Epoxidation of α,β-Unsaturated Carbonyl Compounds by Dimethyldioxirane

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Dioxiranes, three-membered cyclic peroxides, are versatile and highly reactive oxygen-atom transfer reagents.[1] Historically, Curci determined[2] that dimethyldioxirane was the oxygen-atom transfer agent in the peroxymonosulfate (caroate)–acetone system. Murray showed[3] that dialkyldioxiranes could be isolated by low-temperature distillation of the dioxirane from the peroxymonosulfate (caroate)–ketone reaction mixtures. Dimethyldioxirane has been found[1] to be the reagent of choice for epoxidation of electron-rich alkenes. Our studies[4] on epoxidation of simple alkenes with isolated dimethyldioxirane showed the reaction to be sensitive to steric effects, protic solvent effects, and electrophilic in character. Results with electron-poor systems have shown[1d,2,5,6] that dimethyldioxirane will epoxidize a variety of unreactive substrates in the presence of excess reagent. Recent product studies by Adam and co-workers have shown[5] that dimethyldioxirane will epoxidize α,β-unsaturated ketones, acids, and esters as well as flavones.[6] We report here a study of the kinetics of epoxidation of a series of chalcones and selected α,β-unsaturated carbonyl compounds by dimethyldioxirane.

Results

Dimethyldioxirane (**1**) was prepared[2] by the reaction of potassium monoperoxysulfate (caroate) and acetone, and isolated as an ca. 0.1 M solution in acetone by the general method developed by Murray.[3] The reaction of a series of (*E*)-chalcones **2a–o** (reaction 1) as well as (*E*)-(4-chlorobenzal)pinacolone (**3**), (*E*)-cinnamic acid (**4**), (*E*)-methyl cinnamate (**5**), 4-methyl-3-penten-2-one (**6**), 2-cyclohexen-1-one (**7**), and perinaphthenone (**8**) with excess **1** in acetone at ambient temperature yielded the corresponding epoxides in high yield (~95%). As expected,[1] epoxidation was stereospecific. The epoxides were isolated, purified and identified by comparison of their physical and spectral data with those of authentic samples and/or literature values.

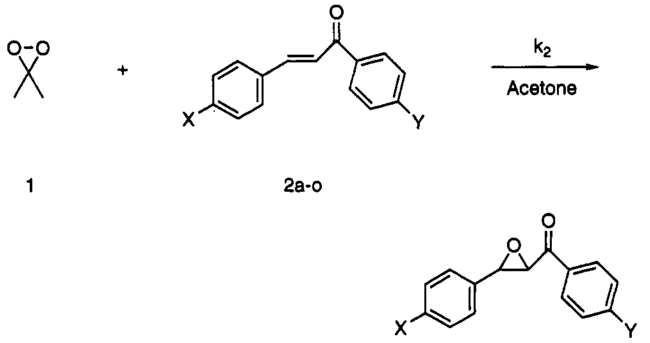
Kinetic studies of the epoxidation of α,β-unsaturated compounds **2–8** were carried out in dried acetone at 30 °C. The reaction was found to be of the second order overall, first order in dioxirane and in α,β-unsaturated carbonyl compound. The second-order rate constants (k_2) were obtained from UV data under pseudo-first order conditions with the dioxirane in, at least, 10-fold excess. Variation of the dioxirane/substrate ratio yielded k_2 values that were within experimental error of one another. The results of the kinetic experiments at 30 °C are listed in Table I for the (*E*)-chalcones and in Table II for the remaining compounds.

Table I. Second-Order Rate Constants (k_2) for the Epoxidation of (*E*)-Chalcones 2a–o by Dimethyldioxirane in Dried Acetone at 30 °C

chalcone	4-X	4′-Y	k_2 M^{-1} s^{-1} (× 10^3)
2a	OMe	H	11.5 ± 0.1
2b	Me	H	3.1 ± 0.2
2c	F	H	1.58 ± 0.01
2d	H	H	1.54 ± 0.13
2e	Cl	H	0.95 ± 0.04
2f	Br	H	1.03 ± 0.05
2g	CN	H	0.36 ± 0.03
2h	NO_2	H	0.25 ± 0.03
2i	H	OMe	2.12 ± 0.06
2j	H	Me	1.86 ± 0.04
2k	H	F	1.54 ± 0.04
2l	H	Cl	1.47 ± 0.03
2m	H	Br	1.39 ± 0.05
2n	H	CN	1.24 ± 0.05
2o	H	NO_2	1.07 ± 0.13

Table II. Second-Order Rate Constants for the Epoxidation of Selected α,β-Unsaturated Carbonyl Compounds by Dimethyldioxirane in Dried Acetone at 30 °C

compound	no.	k_2 M^{-1} s^{-1} (× 10^3)
(4-chlorobenzal)pinacolone	**3**	0.70 ± 0.02
(*E*)-cinnamic acid	**4**	0.66 ± 0.07
(*E*)-methyl cinnamate	**5**	0.63 ± 0.06
4-methyl-3-penten-2-one	**6**	5.7 ± 0.9
2-cyclohexen-1-one	**7**	1.3 ± 0.09
perinaphthenone	**8**	0.68 ± 0.01



For the chalcones, electron-releasing substituents in the para positions of the phenyl rings enhanced the rate of epoxidation, while electron-withdrawing groups had the opposite effect. This phenomena was more pronounced in the 4-substituted chalcones (**2a–c, e–h**) than with their 4′-substituted analogues (**2i–o**). The second-order rate constants (k_2) for the epoxidation of **2a–c,e–o** displayed excellent-to-good LFERs against $\sigma+$ in Hammett-type plots. A linear regression analysis of the data provided ρ^+ values and correlation coefficients (r) of −1.03 and r = 0.995, respectively, for the 4-substituted chalcones, and −0.182 and r = 0.981 for the 4′-substituted chalcones (Figure 1). The k_2 values for epoxidation of **3–8** were similar to those of the chalcones. The k_2 values for epoxidation of the α,β-unsaturated acid and ester **4** and **5** were essentially identical to that of chalcone **2d**. Formal

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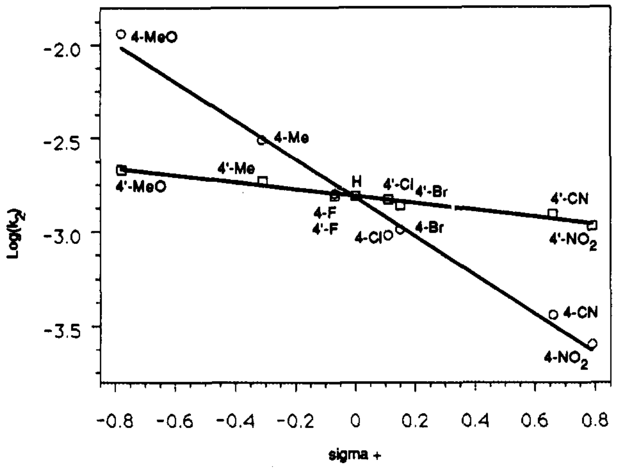

Figure 1. Plots of the k_2 values vs $\sigma+$ constants for epoxidation of 4-substituted (open squares) and 4′-substituted (open circles) chalcones by isolated dimethyldioxirane in dried acetone at 30 °C.

Table III. Second-Order Rate Constants (k_2) for the Epoxidation of Chalcone 2d by Dimethyldioxirane in Dried Acetone at Various Temperatures

temperature ±0.3 °C	k_2 M^{-1} s^{-1} ($\times 10^3$)
25.0	1.24 ± 0.12
27.5	1.35 ± 0.14
30.0	1.54 ± 0.13
35.0	2.3 ± 0.2
37.5	2.3 ± 0.2
40.0	3.0 ± 0.2
45.0	3.56 ± 0.26
47.5	4.0 ± 0.3
50.0	4.4 ± 0.4

replacement of the aryl′ group on a chalcone by an alkyl group had little or no effect. Perinaphthenone 8 was found to be of lower reactivity despite the (*Z*)-configuration. The aliphatic α,β-unsaturated compounds showed a slight increase in reactivity over the aryl analogs. The k_2 values for epoxidation of the α,β-unsaturated systems by 1 were, in general, approximately 2 orders of magnitude slower than those[4] of a simple *trans*-alkenes.

The rate constants for the epoxidation of the parent chalcone **2d** in dried acetone were measured over the temperature range of 25–50 °C (Table III). The Arrhenius method was used to determine an activation energy (E_a) of 10.1 ± 0.4 kcal mol^{-1} ($r = 0.993$). The enthalpy of activation (ΔH^*) and the entropy of activation (ΔS^*) were calculated at 30 °C to be 9.5 ± 0.4 kcal mol^{-1} and −40.4 eu, respectively [k_2 (30 °C) = 1.54×10^{-3} M^{-1} s^{-1}].

As observed previously[4] for the epoxidation of simple alkenes by 1, consistent second-order rate constants could only be obtained with dried solutions of acetone. Addition of water resulted in measurable increases in the k_2 values for epoxidation. Data from experiments with added water in the reaction of 1 and chalcone 2a are listed in Table IV. The chalcone proved to be insoluble at higher mole fractions (>0.25) of added water. A plot of k_2 vs χ_{H_2O} appears linear, presumably due to the limited range of χ_{H_2O} values available. For epoxidation of the simple alkenes,[4] data at low χ_{H_2O} also appeared to be linear in this range but curved upward sharply at higher quantities of added water.

Discussion

An understanding of the nucleophilic and electrophilic characteristics of dimethyldioxirane is necessary to evaluate the oxygen-atom transfer reactivity. Measurement of the electrophilic/nucleophilic character of dioxirane 1 by Adam[7] employing the thianthrene 5-oxide method yielded a χ_{nu} of 0.85 indicative of a dominating nucleophlic character. Murray's S-oxidation results[8] clearly indicated that sulfide and sulfone oxidation by dimethyldioxirane was an electrophilic process. Our work[4] with aliphatic and aryl alkene epoxidation showed that process to be electrophilic in nature and to occur via a spiro "butterfly"-type mechanism. Epoxidation of α,β-unsaturated carbonyl systems is usually accomplished via a nucleophilic process (alkaline hydrogen peroxide) rather than by electrophilic routes. Product studies have shown[1d,2,5,6] that epoxidation of α,β-unsaturated compounds by dimethyldioxirane, in excess, is a useful preparative method. However, the present study has found that the absolute magnitude of the k_2 values for epoxidation of the various α,β-unsaturated systems by 1 is relatively low when compared to that of simple alkenes. In addition, the rates of epoxidation of the α,β-unsaturated compounds (Table II) seem relatively insensitive to structural changes. These factors must be taken into account to maximize the synthetic utility of the reagent for this application.

Table IV. Second-Order Rate Constants for the Epoxidation of 4-Methoxychalcone (2a) by Dimethyldioxirane (1) in Acetone[a] in the Presence of Added Water at 30 °C

vol H_2O added (μL)	χ_{H_2O}[b]	k_2 M^{-1} s^{-1} ($\times 10^3$)	k_{rel}
0	0	11.5 ± 0.1	1
32	0.091	18.4 ± 0.2	1.6
64	0.167	24 ± 1	2.1
96	0.231	29 ± 1	2.5

[a] Dried over anhydrous Na_2SO_4. [b] Mole fraction of added water.

Our previous kinetic study on the reaction of a series of substituted styrenes with 1 showed[4a] an excellent LFER with a ρ^+ value of −0.90 in dried acetone and −1.0 in slightly moist acetone (~0.15 mole fraction of water). The present study yielded an excellent LFER for the 4-substituted chalcones with a ρ^+ of −1.03. The epoxidation of chalcones by peroxybenzoic acid in benzene at 30 °C has been found[9] to correlate with σ^+ values. However, the ρ^+ value (−0.45) for the peroxybenzoic acid case was much smaller than that for the dioxirane reaction. A recent study by Murray[10] on epoxidation of (*E*)-ethyl 4-substituted cinnamates found an excellent correlation with σ values and obtained an ρ of −1.53. A ρ^+ value of −1.3 can be extracted from the ethyl cinnamate data.[10] For that case, a σ^+ fit can not be proven due to the nature of the substituents investigated. Our result and that of Murray show that the electronic requirements at the β-carbon of the two α,β-unsaturated systems are essentially identical to that in the styrene system. Nucleophilic and electrophilic processes would be expected to show substantial bonding to the β-carbon in the transition state, but with opposite electronic requirements. For example, the ρ value for epoxidation of chalcone by alkaline hydrogen peroxide (nucleophilic) in methanol was found[11] to be +0.92 at 30 °C.

The LFER for the 4′-substituted chalcones also yielded a σ^+ relationship with a ρ^+ of −0.18. This is a significant

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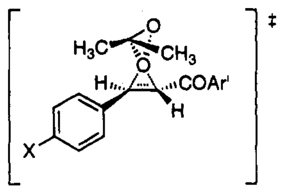
Chart I



finding. The 5-fold reduction in ρ value can be attributed, in large part, to the formal insertion of a carbonyl "spacer" group between the carbon–carbon double bond and the substituted phenyl group. Furthermore, the σ^+ correlation indicates that the electronic requirements for the α-carbon are similar to those for the β-carbon. This clearly shows that the α-carbon is involved directly with the oxygen-atom under transfer. The extent of partial bonding of the dioxirane oxygen atom to both the α- and β-carbons appears similar. This requires an electrophilic transfer of oxygen to the α,β-unsaturated system and is consistent with a transition state as shown in Chart I.

The effect of added water on the kinetics of epoxidation of simple alkenes[4] and α,β-unsaturated compounds is suggestive of a polar solvent effect. If this is the case, then the observed rate enhancements would be consistent with an electrophilic process. However, hydrogen-bonding effects or a change in mechanism can not be ruled out.

The activation parameters at 30 °C for epoxidation of chalcone **2a** ($\Delta H^{\ddagger} = 9.5 \pm 0.4$ kcal/mol; $\Delta S^{\ddagger} = -40$ eu) by dioxirane 1 are in good agreement with those[10] for epoxidation of (*E*)-ethyl cinnamate by 1 (calcd from data: $\Delta H^{\ddagger}$ = 13.5 kcal/mol; $\Delta S^{\ddagger}$ = −27 eu). The activation parameters[12] for epoxidation of *trans*-stilbene by peroxybenzoic acid [$\Delta H^{\ddagger}$ = 15.2 kcal/mol, $\Delta S^{\ddagger}$ = −23] are similar to those of dioxirane with the α,β-unsaturated systems. The activation parameters for the alkaline H_2O_2 epoxidation of chalcones in methanol ($\Delta H^{\ddagger}$ = 15.1 kcal/mol; $\Delta S^{\ddagger}$ = −14 eu)[11] show a substantially different entropy requirement. The large negative $\Delta S^{\ddagger}$ term seems consistent with the electrophilic, spiro process shown in Chart I.

Experimental Section

All solvents were either of spectral or HPLC grade (Aldrich). Melting points were recorded on a Thomas-Hoover (Uni-melt) capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on the Varian EM-360L and JEOL GX-270 NMR spectrometers (tetramethylsilane as an internal standard). Caroate (Oxone-Aldrich) was used without further purification. (*E*)-Chalcones **2a–o** were prepared by alkaline aldol condensation of the appropriately para-substituted benzaldehydes and/or para-substituted acetophenones as previously described.[13a] (4-Chlorobenzal)pinacolone (**3**) was prepared by the method of Hill and Bramann.[13b] The spectral and physical data for compounds **2a–o** and **3** were in excellent agreement with literature values.[14] (*E*)-Cinnamic acid (**4**), (*E*)-methyl cinnamate (**5**), mesityl oxide (**6**), 2-cyclohexen-1-one (**7**), and perinaphthenone (**8**) were commercially available (Aldrich) and purified by recrystallization or distillation before use. UV kinetic experiments were performed on a Perkin Elmer Lambda-6 UV/VIS spectrophotometer equipped with jacketed cell holder. The temperature was maintained (±0.3 °C) with a circulating constant temperature bath and monitored by a Markson digital thermometer with the probe placed inside the sample chamber.

Dimethyldioxirane (1). Dimethyldioxirane (1) was prepared by the general method developed by Murray.[3a] The acetone solutions of 1 were dried over anhydrous Na_2SO_4, filtered, and stored at −17 °C over fresh anhydrous Na_2SO_4 until needed. The concentration of 1 was determined as follows: 1.50 mL of dioxirane stock solution was added to 20 μL of methyl phenyl sulfide at room temperature. After 1 min, the acetone was removed under reduced pressure. The reaction products were methyl phenyl sulfoxide (major) and methyl phenyl sulfone (minor, varying amounts). Integration of the product's methyl signals vs those of the methoxy group of 2-bromoanisole and the methine group of triphenylmethane (added internal standards) was used to determine the molar equivalents of oxygen transferred by 1. All glassware used for dioxirane preparation had been pretreated with boiling aqueous Na_2EDTA, followed by an acetone rinse. No difficulties have been encountered in the preparation, handling, and storage of dimethyldioxirane. However, normal precautions associated with the handling of peroxides should be followed.

Product Studies

The epoxidation of the α,β-unsaturated systems **2(a–o)–8** by dimethyldioxirane produced the corresponding epoxides as the sole observable products. Epoxide yields of 95% or greater were obtained as follows: 0.3 mmol of the α,β-unsaturated carbonyl compound was added to 5 mL of acetone in a dry flask under nitrogen. Three molar equivalents of 1 (stock solution) were added via syringe at ambient temperature. The reaction mixture was stirred overnight in the dark. Longer reaction times (up to 36 h) were employed for the less-reactive compounds. Two additional molar equivalents of 1 were added to the reaction flask as above and the mixture was stirred another 6–12 h. The volatile components were removed under reduced pressure to yield the epoxides in a high state of purity and in essentially quantitative yields (≥95%). Omission of the second addition of excess dioxirane solution resulted in substantially lower yields of epoxide (81 ± 5%). The results for epoxidation of **2a**, **2b**, **2d**, **2h–j**, **2m**, and **4** were in excellent agreement with those reported by Adam.[5] The epoxides were identified by comparison of spectral and physical data[15] with those of authentic samples.

Kinetic Studies

The kinetic studies of the epoxidation of chalcones **2a–o**, (4-chlorobenzal)pinacolone (**3**), (*E*)-cinnamic acid (**4**), (*E*)-methyl cinnamate (**5**), 4-methyl-3-penten-2-one (**6**), 2-cyclohexenone (**7**), and perinaphthenone (**8**) were done under pseudo-first-order conditions with dioxirane 1 in ≥10-fold excess at 30 °C. The kinetic experiments were carried out as follows: 1.30 mL of a dried acetone

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solution of 1 (known concentration) was allowed to equilibrate to 30 °C in the UV cell in the spectrometer for 10 min. A stock solution in dried acetone of the alkene at the desired concentration was prepared by weight. Then 0.100 mL of the alkene stock solution was added to the cell via syringe and rapidly mixed. The kinetics for the epoxidation of **2a–o**, **3**, and **8** were monitored by observing the loss of the alkene absorbance at 400 nm. The epoxidations of **4** and **5** were followed by observing the loss of dimethyldioxirane at 328 nm (λ_{max} 328; ϵ 13.6 M^{-1} cm^{-1}). The epoxidation of **6** was followed by observing the loss of **1** at 360 nm. The kinetic experiments for the epoxidation of **7** were preformed in a similar manner. However, the kinetics runs were monitored when **1** was in >10-fold excess of **7** and when **7** was in >10-fold excess of **1**. The k_2 values determined at the extremes were within experimental error. For the experiments with added water, deionized water was added to 1.20 mL of the stock solution of **1** in the UV cell via syringe before addition of the alkene.

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