

Theoretical Investigation of Linalool Oxidation

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This study concerns the autoxidation of one of the most used fragrances in daily life, linalool (3,7-dimethyl-1,6-octadien-3-ol). It reacts with O₂ to form hydroperoxides, which are known to be important contact allergens. Pathways for hydroperoxide formation are investigated by means of quantum mechanical electronic structure calculations. Optimized molecular geometries and harmonic vibrational frequencies are determined using density functional theory (DFT). Insight into how the addition of O₂ to linalool occurs is obtained by establishing a theoretical framework and systematically investigating three smaller systems: propene, 2-methyl-2-butene, and 2-methyl-2-pentene. 2-Methyl-2-pentene was chosen as a model system and used to compare with linalool. This theoretical study characterizes the linalool-O₂ biradical intermediate state, which constitutes a branching point for the further oxidation reactions pathways. Thus, the observed linalool oxidation product spectrum is discussed in terms of a direct reaction path, the ene-type mechanism, and the radical mechanism. The major hydroperoxide found in experiments is 7-hydroperoxy-3,7-dimethyl-octa-1,5-diene-3-ol, and the calculated results support this finding.

1. Introduction

This work is the first computational study in a series of investigations on the activation of common nonallergenic compounds into skin sensitizers due to air-oxidation when these compounds are handled and stored. The goal is to obtain a mechanistic understanding on how certain harmless organic compounds are oxidized by O₂ and form, for example, hydroperoxides in one case, epoxides in a second, aldehydes in a third, and so on, despite the small differences in their chemical structure. More knowledge on the exact reaction route will increase the possibilities to minimize the formation of the oxidation products that are prone to cause contact allergy. Moreover, to join computational calculations with experiments will provide more knowledge and insight into autoxidation on organic compounds. This will increase the possibility to predict the risk that a compound is prone to be a contact allergen. It will also contribute to reduce the number of experiments where animals are needed.

1.1. Chemistry of Linalool. Fragrances find widespread and increasing use in household products, such as soaps and detergents, and also in cosmetics and toiletries. These compounds are also natural components in many food-stuffs; in particular they are found in common fruits and vegetables. Their ubiquitous presence brings us into daily contact with compounds known to be among the most common causes of contact dermatitis. About 1% of the population in Europe is sensitized

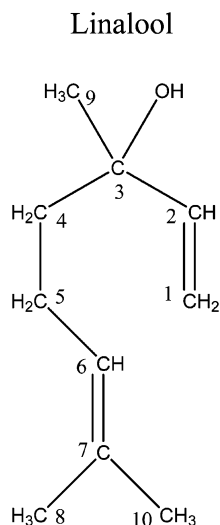


Figure 1. The linalool molecule.

to fragrance chemicals today. These chemicals are already a problem, and there is a potential risk that increased use will worsen the situation. To find a means to control these risks, there is a need for a better understanding of the chemistry of fragrant compounds.

The fragrance chemical in focus in this study is linalool (3,7-dimethyl-1,6-octadien-3-ol), a doubly unsaturated alcohol (Figure 1). Linalool is a colorless and relatively volatile liquid at room temperature, and it is one of the most frequently used fragrances. The linalool molecule is a functionalized monoterpene with two isomeric forms, *S*(+)-linalool and *R*(-)-linalool. The two stereoisomers have different scents and contributes to the aroma of many common plants. *S*(+)-Linalool, found e.g.

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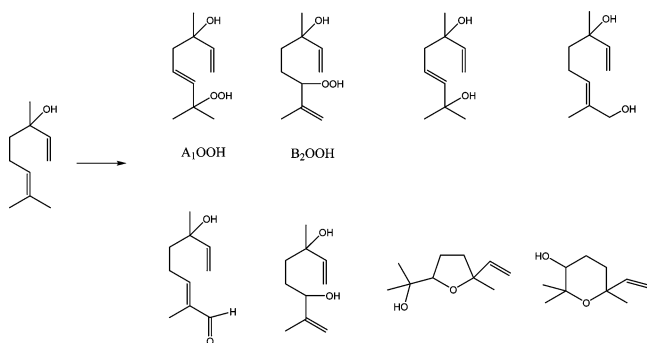


Figure 2. Linalool and the different oxidation products found in experiment.

in tomatoes and the flowers of orange, has a scent which is associated with flowers/orange, while *R*(-)-linalool has a scent of lavender and is typically found in lavender and basil. *S*(+)-linalool and *R*(-)-linalool are equally stable, so below we will not distinguish between them.

Linalool can be oxidized in the presence of air at normal temperature and pressure. It has been shown that the content of linalool in a highly concentrated solution (98%) decreases to about 80% after oxidation for 10 weeks under standard conditions.¹ After about 30 weeks, 50% of the original compound was consumed, and after 80 weeks only about 4% remained.^{1,2}

In experimental studies, pure linalool was shown to be a weak sensitizer, while air-exposed samples of linalool were shown to be allergenic.² Several different oxidation products of linalool (see Figure 2) were identified, and hydroperoxides were shown to be the strongest allergens of the oxidation products tested. The ability to form hydroperoxides is probably the largest risk associated with linalool in the context of contact allergy. In a clinical study on consecutive dermatitis patients, oxidized linalool was shown to be a common contact allergen, and 64% of the patients allergic to oxidized linalool showed positive reactions to the hydroperoxides.³ Therefore, the current study has focused on the hydroperoxides produced in the oxidation process.

The dominating hydroperoxide formed is 7-hydroperoxy-3,7-dimethyl-octa-1,5-diene-3-ol (A_1OOH), but 6-hydroperoxy-3,7-dimethyl-octa-1,7-diene-3-ol (B_2OOH) is also found, although to a lesser extent, together with secondary products of 8-hydroperoxy-3,7-dimethyl-octa-1,6-diene-3-ol (B_1OOH). No 5-hydroperoxy-3,7-dimethyl-octa-1,6-diene-3-ol (A_2OOH), which constitutes an apparently analogous oxidation product, has been found (Figure 3).²

The reaction between linalool and O_2 occurs in the vicinity of the double bond at C_6-C_7 . Oxidation processes that involve unsaturated hydrocarbons constitute a large class of chemical reactions. There have been extensive investigations regarding the general properties of the reaction between $R_1-HC=CH-R_2$ and O_2 . However, there are only a few experimental investigations on the oxidation of linalool,^{1,2} and to the best of our knowledge, linalool is still an unexplored field with regard to computational studies.

The aim of this study is to better understand the oxidation process of linalool. Why is A_1OOH the main hydroperoxide found? Why is no B_1OOH found, but only its secondary products? Why is no A_2OOH found at all? We therefore investigate the basic factors governing the addition of O_2 to linalool. In particular, we evaluate two possible interconnected reaction pathways and point out the bottlenecks of the processes.

To develop a mechanistic understanding we investigate whether the essential properties of O_2 addition to linalool can

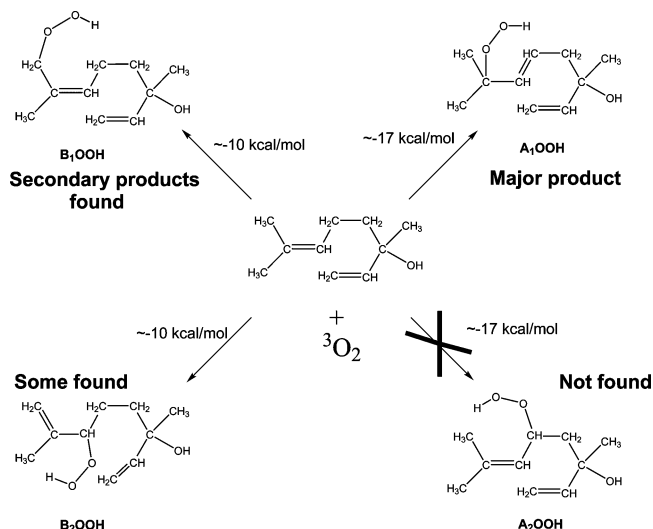


Figure 3. Linalool and the four different hydroperoxides investigated in this study. Enthalpy changes are given.



Figure 4. Allyl hydroperoxide formation by an *ene*-reaction between a singlet oxygen molecule and a C–C double bond system, which contains at least one allylic hydrogen atom.

be modeled by using model hydrocarbons. The smaller systems enable us to investigate the effects on reactivity of carbon chain length, chain branching, and substituents attached to the C=C bond. This is complemented by investigations of the oxidative chemistry of the linalool molecule itself. Comparisons on relative stabilities of different intermediates/products give detailed insight into the proposed scenario.

1.2. Possible Reaction Mechanisms. Earlier studies on the oxidation process of unsaturated hydrocarbons have revealed two main reaction pathways which lead to the formation of hydroperoxides. Here, a third pathway will be included. Common to the three oxidation pathways is an intermediate biradical state, which provides a source of singlet O_2 molecules feeding the *ene*-type mechanism and comprises an initiator for the radical mechanism.

1. The so-called *ene*-type⁴ or Schenck^{5,6} reaction (Figure 4) requires an oxygen molecule excited to its singlet ($^1\Delta_g$) state, which easily reacts with a compound containing an allylic hydrogen atom. The product of such a reaction is an allylic hydroperoxide, in which the double bond has shifted to a position adjacent to the original double bond. The *ene*-type reaction is straightforward and commonly used for industrial manufacture of hydroperoxides. However, singlet oxygen is rare in a standard environment, as the $^1\Delta_g$ state is 22.6 kcal/mol above the $^3\Sigma_g^-$ ground-state. In addition the transition is forbidden by spin, symmetry, and parity selection rules. This means that direct excitation of ground state oxygen by light to form singlet oxygen is very improbable. Instead, the excitation (corresponding to 1263 nm) normally requires a sensitizing compound, e.g. methylene blue, which utilizes photons for a singlet–singlet excitation. The excited singlet state can subsequently interact with $O_2(^3\Sigma_g^-)$ to produce $O_2(^1\Delta_g)$ and a triplet state for the sensitizer. The requirement for the reaction to occur is that this triplet is at least 22.6 kcal/mol lower in energy than the excited singlet state. The exact mechanism by which the

ene-type reaction occurs has still not been fully understood. It will not be further investigated here, but the *ene*-type reaction will be referred to in the discussion part.

2. The slow free-radical chain process follow the reaction steps R1–R3.



The first step is the initiation, where a reactive radical, $R\cdot$, is formed by, for example, a hydrogen abstraction by an O_2 molecule according to $RH + O_2 \rightarrow R\cdot + HOO\cdot$. Once free radicals are formed, they react with O_2 in a chain process. In step (R2), a peroxy radical ($ROO\cdot$) is formed, which can be converted to a hydroperoxide ($ROOH$) in step (R3). In step (R3) a reactive radical $R'\cdot$ is generated. Steps (R2) and (R3) propagate the reaction, where the last step is the slowest of the two.

3. In addition to pathway 1 and 2, we consider a third pathway, which provides a direct route to hydroperoxy-linalool formation (see section 1.2.1 below).

In this study, we investigate the possibilities for linalool to form hydroperoxides by the radical mechanism and by the direct route. However, all three mechanisms will be discussed in connection to a linalool- O_2 transient.

1.2.1. The Biradical Intermediate and Its Implications for the Oxidation of Linalool. The oxidation of linalool to a hydroperoxide involves the breaking of the $C=C$ π bond. For the chemical reaction between molecular oxygen and linalool, the interconversion of the internal $C=C$ double bond into a $C-C$ single bond is expected to be facilitated if an $O_2-C=C$ complex is initially formed, where the π systems of the two reactants are allowed to interact.

Linalool is a singlet in its ground-state, whereas the oxygen molecule has a triplet ground-state. A triplet–singlet interconversion must occur at some point along the reaction coordinate, since the reactants taken together have a triplet potential energy surface (PES), while the hydroperoxide product resides on a singlet PES. If an intermediate triplet state is formed, it may undergo a triplet–singlet interconversion, producing hydroperoxy-linalool (Figure 5), dissociate to 1O_2 + linalool, or may undergo hydrogen abstraction by a second oxygen to produce an $ROO\cdot$ peroxy radical and a hydroperoxyl $HOO\cdot$ molecule. In the latter case, the biradical intermediate state splits into two separate molecular radicals. This is the essence of the autoxidation mechanism, which is further explained below and in Figure 6.

In contrast, in the *ene* reaction, the triplet–singlet excitation occurs prior to the $O_2-C=C$ complex formation. Thus the excitation of the O_2 molecule to the singlet state results in a singlet PES already for the reactants. No change of multiplicity is subsequently required during the addition reaction. In the radical mechanism, the total reaction is split into several steps, which have different but conserved multiplicities during the reaction step in question.

There are two critical steps in the biradical associated reactions. First, the reaction between O_2 and the $C=C$ bond requires an electronic rearrangement, and a barrier can be expected for this process, where a metastable triplet biradical state is formed (Figure 5).⁷ This suggests this reaction step to be quite slow. Having obtained the metastable triplet biradical intermediate, the three reaction paths described in section 1.2. are anticipated, see Figure 6.

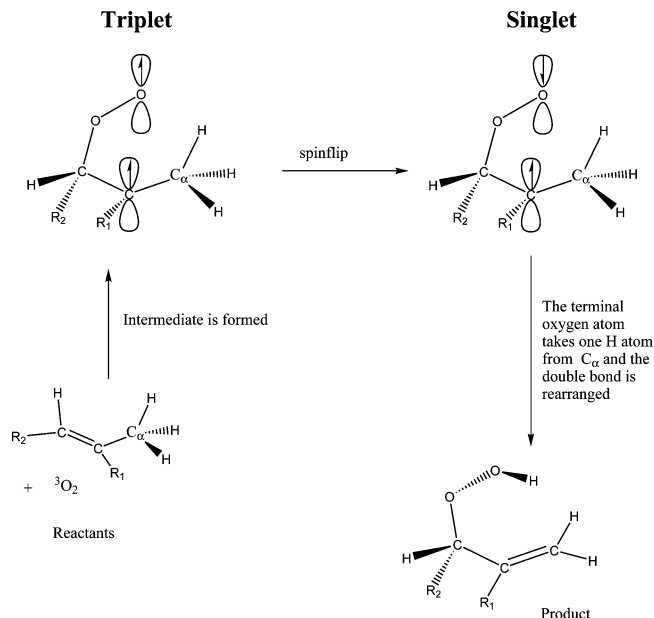


Figure 5. The direct pathway for hydroperoxide formation. The ground-state oxygen molecule attaches to one of the carbon atoms in the double bond and an intermediate is formed. Thereafter a spin flip takes place whereafter the final hydroperoxide is formed immediately.

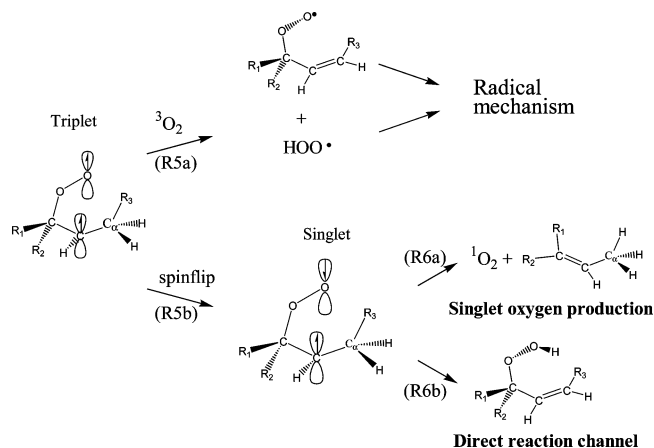


Figure 6. The autoxidation scheme. The three reaction channels associated with the biradical state are depicted.

Change of multiplicity of the biradical from a triplet to a singlet is necessary in order to allow for direct hydroperoxide formation. Transition between triplet and singlet states are forbidden as long as spin is a good quantum number. The fact that the unpaired electrons in the intermediate biradical are located on atoms which are spatially well separated suggests that the coupling between the triplet and singlet electronic states is small. The degree of smallness is controlled by the overlapping π systems of the O_2 and the $C=C$ subsystems, and this determines the probability for reaction to occur. The spin-flip could take place due to spin–orbit coupling or as a consequence of a collisional event with a radical. The process is expected to be slow, but once a singlet is formed, the intermediate is no longer metastable, and structural stabilization is achieved by the migration of a C_α hydrogen atom to the terminal oxygen atom, thus forming the hydroperoxide.

The three pathways presented in section 1.2 can be understood to have a common origin in the triplet biradical intermediate formed according to R4:



This triplet biradical intermediate may react with a second $^3\text{O}_2$ molecule according to

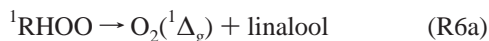


The peroxy-radical ($^2\text{ROO}\cdot$) and $\text{HOO}\cdot$ species formed in R5a may sustain the radical mechanism. In this way, a separation of the two unpaired electrons on the $^3\text{RHOO}$ biradical into two free radicals has been achieved.

Alternatively, the intermediate may undergo triplet–singlet conversion:



This singlet can in turn either dissociate to form $^1\text{O}_2$ which would feed the *ene*-pathway



or rearrange according to direct reaction channel



The reactions R5 and R6 are represented schematically in Figure 6, where the exclusive nature of the biradical intermediate is emphasized.

2. Methods

In this section, the difficulty to obtain an accurate description of the different molecules are discussed, and the computational methods employed are presented.

2.1. Theoretical Background. Linalool ($\text{C}_{10}\text{H}_{18}\text{O}$) possesses many internal rotational degrees of freedom and a relatively flexible 3D structure. The possibility of many conformational isomers makes the electronic structure calculations demanding with regard to the flexibility of the molecule as well as the number of atoms. Hence, it is difficult to conclude whether the most stable conformation has been located or not. Further, the large number of electrons in the linalool molecule makes use of explicit electron correlation methods computationally expensive and difficult.

To minimize the risk for overseeing important conformations of the oxidation products of linalool, we have performed molecular dynamic (MD) simulations.⁸ In this way we obtain different starting geometries for the geometry optimization. Thus, 10 MD simulations were made for each of the key reactants/intermediates/products. For each of the 10 geometries that were obtained by the MD simulations, single point calculations were made, and then the two geometries with lowest energy were chosen for a complete optimization. In some cases we have made complete geometry optimization of all 10 geometries.

Further, to establish a conceptual framework, we systematically investigate three simpler molecules as models for linalool. First we select propene, which is the smallest unsaturated system where there can be a rearrangement of a double bond. Second, a slightly larger system, 2-methyl-2-butene, is analyzed. Finally 2-methyl-2-pentene is investigated. These molecules are used as reactants in the oxidation process, and the intermediates and products are compared with the intermediates and products in the oxidation of linalool. The results for the model systems can be found as Supporting Information.

The chemical modeling in this study serves two purposes. As small a prototype as possible is sought, which is sufficient to describe the essential features in the oxidation of linalool,

and which may be useful for understanding the reactivities of other terpenes. Also, modeling is employed here as a tool to understand how the energetics, which determine the reactivity of linalool, develops upon increasing the molecular complexity.

In the present study, we consider reaction between linalool oil and dissolved molecular oxygen. Because all calculations are performed in gas phase at 298 K, the translational and rotational contributions to the entropy of O_2 and linalool become greatly exaggerated. Qualitative cancellation of errors is observed if the number of reactant molecules equals that for the product. However, when this is not the case, we seek to estimate the difference in entropy of the $\text{O}_2 + \text{linalool}$ system in linalool oil relative to that of the gas phase. We understand this to constitute two logical steps: first, there is the general dissolution of a gas-phase molecule O_2 in a solvent, and second we consider the solvent to be a condensate of reactant molecules (linalool).

The former constrains the O_2 dynamics, thereby reducing its entropy. The latter means that the migrating O_2 molecule is constantly in contact with the second reactant, i.e., a linalool molecule. Thus, the effective translational relative motion of the O_2 and linalool reactants is small. The latter effect can be understood as effective translational cooling, to the extent that the two reactants are at rest relative to one another. Thus, the relevant entropy change for the $\text{O}_2 + \text{linalool}$ reaction in the linalool oil is expected to be much reduced as compared to the gas phase.

We estimate a corrected entropy from the perspective of the O_2 molecule by removing translational and rotational entropy contributions from the free energy of $\text{O}_2(\text{g})$, for which the calculated values at $T = 298$ are

$$T \cdot S_{\text{trans}}[\text{O}_2(\text{g})] = 11 \text{ kcal/mol}$$

$$T \cdot S_{\text{rot}}[\text{O}_2(\text{g})] = 3 \text{ kcal/mol}$$

The sum of these contributions constitutes an upper limit to the entropy correction. In what follows, a value of 10 kcal/mol is employed. Shifted $\Delta_r G^\circ$ values are given in the tables as $\Delta_r G_{\text{corr}}^\circ$ in all cases where the number of particles change upon reaction.

2.2. Computational Method. In this work, ab initio quantum chemical calculations were performed using GAUSSIAN 98.⁹ It has been shown that density functional theory (DFT) employing the hybrid functional B3LYP^{10,11} provides reasonable energies at a low computational cost.^{12–15} It was therefore chosen for this computational study.

The calculations were carried out with the 6-31G(d,p) basis set.¹⁶ To verify the character of the stationary points, analytical Hessians were calculated at the same level of theory. These calculations produce the vibrational frequencies as well as data for the thermochemistry, from which we obtain ΔH (0 K), ΔH (298 K), and ΔG (298 K). The vibrational spectra of the optimized structures were particularly checked for imaginary eigenvalues, which would reveal that a saddle point had been found rather than an energy minimum. Some higher level calculations using complete active space self-consistent field (CASSCF) were also performed.

3. Results and Discussion

This section presents the results of linalool oxidation for the radical mechanism and the direct reaction channel. Our investigation of the radical mechanism begins with the abstraction of hydrogen from linalool by an unspecified radical, which comprises $^3\text{O}_2$ in the autoxidation mechanism. The fate of this

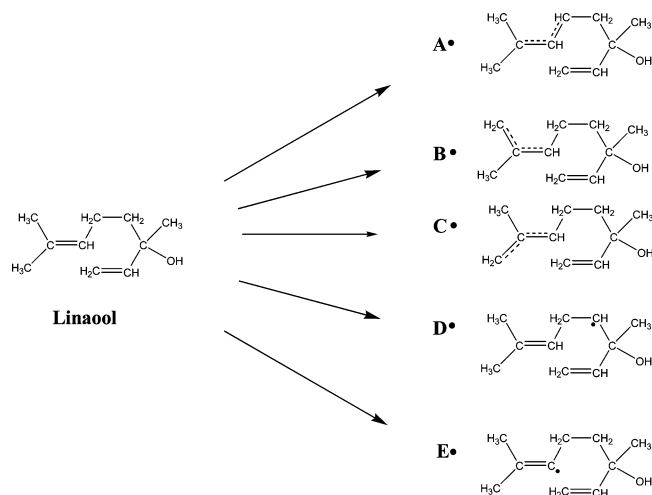


Figure 7. The five radicals investigated in this study that can be formed from linalool by abstracting a hydrogen atom.

system upon reaction with an additional molecular oxygen and the propagation of the linalool radical is described with emphasis on the products formed. Initiation of the autoxidation mechanism involves the formation of a biradical intermediate, which may feed the radical mechanism or provide a direct pathway towards formation of hydroperoxy-linalool. The possible 2-fold role of linalool to act as sensitizer and substrate in the *ene*-type mechanism will be discussed.

3.1. Radical Mechanism – Linalool. *3.1.1. The Initiation Step (R1).* The initiation of a radical chain reaction is the very first bottleneck of this autoxidation pathway. It is due to the high energy required to break a C–H bond. In general this may be caused by exposing the linalool–O₂ system to light, heat, or catalytical levels of redox-active transition metals. In this section, the energetics of the possible radicals that might be formed from linalool are presented according to the initiation step (R1). The energetics for radical generation provides information on which radicals that are interesting in the next step of the radical chain reaction, the propagation step. It will also allow us to compare the energy needed to form R• + HOO• with that for the intermediate biradical state.

In the radical mechanism, the radicals are generated by the abstraction of a hydrogen atom from linalool. C–H bonds at five different carbon atoms in linalool are possible targets for hydrogen atom abstraction in the vicinity of the C₆–C₇ double bond (see Figure 1). Three of the sites (C₅, C₈, C₁₀) are allylic, one (C₆) is vinylic, and one (C₄) is alkylic. All these hydrogen atom abstractions can be expected to yield radicals which are relevant to the hydroperoxide formation. The stability of the various radicals may influence both their rate of formation and the yield of hydroperoxide product.

The positions of the C–H bonds in linalool affect the ease by which these can be broken. The easier H atom abstractions are found in the allylic positions, adjacent to the internal double bond. The allylic radicals, produced by such H atom abstractions, are stabilized by conjugation of the p orbitals on the allylic C atom and the C atoms of the C=C bond. This means that the unpaired electron becomes delocalized in a π system which involves three C atoms. The more delocalized the electron, the more stable the radical, and as a consequence allylic radicals are more easily formed than alkylic and vinylic radicals.

A• is the most stable of the radicals shown in Figure 7. It requires 32 kcal/mol to produce according to reaction R1, see Table 1. The relative stability of A• is due to the possibility for the electrons to delocalize in the π system of the carbon atoms

TABLE 1: Summary of B3LYP/6-31G(d,p) Calculated Energies in kcal/mol for the Initiation Step According to the Radical Mechanism in the Case of Linalool (RH=AH=BH=CH=DH=EH=Linalool)^a

RH + ³ O ₂ → R• + HOO•	ΔH (0 K)	ΔH (298 K)	ΔG° (298 K)
AH + ³ O ₂ → A• + HOO•	31	32	29
BH + ³ O ₂ → B• + HOO•	39	39	37
CH + ³ O ₂ → C• + HOO•	38	38	35
DH + ³ O ₂ → D• + HOO•	49	49	47
EH + ³ O ₂ → E• + HOO•	58	59	56

^a The species are shown in Figure 7.

C₅–C₇ as well as to the electron donating substituents on carbon atom C₇ and carbon atom C₅. Also B• and C• have the possibility to form a π system. In these cases, however, the terminal carbon atom, which has no substituent, is involved. Hence B• and C• are less stable than A•. To form B• or C• requires about 39 kcal/mol.

The radicals D• and E• both have their unpaired electrons localized. There is no suitable p orbital available to form a delocalized system, and the needed energy to form D• or E• is at least 17 kcal/mol higher than to form A•. Hence neither D• nor E• or their products will be further considered in the propagation steps ((R2) and (R3)) of the present study. Since B• and C• are simply trans and cis isomers of each other and have very similar energies, C• and the products of C• will not be further examined here either.

High endergonicities in the range 29–56 kcal/mol are observed for the initiation reactions involving ³O₂, as presented in Table 1. These numbers would be reduced by 23 kcal/mol if ³O₂ were replaced by ¹O₂. The degree to which ¹O₂ is available depends on the presence of sensitizing agents. Issues related to linalool as a sensitizer catalyzing the conversion of ³O₂ to ¹O₂ are discussed in section 3.3.

3.1.2. The Propagation Steps (R2) and (R3). Pathway A. Once A• is formed, it reacts with a ground state ³O₂, reaction R2, to form either ²A₁OO• or ²A₂OO•, see Figure 8. Both reactions are exothermic, with ²A₁OO• being favored over ²A₂OO• by about 3 kcal/mol. Also, the Gibbs free energy (ΔG°) favors ²A₁OO• by 2 kcal/mol (see Table 2). The addition of ³O₂ occurs readily without any barrier, hence, step (R2) is not the rate determining step. Instead, the next step (R3) is the second bottleneck of the radical chain reaction. In the propagation step the peroxy radical, ²A₁OO• (or ²A₂OO•), abstracts a hydrogen atom from a neighboring linalool molecule. This step has two obstacles in its way. First, a hydrogen atom needs to be in the neighborhood, preferable an allylic hydrogen atom. Second the abstraction of a hydrogen atom has an activation barrier to overcome. This implies that step (R3) is slow and that the peroxy radical has a noticeable lifetime, and a quasi equilibrium between the peroxy radicals may be established according to



The mechanism of the interconversion between ²A₁OO• and ²A₂OO• is still under debate, and several mechanisms have been suggested.^{17–24}

If we obtain a thermodynamical equilibrium we may apply the formula

$$-\Delta G^\circ = RT \ln K \quad (2)$$

where *G* stands for Gibbs free energy, *R* is the gas constant, *T* is the temperature, and *K* the equilibrium constant. For linalool oxidation there is a difference in Gibbs free energy of approximately 2 kcal/mol between ²A₁OO• and ²A₂OO•, which

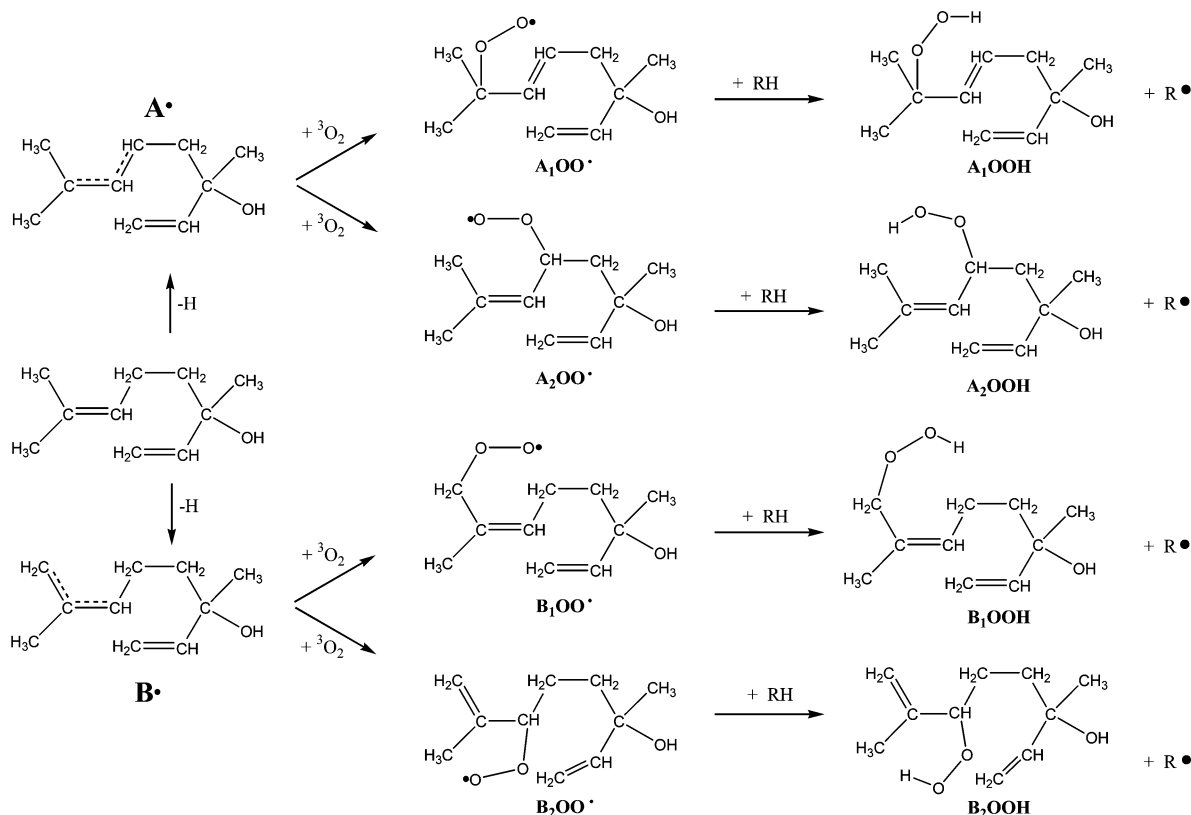


Figure 8. The two pathways, A and B for hydrogen abstraction in linalool, investigated in this study.

TABLE 2: Summary of B3LYP/6-31G(d,p) Enthalpy Changes and Standard Free Energy Changes Relevant in the Oxidation of Linalool (RH=AH=BH) According to the Radical Mechanism, Step (R2), Step (R3), and the Total Reaction (R2) + (R3)^a

RH + O ₂ → ROO•	ΔH (0 K)	ΔH (298 K)	ΔG° (298 K)	ΔG° _{corr} (298 K)
A• + O ₂ (³ Σ _g ⁻) → A ₁ OO•	-16	-17	-4	-14
A• + O ₂ (³ Σ _g ⁻) → A ₂ OO•	-13	-14	-2	-12
B• + O ₂ (³ Σ _g ⁻) → B ₁ OO•	-15	-16	-5	-15
B• + O ₂ (³ Σ _g ⁻) → B ₂ OO•	-18	-18	-7	-17
RH + ROO• → R• + ROOH				
AH + A ₁ OO• → A ₁ OOH + A•	-1	0	0	
BH + A ₁ OO• → A ₁ OOH + B•	7	7	8	
AH + A ₂ OO• → A ₂ OOH + A•	-2	-3	-2	
BH + A ₂ OO• → A ₂ OOH + B•	5	5	6	
AH + B ₁ OO• → B ₁ OOH + A•	-5	-5	-4	
BH + B ₁ OO• → B ₁ OOH + B•	3	2	4	
AH + B ₂ OO• → B ₂ OOH + A•	-2	-1	-2	
BH + B ₂ OO• → B ₂ OOH + B•	6	6	7	
RH + O ₂ → ROOH				
AH + O ₂ (³ Σ _g ⁻) → A ₁ OOH	-16	-17	-4	-14
AH + O ₂ (³ Σ _g ⁻) → A ₂ OOH	-16	-17	-4	-14
BH + O ₂ (³ Σ _g ⁻) → B ₁ OOH	-13	-14	-1	-11
BH + O ₂ (³ Σ _g ⁻) → B ₂ OOH	-12	-12	0	-10

^a The species are shown in Figure 8. Energies in kcal/mol.

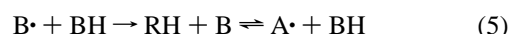
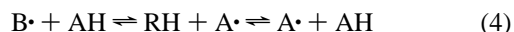
would yield a factor 20–30 more of ²A₁OO• if a quasi-equilibrium is established. It is then plausible that the higher concentration of ²A₁OO• would favor formation of the A₁OOH product, perhaps enough that A₂OOH is not observed.

In step (R3) the hydroperoxide ¹A₁OOH (or ¹A₂OOH) is formed at the same time a new radical (A• or B•) is generated. The energies for propagation step (R3) (Table 2) show that the reaction is exothermic (0–2 kcal/mol) and favorable in the case when radical A is formed but endothermic (5–7 kcal/mol) and less favorable, but possible, when radical B is formed. The Gibbs

free energy shows the same trend; it is negative (0–2 kcal/mol) in the case when radical A• is formed but positive (6–8 kcal/mol) when radical B• is formed. If an equilibrium would be established according to (3), it would be shifted toward the formation of A• because of the difference of ΔG°. The difference of about 5–8 kcal/mol is large enough that no B• would have been detected in the experiments. However, the fast nature of step (R2), where A• or B• reacts further, will prohibit such an equilibrium in the presence of oxygen.



Because of the high concentration of linalool, we also need to consider if A• or B• not only react with oxygen but also abstract a hydrogen atom from another, neighboring, linalool molecule according to (4) and (5).



As ΔG° for the formation of B• is 8 kcal/mol higher than that of A•, if an equilibrium would be established it would be shifted to the right, favoring A•. But again, the fast nature of step (R2) would prohibit such an equilibrium. Since we in this way may rule out the possibility of an equilibrium, which would have implied that the hydroperoxide B₂OOH found in experiment did not originate from B•, we need to consider the activation barrier for the formation of A• and B•. The differences of the barrier to abstract a hydrogen atom from linalool would be important for the product distribution, because if the difference is as large as 5–8 kcal/mol, similar to the difference in stabilization energies of A• and B•, we cannot expect to obtain any of B's products. On the other hand, if the difference is small (1–2 kcal/mol), we would obtain significant amount of B's

products as well. However, to obtain a transition state (TS) is computationally demanding in the case of linalool, and, therefore, we limit ourselves to investigating the corresponding TS for the model system, 2-methyl-2-pentene, to have a qualitative analysis.

The results are presented in the Supporting Information, but in summary, we note that the $A\cdot$ and $B\cdot$ radicals differ in Gibbs free energy by 7 kcal/mol, both for linalool and for 2-methyl-2-pentene. For 2-methyl-2-pentene we found the activation barriers to differ by 2–3 kcal/mol for the formation of $A\cdot$ and $B\cdot$. It would seem likely that the difference would be similar for linalool. In that case the experimentally found excess of A_1OOH compared to B_2OOH would be explained.

The total linalool oxidation reaction (R2 + R3) in the case of pathway A is exothermic by 17 kcal/mol and Gibbs free energy is -4 kcal/mol.

Pathway B. To form $B\cdot$ from linalool, 39 kcal/mol is required, which is 7 kcal/mol more than to form $A\cdot$. The higher energy should make formation of $B\cdot$ less likely. $B\cdot$ can react in a similar way to $A\cdot$, forming ${}^2B_1OO\cdot$ and ${}^2B_2OO\cdot$. The formation of these peroxy radicals is also exothermic, and the released energies are between -16 kcal/mol and -18 kcal/mol, favoring ${}^2B_2OO\cdot$. In this case ΔG° favors ${}^2B_2OO\cdot$ over ${}^2B_1OO\cdot$ by 2 kcal/mol. If we apply the same argument as in the case of $A_1OO\cdot \rightleftharpoons A_2OO\cdot$, this would imply that the equilibrium would be shifted toward ${}^2B_2OO\cdot$, which would favor the 2B_2OOH product.

Within the accuracy of DFT, these small differences of only a couple of kcal/mol is not reliable to make safe conclusions, but we note that they are in agreement with experiments.

The next step, (R3), abstracting a hydrogen atom to form a hydroperoxide, is similar to the case of pathway A. The complete oxidation reaction is exothermic also in the case of pathway B but less so than in the case of pathway A.

In summary, the energetics of the propagation step show that more of $A\cdot$ should be formed if the barrier to abstract a hydrogen atom to form $A\cdot$ is not higher than the barrier to form $B\cdot$. If the barrier for the abstraction of a hydrogen atom to form $B\cdot$ is not more than 2 kcal/mol higher than to form $A\cdot$, we may also expect that $B\cdot$ and its products form. The energetics also suggest that the chain reaction can proceed, and new radicals form. Thereby the initiation step (R1) is not the main source for radical formation.

3.2. The Role of the Biradical Intermediate for Linalool Oxidation. In the oxidation of linalool to form hydroperoxides according to the direct reaction channel, a double bond migrates to an adjacent position. Linalool has one terminal and one internal double bond (Figure 1). However, the terminal double bond is adjacent to a carbon atom (C_3) with four substituents, which implies that the terminal double bond cannot migrate since this requires that a hydrogen atom is attached to the C_3 carbon atom. Therefore, this oxidation must involve the internal double bond. Further, to achieve oxidation according to the direct reaction pathway, the 3O_2 must attach to one of the two carbon atoms in the internal double bond, see Figure 5.

In Figure 9 it is illustrated how the oxygen molecule can attach to either of the two sites, C_2 and C_3 , leading to reactions S1 or S2. Thus, contrary to the radical mechanism, the direct reaction channel can only yield two products, 1A_1OOH and 1B_2OOH . The first step in the two reaction paths, where the intermediates denoted I_1 and I_2 are formed, is endothermic by 25 and 27 kcal/mol, respectively. The complete reaction is exothermic by 12 kcal/mol for (1B_2OOH) and by 16 kcal/mol for (1A_1OOH), and the endergonicity comes out similar, after

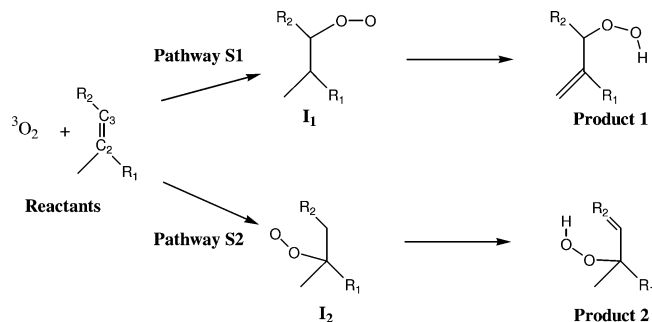


Figure 9. The two pathways, S1 and S2, for the addition of O_2 to the double bond in linalool according to the direct reaction channel.

TABLE 3: Summary of B3LYP/6-31G(d,p) Enthalpy Changes and Standard Free Energy Changes for the Oxidation of Linalool According to the Direct Reaction Channel^a

	$\Delta_r H$ (0 K)	$\Delta_r H$ (298 K)	$\Delta_r G^\circ$ (298 K)	$\Delta_r G^\circ_{\text{corr}}$ (298 K)
linalool + ${}^3O_2 \rightarrow {}^3B_2HOO$ (S1)	25	25	34	24
linalool + ${}^3O_2 \rightarrow {}^3A_1HOO$ (S2)	27	27	38	28
linalool + ${}^3O_2 \rightarrow B_2OOH$ (S1)	-12	-12	0	-10
linalool + ${}^3O_2 \rightarrow A_1OOH$ (S2)	-15	-16	-4	-14

^a Energies in kcal/mol. S1 and S2 indicate pathways, see Figure 9.

correcting for estimated loss of entropy due to the dissolution of 3O_2 in linalool oil (Table 3).

The direct reaction channel requires the conversion from the triplet state of the entrance channel to the singlet state of the product. This occurs via the intermediate biradical states I_1 and I_2 . To learn about the strength of the coupling between the two unpaired electrons at these geometries, first a CASSCF calculation including only two electrons in two orbitals was performed. This treatment assumes cancellation of (a) the dynamic as well as static correlation energy contributions to the excitation energy from the $n-2$ electrons not included in the CASSCF active space, (b) the dynamic correlation energy contribution for the two-electron system at hand, and (c) the combined static and dynamic correlation energy contribution due to the coupling between the two subsystems. The detailed validity of these assumptions relies on the similarity in electronic structure of the singlet and triplet states at the geometry of the intermediate. (b) was tested by performing a CASSCF[2,4] calculation, and negligible effects were observed as indeed is supported by the orbital occupations for the singlet state, which come out 1.07/0.93 and 1.04/0.96 for I_1 and I_2 , respectively. The triplet–singlet excitation of 8 kcal/mol for either intermediate, obtained for CASSCF[2,2], provides a measure of the “through-bond” interaction of the biradical state. The large splitting was subject to further investigation. Inclusion of the mediating orbital in the active space by performing CASSCF[4,4] calculations, thus lifting the static correlation constraint in (a) and (c) above, results in a dramatic lowering of the triplet–singlet splitting to 0.5 and 0.8 kcal/mol for I_1 and I_2 , respectively, while preserving the biradical natures of the singlet states. The effective annihilation of the 8 kcal/mol triplet–singlet splitting discussed above results from the inclusion of the C–H bonding and antibonding orbitals in the active space.

Still, although the degeneracy requirement for spin interconversion is satisfied,²⁵ low rates for the intramolecular isomerization reactions are expected. This is due to the dissimilarity between the open shell singlet intermediate wave functions and the closed shell product states. It increases the probabilities for any competing reactions to occur, which share I_1 and I_2 as branching points on the PES.

To initiate the radical mechanism via reaction R1 requires at least 32 kcal/mol. However, radicals may be formed at a lower cost via the biradical intermediate state, i.e., through reaction R5a (see Figure 6), for which an exothermicity of 12 kcal/mol is observed. Here, the high cost of abstracting a hydrogen is overcome by the formation of a double bond in conjunction with the formation of a hydroperoxy molecule HOO•. The two resulting radicals may feed the radical mechanism.

4. Summary and Conclusion

Selected regions on the free energy landscape related to linalool oxidation were considered, resulting in four different hydroperoxide products, viz. 7-hydroperoxy-3,7-dimethyl-octa-1,5-diene-3-ol (A₁OOH), 5-hydroperoxy-3,7-dimethyl-octa-1,6-diene-3-ol (A₂OOH), 8-hydroperoxy-3,7-dimethyl-octa-1,6-diene-3-ol (B₁OOH), and 6-hydroperoxy-3,7-dimethyl-octa-1,7-diene-3-ol (B₂OOH). The computationally most stable hydroperoxides are A₁OOH and A₂OOH.

The present study has discussed the oxidation of linalool via the formation of a biradical intermediate state. A direct reaction channel was described and shown to give the A₁OOH and B₂OOH products in approximately equal amounts. The biradical (I₁ and I₂ in Figure 9) constitutes a link between the direct reaction path and both the *ene*- and the radical mechanism.

The free energies required to form the biradical intermediates (24–28 kcal/mol) are comparable to those required to form ¹O₂ for the *ene*-type reaction (22.6 kcal/mol). Two scenarios are envisaged, one where thermal energy drives the formation of the biradical intermediates, and a second where a ³O₂ + linalool adduct absorbs a photon in order to reach the TS region. Connection between the direct pathway and the *ene*-type reaction is made if the triplet–singlet interconversion formally allows dissociation of the adduct to form ¹O₂ + linalool. What distinguishes the former from the *ene*-mechanism is that ¹O₂ never forms but rather the adduct directly undergoes further reaction, to produce hydroperoxides. Thus, linalool functions both as sensitizer and substrate.

In the case of the radical mechanism, an allylic C–H unit may undergo abstraction by ³O₂ to form R• + HOO• at a cost of 32 kcal/mol. Alternatively, the intermediate biradical may constitute the initiator for the radical chain reaction. Sitting at the TS, a second ³O₂ may abstract the hydrogen to form the HOO• and the peroxy-linalool radicals. The latter reaction is exergonic by 12 kcal/mol. The A₁OO•, B₂OO•, and HOO• would in turn feed the radical chain mechanism.

In as much as the biradical TS's do indeed comprise crossroads for the different reaction paths, the detailed experimental conditions become essential to the observed product distribution. In the experimental situation considered here, the linalool decomposition in air was monitored for the duration of 80 weeks at normal pressure and room temperature. Under these conditions, A₁OOH was found as the main hydroperoxide product², while B₂OOH was formed to a lesser extent. Although the B₁OOH species is not seen, secondary products are observed. Neither A₂OOH nor secondary products of it are observed.

Taking the common intermediates to constitute branching points, initiating the *ene*- and radical mechanisms as well as the direct reaction channel, it becomes interesting to compare the predictive powers of the three different pathways in describing linalool oxidation.

(1) Were the *ene*-mechanism (section 1.2) to determine the product distribution then the A₁OOH and B₂OOH products would be the only ones formed. As this is in contradiction to

experiment where decomposition products of B₁OOH are also seen, this mechanism cannot be exclusive for the oxidation of linalool.

(2) In the radical chain reaction (section 1.2), the most probable radical to be formed (abbreviated A•) will produce A₁OOH or A₂OOH. A less likely radical (abbreviated B•), 7 kcal/mol higher in energy, will produce B₁OOH or B₂OOH. Comparison with a model system, where activation barriers could be determined, suggests that the amount of A• and B• formed is consistent with the observed product distribution, i.e., excess of A₁OOH as compared to B₂OOH.

However, in experiments, no A₂OOH was detected. The Gibbs free energy of ²A₁OO• is about 2 kcal/mol lower than that of ²A₂OO•. It was argued that the equilibrium in eq 1 is plausible. This would imply that there would be 20–30 times more of ²A₁OO• than of ²A₂OO•. The same A₁OOH/A₂OOH product ratio is obtained if the activation barriers for hydrogen abstraction are the same for both radicals. This would explain why no A₂OOH was seen in experiments. We note here that the uncertainty associated with the DFT calculated energies is about 2 kcal/mol.

Under equilibrium conditions, B₁OO• ⇌ B₂OO•, the change in standard Gibbs free energy is 2 kcal/mol in favor of B₂OO•. Again, considering the uncertainty in the DFT energies this is still consistent with B₁OOH forming. Moreover, we note that both B• and C• can form B₁OO•, which would act to even out the product distribution to the extent that also products of B₁OO• should be detected in experiment. Experimentally B₂OOH but not B₁OOH is observed. However, secondary products of B₁OOH are found, supporting the understanding that the reaction channel for B₁OOH formation displays a significant probability.

(3) The direct reaction channel predicts a similar product spectrum as the *ene*-mechanism, i.e., it does not explain the observed formation of secondary products.

This work focused on the reaction mechanism in the linalool oxidation process. Based on the energetics, all three reaction pathways are understood to contribute. Future work will investigate the stabilities of the different hydroperoxides of linalool and their possible decomposition pathways.

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Supporting Information Available: Results and discussions of the model systems investigated. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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