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Computational Studies of the Epoxidation of cis-/trans-Alkenes by Dimethyldioxirane

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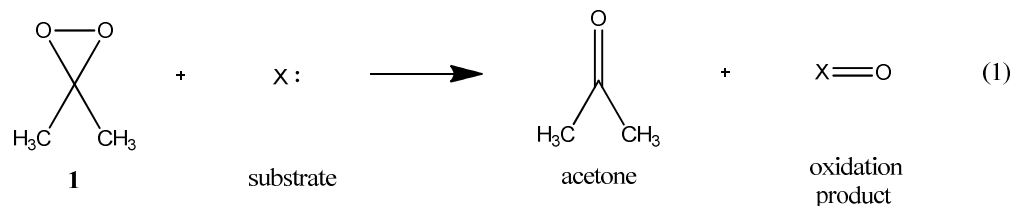
Computational Studies of the Epoxidation of cis-/trans-Alkenes by Dimethyldioxirane

Cover Page Note

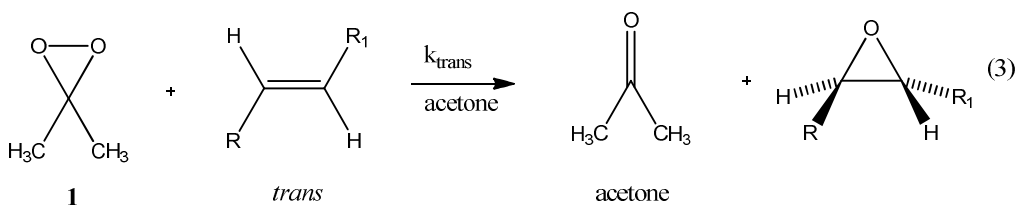
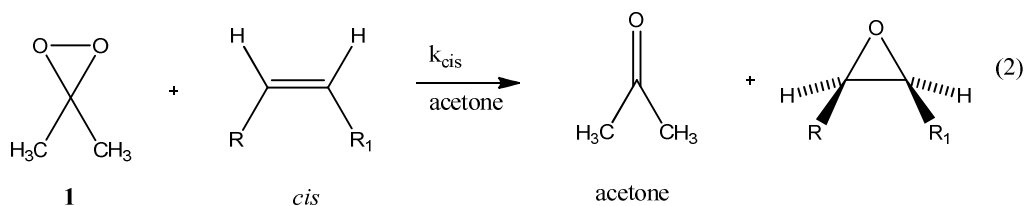
Acknowledgment is made to the Georgia State Research Fund and to GAANN (Davita McTush-Camp) for support of this research. Valerie Stone will be awarded distinction in chemistry for this undergraduate senior research project (designation shows up on the transcript upon graduation)

Introduction

Dimethyldioxirane (**1**), a cyclic three-membered peroxide, has been shown to be a powerful oxidant for numerous substrates, transferring one oxygen atom to yield acetone and an oxidized substrate in high yield (Reaction 1).^[1]



These oxidations can be carried out with ‘isolated’ dimethyldioxirane in acetone or by generating the dioxirane “in situ”, under mild conditions.^[2] The use of isolated dioxirane solutions offers the additional advantage of yielding essentially pure oxidation products in acetone since the dioxirane undergoes conversion to the solvent during the reaction. Removal of the solvent under reduced pressure often yields analytically pure substrate oxidation products. One of the most useful applications of this methodology is the stereospecific epoxidation of alkenes to epoxides. Kinetic studies with isolated dimethyldioxirane showed that alkyl substituted *cis*-alkenes underwent epoxidation approximately 8 fold faster than the analogous *trans*-compounds (Reactions 2 and 3) respectively.^[3]



This observed reactivity difference is of synthetic utility and is not observed for epoxidations with peracids.^[4] This reactivity difference led to the postulation of a concerted mechanism involving a ‘spiro’ transition state (π bond plane of the alkene and the dioxirane ring at a 90° angle).^[3] Thus the faster *cis*-alkene epoxidation involves dioxirane attack from the least hindered side while that of the slower *trans*-alkene reaction always involves steric interactions of the dioxirane with one of the R groups. An early computational study on epoxidation found an optimized (HF/6-31G*) spiro transition for the theoretical reaction of **1** and ethylene.^[5] High level (‘ab initio’) calculations carried out on the theoretical reaction of **1** and *cis/trans*-2-butenes, also supported the spiro transition state mechanism and predicted an energy difference between the *cis*- and *trans*-reactions that was in reasonable agreement^[6] with the experimental data for known *cis/trans* epoxidations.^[3] Studies showed that Density Function Theory (DFT) calculations were sufficient to model the theoretical epoxidation of *cis/trans*-2-butene by **1** in the gas phase and that the relative energy difference was similar to that which included corrections for the solvent.^[7] Concurrent studies using the simpler AM-1 approach also yielded spiro transition states and could predict relative reactivities within a series of structurally similar *cis*-alkenes but not for configurational isomers.^[8] Recently, we have reported the experimental activation parameters for the epoxidation of *cis/trans* pairs of 1,2-dialkylalkenes by dimethyldioxirane.^[9] We report here the results of a DFT computational study of the epoxidation of two series of *cis/trans*-dialkylalkenes by dimethyldioxirane in which the steric size of one of the substituents increases across the series with the other remaining constant.

Experimental (Computational Methodology)

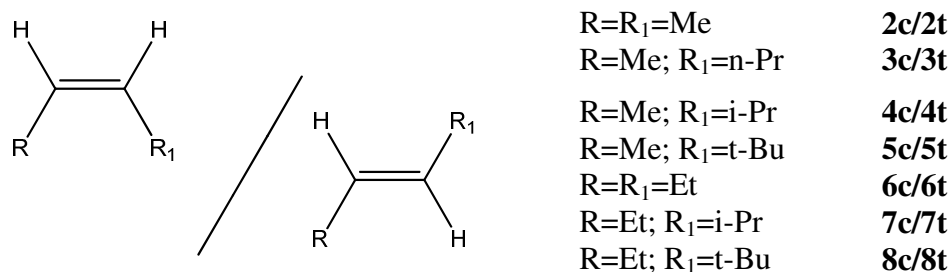
All calculations reported in this paper were performed with the Spartan’10 program. The calculations were made using Density Function Theory (DFT), Becke approach, using the B3LYP/6-31G* basis set.^[10] The structures of the starting materials (dimethyldioxirane, *cis*-alkenes, *trans*-alkenes), transition states and products (epoxides and acetone) were optimized and the energies were calculated in the gas phase at 23° C. As expected, all the transition states converged on the spiro geometry regardless of the initial orientations of the dioxirane and alkene. To save time, and as previously reported^[7], the approach of the dioxirane from the least hindered side of each alkene was taken to be the major contributor to the overall reactivity. The conformations of the alkyl groups of the optimized alkenes were checked versus those of the alkyl groups in the transition state to minimize conformational corrections. Structures in which the starting material and transition state conformations were not the minimum did not affect the electronic activation energies as long as there were no significant

additional steric interactions with the dioxirane and the basic orientations were the same in both the transition state and the alkene. In those cases, the calculated energies of the starting materials and the transition state both reflected the increased conformational effects but the electronic E_a was unchanged. Each transition state gave only one imaginary frequency (μ), which when animated, smoothly connected the reactants and products for each epoxidation. The reaction coordinate profiles were calculated using the HF 6-31G* basis set, which also showed the smooth transition from reactants to products for each epoxidation. The entropies and correction for solvation on the energies were not determined. To obtain the angles of the plane of the alkene and the oxygens of the dioxirane a phantom atom (Z) was placed in the center of the double bond along the C-C axis.

Results/Discussion

The epoxidation of seven *cis/trans* alkenes (**2c/2t** - **8c/8t** see Figure 1) by **1** were modeled by the DFT approach. The first series contains: *cis/trans*-2-butene (**2c/2t**); *cis/trans*-2-hexene (**3c/3t**); *cis/trans*-4-methyl-2-pentene (**4c/4t**); and *cis/trans*-4,4-dimethyl-2-pentene (**5c/5t**), in which number of the branching alkyl groups increase (0,1,2,3, respectively)^[11] along the series with the other methyl group as a constant. The second series contains: *cis/trans*-3-hexene (**6c/6t**); *cis/trans*-4-methyl-3-hexene (**7c/7t**); *cis/trans*-4,4-dimethyl-3-hexene (**8c/8t**), which all have an ethyl group as a constant and the size and branching of the second substituent is increasing (1,2,3, respectively).^[11]

Figure 1: The structures of *cis/trans* pairs of alkenes for the DFT computational study.



The DFT calculated transition states structures with the selected bond angles for the epoxidation of **2c/2t** by **1** are displayed in Figure 2. The transition state (TS) structure calculated for the *cis* alkene, **2c** shows essentially ideal spiro geometry.

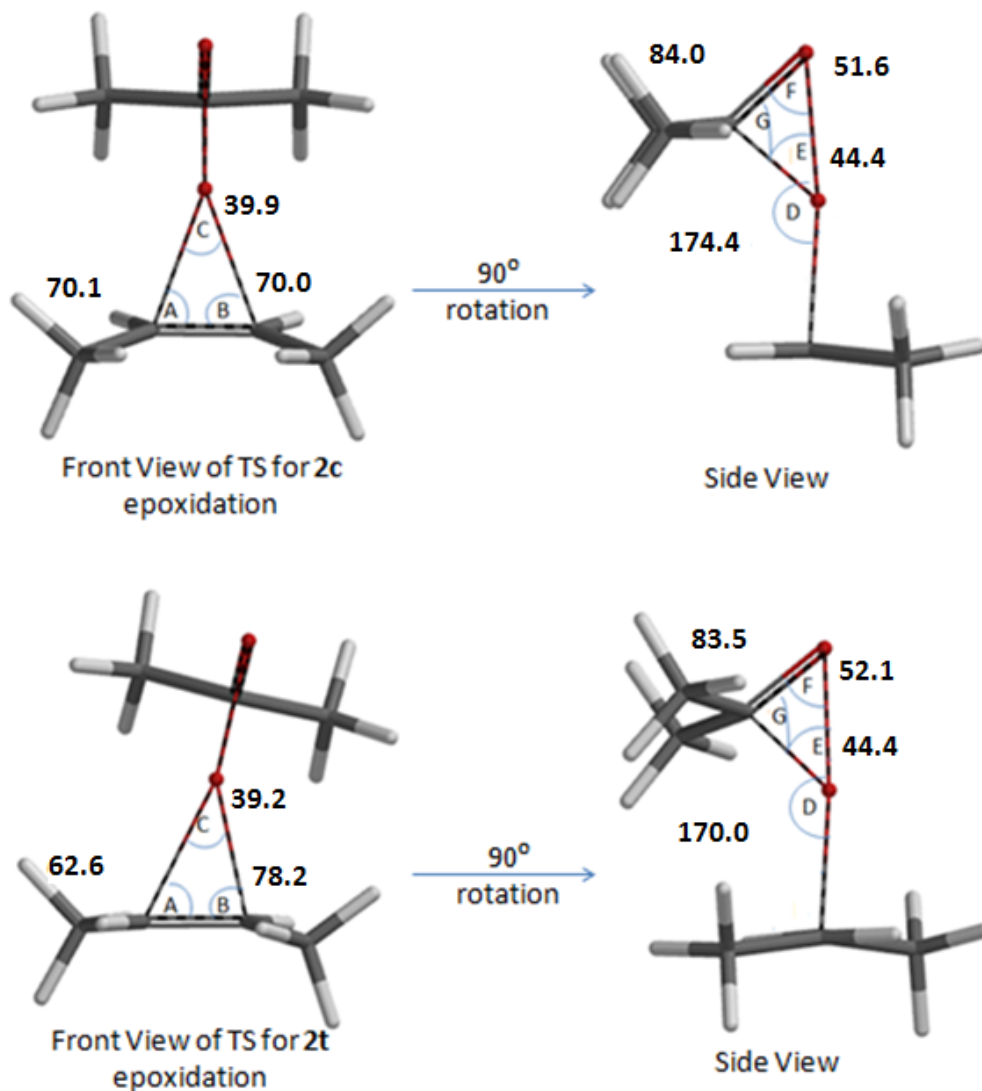
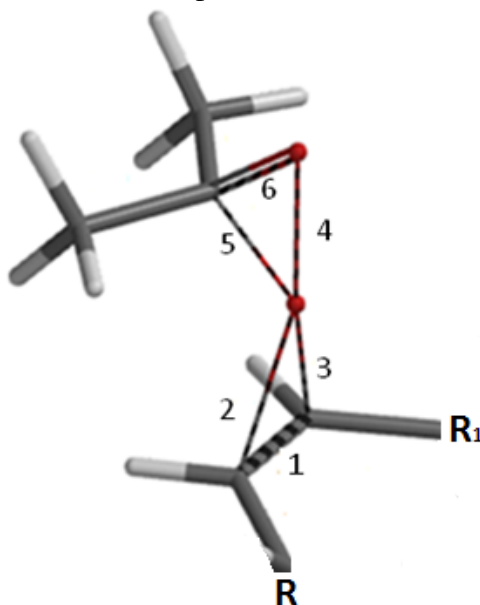


Figure 2: The front and side views (90° rotation, left to right around center of C=C bond) of the calculated transition states (TS) of the epoxidation of *cis*-/*trans*-2-butene (**2c**/**2t**) with **1**, including selected bond angles in degrees (°).

The side view shows that the angle on O-O-Z (center of C=C bond) to be ~174°. The transition state geometry for epoxidation of the *trans* alkene, **2t**, is somewhat distorted from the 'ideal' by tilting away from the R group on the side of the methyl groups of **1** by ~15°. The results are in good agreement with the previously published computational results for the epoxidation of these two alkenes^[6,7]. The transition state structures calculated for the epoxidation of the remaining *cis*/*trans* pairs were essentially analogous to those shown in Figure 2.

The DFT calculated bond lengths and imaginary frequencies, μ , for the transition states (TS) for the seven *cis/trans* pairs for the alkenes are listed in Tables 1 and 2, respectively.

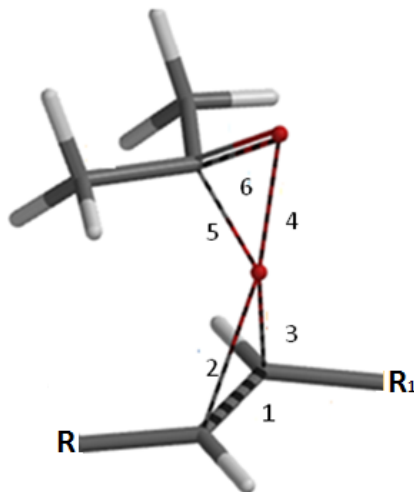
Table 1: Calculated Bond Lengths (Å) and Imaginary Frequencies (μ , cm^{-1}) for the Transition States (TS) for **2c-8c** Epoxidation.



Bond number	TS- <i>cis</i> -Alkene							
	<i>2c</i>	<i>3c</i>	<i>4c</i>	<i>5c</i>	<i>6c</i>	<i>7c</i>	<i>8c</i>	
1	1.380	(1.380 ^a)	1.380	1.380	1.381	1.380	1.379	1.381
2	2.023	(2.026 ^a)	2.033	2.034	2.048	2.029	2.042	2.084
3	2.026	(2.026 ^a)	2.021	2.040	2.043	2.024	2.040	2.022
4	1.886	(1.886 ^a)	1.883	1.879	1.876	1.883	1.875	1.873
5	1.487	(1.485 ^a)	1.485	1.484	1.482	1.485	1.481	1.482
6	1.327	(1.327 ^a)	1.327	1.329	1.330	1.327	1.330	1.331
$\mu(\text{cm}^{-1})$	464	(466.7 ^a)	464	443	441	462	440	435

a) From Reference [7b]

Table 2: Calculated Bond Lengths (Å) and Imaginary Frequencies (μ , cm^{-1}) for Transition States (TS) for **2t-8t** Epoxidation.



Bond number	<i>TS-trans-Alkene</i>							
	<i>2t</i>	<i>3t</i>	<i>4t</i>	<i>5t</i>	<i>6t</i>	<i>7t</i>	<i>8t</i>	
1	1.378	(1.378 ^a)	1.378	1.378	1.377	1.378	1.378	1.376
2	2.137	(2.140 ^a , 2.156 ^b)	2.133	2.136	2.154	2.145	2.129	2.141
3	1.937	(1.935 ^a , 1.985 ^b)	1.943	1.951	1.968	1.936	1.956	1.978
4	1.883	(1.883 ^a ,1.879 ^b)	1.883	1.881	1.871	1.880	1.882	1.869
5	1.496	(1.494 ^a)	1.495	1.494	1.488	1.493	1.496	1.489
6	1.328	(1.325 ^a)	1.325	1.326	1.330	1.326	1.326	1.330
$\mu(\text{cm}^{-1})$	484	(479.7 ^a)	477	470	447	471	474	445

a) From reference [7b]; b) From reference [7c].

For the *cis*-alkene transition states, the bond distances and frequencies do not show appreciable differences as the structures of the alkenes are varied. The bond lengths for 2 and 3 (Table 1) are essentially identical for each transition state as expected for a symmetrical (synchronous) spiro transition state. For the *trans*-alkene series, there is a slight asynchrony in the transition state as demonstrated by the longer bond lengths (~ 2.14 Å) for bond 2 and shorter ones for bond 3 (1.94 - 1.98 Å) for all cases (Table 2) and the tilt of the dioxirane ring plane. The results for the TSs of **2c/2t** epoxidation are comparable with those reported in the literature^[7]. The reaction profiles for the epoxidation of each pair of *cis/trans* alkenes were calculated.

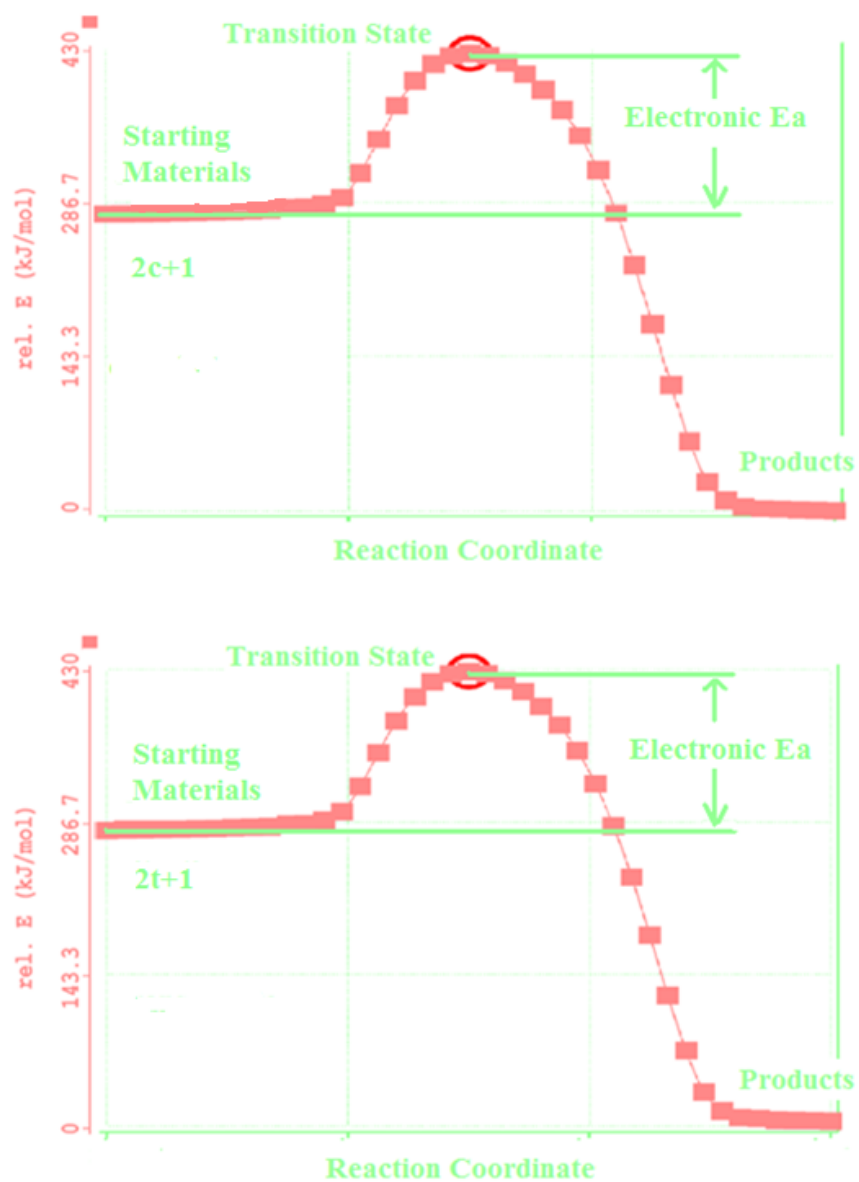


Figure 3: Calculated reaction profiles for the epoxidation of 2c/2t by 1. The profiles fit a classic concerted exothermic reaction model.

The results fit a classic S_N-2 exothermic mechanism; with the alkene π -bond nucleophilically attacking one of the peroxide oxygens along the axis of the O-O bond. There is a continuous smooth increase in energy from the starting materials to the spiro transition state and a smooth decrease in energy to the products. The electronic activation energy (E_a) is calculated by subtraction of the relative energies of the starting materials from that of the transition state. Figure 3 shows the reaction profiles for the epoxidation of **2c/2t** by **1** that are representative for all the pairs of alkenes.

For each pair, the electronic activation energy for the epoxidation of the *cis* alkene was found to be lower than the analogous *trans*-alkene, consistent with expectations based on the greater reactivity of the *cis* compound. The results are listed in Table 3 along with the experimental values^[9] if known. As previously observed^[6,7] the electronic E_a values are substantially higher than the experimental values.

For the series, **2c/2t** to **5c/5t**, the electronic ΔE_a values are essentially constant (-1.5 to -1.7) except for the case (**5c/5t**) with the *t*-Bu groups (largest branched group of the series) which is slightly larger (-2.2). For the series **6c/6t** to **8c/8t** these appear to be a slight increase in electronic ΔE_a as the R₁ group gets larger (more branched). The experimental $\Delta\Delta H^\ddagger$ values are in reasonable agreement with the predicted values (electronic ΔE_a s) especially considering the large experimental errors on the former. The calculated ΔE_a values may be used to predict relative reactivity for each pair of alkenes. Since each rate constant is proportional to $e^{-E_a/RT}$, relative reactivity can be predicted by dividing the respective equations for k_{cis} by that for k_{trans} . Normalizing k_{trans} as 1 and assuming that all the additional factors cancel, yields the following expression: $rel. k_{cis} = e^{-\Delta E_a/RT}$. For all but **2c/2t** experimental normalized k_{cis}/k_{trans} ratios have been reported. Comparison of the predicted $rel. k_{cis}$ ratios vs. the experiment ratios allows for evaluation to calculations. The results are listed in Table 4.

Table 3: DFT calculated electronic activation energies (gas phase) for epoxidation of **2c/2t-8c/8t** with **1** at 23°C.

Alkene	Electronic Ea	Electronic ΔE_a^a	Experimental ΔH^\ddagger	Experimental $\Delta\Delta H^\ddagger$
2c	13.87 (13.8 ^b ,13.85 ^c ,14.1 ^d)	-1.65 (-1.7 ^b)	N/A ^e	N/A ^e
2t	15.52 (15.5 ^{b,d} , 15.50 ^c)	(-1.65 ^c) (-1.4 ^d)	N/A ^e	N/A ^e
3c	13.72	-1.54	NR ^f	NR ^f
3t	15.26			
4c	14.24	-1.58	7.28	-2.1±0.4
4t	15.82		9.42	
5c	12.32	-2.18	7.37	-1.9±1.0
5t	14.50		9.27	
6c	13.96	-1.35	7.14	-1.1±1.1
6t	15.31		8.25	
7c	13.26	-2.41	7.92	-2.0±0.4
7t	15.67		9.92	
8c	12.95	-2.53	7.51	-2.0±0.9
8t	15.48		9.47	

a) Electronic Ea for the cis epoxidation minus the electronic Ea for the trans reaction; b) From reference 6; c) From reference 7b; d) From reference 7c; e) No data available for these two alkenes because they are gases at ambient temperature; f) Only kinetics at 23°C have been carried out.

Table 4: Predicted reactivity differences ($k_{2-cis}/k_{2-trans}$) for the epoxidation of *cis/trans* pairs of alkenes versus normalized experimental values at 23° C.

Alkene Pair	2c/2t	3c/3t	4c/4t	5c/5t	6c/6t	7c/7t	8c/8t
Predicted ^a relative $k_{2-cis}/k_{2-trans}$	16/1	13/1	14/1	41/1	10/1	57/1	74/1
Normalized experimental $k_{2-cis}/k_{2-trans}$	N/A	8.8/1	8.8/1	14/1	8.2/1	11/1	22/1

Relative $k_{2-cis} \approx e^{-\Delta E_a/RT}$ assuming $k_{2-trans} = 1$ and that all the other factors cancel; ΔE_a 's are listed in Table 3.

In general the electronic ΔE_a s yields predictions that are surprisingly close (20-40%) to the experimental values except for the $R_1 = t\text{-Bu}$ containing pairs (**5c/5t**, **8c/8t** and for **7c/7t** approximately 3 to 5 times larger). Arrangement based on the magnitude of the ratio gives essentially the correct order for both experimental and predicted values with only **5c/5t** and **7c/7t** positions switched. The over estimation of the predicted relative k_{cis} 's for the large groups is likely due to the lack of cancellation of the non-energy terms in the calculation. Nevertheless, the methodology provides useful insights.

Summary

In conclusion, the DFT modeling of the epoxidation of *cis/trans*- dialkylalkenes by **1** is consistent with a concerted exothermic process. For the *cis* compounds, the predicted geometry is essentially ideal for a symmetrical, synchronous spiro transition state, independent of the size of the alkyl groups. For *trans* compounds, there is a slight asynchrony in epoxide ring formation and the tilting of the dioxirane portion away from the R group. Nevertheless, the **TS** is still essentially a spiro orientation. The electronic E_{as} , as expected, are higher than the experimental data. The electronic ΔE_a s for each pair are consistent with the experimental data. Prediction of relative k_{cis}/k_{trans} based on the calculated ΔE_a s was in reasonable agreement with experimental values but greatly over predicted the value for the t-Bu containing pairs. Overall, the DFT approach is a reliable method to model this type of reaction and for predicting relative reactivities.

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- [11] Each branch is defined as formal replacement of the H's on the R₁ methyl group by a carbon containing group. Since the geometry of a methyl group is tetrahedral, the steric size essentially increases as the number of branches increases. Thus the t-Bu group (-C(CH₃)₃) with three formal branches has the most steric bulk.