Theoretical Studies of Autoxidation of 2-Alkylidene-1,3-cyclohexadione Leading to Bicyclic-Hemiketal Endoperoxides

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ABSTRACT: Mechanism of the addition of molecular oxygen on the dienolic form of the 2-alkylidene-1,3-cyclohexadione was investigated by quantum chemical calculations using the approximate projection method developed by Yamaguchi. The complete reaction pathway of the formation of the endoperoxide is described. The crossing between triplet and singlet potential energy surfaces has been located. A multireference complete active space self-consistent field calculation has been performed to strengthen the results.

INTRODUCTION

G3 factor is a natural endoperoxide extracted from the leaves of Eucalyptus grandis, where it plays the role of phytohormones and a growth regulator.1 Modifications of its structure afforded new endoperoxides with interesting antimalarial properties.2 The synthesis of G3 factor and its analogues is based on a biomimetic spontaneous oxygen uptake on the enedione in equilibrium with its ketodienolic form (Scheme 1). The autoxidation occurs in mild conditions, at room temperature, without photoactivation, whatever the solvent used, also in solid state and in the dark, and is quantitative and selective.3 Previous studies have shown the implication of fundamental oxygen in its triplet state3−g O2 and have discarded the alternative of a radical reaction.4 This spin-forbidden reaction constitutes the key step to prepare endoperoxides with antimalarial properties and an alternative green process. To elucidate the mechanism of this intriguing reaction, a precedent electron paramagnetic resonance (EPR)/spin-trapping study combined with mass spectroscopy has been undertaken, using two spin traps and starting from the precursors labeled with 13C in different positions.5 For instance, when the 13C-labeled precursor was incubated with dioxygen during 1 h in the presence of the nitrone (TN),6 the EPR spectrum given in Figure 1 was recorded. Its simulation allowed us to undoubtedly identify the radical center in the intermediate detected, and its structure was confirmed by the tandem mass spectrometry analysis. The whole spin-trapping study highlighted the presence of the diradical species within a mechanism in which pathway I (named pathway B in ref 5) was implicated (Scheme 1).

To gain an insight into the mechanism of addition of dioxygen with dienol, a computational approach was employed. The calculations are performed on the simplified 2-alkylidene-1,3-cyclohexadione in equilibrium with its ketodienolic form, which is also subject to autoxidation (Scheme 2).7

The addition of a triplet dioxygen on a singlet dienol will be considered, furnishing a triplet diradical. Because the reactants taken together have a triplet potential energy surface (PES), whereas the endoperoxide product resides on a singlet potential energy surface, a triplet–singlet interconversion must occur at some point along the reaction coordinates. In this way, a change in multiplicity from triplet to open-shell singlet of the obtained diradical is necessary to finally obtain the closed-shell singlet endoperoxide. It is worth noting that the crossing between triplet and singlet potential energy surfaces arises and has to be located. We report herein a density functional theory (DFT) study of the complete pathway leading to bicyclic-hemiketal endoperoxides.

COMPUTATIONAL METHOD

Gaussian 09 was used for all of the computations and analytical frequencies were calculated for all of the stationary points.8 The energy of the singlet diradical after correction of the spin contamination was provided by the approximate spin projection method developed by Yamaguchi.9 The spin-corrected energy value, 1ESO, can be obtained as follows.
In addition, recently, Tantillo has used the DFT with Yamaguchi method to study the intramolecular (2 + 2) cycloaddition reaction, which involves the diradical intermediates from zwitterionic transition state structures.11

As a result, we decided to use the DFT calculations with restricted B3LYP/6-311+G(d,p)12 and unrestricted broken symmetry UB3LYP/6-311+G(d,p) levels for all of the closed-shell and open-shell species, respectively, to study the spontaneous oxygen uptake on the dienol precursor.13 Structures of the singlet diradicals were optimized at the UB3LYP/6-311+G(d,p) level with the broken symmetry method (initial guess $\langle S^2 \rangle = 1$) and the structures of the triplet state of diradicals were calculated with the unrestricted method (initial guess $\langle S^2 \rangle = 2$). Spin-projected energies were
used throughout this paper. To further explore the validity of our results, a multireference complete active space self-consistent field (CASSCF)(8/8)/6-31G(d) calculation was also performed on some points chosen along the intrinsic reaction coordinate (IRC).

Solvent effects were not investigated, as the autoxidation occurred with or without a solvent.

Table 1. Triplet Enthalpies of the Six Minima $M_1$–$M_6$ and the Singlet Spin-Corrected Enthalpy of $M_2$

| Structure | $M_1$ | $M_2$ | $M_3$ | $M_4$ | $M_5$ | $M_6$ |
|-----------|-------|-------|-------|-------|-------|-------|
| Geometry  | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png) |
| $<S^2>$   | 2.02  | 1.02  | 2.02  | 2.03  | 2.03  |       |
| $H$ (au)  | -690.175531 | -690.178658 | -690.179852 | -690.167892 | -690.172619 | -690.173090 |
| $\Delta H$ (kcal/mol) | 21.6 | 19.5 | 19.9 | 26.3 | 23.3 | 23.1 |

*Calculated with the approximate spin-correction procedure proposed by Yamaguchi computed at the UB3LYP 6-311+G(d,p).

Table 2. Triplet Enthalpies of Transition States between $[^3]([\text{Dienol} + \text{O}_2])$ and $[^3]M_1$ or $[^3]M_2$, Respectively. Noted $[^3]TS_1$ and $[^3]TS_2$ and Singlet Spin-Corrected Enthalpies of Transition States $[^1]TS_2$ and $[^1]TS_{\text{form}}$ between, Respectively ($[^1]\Delta_g = \text{O}_2$, Dienol), and $[^1]M_2$ and $[^1]M_2$ and Endoperoxide

| Structure | $[^3]TS_1$ | $[^3]TS_2$ | $[^3]TS_2$ | $[^1]TS_{\text{form}}$ | $[^1]TS_{\text{form}}$ |
|-----------|------------|------------|------------|------------------------|------------------------|
| Geometry  | ![Image](image7.png) | ![Image](image8.png) | ![Image](image9.png) | ![Image](image10.png) | ![Image](image11.png) |
| Imaginary frequency (cm$^{-1}$) | -361.60 | -299.96 | -199.17 | -105.71 | -102.83 |
| $<S^2>$   | 2.04       | 2.04       | 1.02       | 2.02       | 0.96       |
| $H$ (au)  | -690.171608 | -690.175236 | -690.169526 | -690.169304 | -690.173422 |
| $\Delta H$ (kcal/mol) | 24.0 | 21.7 | 25.3 | 25.4 | 22.8 |

**RESULTS**

The different conformations of the singlet ground state dienol were first calculated (see the Supporting Information) and the lowest one’s geometry was retained. The addition of a triplet oxygen $[^3]\sum_{E} = \text{O}_2$ on the dienol can afford three possibilities of geometries in each pathway (A and B). Three triplet minima were found for the pathway noted $[^3]M_{1-3}$ and only two for pathway II noted $[^3]M_4$ and $[^3]M_5$. Despite our efforts, no
minimum could be found for $M_6$, for which the initial guess always converged to $M_4$ or $M_5$ geometries. Triplet enthalpies (au) and the relative enthalpies (kcal/mol) with respect to the starting material ($3\text{dienol} + O_2$) are given in Table 1.

From all of the minima, $3\text{M}_2$, the lowest in energy was located at 19.5 kcal/mol higher than the ground state of the starting material $3\text{(dienol} + O_2)$. The relative enthalpies for $3\text{M}_1$ and $3\text{M}_3$ were, respectively, located at 21.6 and 26.3 kcal/mol. This last value is quite high (7 kcal/mol higher than that of $3\text{M}_2$) and could be explained by the destabilizing Pauli repulsion. So, the research of the transition states were first carried on between both $3\text{M}_1$ and $3\text{(dienol} + O_2)$ and then $3\text{M}_2$.

Figure 2. Complete reaction pathway of the autoxidation. Relative enthalpies are in kcal/mol at the (U)B3LYP/6-311+G(d,p).

Figure 3. IRC plots connecting the transition state $TS_{form}$ to the two minima $M_2$ and the endoperoxide on the singlet potential energy surface ($^1E_{UB}$). Singlet energies vs reaction coordinate plots are shown in blue, single points triplet energies ($^3E_{UB}$) in red, and singlet $\langle S^2 \rangle$ values vs reaction coordinate plots in green.
The conditions are fulfilling singlet and triplet states could be considered as degenerated. On the singlet potential energy surface, allowing the possibility that the reaction pathway continues (Figure 2). The crossing between triplet and singlet potential energy surfaces will be studied in the area of the endoperoxide. The crossing of the triplet and singlet pathways located between M2 and TSform. To further explore the validity of our results, a multireference calculation at the CASSCF(8,8) level was also performed on five chosen geometries on the singlet PES, 1−5, in both singlet and triplet states. The occupation numbers of the eight orbitals of the active space are given in Table 3 for the singlet and the triplet state. In the singlet state, orbitals 3 and 4 are singly occupied for point 1 (M2) to point 3 (TSform), expressing the open-shell character at the onset of closing, then the occupation number increases for orbital 3 and decreases for orbital 4 (points 4 and 5) until the formation of the C−O bond. These results strengthen our previous calculations at the UB3LYP level using Yamaguchi’s method. The ⟨S^2⟩ value of ≈1.0 (equal mixture of singlet and triplet) found for points 1−3, characterizing singlet open-shell diradical structures, is well correlated with the occupation numbers of orbital 3 and 4. Then ⟨S^2⟩ decreases to 0 (0.675 for point 4 and 0 for point 5), characterizing closed-shell structures. Concomitantly, the two electrons fill the orbital 3 and orbital 4 becomes empty, indicating no more diradical character. As can be seen from Figure 4, orbital 3 of point 5 with the occupation number of 1.8 in its singlet state shows the C−O bond formation. For the triplet state of point 5, the energy of one singly occupied orbital drops below that of a

![Figure 4. Orbital S3 of the CASSCF(8/8)/6-31G(d) calculation for the point 5 in its singlet state with the occupation number 1.8.](Image)

Table 3. Occupation Numbers of Orbitals 50−57 of the CASSCF(8,8)/6-31G(d) Calculation on Points 1−5 in the Singlet and Triplet State and Total Energies E^a

| Number | Singlet | S1 | S2 | S3 | S4 | S5 | S6 | S7 | E (au) | ΔE (kcal/mol) |
|--------|---------|----|----|----|----|----|----|----|-------|---------------|
| 1      | 1.90    | 1.93| 1.97| 1.02| 0.97| 0.10| 0.06| 0.03| -686.18868| 0             |
|        | 1.90    | 1.93| 1.97| 1.00| 1.00| 0.10| 0.06| 0.03| -686.18903| -0.22         |
| 2      | 1.90    | 1.98| 1.97| 1.03| 0.97| 0.09| 0.03| 0.01| -686.17679| 7.46          |
|        | 1.91    | 1.98| 1.97| 1.00| 1.00| 0.09| 0.01| 0.03| -686.17729| 7.14          |
| 3      | 1.91    | 1.98| 1.97| 1.21| 0.79| 0.09| 0.01| 0.03| -686.17474| 8.75          |
|        | 1.91    | 1.98| 1.97| 1.00| 1.00| 0.09| 0.01| 0.03| -686.17247| 10.72         |
| 4      | 1.91    | 1.97| 1.98| 1.46| 0.55| 0.09| 0.01| 0.03| -686.17763| 6.93          |
|        | 1.90    | 1.98| 1.97| 1.00| 1.00| 0.10| 0.01| 0.03| -686.16465| 15.08         |
| 5      | 1.91    | 1.98| 1.94| 1.79| 0.23| 0.07| 0.01| 0.06| -686.21144| -14.28        |
|        | 1.94    | 1.97| 1.02| 1.90| 1.00| 0.09| 0.01| 0.06| -686.15387| 21.84         |

^aElectrons implicated in the C−O bond formation are shown in bold.

and 1(diol + O2) and are, respectively, noted 3TS1 and 3TS2. They were, respectively, found at 24.0 and 21.7 kcal/mol higher than the ground state (Table 2). These transition states are characterized by only one imaginary frequency at, respectively, −361.6 and −299.96 cm⁻¹, which are both along the reaction coordinates of the C−O bond formation. 3TS1 is located below the other minima and below 3TS2. As a consequence, the research of other transition states was not further investigated. Using the approximate spin-correction procedure, the enthalpy of the singlet diradical 1M2 was found to be close in energy to the triplet structure (only 0.5 kcal/mol higher). The singlet 1M2 with the same geometry as the triplet 3M2 was also a minimum, as its optimized geometry stays unchanged (ΔH less than 0.01 kcal/mol) with no negative frequency. Therefore, singlet and triplet states could be considered as degenerated. The conditions are fulfilled for the intersystem crossing, allowing the possibility that the reaction pathway continues on the singlet potential energy surface, finally leading to endoperoxide. The crossing between triplet and singlet potential energy surfaces will be studied in the area of the reaction pathway (Figure 2).

Futhermore, on the singlet potential energy surface, we found the transition state 1TS2, which relies (Δg = O₂ diole) to 1M2 with a relative activation enthalpy of 25.3 kcal/mol, a significantly higher barrier than for 3TS2 on the triplet surface. This result is in good agreement with the experimental facts in favor of the implication of fundamental oxygen during this autoxidation.

Continuing on the singlet potential energy surface, the transition state (TSform) between 1M2 and endoperoxide was located at 22.8 kcal/mol above the ground state (and lying only 3 kcal/mol above 1M2).

An intrinsic reaction coordinates (IRCs) calculation was performed to connect both the transition state TSform with the endoperoxide in the reverse direction and the minimum 1M2 in the forward direction on the singlet potential energy surface. The results are consigned in Figure 3. To characterize the singlet diradical character along the reaction coordinate before the closing of the ring, the ⟨S^2⟩ value was reported versus IRC points. The ⟨S^2⟩ value of 1.0 in the DFT calculations indicates an equal mixture of singlet (⟨S^2⟩ = 0) and triplet (⟨S^2⟩ = 2). This value of 1 is expected for singlet open-shell diradical structures. At the onset of the closing, the transition state TSform in its singlet state possesses a diradical character with a ⟨S^2⟩ value of approximately 1; this value then quickly decreases as the peroxide bond is formed. It is worth noting that a singlet PES is very flat as long as ⟨S^2⟩ ≠ 0 and becomes steep as soon
doubly occupied orbital. Thus, for this point only, orbitals 52 and 54 are singly occupied. Yet, as can be seen from their shapes in the Supporting Information, they do correspond to orbitals 53 and 54 of the four previous points (1–4).

The orbitals 53 (or 52 for the triplet last point) and 54 of the five points (1–5) at CASSCF(8,8)/6-31G(d) level both in singlet and triplet state are shown in the Supporting Information.

■ CONCLUSIONS
A plausible reaction pathway of the autoxidation of the ketoalcohol has been investigated by using the unrestricted B3LYP/6-311+G(d,p) level of theory, which appears to perform well for diradicals using the spin-projected Yamaguchi's method and the results have been strengthened by the CASSCF(8,8) calculations. We theoretically demonstrated that the oxygen uptake occurred between singlet dienol and fundamental triplet dioxygen following pathway I, with an overall barrier reaching 22.8 kcal/mol. The crossing between triplet and singlet PES has been located. This computational study is in good agreement with the experimental reaction conditions and our previous spin trap experiments. The DFT method, low in cost, seems convenient to qualitatively describe the autoxidation.

■ ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00989.

Geometries and electronic energies and enthalpies at the B3LYP/6-311+G(d,p) level of all of the stationary points; orbitals 53 and 54 of the five points 1–5 chosen on the singlet IRC, at the singlet and triplet states at the CASSCF(8,8)/6-31G(d) level (PDF)

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Notes
The authors declare no competing financial interest.

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