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The reaction of dimethyldioxirane with 1,3-cyclohexadiene and 1,3-cyclooctadiene: monoepoxidation kinetics and computational modeling

Abstract: The reaction of dimethyldioxirane (**1**) with excess 1,3-cyclohexadiene (**2a**) and 1,3-cyclooctadiene (**2b**) in dried acetone yielded the corresponding monoepoxides in excellent yield. Second-order rate constants for monoepoxidation were determined using UV methodology. The k_2 value for the monoepoxidation of 1,3-cyclohexadiene was found to be 1.14±0.06 M^{-1} s^{-1}, whereas that for the monoepoxidation of 1,3-cyclooctadiene was 0.31±0.03 M^{-1} s^{-1}. Basic density functional calculations at the B3LYP/6-31G level were employed to model the monoepoxidations. As expected, the calculations were consistent with a concerted, electrophilic process with a spiro-transition state. As found for the epoxidation of simple alkenes, the calculated transition-state geometry showed a slight asynchronous tilt of the dioxirane plane relative to that of the remaining alkene portion of the diene and a slight tilt back from the face of the diene. Relative reactivities (relative k_2 values) were determined using the difference in the calculated electronic activation energies and were consistent with the experimental relative k_2 values without the need to correct for the medium (solvent). Reactivity differences for epoxidation can be quickly predicted by this approach as long as there are reasonable structural similarities between the substrates.

Keywords: density functional theory (DFT) calculations; dimethyldioxirane; epoxidation; kinetics.

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Introduction

Studies have shown dioxiranes to be powerful oxidants [1–4]. Dimethyldioxirane (**1**), in particular, has been useful in carrying out many synthetic transformations, adding an oxygen to a variety of substrates [1–4]. One of the most studied reactions of **1** is the epoxidation of olefins. Dimethyldioxirane epoxidations have been shown to be sensitive toward steric and substituent effects [1–4]. Kinetic studies have shown the relative reactivities for *cis* vs. *trans* epoxidation by **1** of simple alkyl substituted alkenes to be approximately 8:1 or greater [5]. The reverse reactivity trend for the epoxidation of phenyl-substituted alkenes was noted as the major exception [6]. However, all epoxidations by **1** have been shown to be quantitative and stereospecific. Mechanistically, the epoxidations have been postulated to occur *via* a spiro-transition state [1–7]. Semiempirical (AM1) calculations have been shown to be useful in modeling dimethyldioxirane epoxidation of simple alkenes within a structurally homologous series [8]. Density functional theory (DFT) calculations were used to model the epoxidation of ethylene, propene, and *cis*- and *trans*-2-butene by both the parent unsubstituted dioxirane and **1** and predicted a spiro-transition state in agreement with the mechanism postulated based on experimental data [9–12]. *Ab initio* calculations, employed to model *cis* and *trans* epoxidations by **1** also predicted a spiro-transition state and the correct relative reactivity of *cis* vs. *trans* simple alkenes [13]. Semiempirical (AM1) calculations failed to predict the relative reactivities of the epoxidation of alkenes by **1** within a series in which there were only minor reactivity differences as well as across two series for which there are small reactivity differences [14]. Basic gas phase DFT calculations proved to be effective for modeling the epoxidation of α,β-unsaturated esters by **1** as well as for the epoxidation of several acyclic conjugated dienes (*s-trans* systems) by dioxirane, systems for which steric effects are minimized [15, 16]. No studies have been reported for the epoxidation of cyclic

conjugated *s-cis* dienes. We report here the results of a kinetic study with computational modeling of the epoxidation of 1,3-cyclohexadiene (**2a**) and 1,3-cycloctadiene (**2b**) by dimethyldioxirane (**1**).

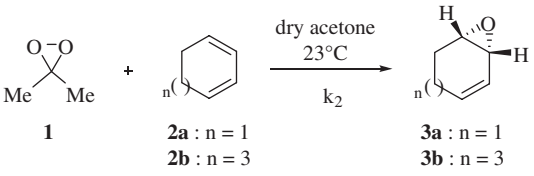
Results and discussion

The reaction of **1** with excess 1,3-cyclohexadiene (**2a**) and 1,3-cyclooctadiene (**2b**) were carried out in dried acetone (Scheme 1). Under these conditions, the monoepoxide was the major product in either case. The monoepoxides were isolated in low yield and characterized by ^{1}H NMR and GC-MS data. The spectroscopic data were in agreement with the literature values [17].

Kinetic studies with **2a** and **2b** were carried out using UV methodology in dried acetone at 23°C. The epoxidations by **1** were shown to be of the first order in dioxirane and in diene; second-order overall. 1,3-Cyclohexadiene was found to be more reactive toward monoepoxidation than 1,3-cyclooctadiene.

Pseudo-first-order conditions with a 10:1 diene/dioxirane ratio were employed to determine the k_2 value for the monoepoxidation of 1,3-cyclooctadiene. Owing to the greater reactivity, second-order conditions were employed to determine the k_2 value for the monoepoxidation of 1,3-cyclohexadiene. Representative plots of the kinetic data are shown in Figures 1 and 2. The k_2 values for the monoepoxidation of 1,3-cyclohexadiene and 1,3-cyclooctadiene are 1.14±0.06 and 0.31±0.03 $M^{-1} s^{-1}$, respectively. The k_2 value for the monoepoxidation of 1,3-cyclohexadiene is comparable to those for the monoepoxidation of disubstituted acyclic conjugated dienes (1.29–1.42 $M^{-1} s^{-1}$) by **1** [14]. The k_2 value for the monoepoxidation of 1,3-cyclooctadiene is comparable to that for the epoxidation of simple *cis*-alkenes by **1** [8].

The monoepoxidations of the cyclic dienes were modeled by applying a basic DFT approach using the B3LYP/6-31G basis set. Regardless of the initial orientation of the reactants, minimized transition-state calculations yielded a spiro-transition state with a slight asynchrony tilt for the monoepoxidation of



1 **2a** : n = 1 **2b** : n = 3 **3a** : n = 1 **3b** : n = 3

Scheme 1

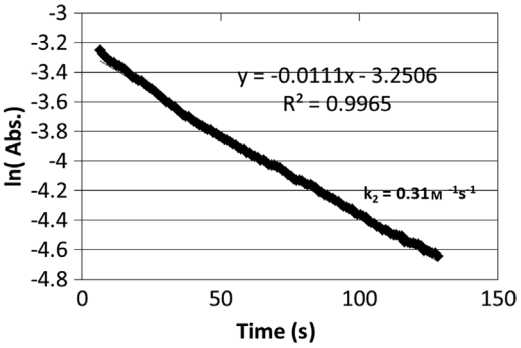


Figure 1 Representative pseudo-first-order plot for the monoepoxidation of 1,3-cyclooctadiene (**2b**) by **1** in acetone at 23°C.

1,3-cyclohexadiene and 1,3-cyclooctadiene as shown in Figure 3. The calculated transition-state geometries for these cases are consistent with previous results for the epoxidation of simple alkenes by **1**, which also show similar asymmetry and tilts for the spiro-transition states [9–14].

The basic DFT approach was employed to quickly predict relative reactivities. These calculations were carried out in the gas phase because solvent corrections have been shown to lower the individual values but not affect the difference between values [18]. The predicted activation energies were determined by taking the difference between the calculated energies of the transition state and those of the ground states of the reactants while controlling for conformational effects. The predicted activation energies for 1,3-cyclohexadiene and 1,3-cyclooctadiene were found to be 13.37 and 14.14 kcal, respectively. The k_{rel} predicted values were calculated from the electronic activation energy difference for the two cyclic dienes. The ground-state geometry calculations of 1,3-cyclohexadiene and 1,3-cyclooctadiene show that 1,3-cyclohexadiene resembles a relatively flat *s-cis*

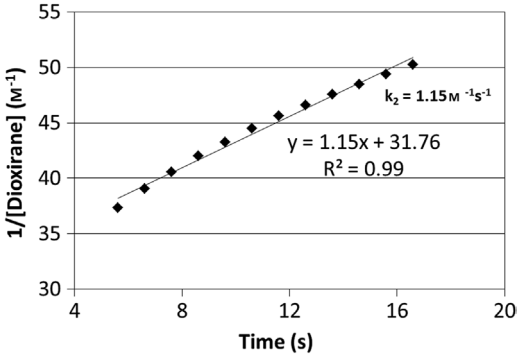


Figure 2 Representative second-order plot for the monoepoxidation of 1,3-cyclohexadiene (**2a**) by **1** in acetone at 23°C.

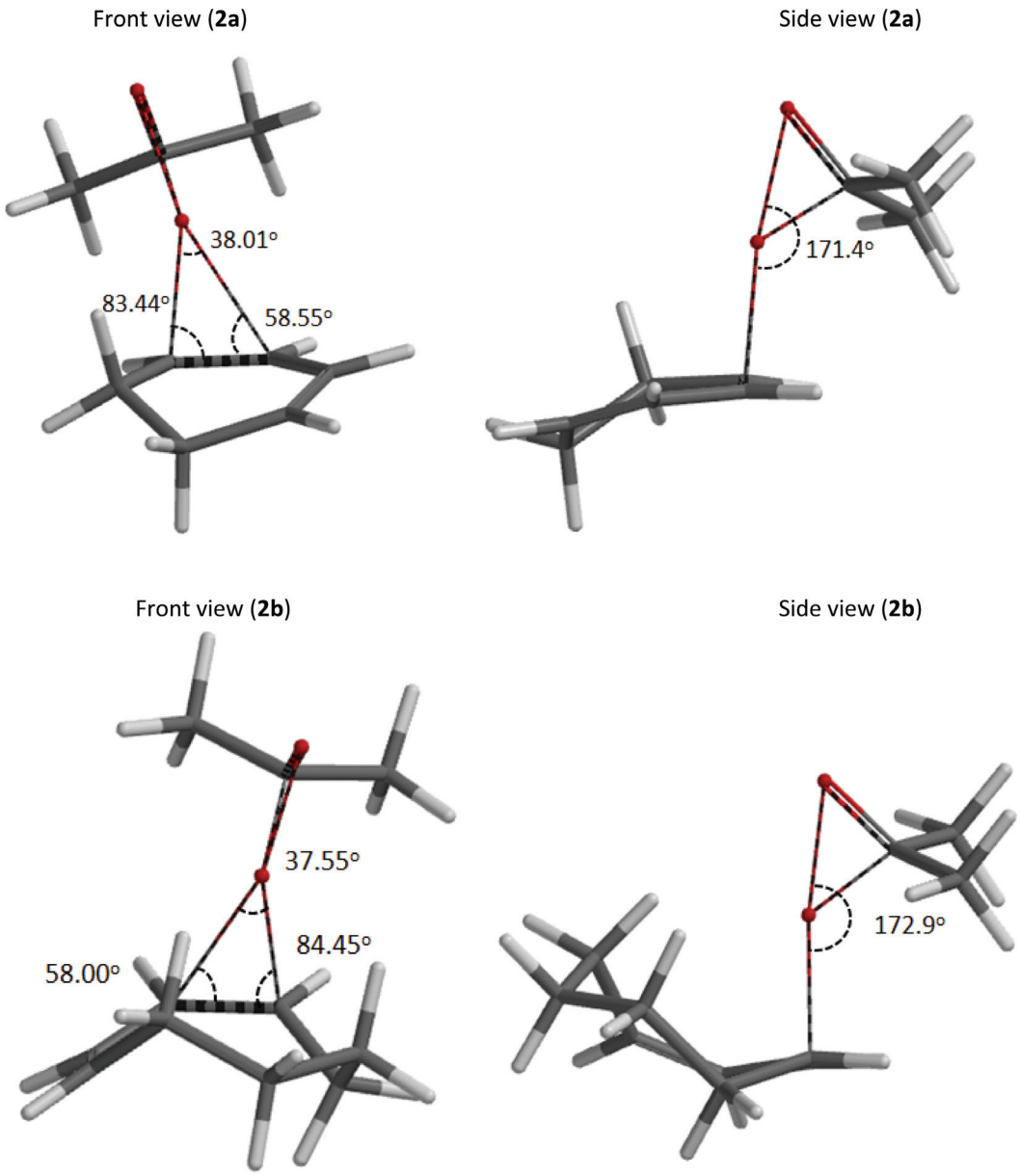


Figure 3 Calculated density functional B3LYP 6-31G* transition-state structures for the monoepoxidation of 1,3-cyclohexadiene (**2a**) and 1,3-cyclooctadiene (**2b**) by **1**.

system. The ground-state structure of the 1,3-cyclooctadiene shows the two double bonds to have a torsion angle of 51°, reducing conjugation. The predicted relative rates for **2a**/**2b** of 3.9: 1 are consistent with the experimental kinetic data for **2a**/**2b** of 3.7:1. The kinetic and predicted data are shown in Table 1. The HOMO-LUMO energies were taken from the DFT B3LYP 6-31G optimized geometries of 1,3-cyclohexadiene, 1,3-cyclooctadiene, and dimethyldioxirane. The HOMO energies of 1,3-cyclohexadiene and 1,3-cyclooctadiene are -5.59 and -6.05 eV, respectively. The LUMO energy of dimethyldioxirane is -0.47 eV. These data are consistent with the DFT results predicting that the 1,3-cyclohexadiene would be more reactive than the 1,3-cyclooctadiene.

On the basis of the successful modeling of the cyclic dienes, the relative rate constants for *cis*-/*trans*-phenyl-substituted alkenes **4a**,**b** were evaluated using this quick, gas-phase calculation method. The transition-state geometries of the epoxidation of *cis*-1-phenylpropene and *trans*-1-phenylpropene by **1** were determined (Figure 4). The second-order rate of the epoxidation of *cis*-1-phenylpropene and *trans*-1-phenylpropene by **1** (Scheme 2) have

Table 1 Experimental and predicted (DFT) data for the monoepoxidation of 1,3-cyclohexadiene (**2a**) and 1,3-cyclooctadiene (**2b**) by compound **1**.

Molecule	k_{2expt} (M^{-1} s^{-1})	Total ground-state energies[a] (kcal/mol)	Transition-state energy[a] (kcal/mol)	Activation energy[a] (E_{elect})	ΔE_{elect}	k_{2rel}	
						Predicted	Experimental
2a	1.14±0.06	314 809.20	-314 795.83	13.37	0.80	3.9±0.3	3.7±0.6
2b	0.31±0.03	-364 143.10	-364 128.96	14.14		≡1[b]	≡1[b]

[a] Calculated.

[b] Normalized.

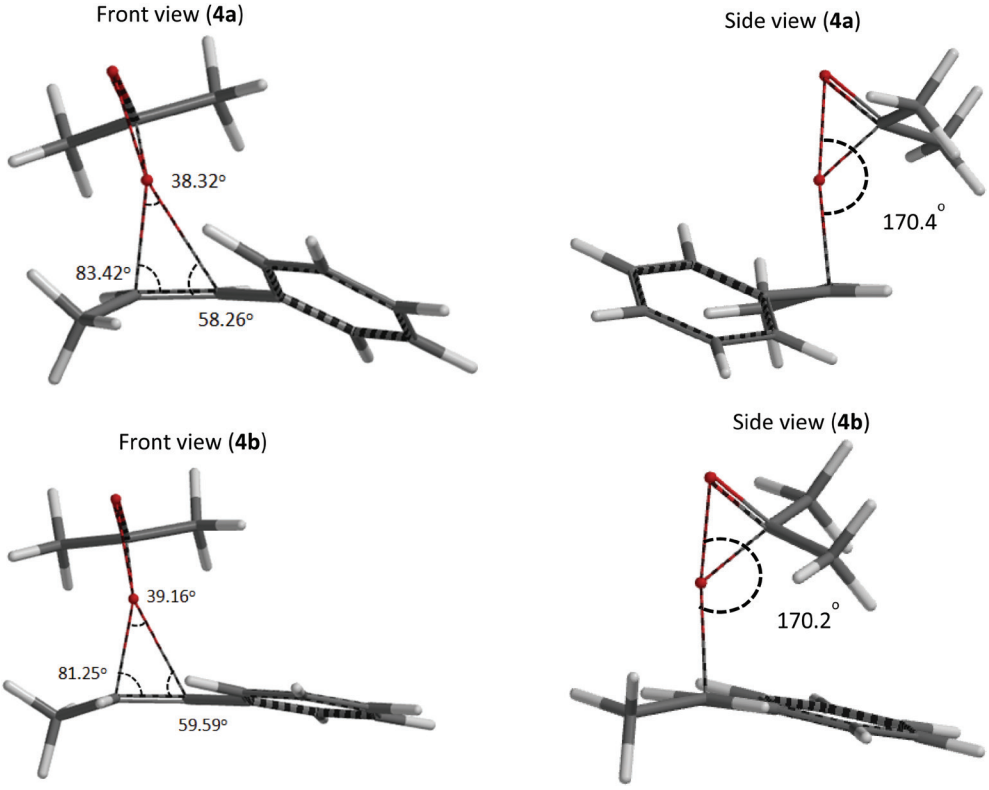
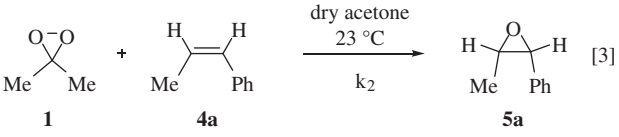


Figure 4 Calculated density functional B3LYP 6-31G* transition-state structures for the epoxidation of *cis*-1-phenylpropene (**4a**) and *trans*-1-phenylpropene (**4b**) by **1**.

been previously reported as 0.18±0.01 and 0.29±0.02, respectively, and noted as an exception of the overall trend of the reactivity of epoxidation by **1** of *cis* vs. the corresponding *trans*-alkene [6]. As expected, the calculation predicted that the epoxidation occurs *via* a concerted, electrophilic process with a spiro-transition state including a slight asynchrony tilt in the oxygen insertion bond formation.



Scheme 2

The electronic activation energies for the epoxidation of *cis*-1-phenylpropene and *trans*-1-phenylpropene were determined to be 14.00 and 13.80 kcal, respectively. The calculated relative reactivity was calculated to be 1.2:1, *trans*-1-phenylpropene/*cis*-1-phenylpropene, whereas the experimental relative reactivity was 1.6:1, thus successfully predicting the greater reactivity of the *trans* isomer. Table 2 summarizes the electronic and experimental data. The DFT results show that the exception in relative reactivity for **4a** and **4b** is actually consistent with the steric

Table 2 Experimental and predicted (DFT) data for the epoxidation of *cis*-1-phenylpropene (**4a**) and *trans*-1-phenylpropene (**4b**) by compound **1.**

Molecule	k_{2expt} (M^{-1} s^{-1})	Total ground-state energies[a] (kcal/mol)	Transition-state energy[a] (kcal/mol)	Activation energy[a] (E_{elect})	ΔE_{elect}	k_{2rel}	
						Predicted	Experimental
4a (*cis*)	0.18±0.01	-387 313.44	-387 299.44	14.00	0.20	≡1[b]	≡1[b]
4b (*trans*)	0.29±0.02	-387 316.19	-387 302.39	13.80		1.2±0.2	1.6±0.2

[a] Calculated.

[b] Normalized.

effect argument, but in this case, the *trans* isomer has the least steric interactions leading to the apparent reversal.

Conclusions

1,3-Cyclohexadiene (**2a**) was found to be more reactive than 1,3-cyclooctadiene toward monoepoxidation by **1.** Kinetic studies showed that the overall reactivity for the monoepoxidation of the essentially *s-cis* 1,3-cyclohexadiene is comparable to that of the *s-trans* acyclic conjugated dienes with similar number of substituents. The results of the study of the less reactive substrate, 1,3-cyclooctadiene (**2b**), are similar to the second-order rate constants of simple *cis*-alkenes. It appears that the two double bonds behave as if they are isolated alkenes for this case. Basic DFT calculations (gas phase) are consistent with the concerted (spiro) mechanism for the monoepoxidation of the dienes and predicted the relative reactivity with reasonable agreement with experimental data. Application of this approach to epoxidation of *cis*-/*trans*-1-phenylpropene successfully predicted the previously noted unexpected reactivity for this pair of alkenes. The method appears to be able to detect the effect of subtle steric interactions in these closely related systems. The basic DFT method is a reliable quick approach to model dioxirane epoxidation reactions and for predicting relative reactivities as long as the reactants have reasonable structural similarities and conformational factors are controlled without the need for time consuming solvent corrections. The challenge of predicting the relative reactivities for substrates with vast structural differences toward epoxidation by **1** still remains to be addressed.

Experimental

Dimethyldioxirane was prepared by the general procedure developed by Murray, for the reaction of oxone and acetone, with modifications [5, 7]. Stock solutions (≤0.1 M in acetone) were collected by redistillation of the initial azeotrope [1–4]. The dimethyldioxirane concentration in acetone was determined using UV methodology (λ 330 nm and molar absorptivity of 12.9 cm^{-1} M^{-1}) [6]. Dimethyldioxirane stock solutions were stored at -20°C over anhydrous Na_2SO_4 until use. Stock solutions were stable for months under these conditions. 1,3-Cyclohexadiene and 1,3-cyclooctadiene were commercially available and were distilled before use. Stock solutions of the dienes in dried acetone were prepared under anhydrous Na_2SO_4 at room temperature and used the same day. For kinetic runs, the temperature of the jacketed sample cell (23.0±0.3°C) was monitored *via* an YSI probe. HPLC-grade acetone from Aldrich was stored under Na_2SO_4 until use for all kinetic runs. Care needs to be taken to avoid advantageous water since the k_2 values will increase substantially depending on the amount of water present [6].

Product studies

The monoepoxides, **3a** and **3b**, were identified by GC-MS (Shimadzu GCMS-QP5000, Column: Supelco 2-4001 fused silica capillary SE-54 30 m length, 0.25 mm diameter) and ^{1}H NMR (Bruker-400 MHz) data. To 0.21 mmol of diene (**2a** or **2b**), 0.20 mmol of 0.088 M dimethyldioxirane in acetone was added at room temperature. After several minutes, GC-MS analysis showed that the monoepoxide was formed in excellent yield with slight amounts of unreacted diene present as well as trace amounts of diepoxides for each case. The acetone was carefully removed at 0°C under reduced pressure, yielding the monoepoxide in roughly 50% yield in each case. The ^{1}H NMR spectra were in good agreement with the published data [17].

3,4-Epoxycyclohexene (3a): ^{1}H NMR (400 MHz,$CDCl_3$): δ 5.94 (m, 2H), 3.51 (m, 1H), 3.24 (m, 1H), 2.04 (m, 2H), 1.64 (m, 2H).

3,4-Epoxycyclooctene (3b): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (m, 1H), 5.60 (m, 1H), 3.46 (m, 1H), 3.12 (m, 1H), 2.07 (m, 2H), 1.3–1.8 (m, 6H).

Kinetics

Kinetic studies were carried out on a Shimadzu UV-3101 PC spectrometer with jacketed cells. A solution of dimethyldioxirane in dried acetone (known concentration) was placed in the jacketed sample cell and was allowed to thermally equilibrate at 23°C. The appropriate amount of cyclic diene stock solution in dried acetone was added

rapidly and mixed (~4 s) *via* pipette. The disappearance of dimethyldioxirane was monitored vs. time at 330 nm for at least two half-lives. For 1,3-cyclooctadiene, pseudo-first-order conditions were employed with the diene concentration at least tenfold greater than that of **1**. For the more reactive 1,3-cyclohexadiene, second-order conditions were employed. The k_2 values were the average of at least three experiments. All kinetic runs had correlation coefficients of 0.99 or greater. After completion of each kinetic run, formation of the monoepoxide was confirmed by GC-MS analysis.

Computational methodology

All calculations (gas phase) reported in this paper were performed with the Spartan'10 molecular modeling program. The DFT approach using Becke3-LYP and the 6-31 G basis set was utilized for all calculations. Energies for the minimized ground-state structures were determined for all the reactants [dimethyldioxirane (**1**), cyclic dienes (**2a** and **2b**), and the phenyl-substituted alkenes (**4a** and **4b**)] and the products [acetone, corresponding monoepoxides (**3a** and **3b**), and epoxides (**5a** and **5b**)]. As expected, the computational data predicted that the reactions are exothermic in all cases. The optimized ground-state energy structure of 1,3-cyclohexadiene was predicted to be a relatively flat *s-cis* system. The optimized ground-state energy structure of 1,3-cyclooctadiene is consistent with the two double bonds not in the same plane with a torsion angle of 51°. The HOMO-LUMO energies were obtained from the optimized geometries using the DFT approach using Becke3-LYP and the 6-31 G basis set. As expected, the optimized transition state for each diene resulted in a spiro-orientation with a slight asynchronous tilt away from the other double bond of the cyclic system. Regardless of the initial approach of the dioxirane, all valid transition states resulted in the spiro-orientation. To save time, the calculations were carried out with the methyl groups of the dioxirane oriented away from the most hindered side of the diene, which always yielded the lowest energy spiro-transition state. Each transition-state calculation was checked for validity. A valid transition state had only one negative eigenvalue, which also corresponded to the eigenvector in a separate intrinsic reaction coordinate (IRC) calculation. When animated, the IRC linked the starting materials to the desired products through the spiro-oriented transition state. For the cyclic dienes, two reaction sites are present and can be approached from the top or bottom, yielding different outcomes due to conformational factors. Because 1,3-cyclohexadiene is relatively flat, the transition states for all approaches for monoepoxidation are of similar reactivity. Alternatively, for 1,3-cyclooctadiene, conformation is a major factor. All approaches to the reaction sites were calculated. Due to significant energy differences, one of the approaches was found to have a substantially lower electronic activation energy and therefore was the major contributor to the overall reactivity for that case. Weighted averages of the electronic activation energies for all orientations of attack of **1** on the other substrates were not necessary. For the other cases, the lowest electronic activation energy was taken as representative. As shown for simple *cis*-alkenes [5], the approach to *cis*-1-phenylpropene is with the methyl groups of the dioxirane away from the hindered side. For the *trans*-1-phenylpropene, the transition state with the lowest energy is with the methyl groups of the dioxirane oriented on the side of the phenyl substituent of the alkene rather than the side of the methyl group. Ground-state energy structures of the starting materials and the transition-state conformations were checked and corrected for conformational differences, if present. For **2b**, this was a problem that was solved by constraining the conformation of the starting material during the transition-state calculation. All calculations were completed in the gas phase at 23°C for this study. The electronic activation energies were calculated as follows: E_{elect} = energy of transition state–(ground-state energy of dioxirane+ground-state energy of substrate). To calculate the relative reactivities, the difference in the electronic activation energies was used (Arrhenius equation) in the following manner: $k_{2rel}=(e^{(-\Delta E_{elect}/RT)})(k_2 \text{normalized})$. The substrate with the lower reactivity is normalized to 1. Inclusion of a solvent in calculations, while affecting the individual values, did not affect the electronic activation energy differences, in agreement with the literature [18]. Therefore, all calculations were completed in the gas phase at 23°C for this study.

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