Theoretical Study on the Reactivity and Regioselectivity of the Ene Reaction of $^1\Delta_g$ O_2 with α,β-Unsaturated Carbonyl Compounds

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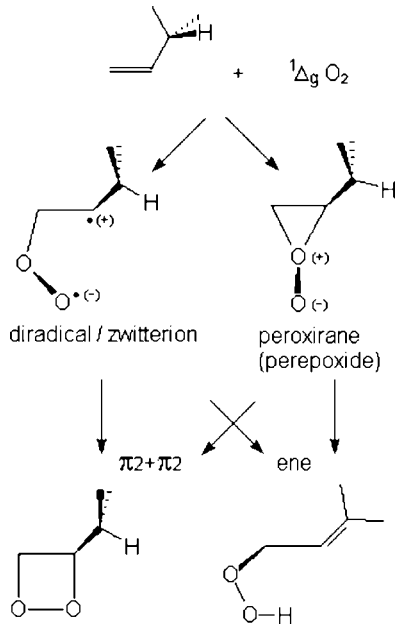
The *ene* reaction of singlet oxygen with α,β-unsaturated carbonyl compounds gives unsaturated hydroperoxides and displays interesting features: Different reactivities of the *s-cis* and *s-trans* reactants and a marked regioselectivity, influenced to some extent by solvent polarity. All of these traits are accounted for by a polar diradical mechanism. A perepoxide intermediate is not a critical point on the reaction's potential energy surface. Also, a trioxene intermediate is located too high in energy to be significantly populated. An alternative pathway leading to dioxetane is not as effective as the ene pathway giving the hydroperoxide.

Introduction

$^1\Delta_g$ O_2 is an important and ubiquitous reactive species in oxidation reactions.[1] It exhibits a diverse reactivity with organic unsaturated molecules, giving particularly the [π2+π2] and [π4+π2] cycloadditions.[2] Wherever an allylic hydrogen is available, an additional reaction channel forming a hydroperoxide is available: this is called the *ene*[3] (Schenck) reaction. These different reactions can compete, but one usually dominates in particular circumstances. For example, electron-withdrawing substituents in alkenes promote the *ene* mode.[4]

With regard to the mechanistic features, the mentioned reactions are in fact related by the possibility of sharing a common open-chain diradical/zwitterionic or cyclic peroxirane (perepoxide) intermediate (the reaction pathways are sketched in Scheme 1).[2c,3b] For the *ene* reaction, both two-step and concerted mechanisms have been proposed in the past.[2c,2d]

The contribution of previous theoretical investigations[5] has flanked the experimental efforts with the aim of elucidating the *ene* reaction mechanism. Among the more recent contributions, the reaction of singlet oxygen with 1,3-cyclohexadiene has been investigated at the DFT(B3LYP) and CASPT2 levels by Sevin and McKee,[6] who find a two-step mechanism to 1-hydroperoxy-2,4-cyclohexadiene and a less-favored concerted transition structure to 1-hydroperoxy-2,5-cyclohexadiene. Then, 2-butene and 2,3-dimethyl-2-butene have been studied by Singleton et al.,[7] who find a concerted mechanism with a bifurcation point after the transition structure at the CCSD(T)//DFT(B3LYP) level.



Scheme 1.

Experimental studies on the singlet oxygen addition to α,β-unsaturated aldehydes, ketones, esters, and carboxylic acids are less frequent than the corresponding investigations involving alkenes and enol ethers. These electron-poor substrates are less reactive towards the electrophilic reagent $^1O_2$. The reaction still appears unusual because of the relatively high reactivity in comparison with other deactivated alkenes.[8] The α,β-unsaturated substrates exhibit two interesting features: a higher reactivity of the *s-cis* conformer

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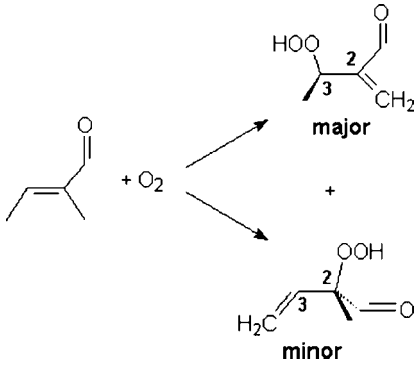
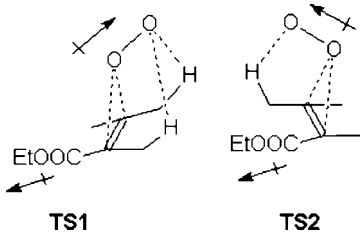
with respect to the *s-trans*[9] and a distinct regioselectivity.[10]

As regards regioselectivity, singlet oxygen is found to add preferably to the distal sp^2 carbon with respect to the carbonyl group, and the product hydroperoxide forms through hydrogen abstraction from the alkyl group geminal to the carbonyl (Scheme 2). Although polar solvents favor the minor product, the molar ratio of the two products depends on the solvent polarity only to a very limited extent. For instance, the $^1O_2$ addition to ethyl 2,3-dimethylbut-2-enoate gives a major to minor product ratio of 95:5 in carbon tetrachloride and of 80:20 in dimethyl sulfoxide. In the reaction with methyl 2,3-dimethylhept-2-enoate, yields of the major product range from 85 to 70% for the isomer *E* and from 95 to 93% for the isomer *Z*. Based on these results, Orfanopoulos[11] put forward a two-step mechanism outlining the slow formation of a peroxirane intermediate, followed by a rapid rearrangement which leads to the products. The transition structures relevant to the first step (Scheme 3) should be associated to different dipole moments: the larger μ of TS2 (which gives way to the formation of the minor product) may be expected to bring about a greater stabilization in a more polar solvent.

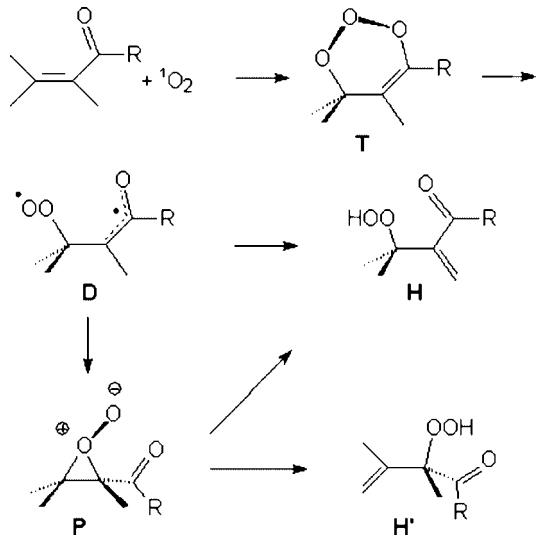


Scheme 2.



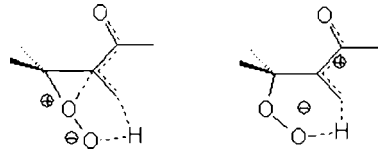
Scheme 3.

The more pronounced reactivity of the *s-cis* conformer has been attributed to the formation of a trioxene intermediate **T** (Scheme 4).[9] The cleavage of its relatively weak O–O bond could produce a diradical **D** which, in turn, could afford either the hydroperoxide **H** (the main product), or a perepoxide **P** that would give the minor product hydroperoxide **H′**. While the intermediate **T**, whose formation would not be possible from the *s-trans* conformer, could rationalize the different reactivity of the two conformers, it could not explain the observed regioselectivity, which is independent of the reagent conformation.



Scheme 4.

It has also been proposed[12] that the observed regioselectivity might originate from the charge distribution of a common intermediate (a perepoxide or a zwitterion, Scheme 5).



Scheme 5.

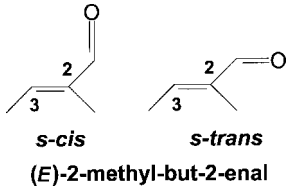
The hydrogen abstraction could be effected by the terminal oxygen in either intermediate. In this situation the breaking C–H bond would be weakened by the conjugation with a partially empty p orbital (in correspondence of the positive charge), and this effect could direct the regiochemistry.

Primary isotope effect studies performed by Elemes and Foote[13] on the reaction of methyl (*E*)-2-methylbut-2-enoate with $^1O_2$ have found a primary kinetic isotope effect (k_H/k_D = 1.30–1.49, depending on the solvent). However, solvent polarity does not influence the extent of the isotope effect, suggesting that polar intermediates and transition structures are not involved in the reaction path. Stratakis and Orfanopoulos[11,14] support a multi-step mechanism displaying the first step forming a peroxirane followed by a rate-determining hydrogen abstraction. A reduced regioselectivity[15] was observed towards alkenes with electron withdrawing groups.

The theoretical work presented in this paper is concerned with the reaction of singlet dioxygen with (*E*)-2-methylbut-2-enal, chosen as a simple model system of an α,β-unsaturated carbonyl compound.

Results and Discussion

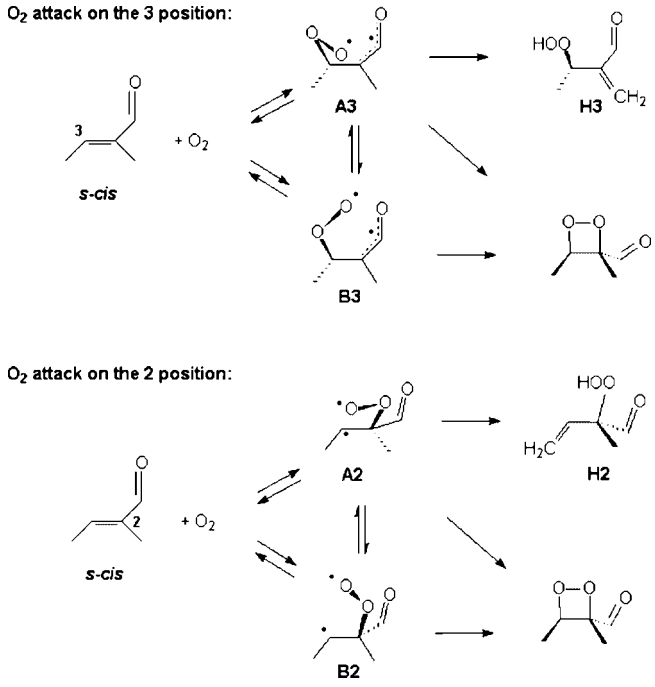
Both the *s-trans* (**1**) and *s-cis* (**2**) conformations of (*E*)-2-methylbut-2-enal were considered to clarify the regioselectivity and the reactivity toward $^1O_2$ addition in position 2 or 3 (Scheme 6).



Scheme 6.

Three different mechanisms for the *ene* reaction were considered: (a) A concerted one; (b) a two-step one, involving a cyclic peroxirane intermediate; (c) another two-step mechanism, involving a polar open-chain diradical.

(a) Considering the $^1O_2$ attack on C^2, a closed shell concerted transition structure (TS) can be found. Yet, its wave function (having $\langle \hat{S}^2 \rangle = 0$) is not stable with respect to orbital rotations.[16] If the wavefunction is consequently relaxed, its $\hat{S}^2$ expectation value becomes close to 1 (in other words, the singlet multiplicity gets contaminated by the triplet). However, the first order saddle point which can be found with the stable spin-contaminated wavefunction does not correspond to a concerted step, but to the formation of a diradical. Similar features had already been observed in a previous theoretical study having propene as a substrate.[17] In conclusion, a minimal energy concerted pathway for the $^1O_2$ attack on C^2, connecting directly the reagents to the products does not exist. By contrast, considering the $^1O_2$ attack on C^3, a closed shell ($\langle \hat{S}^2 \rangle = 0$) concerted transition structure is found, and exhibits a stable wave function. Yet, it cannot correspond to an important reaction pathway, since $\Delta G^{\ddagger} = 29.9$ kcal mol^{-1}. Therefore, the importance of concerted pathways has to be ruled out.



Scheme 7.

(b) A non-concerted pathway passing through a peroxirane (Scheme 4) intermediate cannot be found. A peroxiranic structure does not correspond to an energy minimum, since the delocalization of its unpaired electron on the C–C=O system determines a spontaneous ring opening with formation of the diradical intermediate (see **A3** or **B3** in Scheme 7), as already observed for *s-cis* butadiene.[18] By contrast, peroxirane intermediates were found both for propene[17] and ethenol[19] (but ruled out as intermediates in the *ene* reaction because of their high energy).

(c) The α,β-unsaturated carbonyl compounds seem to follow the diradical mechanism shown in Scheme 7. The diradical pathway nicely accounts for both the regioselectivity and the higher reactivity of *s-cis* isomers, as will be detailed in the following.

Regioselectivity: The *s-cis* conformer of (*E*)-2-methylbut-2-enal is in equilibrium with the most stable *s-trans* conformer, but the free energy difference between the two conformers makes the former species scarcely populated. However, since both conformers of (*E*)-2-methylbut-2-enal are intended here as models for experimentally studied systems, the evolution of each will be dealt with independently. O_2 addition to the C^3 position of the *s-cis* conformer of (*E*)-2-methylbut-2-enal leads to the rather stable delocalized diradical intermediate **A3** (Scheme 7), which is 10.9 kcal mol^{-1} higher. It can be attained through a transition structure which corresponds to a free energy barrier of 19.4 kcal mol^{-1} relative to the preceding minimum (Table 1; TS shown in Figure 1, a). Though this intermediate is thermodynamically unstable with respect to back dissociation, the free energy barrier for the backwards step is 8.5 kcal mol^{-1}). In the diradical **A3** the terminal oxygen can easily extract a methyl hydrogen (Scheme 7; TS shown in Figure 1, b) with a free energy barrier of only 4.8 kcal mol^{-1} (ene pathway). As an alternative, it can undergo ring closure, thus forming a dioxetane ([2+2] reaction, $\Delta G^{\ddagger} = 11.6$ kcal mol^{-1}). A second conformer of the diradical intermediate, **B3**, is less stable than **A3** by 1.4 kcal mol^{-1}. **B3** can form either directly from the reactants ($\Delta G^{\ddagger} = 20.9$ kcal mol^{-1}), or from **A3** ($\Delta G^{\ddagger} = 4.9$ kcal mol^{-1}). This conformer cannot directly abstract the hydrogen from the methyl group and give the ene product, but it can follow three pathways: (a) back dissociation to reactants ($\Delta G^{\ddagger} = 8.6$ kcal mol^{-1}); (b) ring closure to dioxetane ([2+2] reaction, $\Delta G^{\ddagger} = 10.2$ kcal mol^{-1}) or, (c) easily convert to the diradical **A3** ($\Delta G^{\ddagger} = 3.5$ kcal mol^{-1}). This is the easiest transformation for **B3**, and hence the pathway from the reactants through **A3** to finally produce the hydroperoxide **H3** is the most likely.

The addition of O_2 to C^2 (TS shown in Figure 2, a) is more difficult, as can one can expect on the basis of the nature of the diradical intermediates: while **A3** and **B3** are conformations of a π-delocalized system, the unpaired electrons in **A2** and **B2** are localized. The reacting system must overcome a free energy barrier 23.3 kcal mol^{-1} high

Table 1. Relative potential energies, enthalpies, and free energies (with respect to the most stable conformer *s-trans*) for *s-cis* (*E*)-2-methylbut-2-enal at the DFT(B3LYP)/6-311G(3df,2p)//6-311G(d,p) level (units: cal mol^{-1}, T = 298 K).

	O_2 attack on C^3			O_2 attack on C^2		
	ΔE	ΔH	ΔG	ΔE	ΔH	ΔG
s-cis aldehyde + $^1\Delta_g$ O_2	3.5	3.3	3.5	3.5	3.3	3.5
TS to diradical A	12.2	11.8	22.9	16.3	15.3	26.8
peroxyl diradicals A	2.2	3.1	14.4	14.5	14.1	25.3
diradical A – hydroperoxide TS	7.4	5.9	19.2	15.9	14.5	26.1
diradical A – dioxetane TS	13.5	13.5	26.0	22.5	21.6	33.5
hydroperoxide	–29.3	–27.3	–15.7	–22.3	–20.8	–9.5
TS to diradicals B	14.3	13.9	24.4	23.1	22.1	31.9
peroxyl diradicals B	3.9	4.8	15.8	17.2	16.7	27.9
diradical A – diradical B TS	7.0	7.2	19.3	23.3	21.3	32.4
diradical B – dioxetane TS	13.5	13.5	26.0	22.5	21.6	33.5
dioxetane[a]	–22.9	–21.1	–8.8	–	–	–

[a] Relative energies are common to the attack in C^3 and C^2.

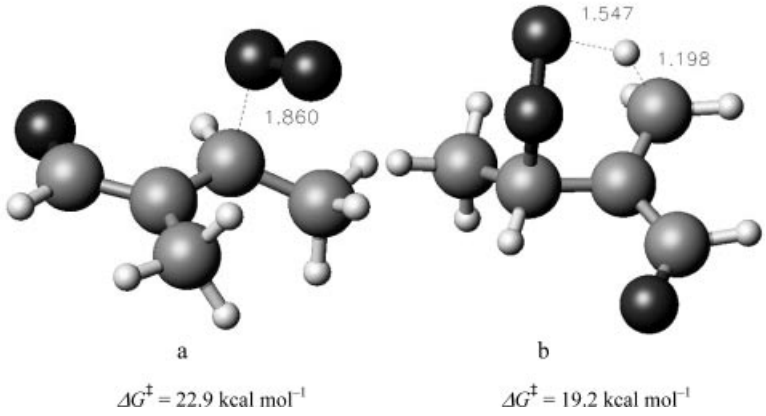


Figure 1. Transition structures for the formation of the diradical **A3** by O_2 addition onto the C^3 of the *s-cis* (*E*)-2-methylbut-2-enal (a), and H abstraction to produce the hydroperoxide (b). Interatomic distances are in Å, free energies are relative to the *s-trans* conformer **1**.

(Table 1), and the diradical intermediate **A2** (Scheme 7) is 21.8 kcal mol^{-1} above the reactants. Back dissociation to the reactants would be easy (1.5 kcal mol^{-1}), but hydrogen abstraction would be even easier (0.8 kcal mol^{-1}; TS shown in Figure 2, b). The **B2** conformer can be obtained directly from the reactants, but the *G* barrier is significant (28.4 kcal mol^{-1}). As an alternative, it could form from **A2**. In this case the *G* barrier is 7.1 kcal mol^{-1}, but the barrier to go back to **A2** is only 4.5 kcal mol^{-1} high. Back dissociation requires a comparable free energy, 4.0 kcal mol^{-1}. Also in this case, the **B2** conformer would be easily converted into the corresponding conformer **A2**.

The reaction products also have different stabilities (–15.7 and –9.5 kcal mol^{-1} with respect to isolated reactants,

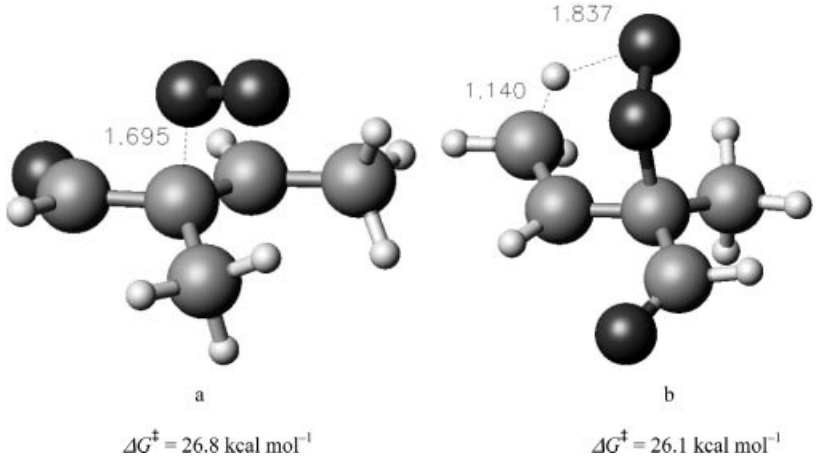


Figure 2. Transition structures for the formation of the diradical **A2** by O_2 addition onto the C^2 of the *s-cis* (*E*)-2-methylbut-2-enal (a), and H-abstraction to produce the hydroperoxide (b). Interatomic distances are in Å, free energies are relative to the *s-trans* conformer **1**.

Table 2. Relative potential energies, enthalpies, and free energies for *s-trans* (*E*)-2-methylbut-2-enal at the DFT(B3LYP)/6-311G(3df,2p)//6-311G(d,p) level (units: kcal mol^{-1}, T = 298 K).

	O_2 attack on C^3			O_2 attack on C^2		
	ΔE	ΔH	ΔG	ΔE	ΔH	ΔG
s-trans aldehyde + $^1\Delta_g$ O_2	0.0	0.0	0.0	0.0	0.0	0.0
TS to diradicals A	10.7	10.4	21.6	17.1	16.1	27.3
peroxyl diradicals A	2.7	3.5	14.9	14.4	14.1	25.2
diradical A – hydroperoxide TS	7.9	6.5	19.8	18.7	17.4	30.3
hydroperoxide	–27.2	–25.2	–13.9	–22.0	–20.7	–9.6
TS to diradicals B	13.0	12.6	22.9	22.0	21.0	31.4
peroxyl diradicals B	5.2	6.0	16.5	14.9	14.6	25.7
diradical A – diradical B TS	7.7	7.8	19.8	19.0	18.1	29.7
diradical B – dioxetane TS	13.8	13.7	26.2	27.0	25.9	36.5
dioxetane[a]	–22.5	–20.6	–8.6	–	–	–

[a] Relative energies are common to the attack in C^3 and C^2.

for the hydroperoxide in **H3** and **H2**, respectively), since the former exhibits a conjugated carbonyl π system. In summary, the addition to C^2 is unfavorable with respect to C^3 both from the thermodynamic and the kinetic points of view.

The *s-trans* isomer exhibits analogous behavior, as can be seen in Table 2. Two kinetic steps characterize the minimum energy mechanism. The first step is a slow addition of O_2 on the C^3 carbon with formation of a π-delocalized diradical intermediate. A subsequent hydrogen abstraction from the methyl group easily affords the product hydroperoxide. In conclusion, the two conformers share the same reaction mechanism.

***cis-trans* Competition:** The above diradical mechanism also explains the observed higher reactivity of the *s-cis* isomer, which forms through a lower barrier with respect to the *s-trans* (19.4 and 21.6 kcal mol^{-1} for the attack to C^3, respectively). This enhanced reactivity may be attributed to the greater stability of the *s-trans* reactant, 3.5 kcal mol^{-1} more stable than the *s-cis*, while the two diradical intermediates have approximately the same free energy. Once the diradicals are formed, they display approximately the same reactivity, since the second step (hydrogen abstraction) implies in both cases the overcoming of a barrier of 5 kcal mol^{-1} (Figure 3).

Although the cyclic intermediate trioxene (**T** in Scheme 4) exists as a stable intermediate, it has a higher free energy than the *s-cis* diradical (ΔG = 26.9 kcal mol^{-1}), and therefore cannot play a role in the mechanism.

In order to compare our results with the experimental data, kinetic isotope effects have been calculated. The steady state approximation on the diradical intermediate in the process

$$alkene + {}^1\Delta_g\,O_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} diradical \xrightarrow{k_2} hydroperoxide$$

gives an observed rate constant expressed as

$$k_{obsd.} = \frac{k_1 k_2}{k_{-1} + k_2}$$

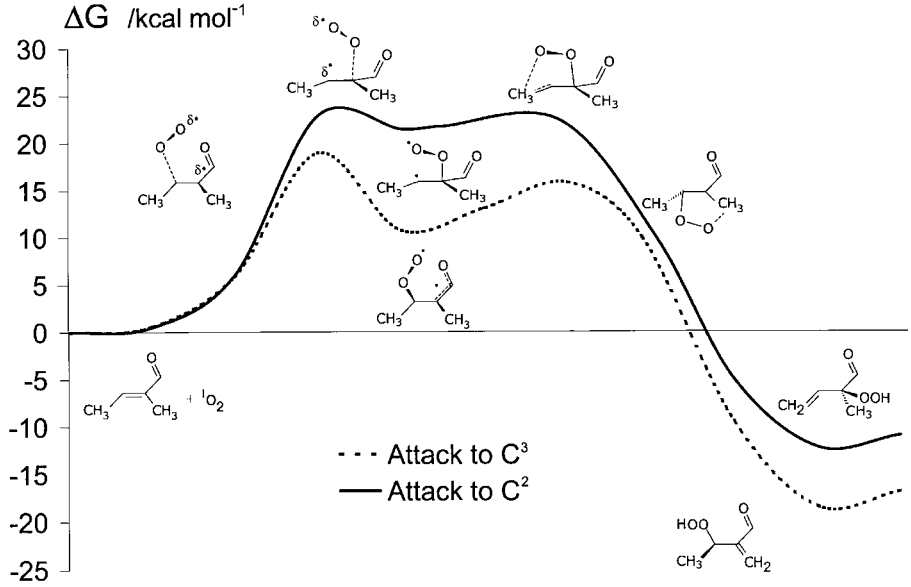


Figure 3. Free energy profiles for diradical formation by O_2 addition onto the C^2 and C^3 of the *s-cis* (*E*)-2-methylbut-2-enal and the subsequent H-abstraction to the product hydroperoxide.

The rate constants for the elementary steps were evaluated according to transition state theory[20] for the two compounds (*E*)-2-methylbut-2-enal and (*E*)-2-trideuteriomethylbut-2-enal. The *s-trans* substrate affords $k_H/k_D = 1.2$ (while the *s-cis* gives $k_H/k_D = 1.1$), in good agreement with the experimental values for methyl (*E*)-2-methylbut-2-enoate (1.30 in benzene and 1.49 in acetone).

Ene vs. [π2+π2] Cycloaddition: Although the cycloaddition product may form from both diradicals **A** and **B** and the corresponding *ene* product only from **A**, the *ene* channel always predominates. For example, we compute $v_{ene}/v_{2+2} \approx 3.1 \times 10^4$ for *s-trans* (*E*)-2-methylbut-2-enal and $v_{ene}/v_{2+2} \approx 3.2 \times 10^3$ for propene,[16] consistently with the reported effects of electron-withdrawing substituents on alkenes.

Solvent Effects: Since the transition structure for cycloaddition is slightly more polar than the TS for the *ene* reaction, we assessed by SCRF calculations the effect of a typical polar solvent (DMSO) in favoring the cycloaddition. The simulation of DMSO does not introduce substantial modifications in the reaction profile (Table 3, Table 4), confirming the hypothesis of an intermediate of low polarity. Yet the solvent affects to a limited extent the reaction rates: for example, the [π2+π2] reaction on the *s-trans* conformer gives $v_{solv}/v_{gas} \approx 15$, while for the *ene* reaction $v_{solv}/v_{gas} \approx 7$. The cycloaddition is thus more sensitive to the solvent effect, even if it never becomes the major process, as testified by the ratio $v_{ene}/v_{2+2} \approx 1.6 \times 10^4$, estimated in DMSO.

Table 3. Free energies in the gas phase and solvent (DMSO), relative to the most stable *s-trans* conformer of (*E*)-2-methylbut-2-enal for the O_2 attack on C^3. IEFPCM DFT(B3LYP)/6-311G(d,p)//6-311G(d,p) level (units: kcal mol^{-1}, $T = 298$ K).

	s-cis		*s-trans*	
	ΔG_{gas}	ΔG_{solv}	ΔG_{gas}	ΔG_{solv}
(*E*)-2-methylbut-2-enal + $^1\Delta_g$ O_2	7.8	3.4	0.0	0.0
TS to diradical A	26.8	21.0	20.9	19.7
peroxyl diradicals A	18.6	12.7	14.5	12.9
diradical A – hydroperoxide TS	23.6	17.9	19.6	18.1
hydroperoxide	–10.7	–19.4	–13.5	–17.3
TS to diradicals B	28.5	21.8	22.4	21.0
peroxyl diradicals B	20.0	14.3	16.3	14.5
diradical A – diradical B TS	23.7	17.5	19.7	17.7
diradical B – dioxetane TS	30.5	23.7	25.9	23.9
dioxetane	–2.9	–9.4	–7.5	–9.3

Table 4. Free energies in gas phase and solvent (DMSO), relative to the most stable *s-trans* conformer of (*E*)-2-methylbut-2-enal for the O_2 attack on C^2. IEFPCM DFT(B3LYP)/6-311G(d,p)//6-311G(d,p) level (units: kcal mol^{-1}, $T = 298$ K).

	s-cis		*s-trans*	
	ΔG_{gas}	ΔG_{solv}	ΔG_{gas}	ΔG_{solv}
(*E*)-2-methylbut-2-enal + $^1\Delta_g$ O_2	7.8	3.4	0.0	0.0
TS to diradical A	30.7	25.1	26.6	25.5
peroxyl diradicals A	29.3	23.8	24.6	10.8
diradical A – hydroperoxide TS	30.2	24.7	29.9	27.5
hydroperoxide	–4.4	–11.6	–9.2	–11.9
TS to diradicals B	35.9	30.0	30.8	30.0
peroxyl diradicals B	32.1	27.4	25.5	25.1
diradical A – diradical B TS	36.5	31.4	29.5	29.2
diradical B – dioxetane TS	37.9	31.2	36.4	34.1
dioxetane	–2.9	–9.4	–10.7	–9.3

Conclusions

The mechanism suggested by the present calculations involves a diradical intermediate for the *ene* reaction. This mechanism seems apt to interpret correctly both the observed regiochemistry and the relative reactivity of the *s-cis* and *s-trans* conformers of the reactant (*E*)-2-methylbut-2-enal. On one hand, the regioselectivity originates from the different stabilities of the two diradical intermediates obtained by O_2 addition. On the other hand, the higher reactivity of *s-cis* species with respect to the *s-trans* is due to the greater stability of the *s-trans* conformation, while the rate-determining step corresponds to transition structures of similar stability. The computed kinetic isotope effect ($k_H/k_D = 1.2$) is in fairly good agreement with the value measured for a similar substrate [$k_H/k_D = 1.30$ for methyl (*E*)-2-methylbut-2-enoate in benzene]. The solvent effect on the energy barriers is small, and favors the addition on C^3. The pathway to dioxetane ([π2+π2] cycloaddition reaction) is found in all cases to lie at higher energy with respect to that for hydroperoxide formation (*ene* reaction).

Computational Methods

Stable and transition structures were located by gradient procedures[21] within the Density Functional Theory (DFT)[22] making use of the B3LYP functional.[23] The polarized 6-311G(d,p) basis set[24] was used in the DFT(B3LYP) optimizations. The critical points were characterized diagonalizing the 6-311G(d,p) analytic Hessian (vibrational analysis). The more extended 6-311G(3df,2p)[25] basis set was used for the final single-point energy calculations. The unrestricted DFT wave function for diradicals, used to provide a qualitatively correct picture in terms of non-zero spin densities, was corrected according to Yamaguchi.[26] The final DFT(B3LYP)/6-311G(3df,2p)//6-311G(d,p) energies were then combined with the 6-311G(d,p) thermochemical contributions from the vibrational analysis to obtain the differences in enthalpies and free energies.[27] All relative energies, enthalpies, and free energies are collected in Table 1 and Table 2. The DFT calculations were carried out with the GAUSSIAN 98 system of programs.[28] The transition structures shown in Figure 1 and Figure 2 are drawn by the MolMol 2.4 program,[29] with the interatomic distances relevant to the discussion reported in Å. The SCRF single point calculations were carried out at the IEFPCM[30] B3LYP/ 6-311G(d,p) level of theory.

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