Epoxidation by Dimethyldioxirane: Electronic and Steric Effects

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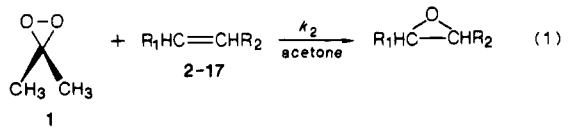
The reaction of dimethyldioxirane (1) with a series of di- and monosubstituted alkenes **2–17** produced the corresponding epoxides in high yield. A kinetic study of the epoxidation of **2–17** by **1** in dried acetone showed the reaction to be of the first order with respect to both alkene and dioxirane. For certain *cis*/*trans*-dialkylalkenes, the cis compounds were found to be of ≈10-fold greater reactivity than the corresponding trans isomers. However, cis/trans pairs of alkenes with phenyl substituents were found to be of similar reactivity. A kinetic study on the reaction of a series of substituted styrenes yielded an excellent LFER with a ρ value of −0.90. Addition of water to dioxirane reactions in acetone increased the observed rates of epoxidation. However, a tertiary allylic alcohol was found to undergo epoxidation slower than expected. The mechanistic implications of the results are discussed.

Dioxiranes,[1] three-membered cyclic peroxides, have been shown to be of high reactivity in oxygen-atom transfer chemistry.[2] Based on extensive kinetic, stereochemical, and labeling data, Edwards and Curci showed[3] that dimethyldioxirane must be the oxygen-atom transfer reagent in the potassium peroxymonosulfate (caroate)–acetone system. Recently, Murray has shown[4] that alkyldioxiranes can be isolated by low-temperature distillation of the cyclic peroxides from the caroate–ketone reaction mixtures. The dioxirane structure of the isolated material has been confirmed by spectral data.[4a,5] Results of a Hammett-type study of S-oxidation by dimethyldioxirane concluded[6] that the reaction was electrophilic in character. However, Adam, measuring the product ratios of the reaction of thianthrene 5-oxide with isolated dimethyldioxirane, has confirmed[5b] his earlier observation[7] that dioxiranes display appreciable nucleophilic character. Our work[8] on epoxidation of simple alkenes with dimethyldioxirane showed the reaction to be electrophilic in character but unusually sensitive to steric factors. We report here a study of the epoxidation of a series of substituted styrenes and selected di- and monosubstituted alkenes by dimethyldioxirane, which shows the unusual characteristics of this oxygen-atom transfer reagent.

Results

Dimethyldioxirane (1) was prepared[3] by the reaction of Oxone (potassium monoperoxysulfate) with acetone and isolated[5] as ≤0.1 M solutions in acetone by the general procedure[4] developed by Murray. Product studies for the reaction of a series of di- and monosubstituted alkenes **2–17** with 1.1 equiv of **1** were carried out by ^{1}H NMR spectroscopy (reaction 1). In all cases except for that of



(1)

Table I. Second-Order Rate Constants for the Epoxidation of Di- and Monosubstituted Alkenes by Dioxirane 1 in Dried Acetone at 23 °C

compd	alkene	$k_2M^{-1}s^{-1}$	rel react.
2	*cis*-3-hexene[a]	0.47 ± 0.03	8.3
3	*trans*-3-hexene[a]	0.057 ± 0.004	≡1.0
4	*cis*-4,4-dimethyl-2-pentene	0.33 ± 0.02	5.8
5	*trans*-4,4-dimethyl-2-pentene	0.023 ± 0.001	0.40
6	*cis*-2,5-dimethyl-3-hexene	0.39 ± 0.02	6.8
7	*trans*-2,5-dimethyl-3-hexene	0.02 ± 0.01[b]	0.4
8	*trans*-2,2,5,5-tetramethyl-3-hexene	0.00024 ± 0.00004	0.004
9	cyclohexene	0.48 ± 0.02	8.4
10	*cis*-1-phenylpropene	0.18 ± 0.01	3.2
11	*trans*-1-phenylpropene	0.29 ± 0.02	5.1
12	*cis*-stilbene	0.040 ± 0.001	0.70
13	*trans*-stilbene	0.043 ± 0.002	0.75
14	indene	0.22 ± 0.01	3.9
15a	4-methoxystyrene	0.57 ± 0.03	10.0
15b	4-methylstyrene	0.25 ± 0.01	4.4
15c	styrene	0.13 ± 0.01	2.3
15d	4-bromostyrene	0.089 ± 0.003	1.6
15e	3-nitrostyrene	0.030 ± 0.003	0.53
16	3,3-dimethyl-1-butene	0.033 ± 0.001	0.58
17	3-methyl-1-buten-3-ol	0.016 ± 0.002	0.28

[a] Included for comparison, see ref 8. Note temperature difference. [b] Initial rate.

trans-2,5-dimethyl-3-hexene (**7**), the corresponding epoxides (stereospecific) were formed in essentially quantitative yield. The yield of epoxide for alkene **7** was only ~50%. Apparently allylic oxidation is competing with epoxidation in this case.

A kinetic study of the epoxidation of **2–17** by **1** in dried acetone was carried out by using UV techniques. The oxygen-atom transfer reaction was shown to be of the first order in both dioxirane and alkene. Alkene **7** again proved to be an exception. After ~20% completion, the reaction of **7** and **1** began to increase in rate, indicative of a competing free-radical process. The kinetic data for epoxidation are summarized in Table I. Since the results for cis/trans pairs **10**/**11** and **12**/**13** did not show the expected 8-fold or greater reactivity[8] of the cis isomers, the rate constants were checked by NMR techniques. One to one mixtures of the cis/trans pairs of alkenes were combined with one-half an equivalent of **1** and the product ratio determined: for **10**/**11** = 0.66; for **12**/**13** = 0.91. These are in excellent agreement with the ratios obtained on the basis of the UV kinetic data.

In an early kinetic experiment, it was noted that dioxirane stock solutions in wet acetone yielded larger k_2 values than those from dried solutions. Furthermore, "drying" (anhydrous $MgSO_4$) of the wet acetone was required to achieve reproducible results. Identical epoxidation yields

(1) (a) Lovas, F. J.; Suenrani, R. D. *Chem. Phys. Lett.* **1977**, *51*, 453. (b) Martinez, R. I.; Hire, R. E.; Herros, J. T. *Ibid.* **1977**, *51*, 457.
(2) For a review, see: Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: Greenwich, CT, in press; Chapter 1, Vol. II.
(3) (a) Edwards, J. D.; Pater, R. H.; Curci, R.; Furia, F. D. *Photochem. Photobiol.* **1979**, *30*, 63. (b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758.
(4) (a) Murray, R. W.; Jeyaram, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Murray, R. W.; Jeyaram, R.; Mohan, L. *Tetrahedron Lett.* **1986**, *27*, 2335.
(5) (a) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699. (b) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Schentzow, O.; Schindler, M. *Ibid.* **1987**, *52*, 2800.
(6) Murray, R. W.; Jeyaram, R.; Pillay, M. K. *J. Org. Chem.* **1987**, *52*, 746.
(7) Adam, W.; Hass, W.; Sicker, G. *J. Am. Chem. Soc.* **1984**, *106*, 5020.
(8) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311.

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Table II. Oxidation of *p*-Methoxystyrene (15a) by Dimethyldioxirane (1) in Acetone[a] in the Presence of Added Water at 23 °C

vol H_2O added (μL)	X_{H_2O}[b]	k_2, M^{-1} s^{-1}	k_{rel}
0	0	0.55	1.0
20	0.073	0.67 ± 0.03	1.2
45	0.15	0.93	1.7
70	0.22	1.21	2.2
120	0.32	1.99 ± 0.03	3.6
150	0.55	6.0	10.9
220	0.64	7.1	12.9

[a] Initial volume 1.00 mL; dried over anhydrous $MgSO_4$. [b] Mole fraction of added water.

were obtained by using either wet or dried acetone as solvent. The effect of added water on epoxidation k_2 values was assessed for the reaction of **15a** and **1** in acetone. The presence of added water in the epoxidation reactions resulted in increased $k_2$values. For solutions containing $\geq$0.5 mole fraction of water, a 10-fold or greater increase in k_2 values was observed. The results are listed in Table II.

The kinetic runs for the remaining substituted styrenes **15b–e** were repeated in acetone containing ~0.15 mole fraction of H_2O, to yield the following k_2 values: for **15b** 0.44 ± 0.01; for **13c** 0.23 ± 0.01; for **15d** 0.13 ± 0.01; for **15e** 0.035 ± 0.002. The effect of added water was not uniform. The effect appeared to be greater for the more reactive styrenes and less for the less reactive compounds. Substitution of added D_2O for H_2O yielded identical rate enhancements.

Discussion

The rate constants for the cis/trans pairs of dialkylalkenes **4/5** and **6/7** confirmed and extended the results of our earlier study.[8] Our earlier work had shown[8] that *cis*-alkenes were of up to 8-fold greater reactivity than the corresponding trans compounds. With the larger alkyl groups, the cis compounds used in the present study showed an even greater reactivity difference compared to that of the trans isomers, up to 20-fold more reactive. Interestingly, this relationship broke down when phenyls were present. In fact, the trans isomers of both the β-methylstyrenes **11** and the stilbenes **13** were slightly more reactive than the cis isomers. The cis phenyl-substituted alkenes **10** and **12** were less reactive than the cis-dialkyl compounds. This does not seem to be a conformational effect since indene (**14**) showed essentially identical reactivity with that of **10**. Interestingly, the trans phenyl-substituted compound **11** showed enhanced reactivity to that of alkyl analogues. Similarly, styrene (**15c**) showed greater reactivity than monosubstituted alkylalkene **16** or 1-nonene.[8]

Although limited to five compounds, the results for the epoxidation of the series of substituted styrenes **15a–e** in dried acetone gave an excellent Hammett-type plot vs σ^+ values. Least-squares analysis yielded a ρ value of −0.90 ± 0.03 with a correlation coefficient (r) of 0.999. This result compared favorably with the ρ^+ values obtained by peracetic acid epoxidation[9a] of styrenes (−1.18)[9b] in acetic acid and perbenzoic acid epoxidation[10a] of stilbenes (−1.01)[10b] in benzene. Interestingly, the results for epoxidation of styrenes **15a–e** by **1** in acetone containing ~0.15 mole fraction of added water gave a slightly larger ρ value of ~1.03 (r = 0.992) even closer to the peracid results. The magnitude and sign of the ρ^+ value seem consistent with a normal electrophilic oxygen-atom transfer mechanism and appear to rule out electron-transfer-type processes.

Murray,[6] based on a LFER (vs σ values) for oxidation of substituted thioanisole by **1** with a ρ of −0.77, concluded that S-oxidation by dioxiranes was electrophilic in character. Interestingly, electrophilic oxygen-atom transfer oxidations of thioanisoles by α-azo hydroperoxides,[11] flavin 4a-hydroperoxides,[12] and hydrogen peroxide[13] showed LFERs with larger ρ values (−1.2, −1.7, −1.2, respectively). The ρ value for S-oxidation by dioxirane may also be a function of water content as found for epoxidation (vide infra). Although of lower magnitude than hydroperoxide electrophilic oxygen-atom transfers, Murray's conclusion[6] is consistent with the epoxidation results.

Recently, Adam has measured the "electrophilic/nucleophilic" character of **1** by the thianthrene 5-oxide method. The nucleophilic character (X_{nu}) of an oxygen-atom transfer reagent was defined[5b] as the mole fraction of nucleophilic attack. Oxidation of the thiathrene 5-oxide sulfoxide function to the sulfone was considered to reflect nucleophilic character while conversion of the sulfide group to the sulfoxide reflected electrophilic oxidation. For example, *m*-CPBA showed[7] a low X_{nu} value of 0.36 (electrophilic) while *t*-BuOO$^-$ gave a value of 1.00 (completely nucleophilic). Dioxirane **1** in acetone[5b] yielded an X_{nu} value of 0.85 while in CH_2Cl_2/buffer the value was found to be 0.68. Thus dioxirane **1** was thought[5b] to show a dominating nucleophilic character since mainly oxidation of the sulfoxide group to the sulfone was observed. However, Murray has found[6] the ρ value (−0.76) of sulfoxide to sulfone oxidation to be larger than that (−0.55) for the similar oxidation by perbenzoic acid[14] suggestive of a electrophilic process. This suggests that interpretation of the X_{nu} results may be more difficult than expected. There may be additional routes to the "sulfone" product other than the expected nucleophilic process. Nevertheless, there are fundamental differences in S-oxidation by **1** from those by other reagents.

The large increases in k_2 values (Table II) observed for dioxirane epoxidation in wet acetone were unexpected. A plot of mole fraction (X_{H_2O}) of added water vs k_2 value showed curvature with greater k_2 increases for larger X_{H_2O} values. In contrast, peracid epoxidations are slowed by protic solvents (presumably due to disruption of the required intramolecular hydrogen bond in the peracid).[15] The dioxirane results appear to represent a polar solvent effect consistent with expectations for an electrophilic process. However, a hydrogen-bonding catalytic effect and/or change in mechanism cannot be completely ruled out at this time. Oxidation by dioxirane in the presence of water has the advantage of being greatly accelerated. However, it is also clear that selectivity depends on the reaction conditions and must be determined for each case.

Interestingly, the epoxidation of **17** containing a *tert*-allylic hydroxy group was slower than that of the *tert*-butyl model compound **16**. This indicates that intermolecular hydrogen bonding to the dioxirane should disrupt or at least slow attack on the side of the alkene syn to the hydroxy function. This results is consistent with the work of Curci[2,16] which showed preferential formation of anti

(9) (a) Fueller, B.; Hampel, M.; Putzkow, W. *J. Prakt. Chem.* **1977**, *319*, 693. (b) A ρ^+ value of −1.18 ± 0.09 can be calculated for the epoxidation[9a] of substituted styrenes by peracetic acid in acetic acid.

(10) (a) Lynch, B. M.; Pausacker, K. H. *J. Chem. Soc.* **1955**, 1525. (b) Calculation of ρ^+ for the epoxidation of substituted stilbenes[10a] by perbenzoic acid in benzene yields a value of −1.01.

(11) Baumstark, A. L. *J. Bioorg. Chem.* **1986**, *14*, 326.

(12) Miller, A. *Tetrahedron Lett.* **1983**, *24*, 753.

(13) Modena, G.; Maiola, L. *Gazz. Chim. Ital.* **1957**, *87*, 1306.

(14) Cerniani, A.; Modena, G. *Gazz. Chim. Ital.* **1959**, *89*, 843.

(15) See: (a) Sheldon, R. A. In *The Chemistry of Peroxides* Patai, S., Ed.; John Wiley: Yew York, 1983; Chapter 6 and references therein. (b) Reference 15a, Plesnicar, B., Chapter 7.

epoxides for fixed allylic alcohols.

In general, the epoxidation data seem consistent with an electrophilic process. The *cis/trans*-dialkylalkene results support a spiro transition state[8] for dioxirane epoxidation. The ρ^+ value obtained for epoxidation of styrenes and the observed rate enhancements vs mole fraction of added water (apparent polar solvent effect) also support an electrophilic mechanism.

Experimental Section

All solvents were of reagent grade. ^{1}H NMR spectra were recorded on a Varian EM-360L NMR spectrometer. UV kinetic experiments were conducted on a Cary 17D spectrometer; cell temperature (±0.3 °C) was maintained via a constant-temperature circulating bath. The alkenes (≥99%, Wiley Organics and Aldrich) and Oxone (Aldrich) were used without further purification. Dimethyldioxirane (1) was prepared in acetone by the general procedure developed by Murray,[4] simplified by slight modification.[5,8] The dioxirane stock solutions were dried twice with anhydrous $MgSO_4$ at −78 °C and at ambient temperature. The concentration (≤0.1 M) of dioxirane 1 was determined by reaction with excess dimethyl sulfide, followed by integration (^{1}H NMR) of the DMSO signal vs that of added internal standard (anisole) and was in good agreement with that determined by UV methods.[5,8] All glassware used in dioxirane preparation had been treated with aqueous $EDTA^{2-}$ followed by acetone wash. Authentic samples of the epoxides were prepared by the reaction of *m*-chloroperbenzoic acid (Aldrich) with 1 equiv of the corresponding alkenes.

Product Studies. Two general procedures were used to determine the yield of epoxide for reaction of 1 with alkenes **2**–**17**. For nonvolatile epoxides, 10.0 μL of the desired alkene were added to 1.1 equiv of 1 in acetone. After complete oxidation, the solvent was removed under reduced pressure (ice bath) to yield the pure epoxides in essentially quantitative yield. The compounds were identified by comparison of physical and spectral properties with those of authentic samples. For volatile epoxides, the epoxidation was carried out as above except that dimethyldioxirane-d_6 in acetone-d_6 was used.[8] Epoxide yield was determined by ^{1}H NMR integration relative to internal standard. Except as noted for alkene **7**, the epoxides were obtained in ≥95% yield. As expected,[2,3,8] the epoxidations were stereospecific in all cases.

Kinetic Studies. Dimethyldioxirane solutions (1.00 mL) of known concentration in *dried* acetone were placed in a 1-cm UV cell at 23 °C. The desired equivalents of alkene were added via syringe and rapidly mixed. Pseudo-first-order conditions with 1:10 and 10:1 alkene to peroxide ratios gave identical values of k_2. The loss of dimethyldioxirane vs time was monitored at 332 nm for all cases except for those of **12**, **13**, and **15e**. For these three exceptions, the kinetics were monitored by following the loss of alkene at longer wavelengths. Excellent correlations were obtained for all cases except **7**. For **7**, normal behavior was obtained for roughly the first 20% reaction, and then the reaction increased in rate before slowing. These characteristics indicate that a competing free-radical-like allylic oxidation may be taking place and are consistent with the low yield (50%) of epoxide for this case. For kinetic runs with added water, the desired quantity of deionized water was added via syringe to 1.00 mL of the stock solution and mixed prior to the addition of the alkene.

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(16) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670.

Total Syntheses of (±)-Cephalotaxine and (±)-8-Oxocephalotaxine

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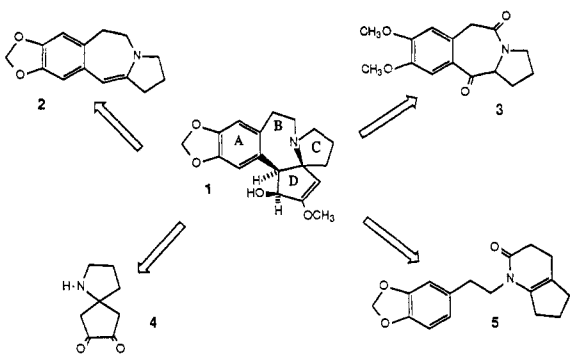
A synthesis of (±)-cephalotaxine (1) was obtained based on a novel oxidative rearrangement of the bicyclic enamide **5** to the spirocyclopentanone lactam **20**. The overall yield from keto ester **6** and amine **7** was 28%, in nine steps, or 41% in ten steps. Double-bond isomerization of minor side product ene lactam **9**, with formation of the key ene lactam intermediate **5**, increased the overall yields of the synthesis to 45% (nine steps) or 66% (ten steps). The racemate of the natural product 8-oxocephalotaxine (**40**) was obtained in an alternative last step by a selective reduction of the keto lactam **39**.

Cephalotaxine (1),[1-12] the major alkaloid constituent of the Chinese plum yew *Cephalotaxus fortunei* and of the Japanese plum yew *Cephalotaxus drupacea* has become an interesting synthetic target, not only because of its unique ring skeleton but also as a result of the anticancer activity found for some of its derivative esters (harringtonine, homoharringtonine, etc.), with leukemia L-1210 and, particularly, P-388 in mice.[13,14] This anticancer activity is currently undergoing clinical evaluation.

Scheme I



The most extensively explored approach to cephalotaxine has focused on use of the ABC tricyclic enamine **2**

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