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Computational study on the ring-opening reaction of protonated oxirane and methylpropene

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Abstract—A computational study on the intermolecular reaction of protonated oxirane with methylpropene, as a model for initiation of oxidosqualene cyclisation, shows that the S_N2-like ring opening is strongly exothermic with a low barrier to reaction and establishes the geometry of the intermolecular reaction.

1. Introduction

As part of an ongoing interest in computation as a method of understanding of reactions initiated by oxirane cleavage,[1–6] we became interested in the cyclisation of 2,3-(*S*)-oxidosqualene **1** to form the tetracyclic steroid precursor lanosterol **2**. This important biochemical reaction is catalysed by the enzyme oxidosqualene cyclase[7–9] (Fig. 1). The substrate is considered to be held by the active site of the enzyme in a reactive conformation, and the epoxide is activated by an acidic amino acid residue.[10] The initial step of the cyclisation is considered to be the ring opening of the activated epoxide, in concert with S_N2-like nucleophilic attack by the proximate 6,7-double bond, leading to closure of the A-ring in lanosterol.[10–12]

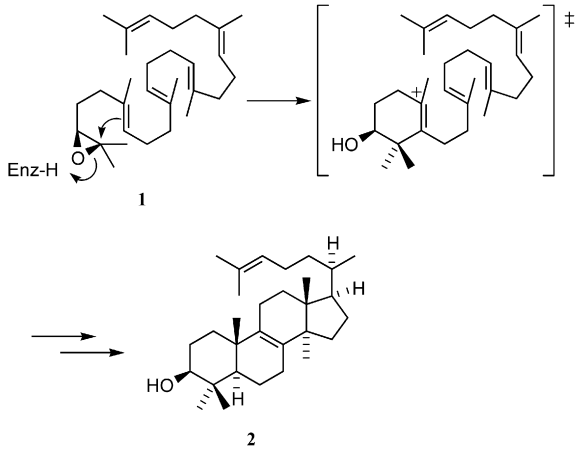

Figure 1. Cyclisation of 2,3-(*S*)-oxidosqualene (**1**) to lanosterol (**2**) is initiated by intramolecular attack of the alkene on the epoxide.

We now report a computational study of the reaction of protonated oxirane **3** with methylpropene **4** (Fig. 2) as the simplest model for the initiation of the biosynthesis of lanosterol. Studies on this intermolecular analogue will allow an analysis of the geometry distortions and energy cost of the intramolecular reaction of oxidosqualene cyclisation, which is prevented by ring strain from achieving optimal orbital overlap.

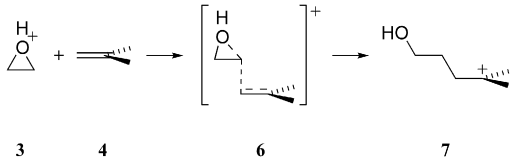

Figure 2. Nucleophilic ring opening of protonated oxirane **3** with methylpropene **4**.

2. Results and discussion

The gas-phase stationary points on the potential energy surface for the nucleophilic ring-opening reaction of protonated oxirane **3** and methylpropene **4** were established at the MP2(Full)/6-31G(d) level of theory (Fig. 3). Transition states have been confirmed by frequency and intrinsic reaction coordinate (IRC) calculations. All calculations were performed using the Gaussian 94[13] program.

Protonated oxirane and alkene collapse spontaneously to the dipole–dipole complex **5**, which reacts via transition state **6** to give product **7a**. Product conformation **7b** is the global

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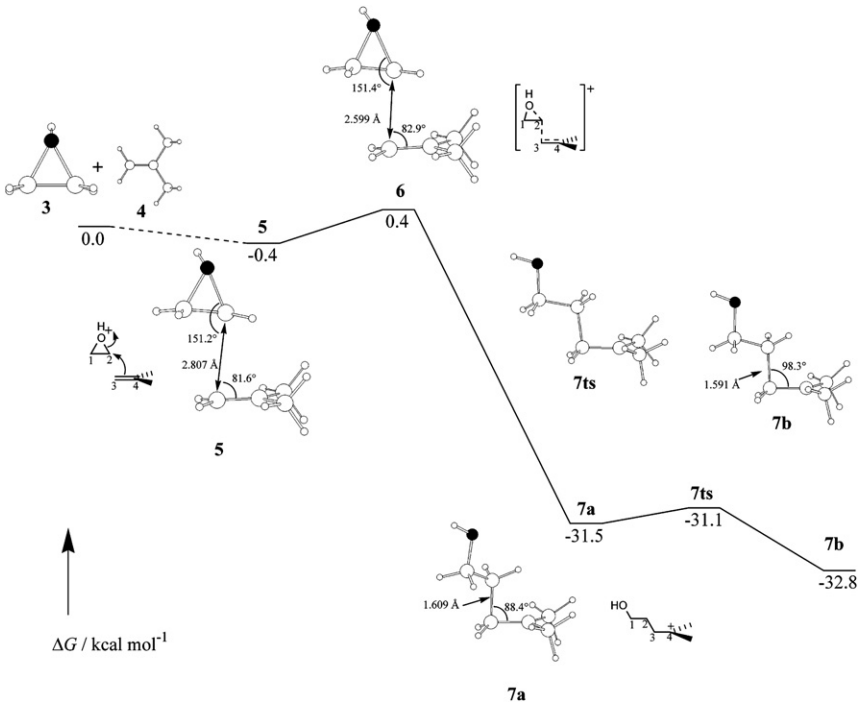


Figure 3. Optmised stationary points on the potential energy surface of protonated oxirane (**3**) and methylpropene (**4**); energies are Gibbs free energies (MP2(Full)/6-31G(d)//MP2(Full)/6-31G(d)).

minimum conformation and is connected to **7a** by rotational transition state **7ts**.

Correction of the calculated stationary point energies by zero-point electronic energies (ZPE) gives rise to incongruities in calculated activation energies (see Table 1).[†] Transition state **6** is calculated to have a ZPE-corrected energy of ΔE=−9.4 kcal mol^{-1} relative to reactants **3** and **4** but complex **5** has a ZPE-corrected energy of ΔE=−9.3 kcal mol^{-1} relative to **3** and **4**, resulting in an apparent anomalous negative activation barrier of $\delta\Delta E$=−0.1 kcal mol^{-1} for complex **5** to reach transition state **6**. Product conformation **7a** exhibits a similarly anomalous negative ZPE-corrected activation barrier of $\delta\Delta E$=−0.2 kcal mol^{-1} to transition state **7ts**.[‡]

The phenomenon of apparent inversion in relative energy of the ZPE-corrected electronic energy of transition state and associated minima has been recognised by Lee for other very flat potential energy surfaces.[15] [§] It is considered to arise for zero-point corrected electronic energies since no allowance is made for enthalpy and entropy corrections, and Lee has reported that the problem is avoided when the vibrational energy contribution of enthalpy and entropy (i.e., Gibbs free energy, ΔG) are included in the energy corrections.

[†] These anomalous negative activation energies also appear in B3LYP/6-31+G(d,p)//MP2(Full)/6-31G(d) single-point energies.

[‡] This type of incongruity, namely apparent negative activation barriers, appears without explanation in a study of the ring-opening nucleophilic reaction of unprotonated and protonated oxirane with ammonia (see Ref. 14).

[§] The phenomenon is significant only when comparing stationary points with very small energy differences in a flat transition state region of a potential energy surface.

Table 1. Calculated electronic energies and Gibbs free energies (MP2(Full)/6-31G(d)//MP2(Full)/6-31G(d))

Structure	E[a,b]	ΔE[c]	G[a]	ΔG[c]
3	−153.547092	0.0[d]	−153.571437	0.0[d]
4	−156.539630		−156.567008	
5	−310.101596	−9.3	−310.139124	−0.4
6 (TS)	−310.101770	−9.4	−310.137838	0.4
7a	−310.154161	−42.3	−310.188680	−31.5
7ts (TS)	−310.154398	−42.5	−310.187971	−31.1
7b	−310.154801	−42.7	−310.190698	−32.8

[a] Values in hartrees.
[b] Includes zero-point correction.
[c] Values in kcal mol^{-1}.
[d] Sum of energies for protonated oxirane **3** and methylpropene **4**.

For this reason, we report Gibbs free energies for the MP2(Full)/6-31G(d) optimised structures (Fig. 3), calculated with frequency calculations using the ReadIsotopes option[16,17] at 298.15 K and 1 atm, with the naturally most abundant atomic isotopes and a scaling factor of 0.9646.[17] The reaction coordinate, after corrections for electronic and thermal enthalpies and entropies are made, shows that reactant complex **5** is lower than reactants **3** and **4** by ΔG=−0.4 kcal mol^{-1} (Fig. 3). Transition state **6** has a positive activation barrier from complex **5** of $\delta\Delta G$=0.8 kcal mol^{-1} and the overall reaction to give product **7a** is exothermic (ΔG=−31.5 kcal mol^{-1}). The low transition state and high exothermicity can be attributed to the inherent reactivity of three-membered rings, primarily arising from relief of ring strain, and protonation of the epoxide oxygen increasing the power of the leaving group and eliminating charge separation in the transition state.

The C1–C2–C3–C4 carbon skeletons of complex **5** and transition state **6** are non-planar with a dihedral angle of −159.3°

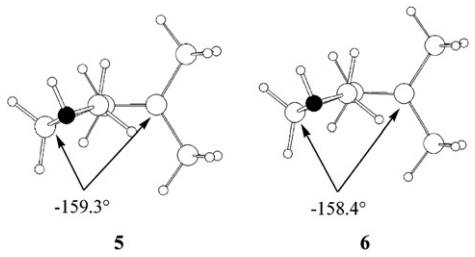


Figure 4. Reactant complex **5** and transition state **6** showing non-planarity of the carbon skeleton.

and −158.4°, respectively (Fig. 4), and these deviations of the dihedral angle from 180° show the alkene rotated away from the face of the oxirane to which the proton is bound. A structure optimisation of the complex with the C1–C2–C3–C4 dihedral angle fixed at 180° resulted in a structure marginally higher in energy than **5** ($\delta\Delta E$=0.02 kcal mol^{-1}), indicating that the barrier to rotation about C1–C2–C3–C4 is low.

An energy difference calculated for *syn* and *anti* protonated methyloxirane[1] shows that the *syn* protonated stereoisomer is 0.2 kcal mol^{-1} higher in energy than the *anti* isomer (MP2/6-31G(d)), similarly reflecting the small interaction energy of an epoxide-bound proton with a proximate methyl.

The trajectory of approach of epoxide **3** to alkene **4** is reflected in the C2–C3–C4 angle. In complex **5** this angle is 81.6°, and this changes only slightly to 82.9° in going to the early transition state **6** (Fig. 3). The C2–C3–C4 angle of attack at the alkene in **5** and **6** is notably less than 90° as the donor π orbital is a molecular orbital centred between C3 and C4 (Fig. 5).

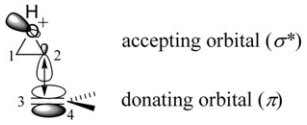


Figure 5. Schematic of the frontier orbital interaction of **3** and **4**: note that the HOMO π orbital is not centred on a single atom and that the LUMO σ* orbital is bent towards C1.

The trajectory of nucleophilic attack at the epoxide, namely the O–C2–C3 angle, for complex **5** (151.2°) and transition state **6** (151.4°) is significantly less than the near-linear arrangement found in a normal S_N2 reaction.[18] There are three factors that contribute to the reduction of the O–C–Nu angle from 180°. The intramolecular nature of the leaving oxygen restricts the ability of the oxygen to leave at and maintain an angle of 180°.[¶] Secondly, the oxygen–carbon σ* orbital of the strained oxirane is a 'bent bond'[19] such that the acceptor orbital is not collinear with the formal oxygen–carbon bond (Fig. 5). In ring-opening nucleophilic substitutions of protonated and unprotonated epoxides with conventional atom-centred nucleophiles[14,20–24] the O–C–Nu angle is less than 180° but larger than the O–C2–C3 angle calculated for **6**. The third contributing factor, unique to reactions in which the nucleophile is an alkene or alkyne, is that the reaction occurs by overlap of the protonated oxirane LUMO with the alkene/alkyne π orbital centred between C3 and C4, further moving C3 from linearity with the C2–O bond.

IRC calculation of transition structure **6** leads, on the product side, to local minimum **7a** with an almost eclipsed C1–C2–C3–C4 dihedral angle of −131.8° (Fig. 6). A study[25] on the nucleophilic ring opening of aziridinium with chloride found two sequential transition states without an intervening intermediate. Ring opening occurs during the first transition state, and the second transition state involves a rotation about the C–N bond to relieve steric interactions between the *N*-methyl groups and the neighbouring hydrogens. A similar rotation about the C1–O bond occurs between **6** and **7a** to move the hydroxyl group to the least-hindered position; the present study did not investigate the nature of this rotation and closer examination may find an inflection point analogous to that for aziridinium opening.[25]

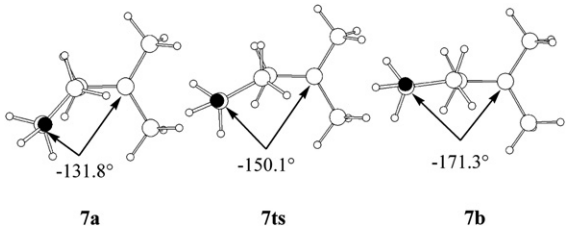


Figure 6. Product conformations **7a** and **7b** and rotational transition state **7ts** showing non-planarity of the carbon skeleton.

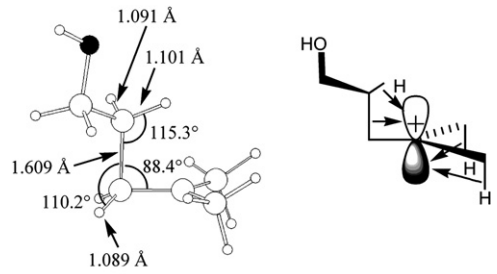
Steric arguments do not explain the deviation from planarity of the carbon skeleton of **7a** as the hydroxyl proton is not in a position where it could interact with either methyl. The deviation of C1–C2–C3–C4 dihedral angle from planarity can be explained as a result of electronic stabilisation of the C4 carbocation by the *syn* C2–H bond (Fig. 7).

The C2–H distance is longer than expected (1.101 Å) and the H–C2–C3 angle is expanded (115.3 °), consistent with loss of electron density from the bond.[‖] Evidence of other hyperconjugative stabilisations of the cation are seen: the C2–C3 bond is aligned with the cation, lengthened to 1.609 Å and the C2–C3–C4 angle is reduced to 88.4°; and carbon–hydrogen bonds of the C5 and C6 methyl groups also show evidence for hyperconjugation of the cation. The C1–C2–C3–C4 dihedral angle of **7b** is −171.3°, closer to planarity than **7a**, and **7b** represents a structure more sterically favoured than **7a** but with less electronic stabilisation of the cation.[††]

[¶] For O–C2–Nu to be even close to linear, the O–C1 bond would need to hugely elongate, however, relief of ring strain in the transition state results in a decrease of O–C1 bond length from 1.525 Å in **3** to 1.410 Å in **7a**.

[‖] The distortions of the C2–H bond cannot be attributed to steric interactions as they do not occur with the similarly eclipsed C3–H bond.

[††] Preliminary calculations in the present study were performed at the HF/6-31G(d) level of theory; at this lower level, the carbocation product is planar through the carbon skeleton with a C1–C2–C3–C4 dihedral angle of 180.0° and shows little evidence of hyperconjugative stabilisation of the carbocation. As the Hartree–Fock method does not include electron correlation in the approximation of the Hamiltonian, the HF/6-31G(d) optimised product adopts the most sterically-favoured conformation of a planar, staggered chain of carbon atoms, strengthening the suggestion that the non-planarity of MP2(Full)/6-31G(d) optimised **7a** arises from electronic stabilisation of the carbocation.



7a

Figure 7. The important hyperconjugations in structure **7a**.

3. Conclusion

The ring-opening reaction of protonated oxirane with methylpropene is shown to be an S_N2-type reaction, computed to occur with a low activation barrier and high exothermicity. The geometry of the reactant complex and transition state is strongly influenced by a low-energy steric interaction between the protonated epoxide and the alkene. Analysis of reaction trajectories in comparison with intramolecular (A-ring) models of oxidosqualene will allow an estimation of the cost associated with the intramolecular nature of lanosterol formation.[26]

Hyperconjugative stabilisation of the carbocation has an important effect on the geometry of the product, dictating that the cation species adopt constrained internal angles thereby influencing conformation and regiochemistry. It is expected that similar interactions exert significant control over conformation and regiochemistry in the biosynthesis of lanosterol.

Acknowledgements

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Supplementary data

Atomic coordinates of all optimised stationary points and calculated energies, zero-point corrections and imaginary frequencies are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.168.

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