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Comparison of the singlet oxygen ene reactions of cyclic versus acyclic β , γ -unsaturated ketones: an experimental and computational study

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Dedicated to Professor Waldemar Adam on the occasion of his 75th birthday

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ABSTRACT

The photooxygenation of two β , γ -unsaturated ketones was studied by experimental and computational methods: 5-methyl-hex-4-en-2-one (1) and cyclohex-3-en-1-one (6) as model compounds for acyclic versus cyclic deconjugated enones. The open-chain substrate delivered a 1:1 mixture of regioisomers **2a,b** following the established *cis*-selectivity model whereas the cyclic substrate reacts with ${}^{1}O_{2}$ to give preferentially the conjugated product 7. This effect is in agreement with the mechanistic two-stage no-intermediate model and on a computational level corresponds to a regioselectivity control following the steepest decent pathway from the corresponding transition stages in a valley ridge potential energy surface region.

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The singlet oxygen $({}^{1}O_{2})$ ene reaction was described for the first time by Günther O. Schenck (therefore often named Schenck reaction) in 1943.¹ In this reaction, ¹O₂ attacks one carbon of a carboncarbon double bond with transfer of an allylic hydrogen with simultaneous allylic shift of the double bond.² Alternatively, an allylic silvl group from a silvl enolether in case of the silvl-ene reaction can be transferred. As products of this reaction, allylic hydroperoxides are formed. Since the first examples of ${}^{1}O_{2}$ ene reactions were reported, this transformation has found numerous applications in modern organic synthesis.³ Furthermore, the mechanistic course of this reaction has been a matter of debate for several decades and still is not completely understood. This situation is largely due to several selectivity features that could not be incorporated into one mechanistic picture (vide infra). Several mechanisms have been postulated for this reaction with concerted or 'two-stage no-intermediate' mechanisms,⁴ as well as two-step processes involving 1,4-biradical,⁵ 1,4-zwitterion,⁶ perepoxide,⁷ or dioxetane intermediates.⁸ Scheme 1 represents a typical textbook presentation involving a reversible primary interaction followed by a short-lived intermediate that collapses to the product.

Orfanopoulos and Stephenson performed classical and elegant inter and intramolecular isotope effect experiments with isotopically labeled tetramethylethylenes that provided strong evidence for the perepoxide intermediate.⁹ Also, the small negative activation enthalpies and highly negative activation entropies observed for the singlet oxygen ene reaction from kinetic measurements have shown that the reaction of ${}^{1}O_{2}$ with electron-rich olefins proceeds 10^{3} times slower than the diffusion rate which accounts for the presence of non-productive encounters between ${}^{1}O_{2}$ and the alkene favoring the participation of a reversibly formed exciplex as intermediate. 10

The *regiochemistry* of the ene reaction between ${}^{1}O_{2}$ and substrates with multiple sites for allylic hydrogen transfer was extensively studied and several general effects can predict the regioselective introduction of the hydroperoxy group:² (a) the *cis*-effect¹¹ (*syn*-effect). In the reaction of ${}^{1}O_{2}$ with trisubstituted alkenes¹² or enol ethers,¹³ the allylic hydrogen atoms on the more substituted side of the double bond are more reactive for H-abstraction by ${}^{1}O_{2}$ (see Scheme 2 indicated by hydrogens



Scheme 1. Ene reaction with singlet oxygen--the mechanistic basis.



Scheme 2. Singlet oxygen ene reaction--the cis effect.



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indicated in blue); (b) the *gem*-effect,¹⁴ that leads to highly selective abstraction of an allylic hydrogen atom from a substituent in α -position of an α , β -unsaturated carbonyl compound; (c) the large-group effect,¹⁵ that leads to selective (moderate) abstraction of an allylic hydrogen from the substituent geminal to a large group. With the exception of hydroxyl groups, substituents in allylic positions do not exhibit appreciable effects on the regiose-lectivity of the ${}^{1}O_{2}$ ene reaction and ca. 1:1 mixtures of secondary and tertiary allylic hydroperoxides are formed (Scheme 2). We have recently reported on the change in regioselectivity that can be observed for photooxygenations in micro-emulsions¹⁶ and in hydrogels.¹⁷

Results and discussion

In the area of open-chain enone photooxygenation, two trends are in agreement with the regioselectivity rule of thumb described above: low regioselectivity (consequence of the *cis*-effect) in the photooxygenation of β , γ -unsaturated ketone **1** (1:1 mixture of regioisomeric hydroperoxides **2a** and **2b**)¹⁶ and the high regioselectivity (resulting from the *gem*-effect) in the photooxygenation of α , β -unsaturated ketone **3** (mixture of hydroperoxide **4** and its isomeric peroxyacetal **5** (Scheme 3)).¹⁸

When applying the cyclic β , γ -unsaturated ketone **6** as substrate, the conjugated product **7** is formed as the major product in polar and nonpolar solvents (methylene chloride, acetone, carbon tetra-chloride) with tetraphenyl-porphyrine (TPP) as singlet oxygen sensitizer. Allylic hydroperoxide **7** is not described in the chemical literature, only mentioned in two patents where **7** is produced by thermal methods.¹⁹ From ¹H and ¹³C NMR the structure of **7** was unambiguously determined. Reduction of the product mixture with Me₂S resulted in 4-hydroxycyclohexenone, well known from the Kornblum–DeLaMare rearrangement of 1,3-cyclohexadiene-endoperoxide.²⁰ The mechanistic question remains whether and why the *cis*-effect breaks down for **6** or a thermodynamic control exists that prefers the formation of the more stable conjugated enone as a major product.

Computational studies

The mechanistic pathways of singlet oxygen $({}^{1}\Delta g - {}^{1}O_{2})$ ene reactions employing **1** and **6** were also investigated by quantum chemical methods in order to rationalize the origin of regioselectivities. All structure geometry optimizations were carried out with the density functional theory using the non empirical TPSS functional (*meta* GGA) developed by Staroverov et al.,²¹ combined with the contracted TZVP basis set from Ahlrich et al.,²² implemented in the program package TURBOMOLE6.3.²³ The grid size for numerical integration was set to m5.



Scheme 3. Ene reaction with compounds 1 (acyclic deconjugated enone), 3 (acyclic Michael system), and 6 (cyclic deconjugated enone).

Apart from discussions in the literature about the first interactions of singlet oxygen and the alkene substrate on the reaction coordinate, there is one characteristic profile for the abstraction of competing hydrogen atoms in allylic positions^{3–5} which is also found in the case of the unsaturated ketones **1** and **6**. The reaction coordinate is running down from the substrates or the preformed adducts and splits into two pathways which are leading to the products of type **A** and **B** (Fig. 1). This splitting does not involve any activation barriers so that regioselectivity is induced by the steepest descent pathways, resulting from the local shape of potential energy surfaces and related dynamic effects.⁴

This energy profiles were analyzed by scans of the potential energy surface starting from the TS-structures leading to **A** and **B** and along the dissociation of the cleaved carbon–hydrogen bond.



Figure 1. Reaction path along the singlet oxygen ene reaction with β , γ -unsaturated cyclic ketone **6** and acyclic ketone **1** TPSS/TZVP. Regioselectivities only result from the descent in the region around the TS **9** and **10** toward the products **A** and **B**. (The attack of singlet oxygen on compound **6** leads to identical transition structures for both possible faces.)

Perepoxide like structures could only be found for an exo aligned attack of singlet oxygen on compound 6 (see Supplementary information for details). Other perepoxide structures were found to be no stationary points on the potential energy surfaces for both substrates. There is a thermodynamic preference for the Michael-type products in both cases. Product 2a is favored by 3.1 kcal/mol and product 7 by 2.7 kcal/mol (including zero point corrections) but the experiment shows that thermodynamic effects are not responsible for regioselectivity. Since the regioselectivities are also not induced by any activation barriers, another model is needed to explain the regioselectivities which elucidates the control via the descent of the particular pathways. The only stationary point in the regions where regioselectivity is created is the transition state (9 and 10 in Fig. 2). It is apparent that the real minimum reaction path is split in a valley ridge inflection point close to the transition state from recent studies.⁴ Scans following the steepest descents from the stationary points 9 and 10 in the direction of both possible products of type **A** and **B** are able to represent the both reaction pathways.

Potential energy profiles in higher resolution of the area around the transition states **9** and **10** are showing markedly different properties. The descent toward the thermodynamic favored products is steeper in both cases but there is a flat plateau like region in the pathway toward the unfavored product **B** for substrate **6** (Fig. 3).



Figure 2. Scans following the steepest descent from transition structures **9** and **10** toward the product regions TPSS/TZVP (resolution higher than in Figure 1). The pathway from **9** to **8** shows a markedly flat shaped region around the transition state.



Figure 3. Transition structures **9** and **10** with depicted atom distances between oxygen and the abstracted hydrogen in allylic positions TPSS/TZVP.

This flat area which has to be crossed on the way to product **8** could diminish the likely hood for the generation of **8** and increase the generation of **7** since the descent toward **7** is almost vertical in the first steps.

A closer look at the transition structures **9** and **10** gives also an advice which reaction path is more favored. The O–H distances of the oxygen that abstracts the hydrogen atoms in the allylic positions of the unsaturated ketone shown in Figure 3 are very similar for the acyclic system **10** (the bond lengths are differing only by 0.1 Å). Structure **9** for the cyclic transition state is of much more asymmetric nature. The oxygen–hydrogen distances are differing by 0.4 Å so that a transition state arises from the cyclic geometry that is early for the generation of **7** and a late transition state for the generation of **8**.

The abstraction of the α -hydrogen by the peroxy group in **9** (Fig. 3) appears to be more favored than the abstraction of the competing β -hydrogens, as the longer $O-H^{\alpha}$ distance indicates a stronger O-H-attraction along the negatively curved normal mode of saddle point **9**. In other words the system starts loosing energy on the reaction coordinate with a still long $O-H^{\alpha}$ distance. Also the lower selectivity observed in the formation of **2a** and **2b**, preferring the thermodynamically disfavored product **2b**, can be explained by the less pronounced asymmetry of the O-H distances in TS **10**.

Conclusion

The divergent regioselectivity effects experimentally determined for the ene substrates **1** and **6**, respectively, are in agreement with the mechanistic two-stage no-intermediate model and on a computational level correspond to a control mechanism following the steepest decent pathway from the corresponding transition stages in a valley ridge potential energy surface region.

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Supplementary data

Supplementary data (The detailed energy profiles for the reaction of singlet oxygen with **1** and **6**, respectively, are described.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.099.

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