Apparently for this reaction to succeed it is important that the halide be on a secondary or tertiary carbon center. This effect has also been noticed[11] in analogous additions of cyanide ion to α-chloroacetaldehyde, -butyraldehyde, and -isobutyraldehyde, in which the yields of epoxynitrile product were 0%, 46%, and 100%, respectively.

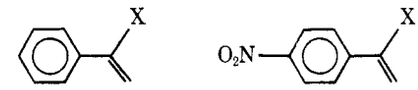


(2)

Eq	X	R, R_1	% yield
2a	Br	$-(CH_2)_5-$	83
2b	Cl, Br	CH_3, H	66
2c	Br	H, H	0

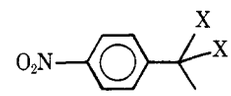
Another potential route to the desired α-substituted styrene oxides involved the peracid epoxidation of the corresponding olefins. Thus we synthesized styrenes **1a–e** using standard procedures and attempted their epoxidation under a variety of conditions at room temperature and below. The reagents and conditions employed included CH_3CO_3H–NaOAc–CH_2Cl_2, various peroxyimidic acids, and *m*-chloroperbenzoic acid (MCPBA), the latter being employed both with and without buffers (solid K_2CO_3 or K_2HPO_4) in pentane, CH_2Cl_2, or ether. In only one instance did NMR examination of reaction mixtures or their extracts suggest the presence of an oxirane methylene group, although in all cases the starting materials were rapidly consumed. In general, the NMR spectra of the product mixtures were consistent with the *formation and rearrangement* of the desired epoxide. Similar results have been reported previously for the peracid epoxidations of 1-chlorocyclohexene.[12] In our hands, various attempts at peracid epoxidation of freshly purified **1e** lead to the isolation of 50–70% yields of α-bromoacetophenone. In the case of **1b**, significant amounts of acetophenone, as well as numerous rearranged oxidized products, were obtained upon workup. This was true even when the epoxidations were carried out under rigorously dry conditions. However, in the NMR spectrum of the product mixture from MCPBA epoxidation of α-acetoxystyrene (**1d**) appeared an encouraging sign, a pair of sharp doublets (J = 5 Hz) at δ = 2.92 and 3.23. While this suggested the presence of the desired epoxide in the reaction mixture, attempts to isolate it were unsuccessful.

Since carbonium ion stability usually plays an important role in governing the reactivity of epoxides, particularly epoxides in which a benzylic center is present, we carried out an analogous series of epoxidation attempts on the α-substituted *p*-nitrostyrenes **2c–i**. For the most part the required styrenes were obtained by modification of the syntheses used for olefins **1a–e**. The enol ethers **2c, 2g,** and **2h,** for example, were obtained by the elimination of alcohol from the corresponding ketal of *p*-nitroacetophenone, **3**. Thus styrene **2c** was easily formed by heating diethyl ketal **3c** in toluene containing pTsOH as catalyst for 30 h. However, these conditions were not sufficient to eliminate CH_3OH or CF_3CH_2OH from the corresponding ketals **3g** or **3h**. In fact, heating **3g** with *p*-TsOH in toluene, even under rigorously dry conditions, consistently led to the formation of *p*-nitroacetophenone. The same was true for the bis(trifluoroethyl) ketal **3h**. The mechanism of this reaction is not known, but the formation of ketones from ketals under nonhydrolytic conditions has

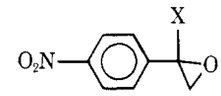


1a-e

2c-i



3c,g,h



4d,h,i

a, X = Cl
b, X = $OSiMe_3$
c, X = OEt
d, X = OAc
e, X = Br
f, X = $OSi(tBu)Me_2$
g, X = OCH_3
h, X = OCH_2CF_3
i, X = F

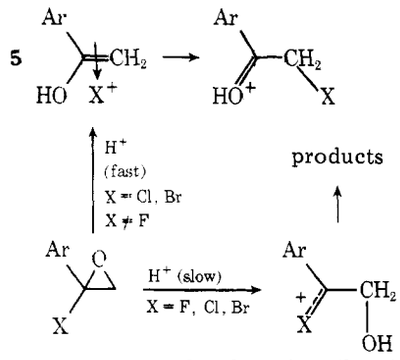
been reported previously.[13] Ultimately these eliminations were effected with $POCl_3$ in refluxing pyridine.[13] Under these conditions dimethyl ketal **3g** reacted smoothly and completely in 6 h, but the bis(trifluoroethyl) ketal **3h** proved exceptionally unreactive and did not react completely even after 1 week. This pattern of reactivity has also been observed, although over a more compressed range, in the acid catalyzed hydrolysis of formaldehyde acetals,[14] and it clearly foretold the properties of the epoxides which eventually were derived from styrenes **2c, 2g,** and **2h.**

As with the α-substituted styrenes **1a–e,** epoxidations of the nitrostyrenes **2c–i** were attempted under a variety of conditions. In general the nitro compounds reacted considerably more slowly, and the reactions were considerably cleaner. For example, epoxidation of **2e** with MCPBA in CH_2Cl_2 over solid K_2CO_3 at 0 °C for 10 min gave an almost quantitative yield of α-bromo-*p*-nitroacetophenone, and epoxidation of **2f** apparently gave only a single product (as judged by the NMR spectrum), the silyl derivative of α-hydroxy-*p*-nitroacetophenone. On the other hand, epoxidation of **2c** led to the formation of α-ethoxy-*p*-nitroacetophenone, along with other unidentified products. In none of these cases did NMR examination of product mixtures suggest the presence of the desired epoxides.

Epoxidation of the methoxystyrene **2g** with MCPBA in CH_2Cl_2 over solid K_2CO_3 not only gave α-methoxy-*p*-nitroacetophenone, but some of the desired epoxide **4h** was also present in the mixture, as judged by a pair of sharp doublets (δ 2.91 and δ 3.43, J = 4.0 Hz) characteristic of oxirane methylene groups. Unfortunately, this epoxide was too reactive to isolate; even on standing in $CDCl_3$ solution in an NMR tube it rearranged completely in 24 h.

Epoxidation of the trifluoroethyl enol ether **2h** using MCPBA in CH_2Cl_2 over solid K_2CO_3 or K_2HPO_4 also gave a mixture of products, but the NMR spectrum suggested that the desired epoxide **4h** comprised ca. 75% of the mixture. The

Scheme I



rest of the mixture appeared to be primarily trifluoroethyl *p*-nitrobenzoate.[15] Attempts to recrystallize **4h** from protic solvents (e.g., MeOH) led to its complete and rapid decomposition; although it could be recrystallized from CCl_4 or chromatographed on silica gel, little purification was achieved in this way. Ultimately **4h** was purified by repeated recrystallization from pentane. Similar results were obtained with the epoxidation of enol acetate **2d.** This olefin was considerably less reactive than the others, and it underwent epoxidation smoothly with *unbuffered* MCPBA in *refluxing* CH_2Cl_2. The resulting epoxyacetate **4d** proved to be an exceptionally stable epoxide and could be recrystallized and chromatographed even more casually than **4h.** No rearrangement products were observed during the epoxidation of **2d** or the subsequent manipulations of **4d;** the only routes of decomposition observed appeared to be hydrolytic, as discussed below.

The final olefin epoxidized in these studies was *p*-nitro-α-fluorostyrene, **2i.** The synthesis of this olefin proved quite straightforward. *p*-Nitrostyrene was fluorobrominated using *N*-bromosuccinimide and polymerized HF in pyridine.[16] Dehydrobromination of the latter using potassium *tert*-butoxide in refluxing *tert*-butyl alcohol afforded **2i** in 80% yield based on *p*-nitrostyrene. Whereas both the epoxidation of bromostyrene **2e** (MCPBA, CH_2Cl_2, 0 °C) and the subsequent rearrangement of the epoxide were complete in less than 10 min, epoxidation of **2i** required 16 h of refluxing in CH_2Cl_2 with an excess of MCPBA. Again, the epoxide was exceptionally stable compared to many of the others discussed above, and it was obtained in good yield despite the fact that no basic buffers were used in the epoxidation. In fact, in our first attempts to epoxidize **2i,** we found that the use of MCPBA–K_2CO_3 in CH_2Cl_2 led mainly to *polymerization* of the olefin. As with epoxyacetate **4h,** but in sharp contrast to the α-chloro or α-bromo epoxides, fluoro epoxide **4i** showed no tendency to rearrange, appearing instead to decompose by solvolytic or hydrolytic mechanisms to compounds devoid of fluorine.

Of the three α-substituted styrene oxides which could be isolated (**4d, 4h,** and **4i**), none proved exceptionally stable in *aqueous* solutions. Their reactions could be conveniently followed at 310 nm. All three epoxides reacted in water to give the same product, as judged by their identical UV spectra. From the reaction of **4i,** the sole reaction product was isolated and shown by IR, UV, and NMR to be α-hydroxy-*p*-nitroacetophenone. In fact, the latter is also somewhat unstable in aqueous solution, decomposing over a period of hours to bright yellow products which were not identified. At a concentration of 0.25 mM in 0.1 M phosphate buffer at pH 8.00, the fluoro epoxide **4i** had a half-life of approximately 0.4 min; the trifluoroethoxy epoxide **4h** was approximately as reactive under the same conditions. In contrast, epoxyacetate **4d** was almost two orders of magnitude *less* reactive, undergoing hydration with a half-life of approximately 35 min.

Although a half-life of 35 min is somewhat less than we had hoped for, this order of reactivity nevertheless gives quite workable nonenzymatic background rates, and using epoxide **4d** with solubilized preparations of epoxide hydrase we have obtained enzymatic hydration rates greater than 11 times the nonenzymatic rate.[17] We have also obtained evidence that microsomal esterases do not affect epoxyacetate **4d,** although enol acetate **2d** is an excellent substrate for these enzymes. The details of these experiments and the development of a photometric assay of epoxide hydrase based on **4d** as the substrate will be reported elsewhere.

From our successes and failures in the attempted syntheses of α-substituted styrene oxides, it is clear that the reactivity of the latter is governed by the effects of the para and α substituents on the stability of the benzylic carbonium ions formed by acid catalyzed opening of the oxirane ring; i.e., H > NO_2, and R_3SiO > EtO > MeO > CF_3CH_2O > AcO. With respect to the halooxiranes, it is interesting that the fluoro compound gave no fluorine-containing rearrangement products, whereas α-haloacetophenones were formed in high yield during the epoxidations of **1a, 1e,** and **2e.** A mechanism which may account for this divergent behavior is given in Scheme I. The essential feature of this mechanism is the intermediacy of the halonium ion π complex, **5.** Its formation provides an obvious role for acid catalysis in these migrations, which has not been accounted for previously.[7] Scheme I *may* also provide an explanation for the paradoxical *decrease*[7] in reactivity of chlorooxiranes as methyl substituents are placed on the ring carbons. The stability of olefin π complexes is a delicate function of electronic, steric, and solvent effects.[18,19] While sufficient data to unravel these effects are not yet available, it may be noted that although increasing the methyl substitution in a series of olefins increases their rates of bromination[20] it *decreases* their affinity for Ag(I)[21] and their rates of hydroxymercuration in solution.[22] The lack of fluorine migration in reaction of **4i** could be a consequence of the extreme electronegativity of F and its reluctance to form fluoronium ions.[23] A related π-complex mechanism may be involved in the NIH shift of a chlorine atom during the hydroxylation of *p*-chlorophenylalanine by phenylalanine hydroxylase to form 3-chlorotyrosine.[2]

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a Varian T-60 instrument using Me_4Si as an internal standard.

α-Chlorostyrene (1a). This compound was prepared in 38% yield by the method of Dufraisse and Viel.[24] NMR ($CDCl_3$) δ 5.44 (d, 1 H, J = 1.5), 5.66 (d, 1 H, J = 1.5), 7.15–7.73 (m, 5 H).

α-Bromostyrene (1e). This compound was prepared in 47% yield by dehydrobromination of styrene dibromide with KOH in refluxing ethanol, followed by chromatography on silica gel with ligroin as eluent: NMR ($CDCl_3$) δ 5.65 (d, 1 H, J = 1.5 Hz), 5.98 (d, 1 H, J = 1.5 Hz), 6.90–7.62 (m, 5 H).

p-Nitro-α-bromostyrene (2e). *p*-Nitrostyrene[25] was dissolved in CCl_4 and treated with an equimolar quantity of bromine for 16 h at room temperature to give a 74% yield of *p*-nitrostyrene dibromide (mp 74–75 °C): NMR ($CDCl_3$) δ 3.99 (d, 1 H), 4.13 (s, 1 H), 5.23 (dd, 1 H), 7.64 (d, 2 H), 8.28 (d, 2 H).

This dibromide (2.7 g, 8.75 mmol) was dissolved in *t*-BuOH containing 1.47 g (13.1 mmol) of *t*-BuOK and the solution was refluxed for 15 h. The mixture was then poured into four volumes of water and extracted with CH_2Cl_2. Evaporation of the extract and recrystallization from hexane gave yellow crystals (1.0 g, 50% yield) which decomposed upon storage for several days at room temperature: NMR ($CDCl_3$) δ 5.95 (d, 1 H, J = 2.0), 6.30 (d, 1 H, J = 2.0), 7.70 (d, 2 H), 8.15 (d, 2 H).

α-Trimethylsilyloxystyrene (1b). The compound was prepared using the method of House,[26] except that the reaction was carried out at room temperature for 4 days. This compound was quantitatively hydrolyzed upon column chromatography (alumina or silica) but could be obtained in ≥95% purity by distillation through a Vigreux column (bp 99–100 °C at 5 Torr): NMR ($CDCl_3$) δ −0.12 (s, 9 H), 4.05 (d, 1 H, J = 1.0 Hz), 4.52 (d, 1 H, J = 1.0 Hz), 6.63–7.80 (m, 5 H).

p-Nitro-α-(*tert*-butyldimethylsilyloxy)styrene (2f). The method of House was used.[26] The workup procedure yielded an orange oil which was purified in ca. 65% yield by column chromatography through silica gel, eluting with 90:10 ligroin–ether, yielding a yellow oil: NMR ($CDCl_3$) δ 0.23 (s, 6 H), 1.02 (s, 9 H), 4.58 (d, 1 H, J = 2.0 Hz), 4.86 (d, 1 H, J = 2 Hz), 7.68 (d, 2 H), 8.13 (d, 2 H).

α-Ethoxystyrene (1c). Acetophenone (10.0 mL, 10.3 g, 85.7 mmol) and triethylorthoformate (20.0 mL, 17.8 g, 120.1 mmol) were dissolved in 25 mL of EtOH, and 1 drop of concentrated HCl was added. The mixture was stirred for 1 day at room temperature. The mixture was poured into water and extracted with ether. The solvent was evaporated to give a yellow oil which was filtered through a column of silica gel using 95:5 ligroin–ether: NMR ($CDCl_3$) δ 1.35 (t, 3 H), 4.32 (q, 2 H), 7.42 (m, 3 H), 8.02 (m, 2 H).

Ketals of p-Nitroacetophenone. Ten grams of p-nitroacetophenone and 25.0 mL of the desired trialkylorthoformate were dissolved in 20 mL of the corresponding alcohol and heated to reflux. The alcohol and trialkylorthoformate were then evaporated, and the remaining mixture was taken up in ether and washed with water.

p-Nitroacetophenone diethyl ketal (3c) was obtained with a 6-h reflux. The crude product was used without further purification: NMR ($CDCl_3$) δ 1.25 (t, 6 H), 1.5 (s, 3 H), 3.63 (dq, 4 H), 7.69 (d, 2 H), 8.18 (d, 2 H).

p-Nitroacetophenone dimethyl ketal (3g) was obtained with a 2-h reflux and used without further purification: yield, 79%; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 3.19 (s, 6 H), 7.68 (d, 2 H), 8.18 (d, 2 H).

p-Nitroacetophenone bis(trifluoroethyl)ketal (3h) was obtained with a 24-h reflux and used without further purification: yield, 61%; mp 50–51 °C; NMR ($CDCl_3$) δ 1.79 (s, 3 H), 3.91 (dq, 4 H), 7.79 (d, 2 H), 8.32 (d, 2 H).

Tris(trifluoroethyl)orthoformate. This orthoformate was prepared by the method of Hill[27] from trifluoroethanol, ferric chloride, and chloroform: yield, 17%; bp 132–133 °C; NMR (CCl_4) δ 4.03 (m, 6 H), 5.57 (s, 1 H).

p-Nitro-α-ethoxystyrene (2c). Crude ketal **3c** was heated to a gentle reflux in toluene with 500 mg of p-toluenesulfonic acid for 30 h. The mixture was cooled and stirred over solid $NaHCO_3$, and the toluene was evaporated to give yellow crystals which were recrystallized from ligroin and then from CH_3OH: yield, 47% (from p-nitroacetophenone); mp 49–51 °C; NMR ($CDCl_3$) δ 1.62 (t, 3 H), 3.95 (q, 2 H), 4.38 (d, 1 H, J = 3.0), 4.78 (d, 1 H, J = 3.0), 7.75 (d, 2 H), 8.15 (d, 2 H).

p-Nitro-α-methoxystyrene (2g). The enol ether was prepared by the method of Rappaport[13] from dimethyl ketal **3g**, $POCl_3$, and pyridine by heating for 6 h at 100 °C. The compound was purified by recrystallization once from methanol and once from ligroin: yield, 95%; NMR ($CDCl_3$) δ 3.78 (s, 3 H), 4.42 (d, 1 H, J = 3.5), 4.83 (d, 1 H, J = 3.5), 7.73 (d, 2 H), 8.13 (d, 2 H).

p-Nitro-α-trifluoroethoxystyrene (2h). The enol ether was made by a modification of the procedure of Rappaport.[13] The ketal **3h** (1.5 g, 4.3 mmol) and $POCl_3$ (3.2 mL, 5.3 g, 34.6 mmol) were heated to reflux in 30 mL of pyridine and 10 mL of toluene for 7–10 days. The reaction was stopped by adding 10% aqueous NaOH *dropwise* at 0 °C until the solution was neutralized and then extracting with two portions of $CHCl_3$. The solvent was dried and evaporated to yield brown crystals which were filtered through a column of silica gel using 80:20 ether–ligroin as an eluent. Finally, the compound was recrystallized from ligroin: yield, 0.79 g (31%); mp 83–84 °C; NMR ($CDCl_3$) δ 4.33 (q, 2 H), 4.51 (d, 1 H, J = 4.0), 5.05 (d, 1 H, J = 4.0), 7.83 (d, 2 H), 8.27 (d, 2 H). Anal. Calcd for $C_{10}H_8F_3NO_3$: C, 48.53; H, 3.26; N, 5.67. Found: C, 48.85; H, 3.16; N, 5.47.

p-Nitro-α-fluoro-β-bromoethylbenzene. This compound was prepared by the method of Olah[16] from p-nitrostyrene, N-bromosuccinimide, and pyridine·$(HF)_x$ in ether. The reaction was stirred in a polyethylene bottle overnight at room temperature: yield, 85%; mp 73–74 °C; NMR ($CDCl_3$) δ 3.70 (dd, 2 H, J_{HF} = 20), 5.80 (dt, 1 H, J_{HF} = 57.5), 7.62 (d, 2 H), 8.27 (d, 2 H).

α-Fluoro-p-nitrostyrene (2i). The α-fluoro-β-bromo compound (7.5 g., 30.2 mmol) and 4.1 g (36.2 mmol) of potassium *tert*-butoxide were dissolved in 150 mL of *t*-BuOH and stirred at room temperature for 30 min. The mixture was poured into water, the crystals were filtered, and the mixture was then recrystallized first from 80:20 MeOH–H_2O and then from ligroin: yield, 4.6 g (94%); mp 62–63 °C; NMR ($CDCl_3$) δ 4.90 (dd, 1 H, J_{HF} = 7), 5.44 (dd, 1 H, J_{HF} = 30.0), 7.68 (d, 2 H), 8.23 (d, 2 H). Anal. Calcd for $C_8H_6FNO_2$: C, 57.49; H, 3.62; N, 8.38. Found: C, 57.20; H, 3.62; N, 8.23.

p-Nitro-α-acetoxystyrene (2d). The compound was made by the method of Pollack and Noyce.[28] Purification was achieved by first reducing the unreacted p-nitroacetophenone to the corresponding alcohol using sodium cyanoborohydride in 95% EtOH, keeping the pH between 3 and 4 with an AcOH/NaOAc buffer. The mixture was then poured into water and extracted with ether. After solvent evaporation, the crystals were recrystallized once from ethanol and once from ligroin, giving pure **2d:** yield, 20%; mp 51–52 °C (lit.[28] 52–53 °C); NMR ($CDCl_3$) δ 2.32 (s, 3 H), 5.17 (d, 1 H, J = 2.0), 5.52 (d, 1 H, J = 2.0), 7.55 (d, 2 H), 8.12 (d, 2 H).

Epoxidation Methods. m-Chloroperbenzoic acid was dissolved in ether and extracted with pH 8.0 phosphate buffer before use.

Method A. The styrene derivative and a 1.5 molar excess of MCPBA were dissolved in CH_2Cl_2 and stirred at either 0 °C (enol ethers), room temperature (α-halo- and α-acetoxystyrenes), or at reflux (α-fluoro- and α-acetoxy-p-nitrostyrenes). The reaction was stopped by washing once with 10% aqueous $Na_2S_2O_3$ and then with aqueous $NaHCO_3$.

Method B. The styrene derivative and a 1.5 molar excess of MCPBA were dissolved in CH_2Cl_2 at 0 °C and then an excess of solid K_2CO_3 or K_2HPO_4 was added to the mixture. The mixture was stirred at room temperature for ca. 48 h. Periodic additions of small amounts of MCPBA were needed to drive the reaction to completion. After each addition, the mixture was chocked with moist pH paper to make sure it was not acidic. The reaction was stopped by washing once with 10% aqueous $Na_2S_2O_3$.

p-Nitro-α-trifluoroethoxystyrene oxide (4h) was made using method B. The compound was purified by three recrystallizations from pentane and gave satisfactory mass spectral analysis: yield of purified material, 10%; mp 50–51 °C; NMR ($CDCl_3$) δ 2.90 (d, 1 H, J = 4); 3.50 (d, 1 H, J = 4), 3.93 (q, 2 H, J = 9), 7.68 (d, 2 H), 8.28 (d, 2 H). Anal. Calcd for $C_{10}H_8F_3NO_4$: C, 45.62; H, 3.04; N, 5.32. Found: C, 45.69; H, 3.18; N, 5.00.

p-Nitro-α-fluorostyrene oxide (4i) was made using method A. Purification was achieved by recrystallization from ligroin: yield, 73%; mp 62–63 °C; NMR ($CDCl_3$) δ 3.03 (d, 1 H, J = 4.0), 3.55 (dd, 1 H, J_{HF} = 5.0), 7.63 (d, 2 H), 9.27 (d, 2 H). Anal. Calcd for $C_8H_6FNO_3$: C, 52.47; H, 3.30; N, 7.65. Found: C, 52.60; H, 3.25; N, 7.59.

p-Nitro-α-Acetoxystyrene oxide (4d) was synthesized by method A. Purification was achieved by recrystallization from CCl_4 and then from EtOH: mp 100–101 °C; yield, 58%; NMR ($CDCl_3$) δ 2.16 (s, 3 H), 3.01 (d, 1 H, J = 4.5), 3.40 (d, 1 H, J = 4.5), 7.58 (d, 2 H), 8.21 (d, 2 H). Anal. Calcd for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.40; H, 3.90; N, 6.03.

Formation and Rearrangement of α-Methoxy-p-nitrostyrene Oxide (4g). The epoxidation was carried out using method B and solid K_2CO_3 buffer. After workup, the NMR spectrum ($CDCl_3$) contained peaks corresponding to unreacted starting material, as well as the following peaks which were attributed to either α-methoxy-p-nitrostyrene oxide or α-methoxy-p-nitroacetophenone: δ 2.91 (d, J = 4 Hz, epoxide methylene), 3.35 (s, epoxide α-methoxyl), 3.43 (d, J = 4 Hz, epoxide methylene), 3.74 (s, acetophenone α-methoxyl), 5.61 (s, acetophenone methylene), 7.17–8.45 (m, aromatic protons).

The $CDCl_3$ solution was allowed to stand for 24 h in the NMR tube and the spectrum was retaken. It was identical with the above spectrum except that the peaks at δ 2.91, 3.35, and 3.43 had disappeared.

Hydrolysis of 4i. A solution of 200 mg of the epoxide in 15 mL of THF and 30 mL of H_2O was stirred for 10 min at room temperature. The reaction was extracted with two portions of CH_2Cl_2. The solvent was evaporated and the crystals were recrystallized once from CCl_4: mp 120–125 °C; NMR (CD_3COCD_3) δ 5.01 (s, 2 H); 8.35 (q, 4 H); IR ($CHCl_3$) 3505 m (OH), 1710 s(C=O); UV (H_2O) λ_{max} 267 nm (ε 9100).

The solid from the above reaction was subjected to the same conditions except that the time was extended to 8 h. The resulting solid was bright yellow and showed several new spots on TLC.

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Registry No.—**1a,** 618-34-8; **1b,** 13735-81-4; **1c,** 6230-62-2; **1d,** 2206-94-2; **1e,** 98-91-7; **2c,** 59938-04-4; **2d,** 22391-01-1; **2e,** 64600-19-7; **2f,** 64600-20-0; **2g,** 3440-23-1; **2h,** 64600-21-1; **2i,** 64600-22-2; **3c,** 64600-23-3; **3g,** 53577-98-3; **3h,** 64600-24-4; **4d,** 64600-25-5; **4g,** 64600-26-6; **4h,** 64600-27-7; **4i,** 64600-28-8; α-hydroxy-p-nitroacetophenone, 64611-67-2; styrene dibromide, 6607-46-1; p-nitrostyrene, 100-13-0; p-nitrostyrene dibromide, 64600-29-9; acetophenone, 98-86-2; triethylorthoformate, 122-51-0; p-nitroacetophenone, 100-19-6; trimethyl orthoformate, 149-73-5; tris(trifluoroethyl)orthoformate, 58244-27-2; p-nitro-α-fluoro-β-bromoethylbenzene, 64600-30-2; α-methoxy-p-nitroacetophenone, 7714-12-7.

References and Notes

(1) J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, **28**, 1129 (1972).
(2) D. M. Jerina and J. W. Daly, *Science*, **185**, 573 (1974).
(3) T. C. Bruice and P. Y. Bruice, *Acc. Chem. Res.*, **9**, 378 (1976).
(4) (a) F. Oesch, D. M. Jerina, and J. Daly, *Biochim. Biophys. Acta*, **227**, 685 (1971); (b) G. Belvedere et al., *J. Chromatogr.*, **118**, 387 (1976); (c) V. S. Ganu, S. O. Nelson, L. Verlander, and W. L Alworth, *Anal. Biochem.*, **78**, 451 (1977); (d) D. M. Jerina, P. M. Dansette, A. Y. H. Lu, and W. Levin, *Mol. Pharmacol.*, **13**, 342 (1977).
(5) F. Oesch, N. Kaubisch, D. M. Jerina, and J. W. Daly, *Biochemistry* **10**, 4858 (1971).
(6) R. P. Hanzlik, M. Edelman, W. J. Michaely, and G. Scott, *J. Am. Chem. Soc.*, **98**, 1952 (1976).
(7) R. N. McDonald in "Mechanisms of Molecular Rearrangements", B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1971, pp 67–107.
(8) C. L. Stevens, W. Malik, and R. Pratt, *J. Am. Chem. Soc.*, **72**, 4758 (1950).
(9) T. I. Tennikova and E. N. Kropacheva, *Zh. Obshch. Khim.*, **19**, 1917 (1949); *Chem. Abstr.*, **44**, 1929 (1950).
(10) C. Stevens and E. Farkas. *J. Am. Chem. Soc.*, **74**, 618 (1952).
(11) J. Cantacuzene and D. Ricard, *Tetrahedron Lett.*, 2237 (1966).
(12) M. Mousserson and R. Jacquier, *Bull. Soc. Chim. Fr.*, 698 (1950).
(13) H. Rappaport, C. H. Lovell, H. R. Reist, and M. E. Warren, Jr., *J. Am. Chem. Soc.*, **89**, 1942 (1967).
(14) P. Saloman in "The Chemistry of the Carbonyl Group", S. Patai, Ed., Interscience, New York, N.Y., 1966, pp 177–207.
(15) B. Belleau and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 2816 (1952).
(16) G. A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 780 (1973).
(17) The epoxide hydrase preparations used in these experiments were prepared from both rat and chicken liver microsomes by detergent solubilization (Cutscum) and $(NH_4)_2SO_4$ fractionation as described by P. Bentley and F. Oesch, *FEBS Lett.*, **59**, 291 (1975).
(18) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, pp 87–90.
(19) R. D. Bach, A. T. Weibel, J. Patane, and L. Kevan, *J. Am. Chem. Soc.*, **98**, 6237 (1976).
(20) J. E. Dubois and G. Mouvier, *Bull. Soc. Chim. Fr.*, 1426 (1968).
(21) M. A. Muhs and F. T. Weiss, *J. Am. Chem. Soc.*, **84**, 4697 (1962).
(22) H. C. Brown and P. J. Geohegan, Jr., *J. Org. Chem.*, **37**, 1937 (1972).
(23) R. D. Chambers, "Fluorine in Organic Chemistry", Wiley, New York, N.Y., 1973, pp 54–55.
(24) C. Dufraisse and J. E. Viel, *Bull. Chem. Soc. Fr.*, **37**, 877 (1925).
(25) R. Broos and M. Anteunis, *Synth. Commun.*, **6**, 53 (1976).
(26) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(27) M. E. Hill, D. T. Carty, D. Tegg, J. C. Butler, and A. F. Stang, *J. Org. Chem.*, **30**, 411 (1965).
(28) D. S. Noyce and R. M. Pollack, *J. Am. Chem. Soc.*, **91**, 119 (1969).

π-Complexed β-Arylalkyl Derivatives. 5. Polar Effects in the Formolysis of π-Complexed 9-Benzonorbornenyl and 9-Benzonorbornadienyl Methanesulfonates[1]

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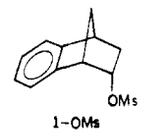
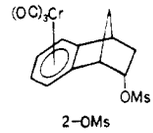
In a search for possible neighboring-group (direct d-orbital) participation by the metal, the formolysis rates of *anti*-9-benzonorbornenyl and *anti*-9-benzonorbornadienyl methanesulfonates (**6**- and **11**-OMs) have been compared with those of the π-complexed derivatives *endo*-tricarbonylchromium (**7**- and **12**-OMs), *exo*-tricarbonylchromium (**8**- and **13**-OMs) and, in the case of **6**-OMs only, the *endo*- and *exo*-trimethyl phosphite dicarbonylchromium derivatives (**9**- and **10**-OMs). At 60 °C the relative reactivities of **6**–**13**-OMs are 1.0, 0.005, 0.02, ~1.6, ~3.4, ~70, 0.06, and 0.07. All appear to yield unrearranged esters as the exclusive primary formolysis product, although formolysis of the complexes is accompanied by extensive oxidative decomplexation which prevents the determination of accurate titrimetric rate constants. It is suggested that the observed rate effects reflect differing ion-dipole interactions in the transition state of the rate-limiting step, rather than direct d-orbital participation by chromium.

In earlier papers in this series[2] we have reported several chromium tricarbonyl complexed β-arylalkyl methanesulfonates which solvolyze with partial or complete π-(aryl)-chromium tricarbonyl migration at rates that exceed those of their noncomplexed counterparts. To rationalize these and other observations, we suggested the possibility of direct d-orbital participation and/or σ–π homoconjugation. Each of these reaction paths, illustrated diagrammatically for the acetolysis of 2-[π-(phenyl)chromium tricarbonyl]-2-methyl-1-propyl methanesulfonate in Scheme I, suggests that the metal moiety should stabilize intermediates in which a positive charge is concentrated in the vicinity of the metal and requires that it precede the migrating aryl in a geometric sense during the rearrangement. We have shown that these conditions are fulfilled by demonstrating that at 75 °C the acetolysis of *exo*-2-[*endo*-π-(benzonorbornenyl)chromium tricarbonyl] methanesulfonate (**4**-OMs) is about 300 times as rapid as that of the exo-complexed methanesulfonate, **5**-OMs, that a portion of the former internally returns to the latter during acetolysis, and that both complexes yield the thermodynamically less stable endo-complexed *exo*-acetate, **4**-OAc, as the major product; cf. Scheme II.[3] We were able to demonstrate conclusively that tricarbonylchromium inductively retards acetolysis in cases where the aryl ring itself cannot participate anchimerically by comparing the acetolysis rate of *endo*-2-[*exo*-π-(norbornenyl)chromium tricarbonyl] methanesulfonate (**2**-OMs) with that of its noncomplexed analogue, **1**-OMs.[3] We were unable, however, to distinguish between direct metal bridging and σ–π homoconjugation as the mode of the metal-complex participation since either interpretation (Scheme I) appeared compatible with our data. In an effort to make such a distinction we have prepared and examined the solvolysis rates and products of a series of exo-π-complexed, *anti*-9-benzonorbornenyl and -norbornadienyl methanesulfonates designed to maximize the possibility of direct metal interaction.



1-OMs



2-OMs

Results

Preparation of Starting Materials. The π-complexed, 9-substituted benzonorbornenyl and -norbornadienyl derivatives were prepared from the known[4] noncomplexed alcohols

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