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Notes

Regio- and Stereoselectivity of *β*-Himachalene Epoxidation by *m*-CPBA. A Theoretical Study

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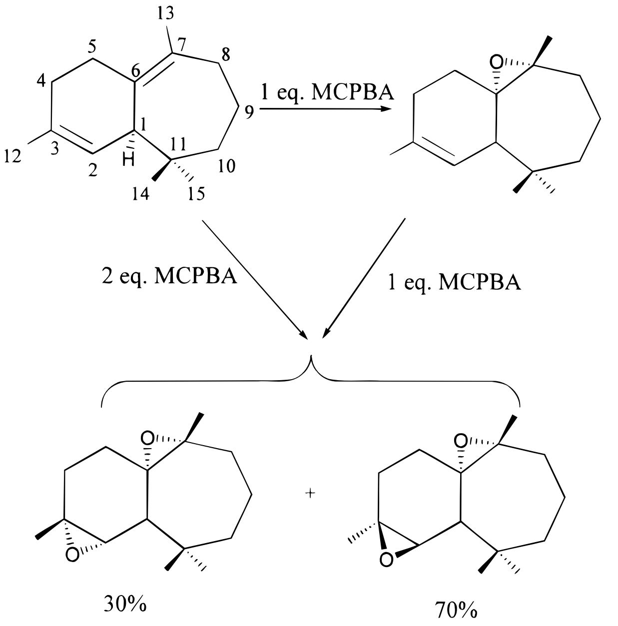
Introduction

The essential oil of the Atlas cedar (*Cedrus atlantica*), one of the raw materials in the perfume industry, has been the object of various important studies.[1−7] This oil is constituted primarily (75%) of three sesquiterpenic bicyclic hydrocarbons: α-*cis*-, *β*-, and *γ*−*cis*-himachalene. The three himachalenes differ from each other only in the position of an ethylenic linkage. The reactivity of these sesquiterpenes has been studied extensively.[8−11] Our group studied the reactivity of *cis*- and *trans*-himachalene.[12−19] The object of this research was the semisynthesis of components with interesting olfactory properties in perfumery. The epoxidation of *β*-himachalene, the most abundant component of cedar oil (50%), with *m*-chloroperbenzoic acid (*m*-CPBA), is regio- and stereoselective.[13] Indeed, when these reactants are used in stoichiometric proportions, only the C_6-C_7 double bond is attacked, on its α-side, giving thus the monoepoxide (α-*(6,7)*-epoxyhimachal-2-ene) in quantitative yield (Scheme 1). With an excess of peracid, the C_2-C_3 double bond is also oxidized on both sides: the α side, with the C_1 hydrogen, and the other (*β*) side. The monoepoxide was identified by spectral analysis (^{1}H and ^{13}C NMR and mass spectrometry). The stereochemistry of the oxiranic bridges was deduced from X-ray study.[14,17]

Scheme 1



To our knowledge, no mechanistic theoretical study of *β*-himachalene has been undertaken and neither regio- nor stereoselectivity studies. A computer search of *Chemical Abstracts* did not offer any help in this matter. To better understand our previous experimental investigations[13] (regio- and strereoselectivity and mechanism) of the *β*-himachalene epoxidation, we carried out quantum chemical calculations, an indispensable tool to supplement the experimental data. In this work, we have done a detailed structural and mechanistic study of *β*-himachalene epoxidation with *m*-CPBA using AM1 calculations.

Computational Details

The structures and heats of formation were obtained from the AM1 semiempirical SCF-MO method at the restricted Hartree−Fock (RHF) level[20] implemented in the AMPAC program.[21] All geometric parameters were optimized without symmetry constraints. Minima and transition states were verified by the number of negative eigenvalues of the Hessian (zero and one, respectively). We therefore carried out ab initio (RHF/6-31G(d) level) and B3LYP/6-31G(d)[22] single-point calculations for all

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Table 1. *E*(HOMO), *E*(HOMO-1), and p_z Weight of C_2, C_3, C_6, and C_7 Atoms in the HOMO and HOMO-1 for Different Conformers of *β*-Himachalene

	conformers					
MO	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**
HOMO						
E (eV)	−8.88854	−8.90727	−8.90497	−8.83791	−8.84712	−8.82776
C_2	0.157	−0.198	0.207	−0.138	−0.147	0.231
C_3	0.159	−0.228	0.239	−0.159	−0.204	0.267
C_6	0.545	−0.495	0.510	−0.455	−0.378	0.491
C_7	0.562	−0.512	0.515	−0.493	−0.380	0.508
HOMO-1						
E (eV)	−9.25701	−9.23786	−9.25292	−9.25948	−9.26722	−9.25176
C_2	0.532	−0.584	−0.585	0.493	0.487	0.570
C_3	0.502	−0.537	−0.537	0.460	0.442	0.519
C_6	−0.205	0.229	0.242	−0.168	−0.192	−0.272
C_7	−0.183	0.209	0.219	−0.162	−0.153	−0.258

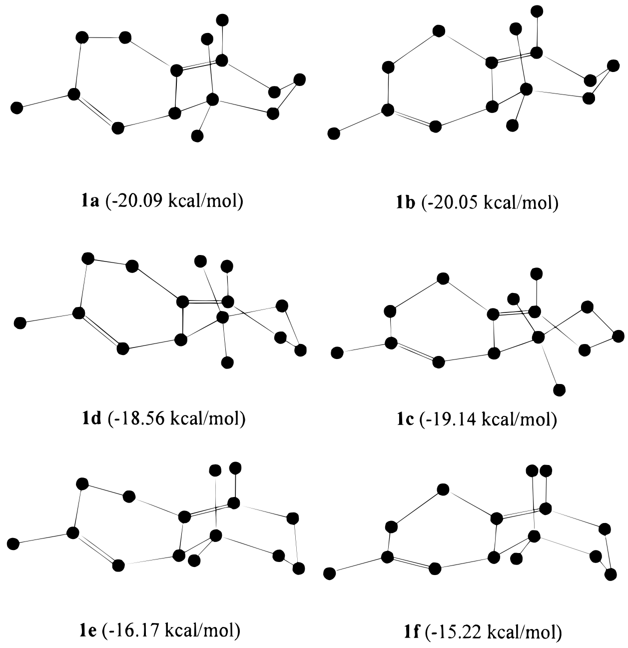
transition-state structures to estimate the activation barriers. We chose these methods to obtain three sets of estimates of activation barriers. The ab initio and B3LYP calculations were carried out using the Gaussain92[23] and the Gaussain94[24] programs, respectively.

Results and Discussion

Structural Study. The ring fusion and the presence of two double bonds are two factors limiting the number of possible conformers of himachalene. Nevertheless, we have identified many conformers, of which we present only six (others have been omitted because they are energetically higher), which are energetically favored **1a**−**f**. In Figure 1, we present them in pairs having nearly the same seven-membered ring structure: (**1a**, **1b**), (**1c**, **1d**), and (**1e**, **1f**). We notice also that, in all these conformers, the six-membered cycle folds along only two directions or creases, C_2-C_5 and C_3-C_5 with opposite orientations, while the seven-membered 1-folds along several directions, i.e., C_1-C_9, C_8-C_{11}, and C_1-C_{10}. The junction of the two cycles prevents such folding modes as C_3-C_6 and C_1-C_8.

Let us now examine the energy−geometry dependence. We notice that the folding mode of the six-membred ring corresponds to an energetic difference of 0.04, 0.58, and 0.95 kcal/mol for the pairs (**1a**, **1b**), (**1c**, **1d**), and (**1e**, **1f**), respectively. If we take **1a** and **1e**, conformers with nearly the six-membered ring structure, the differences in the seven-membered ring have an energetic consequence of about 4 kcal/mol. We can conclude therefore that the energy of *β*-himachalene depends especially on the seven-membered ring geometry.

Regioselectivity. As we mentioned in the Introduction, the *β*-himachalene oxidation occurs exclusively on the C_6-C_7 double bond when stoichiometric quantities of *β*-himachalene and *m*-CPBA are used. The C_2-C_3 double bond is attacked by the *m*-CPBA only when this latter is used in excess. What are the factors behind this regioselectivity? The answer lies in the relative energies of the molecular orbitals (MOs) on these sites (C_2-C_3 and C_6-C_7), taking into account the HOMO(*β*-himachalene)−LUMO(peracid) interaction. We carried out a molecular orbital analysis on all conformers. In Table 1 we present the energies of the HOMO and HOMO-1 and the most important weighting (>15%) of C_2, C_3, C_6, and C_7 p_z atomic orbitals in them. The HOMO appears principally localized on the C_6 and C_7 atoms with an involvement of about 50% while the HOMO-1 is localized especially on the C_2 and C_3 ones. The HOMO orbital is about 0.4 eV higher than the HOMO-1 one; this difference is probably due to strain in the seven-membered ring or to the degree of substitution. This explains the preferred attack on the C_6-C_7 double bond of *β*-himachalene by *m*-CPBA.



1a (-20.09 kcal/mol) **1b** (-20.05 kcal/mol)

1d (-18.56 kcal/mol) **1c** (-19.14 kcal/mol)

1e (-16.17 kcal/mol) **1f** (-15.22 kcal/mol)

Figure 1. AM1-optimized geometries of *β*-himachalene conformers. The heats of formation are given in parentheses.

Stereoselectivity and Mechanistic Considerations. The epoxidation of alkenes by peracids is not as well-understood as their epoxidation by peroxides.[25] The "Butterfly" mechanism of Bartlett[26] for epoxidation by peracids has been generally accepted. In this work, we

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Table 2. AM1 Calculated Reaction Energy E_r (kcal/mol) and Forward and Reverse Activation Barrier Energies E_{af} (kcal/mol) and E_{ar} (kcal/mol) of β-Himachalene + m-CPBA $\longrightarrow$ Monoepoxide + m-CBA

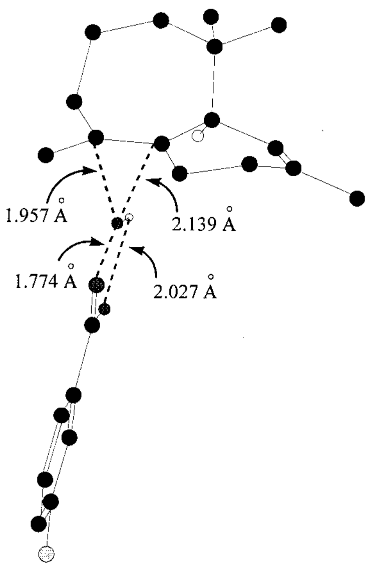
	E_r		E_{af}		E_{ar}	
conformers	α	β	α	β	α	β
1a	−43.54	−40.48	34.57	38.25	78.11	78.73
1b	−44.94	−37.18	34.13	39.30	73.18	76.48
1c	−45.04	−39.73	33.83	38.52	78.87	78.25
1d	−42.93	−42.36	34.44	38.20	77.36	80.56
1e	−44.40	−44.53	33.68	35.15	78.08	79.68
1f	−46.57	−42.56	33.27	37.77	79.84	80.32

Table 3. Activation Barrier Difference Energies (kcal/mol)

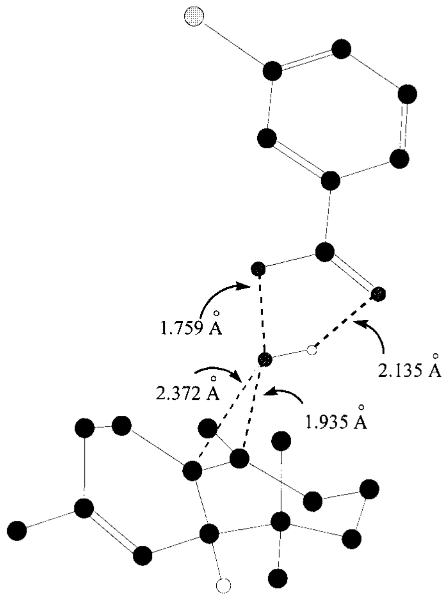
	ΔE^a		
conformers	AM1	6-31G(d)^b	B3LYP^c
1a	3.69	13.13	10.10
1b	5.17	16.49	13.41
1c	4.69	10.35	12.49
1d	3.76	2.00	0.64
1e	1.47	9.10	4.93
1f	4.50	9.42	8.00

[a] $\Delta E = E_{af}(\beta) - E_{af}(\alpha)$ [b] RHF/6-31G(d) single-point calculations on the AM1-optimized geometries [c] B3LYP/6-31G(d) single-point calculations on the AM1-optimized geometries

have examined m-CPBA epoxidation of the β-himachalene. Moreover, we took account of acid spiro arrangement vis-à-vis the targeted double bond, as recently proposed[27,28] and in accordance with Bartlett's concerted model.[26] This approach has been examined for both α- and β-sides. We have localized two transition structures (α and β) for each conformer on the complete potential energy surface. In Table 2, we present the AM1-calculated reaction energy E_r and the forward and reverse activation barrier energies E_{af} and E_{ar} corresponding to α- and β-sides for all conformers **1a**−**f**. These results show that the monoepoxidation reaction is energetically exothermic and the α-monoepoxide formation is favorable. We notice also that the energy barrier corresponding to the approach to the α-side is lower than the corresponding one to the β-side. This result permits us to conclude that the α-attack is kinetically and energetically favored, and this is in good agreement with our experimental results.[13] Lucero and Houk[29] have recently applied this strategy in the epoxidation study of the 1,2-dihydronaphthalenes. They reported that the two-side barriers difference is about 1.2 kcal/mol at the 6-31G(d)/PM3 level of theory. In our case, this deviation is between 1.3 and 5.2 kcal/mol at the AM1 level. At 6-31G(d)//AM1 and B3LYP/6-31G(d)//AM1 levels, this deviation is between 2.0 and 16.5 kcal/mol and between 0.6 and 13.4 kcal/mol, respectively (Table 3). The 6-31G(d) and B3LYP/6-31G(d) single-point energies calculated for the AM1 geometries correctly identify the favored attack. In Figure 2, we have depicted the AM1-optimized structure of the transition state corresponding to the lowest conformer (**1a**).



α-side



β-side

Figure 2. AM1-optimized geometries of α- and β-side transition states corresponding to the lowest conformer (**1a**).

The structural analysis of the transition states shows that C_6−O and C_7−O bonds are both close to 2.0 Å in the α-attack, while they are about 2.2 and 1.9 Å, respectively, in the β-attack. The α-attack seems to occur synchronously. On the other hand, Yamabe et al.[27] have reported that the structure of the transition-state for ethylenic epoxidation is of an asymmetric-bridged type. The same conclusion was previously reported by Plesnicar et al.[30] Nevertheless, a symmetrical transition structure has been reported by Bach et al.[31] and Houk et al.[32,33] A recent DKIE study[34] suggests a relatively symmetrical

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transition state. The geometry is a spiro type with the oxyranic oxygen atom being roughly equidistant from the two olefinic carbons. Our results are thus in good agreement with previous high-level experimental and theoretical investigations.[28,29,32]

In summary, new results for the β-himachalene epoxidation have been found. The stability of the conformers depends mainly on the seven-membered ring. The MO analysis shows that *m*-CPBA attack occurs preferably at the tetrasubstituted C/C double bond, which is also the one with the highest-energy π MO. The calculated activation barriers show that the α−side attack needs less energy than the β-side one. The O−C bonds are synchronously formed in conformity with the “Butterfly” mechanism.

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