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Computational Modeling of a Stereoselective Epoxidation: Reaction of Carene with Peroxyformic Acid

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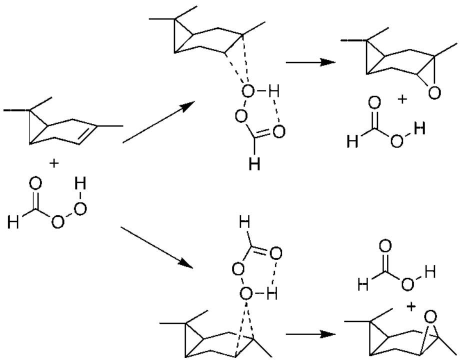

Electronic structure theory was used to model the epoxidation of 3-carene by peroxyformic acid. Reactants, products, and transition states were optimized at the B3LYP/6-31G* level of theory, followed by B3LYP/6-311+G** and MP2/6-311+G** single point calculations. The reaction pathway yielding the *trans*-epoxide product was found to have a significantly lower reaction barrier (7.8 kcal/mol) than that leading to the *cis*-epoxide product (9.4 kcal/mol), in agreement with expectations. Magnetic shieldings of the two isomeric carene epoxides were also calculated, using the GIAO method, and compared to experimental ^{1}H and ^{13}C NMR spectra. Although the calculated carbon spectra proved inconclusive, the proton shieldings calculated for the *trans*-epoxide correlated much more closely to the experimental values for the major epoxidation product than did the shieldings calculated for the *cis*-epoxide, serving to verify the identity of the major product.

Introduction

Ab initio and density functional electronic structure theories have previously been used to model the epoxidation of alkenes by peracids. In the classical transition state, all the atoms of the peracid and the two carbons of the alkene are contained in a single plane that is perpendicular to the plane of the alkene and parallel to the axis of the alkene. This geometry corresponds to Bartlett's "butterfly mechanism", whimsically named for the shape of the transition structure.[1] For many years, experimental studies supported this mechanism.[2] More recently, however, computational methods have been used to determine the transition state structures, and although there has been some debate, [3] it now seems well-established that the reaction indeed occurs via a concerted mechanism (as Bartlett suggested) but that the transition state has a symmetrical spiro geometry rather than a planar geometry.[4–14] In this spiro geometry, the peracid

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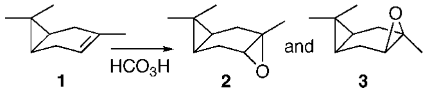

FIGURE 1. Epoxidation of 3-carene (**1**) by peroxyformic acid to yield *trans*-carene epoxide (**2**) and *cis*-carene epoxide (**3**).

lies in a plane that is perpendicular to both the plane of the alkene (the horizontal plane) and the axis of the alkene double bond.

Bach's group has extensively studied the transition states for the epoxidations of ethylene, propene, and 2-butene.[5] Both this group and also those of Freccero and of Sarzi-Amadè have successfully extended the approach to more complex alkenes, as well, including bicyclic structures such as norbornene in which issues of facial selectivity arise.[6,7] The frequently diastereoselective and synthetically useful peroxyacid epoxidations of allylic and homoallylic systems have also attracted considerable computational attention.[8–11] We wished to see if the same methodology could successfully be applied to the case of 3-carene (Figure 1). Carene, one of the monoterpenes that constitutes turpentine,[15] has often been epoxidized as the first step in a synthetic pathway, either as a precursor for ligand preparation or as the starting point for natural product total synthesis.[16] Carene epoxidation has also recently been shown to have biological significance.[17]

The laboratory epoxidation of carene is frequently carried out using a peracid, most commonly MCPBA,[18,19] which produces exclusively the *trans*-carene epoxide (also known as the α-epoxide).[18] Here, we have modeled the epoxidation reaction using the much smaller peroxyformic acid as the oxidant. It has been reported that, for the reaction involving simple peracids, the major product makes up roughly 80% of the mixture.[20] Using GC/MS and NMR, this major product has been identified with a fair degree of certainty as the *trans*- rather than the *cis*-epoxide.[21] However, it is worth noting that under different reaction conditions the ratio of products can vary greatly.[22]

TABLE 1. Calculated Reaction Barriers for Epoxidation by Peroxyformic Acid (kcal/mol)

theoretical method	ethylene	propene	carene *cis*	carene *trans*
B3LYP/6-31G*//B3LYP/6-31G*	14.7	12.3	10.9	9.2
B3LYP/6-311+G**//B3LYP/6-31G*	15.6	12.7	10.7	8.9
MP2/6-311+G**//B3LYP/6-31G*	19.3	15.4	9.4	7.8
QCISD(T)/6-31G*//QCISD/6-31G*[a]	18.8	16.0		

[a] Values taken from ref 5.

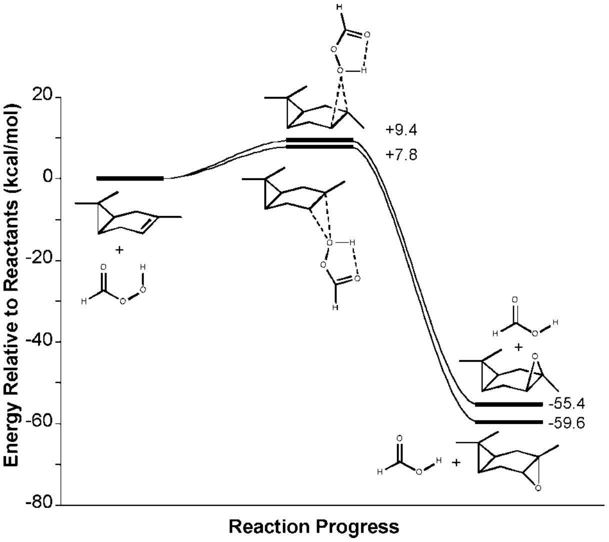

FIGURE 2. Reaction coordinate energy diagram for the epoxidation of carene showing both possible reaction pathways. Labeled energies were calculated at MP2/6-311+G**//B3LYP/6-31G*.

We were interested to see whether computational methods could reproduce the experimentally observed stereoselectivity of this reaction. Furthermore, we wished to determine whether computation of the NMR spectroscopic properties of the two isomeric products, followed by comparison to the experimental spectra, could be used to verify the identity of the major product. Both procedures are potentially useful for predicting and evaluating the outcomes of stereoselective epoxidation reactions of practical experimental interest.

Results and Discussion

As a starting point, energies were calculated for the reactants, products, and transition states for epoxidation of ethylene and propene, using the structures reported by Bach et al.[5] These authors showed that reaction barriers calculated at QCISD(T)/6-31G*//B3LYP/6-31G* closely approximated those calculated at QCISD(T)/6-31G*//QCISD/6-31G*.[13] The calculations reported here indicate that even MP2/6-311+G**//B3LYP/6-31G* reaction barriers serve as a good approximation of those calculated at QCISD(T)/6-31G*//QCISD/6-31G*[5] for the ethylene and propene epoxidations (Table 1). Accordingly, the more economical MP2/6-311+G**//B3LYP/6-31G* procedure was used to compute barriers in the larger carene system, for which QCISD(T) calculations would have been impractical.

The activation barriers for epoxidation of carene to yield the *cis* and *trans* products are listed in Table 1, and a reaction energy diagram is shown in Figure 2. As expected, the barrier for epoxidation leading to the *trans* product (7.8 kcal/mol) is substantially lower than that for epoxidation leading to the *cis* product (9.4 kcal/mol). Since the reaction is under kinetic

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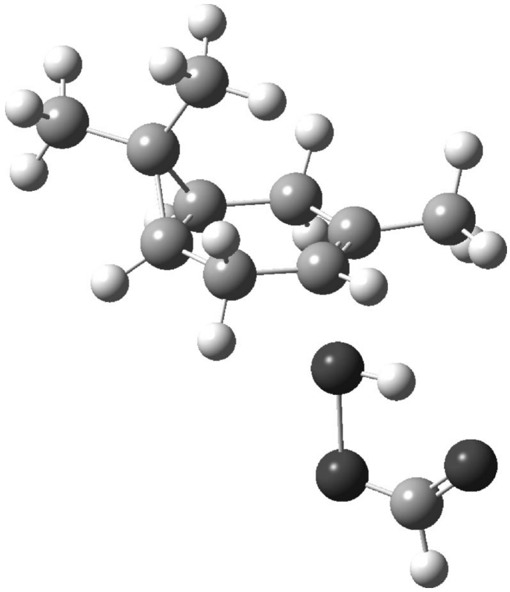

FIGURE 3. Transition state structure for the *trans*-epoxidation of carene determined at B3LYP/6-31G*.

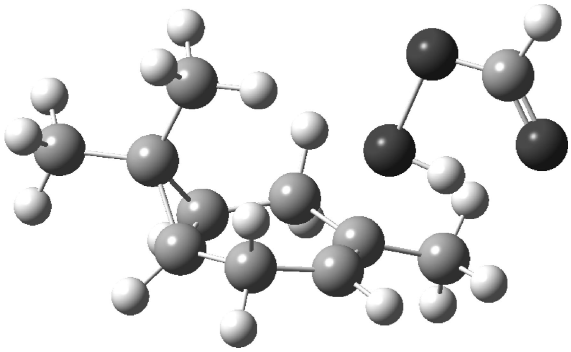

FIGURE 4. Transition state structure for the *cis*-epoxidation of carene determined at B3LYP/6-31G*.

TABLE 2. Experimental and Calculated ^{13}C NMR Resonances of the Carene Epoxides (ppm)

atom	exptl	calcd/*cis*	calcd/*trans*
C_1	15.9	23.5	22.4
C_2	23.2	28.2	27.7
C_3	56.0	59.8	59.8
C_4	58.2	62.6	62.8
C_5	19.2	25.0	24.3
C_6	13.8	22.3	20.0
C_7	16.0	23.5	22.0
C_8	23.1	26.6	25.0
C_9	14.6	16.3	17.1
C_{10}	27.7	32.4	30.4
rms deviation		5.6	4.6

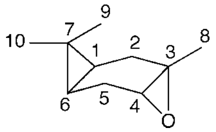

FIGURE 5. Atom numbering scheme for carene epoxide. For hydrogen atoms, exo designates on the same face of the cyclohexane ring as the cyclopropane moiety, and endo as on the opposite face from the cyclopropane moiety.

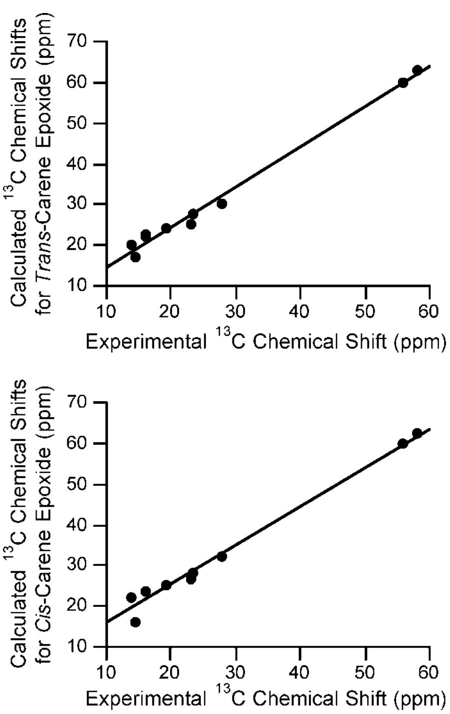

FIGURE 6. Calculated ^{13}C NMR chemical shifts for *trans*- and *cis*-carene epoxides compared to the experimental values obtained from the carene epoxidation major product. Isotropic shielding constants were calculated at B3LYP/6-311++G**//B3LYP/6-31G*. For the *trans*-carene epoxide best fit line: slope = 0.980, intercept = 4.90, correlation coefficient (R^2) = 0.990. For the *cis*-carene epoxide best fit line: slope = 0.954, intercept = 6.48, correlation coefficient (R^2) = 0.985.

TABLE 3. Experimental and Calculated ^{1}H NMR Resonances of the Carene Epoxides (ppm)

atom/group	exptl	calcd/*cis*	calcd/*trans*
H_1	0.54	0.48	0.42
H_{2exo}	2.15	2.05	2.04
H_{2endo}	1.49	1.98	1.42
H_4	2.84	2.69	2.58
H_{5exo}	2.31	2.17	2.27
H_{5endo}	1.64	2.14	1.60
H_6	0.46	0.43	0.31
C_8 methyl	1.27	1.19	1.14
C_9 methyl	0.73	1.14	0.75
C_{10} methyl	1.01	0.93	1.02
rms deviation		0.27	0.12

control, the relative energies of the transition structures are expected to determine the stereochemical outcome. The actual transition structures are shown in Figures 3 and 4. Peroxyformic acid would appear to be an adequate model oxidant, despite being much smaller than those typically used experimentally, since the hydrogen of the formyl group, where a bulkier group would in practice be located, points away from the rest of the structure.

Calculated isotropic magnetic shieldings were used to further corroborate the previously reported experimental conclusion that the major reaction product is *trans*- rather than *cis*-carene epoxide. Comparisons between the calculated and experimental carbon chemical shifts were inconclusive; calculations for both *cis*- and *trans*-carene epoxide correlated equally well with the experimental spectra (Table 2, Figure 6; atomic numbering scheme in Figure 5). However, the ^{1}H NMR results (Table 3) were more helpful. The isotropic shielding values calculated for *trans*-carene epoxide correlated far more closely with the experimental shifts (R^2 = 0.990) than did the isotropic values calculated for *cis*-carene epoxide (R^2 = 0.885) (Figure 7). This

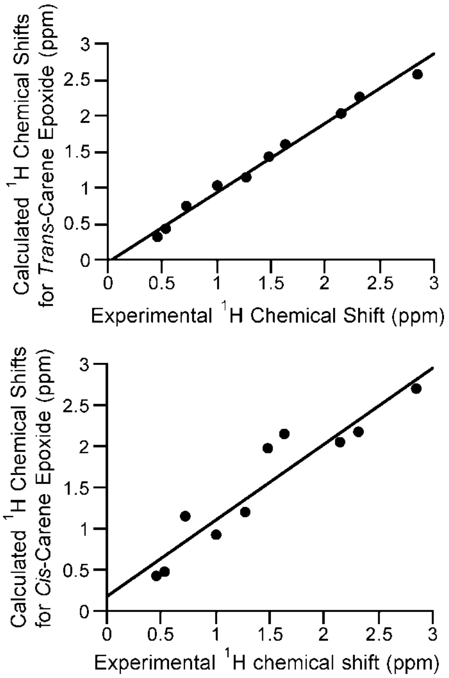

FIGURE 7. Calculated ^{1}H NMR chemical shifts for *trans*- and *cis*-carene epoxides compared to the experimental values obtained from the carene epoxidation major product. Isotropic shielding constants were calculated at B3LYP/6-311++G**//B3LYP/6-31G*. For the *trans*-carene epoxide best fit line: slope = 0.961, intercept = –0.03, correlation coefficient (R^2) = 0.990. For the *cis*-carene epoxide best fit line: slope = 0.923, intercept = 0.19, correlation coefficient (R^2) = 0.885.

correspondence provides strong additional evidence that the major product of carene epoxidation is indeed the *trans*-epoxide. In addition, the observation that calculated ^{13}C NMR shifts were not useful for structure assignment in this case, but that the ^{1}H NMR shifts were, provides a perhaps interesting counterexample to some of the successes recently reported with regard to the use of calculated ^{13}C NMR shifts for structure determination.[23]

Conclusions

The two reaction pathways for the epoxidation of 3-carene by peroxyformic acid, leading to isomeric *cis*- and *trans*-epoxide products, were explored via electronic structure calculations. In agreement with expectations, the transition state leading to the *trans*-epoxide was substantially lower in energy than that leading to the *cis*-epoxide. Furthermore, although calculated carbon NMR spectra did not prove useful, proton magnetic shieldings computed for the *trans*-epoxide correlated much more closely with the experimentally derived spectrum of the major isomer than did the proton shieldings calculated for the *cis* isomer. The present findings further illustrate the potential usefulness of computational study of epoxidation reactions of structurally and stereochemically complex alkenes using the methodology pioneered by Bach and co-workers[4–8,13,14] and by the groups of Freccero and Sarzi-Amadè[7,10,11] and of Houk.[4,9] Perhaps most usefully, this methodology can likely be used to predict with a fair degree of confidence the outcomes of epoxidations in which different stereoisomeric epoxide products are possible, but for which the direction and degree of preference are not known in advance. Furthermore, calculation of the proton magnetic shieldings for the isomeric epoxides, followed by comparison to the experimental proton NMR spectra of the major (and perhaps minor) products, can be used to verify the experimental outcome.

Computational Methods

The Gaussian 03 package[24] was used to carry out all calculations. Standard Pople-type basis sets were employed.[25] All geometries were optimized at the B3LYP/6-31G* level. It has previously been shown that, for alkene epoxidations, B3LYP optimizations are the best of the more affordable methods; MP2 optimizations, for example, yield incorrect structures.[5,12,13] Carene epoxidation transition state structures were determined through a multistep process. First, the two carbon−oxygen distances were fixed at the values for the 2-methyl-2-butene transition state, and all other parameters were allowed to optimize. Second, starting from these partially optimized geometries, unconstrained optimizations (opt = calcfc,ts) were carried out, leading to the fully optimized transition state structures. All transition structures were verified as transition states by the calculation of vibrational frequencies at the B3LYP/6-31G* level of theory; that is, one imaginary frequency was found.

Single point energies were calculated at B3LYP/6-311+G** and MP2/6-311+G** using the B3LYP/6-31G* optimized geometries. Zero point energies calculated at B3LYP/6-31G* and corrected by a scale factor of 0.9804[26] were included, as well.

Isotropic shielding values were computed using the GIAO method[27] in conjunction with the B3LYP/6-311++G**//B3LYP/6-31G* level of theory. Calculated isotropic shielding values for each of the three hydrogen atoms in a methyl group were averaged to produce a single observable value for the methyl group as a whole. The calculated isotropic shielding values were subtracted from the corresponding value for TMS to yield calculated chemical shift values, relative to TMS.

Experimental Section

To obtain experimental ^{13}C and ^{1}H NMR spectra, 117 μL of (+)-3-carene was reacted with 437 mg of magnesium bis(monoperoxyphthalate) in 1 mL of methanol. The product was isolated by diluting the mixture with 10 mL of ether and 2 mL of water. The aqueous layer was removed and the organic layer washed three times and dried over $MgSO_4$. The organic solution was then run through a $MgSO_4$ filter to remove the drying agent. The drying agent was washed with 5 mL of ether, which was added to the

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solution. Finally, the ether was removed by rotary evaporation, leaving a colorless liquid as the product. ^{13}C, ^{1}H NMR, COSY, and HETCOR spectra were collected on a 400 MHz spectrometer. They were assigned using three-bond and four-bond couplings.

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Supporting Information Available: Cartesian coordinates, imaginary frequencies (where applicable), and energies of all stationary points; experimental NMR spectra (^{1}H NMR, ^{13}C NMR, HETCOR, COSY) of carene epoxidation product. This material is available free of charge via the Internet at http://pubs.acs.org.

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