Olefin Epoxidation with α -Substituted Hydroperoxides

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Abstract: A number of α -substituted hydroperoxides were examined for their ability to epoxidize olefins in a stereospecific manner. Hydroperoxy ethers, amines, carbonyl compounds, and nitriles showed this capability. Intramolecular epoxidation was demonstrated in cases where ortho esters of some olefinic alcohols were treated with H₂O₂, and methyl orthooleate-H₂O₂ mixtures also epoxidized the internal olefin in an intramolecular reaction. Attempts to generate chiral hydroperoxides for asymmetric epoxidation are described and structural features required for epoxidation reagents are discussed.

During our study¹ of the action of dehydrating agents on H_2O_2 we found that ortho esters act on H_2O_2 to produce intermediates capable of olefin epoxidation² (eq 1). Here we report further



details on our experiences with these and related systems. Our direction in these studies has been toward the definition of structural features required for oxgyen atom transfer reagents rather than synthetic applications. Consequently, only the more promising reagents have been examined in preparative reactions.

The likely intermediates involved in the epoxidation of eq 1 are the α -hydroperoxy ethers 1. A few members of this class of substances had been isolated and characterized: Rieche³ obtained the crystalline 2 and Milas⁴ distilled the THP derivative of H₂O₂, 3. Epoxidations with 2 or 3 proved that 1 was a viable intermediate; moreover, Kim⁵ had shown that the related 4 would also epoxidize olefins. Thus the nature of the epoxidant in eq 1 seems secure.

Intramolecular Epoxidation

The α -hydroperoxy ethers present unusual opportunities for the study of intramolecular epoxidation. For such epoxidation to occur with peroxy acids, a large number of connecting atoms between the peroxy function and the olefin are required; the first bond from the acyl carbon is directed *away* from the terminal oxygen and entropy renders an arrangement such as 5 unlikely if the connecting atoms are free to rotate. Indeed, the first clear case of intramolecular epoxidation, peroxyarachidonic acid (6), recently reported by Corey⁶ involves a 16.5-membered transition state. Its remarkable success can be attributed, in part, to the restricted rotation provided by the three additional π -bonds. The corresponding situation with α -hydroperoxy ethers is considerably more favorable: the direction of the first bond away from the peroxy carbon (7a or 7b) permits the geometry required for intramolecular

Scheme I



epoxidation to be achieved with fewer connective atoms. Just how few was tested as follows.



The ortho esters 8-10 derived from allyl, homoallyl, and bishomoallyl alcohols were prepared by standard exchange reactions from the ethyl ortho esters while the ketal 11 was prepared similarly from 2,2-dimethoxypropane. A competition experiment was designed as the test for intramolecular epoxidation using the more

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Preparative epoxidations with this reagent have also been recently described:

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Table I

$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$						+ 14
	[8- 11]	[15].	epoxide ratios $(13 + 14)/12$			
expt	M	M	from 8	from 9	from 10	from 11
1	1	5	0.39	1.5	8.8	2.5
2	0.5	2.5	0.35	2.8	16	3.8
3	0.33	1.67	0.33	4.2	27	6.9
4	0.25	0.28	0.28	10	33	9.9
			(allylic, n = 1	(homo- allylic, n = 2)	(bishomo- allylic, n = 3)	(homoallylic ketal, $n = 2$)
	$k_{ m intra}/k_{ m styr}$		<1	$\sim 7 \text{ M}$	~40 M	~11 M

reactive (disubstituted vs. monosubstituted) olefin β -methylstyrene (15). As shown in the generalized Scheme I, the intermediate X, generated from the action of H_2O_2 on 8-10 in the presence of 15, has a number of olefin sites with which to react. Bimolecular reaction with 15 gives the styrene oxide 12, and at low conversions the principal sources of 13 involve k_2 and k_{intra} . The relative importance of inter- and intramolecular reactions of X was examined by determining the effect of dilution on the ratio (13 +(14)/(12)

Each of the ortho esters 8-10 and the ketal 11 were placed in competition with 15 at four different dilutions in THF at ambient temperature. The initial molar ratios [8-11]/[15] were kept constant at 1/5 and low conversions (10%) were ensured by monitoring the epoxide formed by GLC. Ortho esters remaining at the end of the reaction were decomposed by the addition of H_2O and the epoxide products were determined by GLC against internal standards. In practice, the esters 14 represented only a small fraction of the epoxides obtained, yet all products were shown to be stable to the reaction and workup conditions. The results of these competition experiments are summarized in Table I.

The results show that for the allylic case (n = 1) no intramolecular component for epoxidation could be detected while the homo- and bishomoallylic cases show clear evidence for the intramolecular epoxidation pathway. At all concentrations used these latter cases gave more epoxide derived from the intrinsically less reactive olefin; the approximately linear increase in the epoxide ratio with dilution is best accommodated by the rate ratios given in the lowest row of the table. These were obtained from plots of (13 + 14)/12 against 1/[15].

Of particular interest is the case of the ketal 11, since its efficiency in intramolecular epoxidation implies that structure 7a is sufficient to describe the nature of the intermediate involved in these reactions. A more refined picture of how the epoxidation occurs is postulated in structure 17. The π bond can approach



the backside of the terminal oxygen on a line defined by the O-O single bond of the peroxide.⁷ With fewer connective atoms, i.e., the allylic case, this approach cannot be realized. Such geometries have been favored by calculations of peracid-olefin transition states;⁸ in addition, this approach can place a lone pair of the terminal oxygen parallel with the approaching π bond as has recently been proposed for peracid epoxidations by Sharpless. However, this degree of refinement must await further experimental verification.



$18 + 20 \xrightarrow[]{\text{H}_2\text{O}_2}_{\text{THF}}$	19 + 21
[18] = [2 0], M	[19]/[21]
1	7
0.5	12
0.25	27

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In order to examine the possibility of epoxidation via structure 7b we examined an ortho ester derived from an olefinic acid. Specifically, oleic acid was converted to the corresponding ortho ester 18. On treatment with H_2O_2 in CH_2Cl_2 for 24 h, a 40% yield of the corresponding epoxide 19 was obtained.



To establish that epoxidation was indeed intramolecular, a competition experiment was performed along the lines of those previously described. Here the competing olefin was the amide 20. On successive dilutions of a THF solution containing equimolar amounts of 18 and 20 with H2O2, the yield of 19 increased at the expense of **21** (Table II).



Structures such as 22 are, consequently, likely candidates for



this epoxidation. Systematic studies are underway to determine the fewest number of connective atoms necessary for intramolecular oxygen transfer in these cases.

Asymmetric Epoxidations

These α -hydroperoxy ethers offer an opportunity for generating chiral epoxidizing agents in which the asymmetric center is nearer the oxygen-transfer site than is the case with peroxy acids (compare 23 with 24). However, a number of cases examined gave disappointing results. Perhydrolysis of optically active ketals 25¹⁰ and 26^{11} in the presence of the test olefin 15 gave only 3-5% enantiomeric excess in the epoxide 12. Similar results were obtained with 27 or 28.



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Scheme II



Table III. Olefin Epoxidation with 35 (CHCl₃, 24 h, 60 °C)



In addition, a few α -aminohydroperoxides were tested. These substances can be isolated¹² or generated in situ from Schiff's bases and H_2O_2 . While epoxide yields with 29-31 were up to 45%, the asymmetric induction (with 31) was <5% and the competing cyclization to the oxaziridines 32 placed great restrictions on the use of these reagents for synthetic purposes.



A somewhat cleaner system was found in the hydroperoxides 34a,b, derived from the isoindolone 33. These proved quite stable (<10% loss of active oxygen after 2 weeks) and the diastereomers of 34 were readily separated by LC.13



Exposure of either diastereomer to 15 gave epoxide and each gave a single alcohol 33. Surprisingly, neither 33 nor 34 was found to isomerize under the conditions of epoxidation and we conclude that oxygen transfer occurs without opening of the five-membered ring (Scheme II). However, this reagent as well showed insufficient asymmetric induction to warrant further pursuit.

α-Hydroperoxy Carbonyl Compounds

The base-catalyzed oxidation of carbonyl compounds (eq 2) has made α -hydroperoxy esters and ketones readily available.¹⁴ Their decomposition under basic, acidic, and thermal conditions has been extensively explored,¹⁵ yet no reports regarding their

reactions with olefins are known to us. The curious instability of *olefinic* α -hydroperoxy esters vs. their saturated counterparts has, however, been noted.^{14b} This instability is now explained by our finding that either the ester 35, ketone 36, or nitrile 37 are remarkably effective at olefin epoxidation.



Several olefins were examined in this reaction using 35 and results are given in Table III. Like peroxy acid reactions, a preference for syn epoxidation was observed with allylic alcohols and 35 and cyclopentanone gave a 35% yield of the Baeyer-Villiger oxidation product.

Conclusions

A number of α -substituted hydroperoxides have been shown capable of olefin epoxidations and all reagents examined were cleanly stereospecific. In this respect they resemble peroxy acids rather than, say, carbonyl oxides. Moreover, these reagents can all exist in intramolecularly hydrogen bonded form. Whether this feature is the minimum requirement for stereospecific oxygen atom transfer, or is merely a consequence of the electronegative substituent on the hydroperoxy-bearing carbon, has yet to be resolved. We do note, however, the resemblance borne by many of these reagents to flavin hydroperoxides¹⁶ 38 and predict that these latter substances are likewise capable of olefin epoxidation.



Experimental Section

A. Analysis. Gas-liquid chromatography was performed on a Varian Model A-90 (15% OV-101 on Chromosorb W) and Hewlett-Packard 5710A (3% OV-17 on Chromosorb W) using a Varian Model 101 electronic integrator for peak area determinations. High-pressure liquid chromatography was accomplished by using a Waters Associates LC system on a 1-ft µ-Porasil column and Model R401 refractive index detection system. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and high-resolution mass spectra were obtained on a Varian CH-5 instrument.

B. Materials. Literature preparations were followed for 19,¹⁷ 20,¹⁸ **26**, ¹⁹ **27**, ²⁰ **28**, ²³ **29**, ¹² Schiff bases leading to 30, ²¹ **31**, ²² and hydroper-oxides **35**, ^{14a} **36**, ²⁴ and **37**, ²⁵ Hydrogen peroxide (90%) was obtained from FMC Corp. and was used as received. Triallyl orthoformate (8) was purchased from Pfaltz and Bauer.

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Preparation of Unsaturated Ortho Esters. Ortho esters 9 and 10 and ketal 11 were prepared by transesterification of the ethyl ortho esters or 2,2-dimethoxypropane under standard exchange conditions.²⁹

(1) Tri-3-butene Orthoacetate (9): bp 132–136 °C (30 mm); NMR δ 1.47 (s, 3 H), 2.33 (m, 6 H), 3.52 (t, J = 6.0 Hz, 6 H), 5.12 (m, 6 H), 5.80 (m, 3 H); IR 1160, 1050 cm⁻¹; mass (M⁺ – CH₃) 225.3071 (calcd (M⁺ – CH₃), 225.3071).

(2) Tri-4-pentene Orthoformate (10): bp 178-180 °C (30 mm); NMR δ 1.68 (m, 6 H), 2.10 (m, 6 H), 3.42 (t, J = 8.0 Hz, 6 H), 4.72 (m, 6 H), 5.00 (s, 1 H), 5.63 (m, 3 H); IR 1420, 1120, 1250, 1050 cm⁻¹; mass (M⁺ - H) 267.3871 (calcd (M⁺ - H), 267.3875).

(3) 2,2-Di-3-butenoxypropane (11): bp 77–78 °C (25 mm); NMR δ 1.30 (s, 6 H), 2.23 (m, 4 H), 3.40 (t, J = 8.0 Hz, 4 H), 5.10 (m, 4 H), 5.80 (m, 2 H); IR 1630, 1040 cm⁻¹. Anal. Calcd for C₁₁H₂₀O₂: C, 71.70; H, 10.94. Found: C, 71.65; H, 10.90.

Competition Experiments for Intra- vs. Intermolecular Epoxidation of 8–11. The ortho ester (1 mmol) and *trans-* β -methylstyrene (5 mmol) in THF (appropriate amount depending on the concentration desired) were stirred at room temperature as H₂O₂ (90%, 100 µL/mmol of ortho ester) was added slowly. The solution was checked periodically by GLC until the reaction was approximately 10% complete, then water was added and the solution was stirred for 15–30 min. The solution was extracted several times with ether and the combined extracts were dried over Na₂SO₄. The crude reaction mixture was analyzed by GLC for epoxide ratios.

Preparation of Trimethyl Orthooleate (18). 18 was prepared by using the Pinner synthesis.²⁶

(1) Preparation of Methyl Oleoimidate Hydrochloride. Dry HCl (4.02 g, 0.11 mol, through concentrated sulfuric acid) was bubbled into a mixture of commercial oleonitrile (26.35 g, 0.1 mol) in 4.46 mL (0.11 mol) of methanol cooled in an ice bath. The solution was placed in the freezer, when, after 24 h, 38 mL of dry ether was added and the solution was allowed to stand in the refrigerator for an additional 24 h. The suspension of the salt was filtered rapidly, washed with cold, dry ether, then immediately placed in a vacuum desiccator (the salt is extremely hygroscopic). This salt (10.0 g) in 18 mL of methanol was stirred until solution occurred, then ether (95 mL) was added and the solution was refluxed for 24 h. The solution was cooled in an ice bath and filtered through Celite to remove NH4+Cl-. Sodium methoxide (0.54 g) was then added to the filtrate to neutralize acidic residues. Washing the filtrate twice with 10% Na₂CO₃ and once with saturated Na₂CO₃ and drying over K₂CO₃ provided, after evaporation, the ortho ester contaminated with amide and methyl ester. The crude product was triturated with hexane at -10 °C, then filtered free of the solid amine. Evaporation provided the ortho ester as a light yellow oil containing less than 5% methyl ester. Distillation in vacuo provided an analytical sample: 6.54 g (64%); bp 145 °C (0.057 mm); NMR δ 0.9-2.0 (m, 17 H), 3.27 (s, 3 H), 5.37 (m, 2 H); IR 1465, 1380, 1250, 1050 cm⁻¹; mass spectrum (M⁺ CH₃O) 311.2950 (calcd (M⁺ - CH₃O), 311.2950).

Competition Experiment of 18 with 20. Intermolecular Oxidation. The ortho ester 18 and amide 20^{18} (1 mmol each) were stirred in THF (appropriate amount depending on concentration desired) as H_2O_2 (100 μ L/mmol of ortho ester) was added slowly. After the solution was stirred for 24 h at room temperature, 5 mL of H_2O was added and the solution was stirred for 15 min. Ether was added and the layers were separated; the ether was dried over Na_2SO_4 and then evaporated. The residue was analyzed by LC (5:1 hexane/EtOAc) for epoxide ratios.

Preparative Epoxidation, $18 \rightarrow 19$. Ortho ester 18 (1 mmol) in 1 mL of CH₂Cl₂ was stirred and 100 μ L of H₂O₂ was added slowly. The solution was stirred *vigorously* for 24 h, after which time H₂O was added and the solution was stirred for an additional 15 min. The organic phase was dried over Na₂SO₄ and the crude mixture was analyzed by LC (10:1 hexane/EtOAc) and NMR showing a 40% yield of methyl ester peroxide 19, identical with an authentic sample.¹⁷

Preparation of 1-Oxo-2-[(+)-a-methylbenzyl]-3-hydroxy-3-phenylisoindole (33a,b). (+)- α -Methylbenzylamine (6.44 mL, 0.05 mol) was added slowly (dropwise) with cooling to a mixture of the crude pseudochloride (12.25 g, 0.05 mol, prepared by refluxing benzophenone-2carboxylic acid with thionyl chloride) and 4.0 mL of dry pyridine in 30 mL of dry benzene. After the mixture was stirred at room temperature for 12-24 h, 100 mL of chloroform was added and the mixture was washed four times with 1.0 M HCl, twice with 1.0 M NaOH, and once with brine and dried over MgSO₄. The crude product was recrystallized once from CCl₄, giving mostly one isomer as white plates. Repeated recrystallization resulted in a 1:1 mixture of diastereomers which were separated by LC (20% EtOAc/hexane): 10.8 g (66%); mp 167-170 °C; NMR (isomer 1) δ 1.66 (d, J = 7.5 Hz, 3 H), 3.04 (s, 1 H), 4.47 (q, J = 7.5 Hz, 1 H), 7.40 (m, 14 H); (isomer 2) 1.87 (d, J = 6.0 Hz, 3 H), 3.23 (s, 1 H), 4.85 (q, J = 6.0 Hz, 1 H), 7.20 (m, 14 H); IR 3550, 3300 (br), 1690 cm⁻¹. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22, H, 5.81; N, 4.25. Found: C, 80.25; H, 5.89; N, 4.23.

Preparation of 1-Oxo-2-[(+)-α-methylbenzyl]-3-hydroperoxy-3phenylisoindole (34a,b). H_2O_2 (0.340 g, 90%) was added slowly to a solution containing 1.645 g (5 mmol) of 46 (mixture of isomers) and 10 μ L of H₂SO₄ (catalytic amount) in 5–10 mL of CH₂Cl₂ at 0 °C. The solution became homogeneous after 5 min and the cooling bath was removed. After being stirred for 24 h at room temperature the solution was washed with saturated sodium bicarbonate solution (thrice) and once with brine and dried over Na₂SO₄. Evaporation provided 1.54 g (89%) of the hydroperoxide as a mixture of isomers, mp 136-140 °C. Separation of the isomers by LC provided pure 34a,b (25% EtOAc/hexane): NMR (isomer 1) δ 1 80 (d, J = 8.0 Hz, 3 H), 4.38 (q, J = 8.0 Hz, 1 H), 7.25 (m, 14 H), 10.20 (br s, 1 H); (isomer 2) 1.87 (d, J = 6.5 Hz, 3 H), 4.74 (q, J = 6.5 Hz, 1 H), 7.15 (m, 14 H), 10.10 (br s, 1 H). Anal. Calcd for $C_{22}H_{20}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 73.25; H, 5.65; N, 3.89. Individual hydroperoxide isomers did not isomerize after 16 days at room temperature (determined by NMR) and active oxygen content was virtually unchanged (determined by titration²⁷) over this time span.

Reaction of 34 with *trans-* β **-Methylstyrene.** After separation of the isomers **34a,b** by LC, 80.0 mg (0.23 mmol) of a single isomer was added to a solution containing 65 μ L of *trans-* β -methylstyrene (0.5 mmol) in 1 mL of CHCL₃. After the solution was stirred at room temperature for 4 days, the epoxide was isolated by preparative GLC (28.2% yield), $[\alpha]^{22}_{D}$ -3.89° (*c* 1.52, EtOH), 5.5% ee (lit.²⁸ $[\alpha]^{20}_{D}$ -70.8° (*c* 4.44, EtOH)). NMR of the reaction mixture revealed that only isomer 1 of alcohol **35** was obtained from isomer 1 of **34** and only isomer 2 of **33** was obtained from isomer 2 of **34**.

Reaction of 35 with Olefins. The olefin (1 mmol) was added to a solution containing 1 mmol of 35^{14a} in 3 mL of CHCl₃ which was heated to 60 °C (bath temperature). After 24 h the reaction mixture was examined by GLC and NMR for epoxide. For Baeyer-Villiger oxidation, the ketone was added to the hydroperoxide solution containing a catalytic amount of *p*-toluenesulfonic acid. The same procedure was used to prepare epoxides with 36^{24} and 37;²⁵ the latter was the most reactive of these reagents.

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