Epoxidation and Oxygen Insertion into Alkane CH Bonds by Dioxirane Do Not Involve Detectable Radical Pathways

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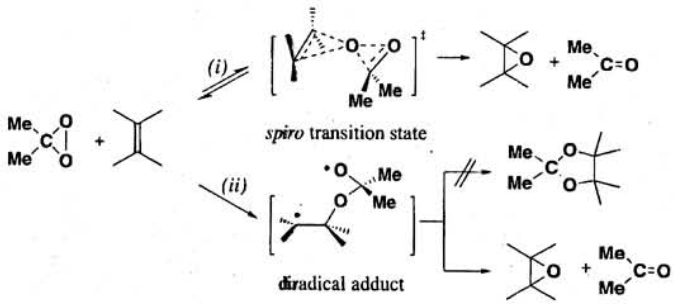
Abstract: The dimethyldioxirane oxidation of α-methylstyrene, *trans*-cyclooctene, and 1-vinyl-2,2-diphenylcyclopropane gave, under all reaction conditions employed, the corresponding epoxides in high yields. No radical products from allylic oxidation, from *trans*/*cis* isomerization, or from cyclopropylcarbinyl rearrangement (radical clock) were observed. Even for these alkenes, which are prone to radical reactions, the previously established electrophilic concerted mechanism applies, rather than the recently proposed radical mechanism. The selective hydroxylation of (−)-2-phenylbutane by dimethyldioxirane gave only (−)-2-phenylbutan-2-ol with complete retention of configuration and no loss of optical purity. Thus, a radical-chain oxidation is also discounted in the oxygen insertion into hydrocarbon C−H bonds for dioxiranes.

Keywords
dioxiranes · epoxidations · insertions · oxenoids · radicals

Introduction

Dioxiranes,[1] especially the isolated dimethyldioxirane (DMD)[2] in acetone solution, are well-established as useful oxidants for a variety of oxyfunctionalizations of organic and organometallic[3] substrates. The epoxidation of olefins under mild and neutral conditions is of particular interest in view of the synthetic value of this transformation. Indeed, the convenient dioxirane route has even provided access to highly sensitive epoxides,[4] which could hitherto not be prepared. Intensive studies have been directed to elucidate the reaction mechanism of the DMD epoxidation, and the overwhelming experimental evidence[1, 5] and theoretical calculations[6] have pointed to a concerted pathway. Thus, instead of the initially proposed diradical mechanism,[1a] a concerted pathway through the *spiro* transition state was suggested (Scheme 1).



Scheme 1. Concerted versus stepwise diradical epoxidation by dioxiranes.

Despite the convincing evidence for an electrophilic attack of the dioxirane on the double bond,[1] a radical mechanism was most recently proposed by Minisci et al.[7] These authors observed allylic oxidation to a significant extent in the reaction of α-methylstyrene with DMD.

The efficient oxyfunctionalization of unactivated C−H bonds of alkanes under extremely mild conditions is undoubtedly a great achievement of dioxirane chemistry.[1] For this remarkable transformation, the high stereochemical selectivities as well as kinetic evidence all point to an oxenoid mechanism for the insertion.[1, 8] Nevertheless, Minisci et al. recently proposed that a radical-chain mechanism also applies in this case;[9] product studies and the effect of radical traps were presented to support this thesis.

These perplexing results demand rigorous experimental scrutiny to establish their reproducibility, and, if reproducible, the generality and scope of such complicated radical side reac-

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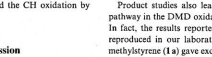
tions must be assessed. Therefore, we decided to reexamine the above transformations by using reliable mechanistic probes for radical pathways. Our present experimental results unequivocally establish that the epoxidation and the CH oxidation by DMD do *not* involve radical processes.

Results and Discussion

The stoichiometry and kinetics of the DMD epoxidation of α-methylstyrene (**1a**) was first studied under a variety of conditions. The strained *trans*-cyclooctene (**1b**)[10] was chosen as a second substrate, since, if radical intermediates were formed, it would be expected to undergo *trans*-to-*cis* isomerization on epoxidation with DMD. The structurally related 1,1-diphenyl-2-vinylcyclopropane (**1c**)[12] was also chosen as a probe for a radical mechanism—should radicals be involved, the classical cyclopropylcarbinyl rearrangement should be observed.[13] The results are summarized in Table 1.

Table 1. Epoxidation of substrates **1a**–**c** with dimethyldioxirane.



1a **1b** **1c**

Entry	SM	Solvent	*T*/°C	*t*/h	Conv./% [a]
1	**1a**	acetone	20	1.0	96
2	**1a**	acetone/N_2 [b]	20	0.6	88
3	**1a**	acetone	56	0.3	85 [c]
4	**1a**	acetone	−78	12	>95
5	**1a**	CCl_4 [d]	20	9	>95
6	**1a**	acetone/$CHCl_3$ [e]	0	12	>95
7	**1b**	acetone	20	<0.1	>95
8	**1c**	acetone	20	1.0	>95

[a] Based on dioxirane initial concentration and determined by ^{1}H NMR and/or GC/MS analysis of the crude reaction mixtures (error limit ±5% of the stated values); mass balance > 90% and yields > 95%. [b] Solvent and reaction solutions were purged with N_2 and yields > 95%. [c] Epoxide and 2-phenylpropane-1,2-diol were obtained in a 90:10 ratio. [d] DMD was used as 0.08 M solution in CCl_4, which was also ca. 0.1 M in acetone; ref. [11]. [e] $CHCl_3$ was employed as cosolvent in a 1:1 solvent mixture with acetone.

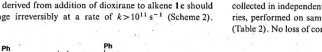
With DMD and α-methylstyrene at initial concentrations in the range of ca. 10^{-2} M, kinetic runs were performed in acetone at 20.00 ± 0.05 °C by following the decay of the dioxirane concentration (iodometry)[11] with time. The reactions followed a clean overall second-order rate law (first order in dioxirane and alkene). Integrated second-order rate-law plots were found to be linear to over 80% reaction and afforded reproducible rate constants, namely, $k_2 = 1.02 \pm 0.04\,M^{-1}s^{-1}$. In separate experiments, also under the conditions given above, the consumption of α-methylstyrene with time was followed by GC analysis. A value of $k_2 = 0.97 \pm 0.04\,M^{-1}s^{-1}$ was determined from second-order rate plots. It is noteworthy that the complex kinetic behavior, which is characteristic for radical decomposition of the dioxirane,[14] was not observed. Even in N_2-purged solvent[7] at 20 °C, a smooth decrease of dioxirane concentration with time was recorded with a second-order constant $k_2 = 1.12 \pm 0.06\,M^{-1}s^{-1}$, which is equal, within experimental error, to the value obtained when the reaction was carried out under air (see above). Clearly, under normal conditions, the α-methylstyrene epoxidation is much faster than DMD radical decomposition[14] and radical-chain processes do not compete.

Product studies also lead to the conclusion that a radical pathway in the DMD oxidation of α-methylstyrene is unlikely. In fact, the results reported by Minisci et al.[15] could not be reproduced in our laboratories. Instead, the oxidation of α-methylstyrene (**1a**) gave exclusively the corresponding epoxide; the reported[7] products 2-phenylpropanal (51%), 2-phenylpropenol (6%), and 2-phenylpropenal (5%) were not detected. Moreover, deliberate attempts to induce the described radical process[7,10] failed for the DMD epoxidation of α-methylstyrene. For example, the oxidation was also performed in refluxing acetone, that is, at the highest possible temperature (ca. 56 °C) for DMD (Table 1, entry 3), by using a high-efficiency condenser (− 30 °C) in order to avoid dioxirane loss by evaporation. Again, α-methylstyrene epoxide was the major product (>95% yield). Furthermore, no significant variation in the product composition (>90% epoxide) could be detected by performing the reaction at low temperature (−78 °C; Table 1, entry 4), in CCl_4 as cosolvent (Table 1, entry 5), or by adding $CHCl_3$ (Table 1, entry 6), which should be the reagent of choice[16] to propagate a radical pathway.

The oxidation of *trans*-cyclooctene (**1b**) was rapid and led stereoselectively to the *trans*-epoxide[10] (Table 1, entry 7); not even traces of the thermodynamically more stable *cis*-epoxide could be detected. A stepwise diradical pathway for the oxidation of *trans*-cyclooctene would imply a substantial diradical lifetime (ca. nanoseconds), long enough for bond rotation. Since the difference in strain energy is so pronounced for the substrate **1b** (9.8 kcal mol^{-1}) as well as for the product (4.2 kcal mol^{-1})[10], *trans*/*cis* isomerization at the stage of the diradical (Scheme 1, path ii) with loss of stereoselectivity would have been expected. In a competition experiment, a 1:1 mixture of *trans*- and *cis*-cyclooctene was treated with DMD (0.5 equiv): only the *trans*-epoxide was observed. Quantitative relative rate measurements established that $k_{trans}/k_{cis} = 100 \pm 14$, a ratio which is essentially the same as reported for *m*CPBA ($k_{trans}/k_{cis} = 112$).[17] For the epoxidation of alkenes with DMD,[18] the *trans* isomer is two orders of magnitude more reactive than the corresponding *cis* isomer. The appreciable strain energy of *trans*-cyclooctene is mainly responsible for its high reactivity,[19] but the comparatively easy access—relative to that in standard *trans* olefins—to the slightly pyramidalized double bond of the fairly rigid *trans*-cyclooctene skeleton also plays a significant role in reversing the *cis*/*trans* reactivity.

Mechanistically more relevant for our purposes is the fact that, were a radical DMD epoxidation to apply (Scheme 1, path ii), cyclooladducts should be formed, since it is well established that a diradical of the intermediate of this type would preferentially cyclize rather than undergo fragmentation.[15] The cyclization would have essentially no activation energy, whereas probably as much as 10–15 kcal mol^{-1} would be required for the fragmentation, because a relatively strong CO bond is broken and a strained product (epoxide) formed.

The third probe for radical activity, alkene **1c**, is an ultrafast radical clock by way of its cyclopropyl ring opening[13] (Table 1, entry 8). The fact that the epoxide with an intact cyclopropane ring was the exclusive product strongly corroborates a concerted mechanism for this oxygen transfer process. Based on the precise chronometrics[16] of model experiments on the (2,2-diphenylcyclopropylmethyl radical ($k_{ream} = 5 \times 10^{11}\,s^{-1}$), the radical derived from addition of dioxirane to alkene **1c** should rearrange irreversibly at a rate of $k > 10^{11}\,s^{-1}$ (Scheme 2).

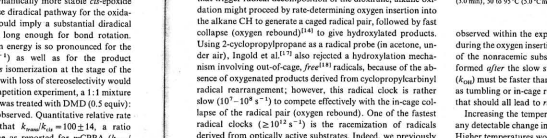


$k_{rearr} = 5 \times 10^{11}\,s^{-1}$ $k_{rearr} > 10^{11}\,s^{-1}$

Scheme 2.

Therefore, the absence of any products derived from such cyclopropylcarbinyl rearrangement renders a radical pathway extremely unlikely. This agrees with the conclusion of the overwhelming majority of reported DMD epoxidations.[1–4]

Despite abundant evidence such as kinetics, kinetic H/D isotope effects, stereoselectivities, and theoretical work, Minisci et al. have also invoked a radical mechanism for the oxygen insertion into carbon–hydrogen bonds in the reaction with dioxiranes with alkanes.[9] Actually, based on early[13] and recent data,[14] we have observed that, provided one avoids conditions that trigger radical decomposition of the dioxirane, alkane oxidation might proceed by rate-determining oxygen insertion into the alkane CH to generate a caged radical pair, followed by fast collapse (oxygen rebound)[14] to give hydroxylated products. Using 2-cyclopropylpropane as a radical probe (in acetone, under air), Ingold et al.[13] also rejected a hydroxylation mechanism involving out-of-cage, *free*[14] radicals, because of the absence of oxygenated products derived from cyclopropylcarbinyl radical rearrangement; however, this radical clock is rather slow (10^7–$10^8\,s^{-1}$) to compete effectively with the in-cage collapse of the radical pair (oxygen rebound). One of the fastest radical clocks ($\geq 10^{12}\,s^{-1}$) is the racemization of radicals derived from optically active substrates. Indeed, we previously showed that hydroxylation of (*R*)-2-phenylbutane (**2**) to (*S*)-2-hydroxy-2-phenylbutane (**3**) by methyl(trifluoromethyl)-dioxirane (TFD) proceeds with 100% retention.[14] Therefore, it was essential to apply this ultrafast radical clock for CH insertions by DMD. Instead of optical rotation measurements (used for TFD[14]), the enantiomeric excess (% *ee*) was assessed by separating the enantiomers of **2** and of **3** on a chiral GC column, and also by ^{1}H NMR spectrometry using shift reagents for **3**. As little as 5% racemization (an error readily encountered



Scheme 3. DMD oxidation of optically active (*R*)-2.

when determining optical rotations) would be indicative of caged radical pairs.[19]

Data for the DMD oxidation of optically active (*R*)-2 were collected in independent experiments in two different laboratories, performed on samples of (*R*)-3 of different optical purity (Table 2). No loss of configuration at the stereogenic center was

Table 2. Enantioselective oxidation of (*R*)-2-phenylbutane by DMD.

(*R*)-2 (*S*)-3

Entry	DMD/equiv [a]	*T*/°C	*t*/h	Conv./% [b]	*ee*(3)/% [c]	*ee*(3)/%
1	7	8	60	58	70.9	71.0 [d]
2	10	25	40	85	61.6	62.2 [e]

[a] Relative to (*R*)-2. DMD added over 10 min. [b] Determined by GC [DB1 column, 30 m × 0.53 mm, 1.5 mm i.d.; *T* prog.: 100 °C (0.5 min), 100 to 280 °C (10 °C min^{-1})] and/or ^{1}H NMR spectroscopy of the crude reaction mixture. [c] As determined (±1%) by high-resolution chiral HRGC employing a Megadex-5 column (30% 2,3-dimethyl-6-pentyl-β-cyclodextrin, 0.20–0.25 mm film, 25 m × 0.25 mm i.d., FID detector, He c.g.) and peak fitting analysis (corr. coeff. 0.999), standardized versus racemic alkane 2. [d] Determined (±2%) by ^{1}H NMR spectroscopy (500 or 400 MHz, $CDCl_3$) using (+)-Eu(hfc)$_3$ [e] As determined by GLC analysis [permethylated β-cyclodextrin, 30 m × 0.25 mm; *T* prog.: 50 °C (3.0 min), 50 to 95 °C (5.0 °C min^{-1})].

observed within the experimental error (i.e., 100% retention!) during the oxygen insertion by DMD into the benzylic CH bond of the nonracemic substrate. Thus, if caged radical pairs are formed *after* the slow step (k_{CH}), their stereorelated collapse (k_{OH}) must be faster than diffusion out of the cage (k_{diff}) as well as tumbling or in-cage rotation (k_{rot}), competitive processes[20] that should all lead to *racemization* (Scheme 3).

Increasing the temperature from 8 to 25 °C did not result in any detectable change in the stereochemical outcome (Table 2). Higher temperatures would be expected to increase out-of-cage diffusional and in-cage rotational processes relative to recombination[21] and, hence, loss of configuration. Thus, the optically active radical probe unequivocally confirms that, at least on a timescale of less than a ps, stereomemory is retained. We cannot definitively conclude whether the stereoretained oxygen rebounds or whether the oxenoid mechanism applies, but *free*[14,18] radicals or even in-cage rotationally randomizing radicals are certainly not involved in the CH oxygen insertion by DMD!

Conclusion

In line with compelling literature data available so far, the results presented herein reinforce the view[11] that—provided care is taken in handling dioxirane solutions to avoid conditions that trigger dioxirane decomposition (e.g., trace metals or other contaminants, exposure to light, depletion of oxygen gas, etc.)[14]—both dioxirane epoxidations and alkane hydroxylations do not involve a radical mechanism. In the case of the DMD oxidation of alkanes, a concerted oxenoid mechanism is kinetically hard to distinguish from a stepwise process with intermediate *fast-collapsing* caged radical pairs (oxygen rebound). We content that further mechanistic work is warranted in this fascinating area to explore these mechanistic details.

Experimental Procedure

Equipment: Boiling points and melting points were not corrected. The ^{1}H NMR spectra were recorded on a Bruker AC200 or AM500 instrument. The ^{1}H NMR were referenced to the residual isotope impurity $CHCl_3$ ($\delta = 7.26$) of the solvent $CDCl_3$ and/or to TMS. Mass spectra were run employing a Hewlett-Packard Model 5970 mass selective detector (EI, 70 eV) connected to a Model 5890 gas chromatograph. GC analyses were performed on a Perkin-Elmer Model 3800 chromatograph, equipped with a Epson Model FX850 data station, by using a DB1 column [30 m × 0.53 mm, 1.5 mm i.d., T_{prog} 100 °C (0.5 min), 100 to 260 °C (15 °C min^{-1})] or an SE30 capillary column (30 m × 0.25 μm i.d.). Optical rotations were measured by employing a Perkin-Elmer Model 241 MC spectropolarimeter. Chiral high-resolution gas–liquid chromatography (HRGC) was performed on a Megadex-5 column (30% 2,3-dimethyl-6-pentyl-β-cyclodextrin, 0.20–0.25 mm film, 25 m × 0.25 mm i.d., FID detector, He c.g.) and a permethylated β-cyclodextrin column by using a Fisons Instruments HRGC Mega Series 2 8560 with peak-fitting analysis ($r^2 = 0.999$). Other equipment and analytical methods have been previously described [3,4,14].

Materials and Reagents: Commercial acetone, carbon tetrachloride, and bromotrichloromethane were purified by standard methods, stored over 3 Å molecular sieves at 4–8 °C, and routinely redistilled prior to use. Oxone triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (a gift from Peroxid-Chemie, Pullach, Germany) was the source of potassium peroxymonosulfate employed in the synthesis of the dioxiranes. Solutions of 0.08–0.16 M dimethyldioxirane in acetone were obtained by adopting procedures, equipment, and precautions that have been already described in detail [2]. High-purity commercial (Aldrich) *n*-methylsiranane (**1a**) was further purified by distillation. Starting materials *trans*-cyclooctene (**1b**) [10], and 1-vinyl-2,2-diphenylcyclopropane (**1c**) [12] were obtained by following known literature procedures; their physical constants and spectral characteristics were in agreement with those given. Optically active (*R*)-(−)-2-phenylbutane [22,23] [(R)-2, b.p. 60–61 °C/20 Torr], with *ee* values of 70.9% [HRGC, $[\alpha]_D = -17.4°$ (neat)] and 62.2% [HRGC], were obtained as previously reported [19].

General procedure for alkene epoxidations by dimethyldioxirane: The alkene (200–500 mg) was dissolved in acetone (5–15 mL) and 1.0–1.1 equiv of dimethyldioxirane (0.05–0.10 M solution in acetone) was rapidly added at the given temperature (Table 1). The reaction solution was monitored by GC or GC/MS and stirred until the peroxide test (KI/starch paper) indicated that the dioxirane had been consumed. The solvent was removed in vacuo (20 °C, 20–100 Torr) to afford the known corresponding epoxides in high purity; these possessed physical constants and ^{1}H NMR spectra in good agreement with the reported ones [24,10]. In the epoxidation of **1a**, the corresponding epoxide was in some instances accompanied by minor amounts of its hydroxyl-ketone, namely, 2-phenylpropane-1,2-diol (GC/MS, ^{1}H NMR).

1-(2,2-diphenylcyclopropyl)-1,2-epoxyethane was obtained as a colorless oil of an inseparable 50:50 diastereomeric mixture: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.40–1.66$ (m, 3H), 2.35–2.58 (m, 1H), 2.65–2.79 (m, 2H), 7.15–7.53 (m, 10H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 17.3$ (t), 18.7 (t), 27.2 (d), 34.7 (s), 35.9 (s), 47.4 (t), 47.6 (t), 52.8 (d), 53.2 (d), 126.1 (d), 126.1 (d), 126.9 (d), 126.9 (d), 127.2 (d), 127.6 (d), 128.4 (2x d), 128.5 (d), 128.6 (d), 130.4 (d), 130.7, 141.1 (s), 141.2 (s), 145.8 (s), 146.0 (s); IR (CCl_4): $\tilde{\nu} = 3060$, 3040, 3010, 2980, 2930, 1585, 1480, 1430, 1410, 1390, 1250, 1120, 1070, 1025, 1000, 950, 810 cm^{-1}; $C_{17}H_{16}O$ (236.3): calcd C 86.41; H 6.82; O 6.77; found C 86.13; H 7.24.

Hydroxylation of (*R*)-(−)-2-phenylbutane by dimethyldioxirane: To a solution of (*R*)-(−)-2-phenylbutane [(*R*)-2] with an *ee* value of 70.9% (188 mg, 1.40 mmol) in acetone (8 mL) at 8 °C was added gradually (over 1 h) via a. sevenfold excess of a standardized cold solution of dimethyldioxirane (0.091 M, 106 mL, ca. 9.8 mmol). The reaction mixture was allowed to stir under an atmosphere of air at the given temperature, the progress of the reaction was monitored by GC and GC/MS analyses. After removal of the solvent in vacuo, ^{1}H NMR spectroscopy (500 MHz, $CDCl_3$) with (+)-Eu(hfc)$_3$ as chiral shift reagent showed that, in the crude starting mixture, the alcohol product was 71.0% optically pure. The identical reaction of 61.6% optically pure (*R*)-2 yielded the alcohol (*S*)-3 with an *ee* value of 62.2%, as determined by chiral GC analysis (≤ 2% on a permethylated β-cyclodextrin column. The physical constants and spectral data of (*S*)-(+)-2-phenylbutan-2-ol [(*S*)-3] [25] isolated from the reaction mixture by column flash chromatography (SiO_2, gel, Et_2O/petroleum ether 1:9) were in full agreement with those reported [19].

Kinetic Measurements: Runs were performed by following the decay of the dioxirane concentration (by iodometry) with time, according to the reported procedure [1f,14]. All experiments were carried out under air (or under a N_2 blanket) under constant stirring conditions, with the dioxirane and alkene initial concentrations kept in the range (4–6) × 10^{-3} M, and differing by 8–20%. At zero time, an aliquot (0.5–1.0 mL) of a thermostated dioxirane solution in acetone was added to 10–20 mL of a solution (also thermostated) of *n*-methylsiranane (**1a**) in the same solvent; aliquots (20–50 μL) of the reaction solution were withdrawn periodically and quenched with excess KI/EtOH. The liberated I_2 concentration was determined by iodometry. In runs performed by following the decay of *n*-methylsiranane substrate by GC, Freon A112 was also present as an internal standard in the reaction mixtures. At regular time intervals, aliquots (5–10 μL) were withdrawn and treated with 0.1 mL of ca. 0.15 M nBu_4S in CH_2Cl_2. The substrate concentration was determined from a previously prepared calibration curve. Linear $\ln([a] - x)/([b] - x)]$ versus time plots were obtained to over 80% reaction, with $r^2 \geq 0.999$; from these data the k_2 ($M^{-1}s^{-1}$) values were calculated. In each case, at least two independent runs were performed and the k_2 values averaged (estimated error ≤ ± 6%).

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