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Electronic effects in the regioselectivity of the singlet oxygen and 4-methyl-1,2,4-triazoline-3,5-dione ene reactions with isobutenylarenes

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Dedicated to Professor Dionis E. Sunko on the occasion of his 80th birthday

Abstract—The regioselectivity of the ene pathway in the photooxidation of several 1-aryl-2-methylpropenes, as probed by stereoselective deuterium-labeling, depends on the electronic nature of the *para* phenyl-substituents. The reaction of the same array of alkenylarenes with 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) gives ene products with an impressive >97% allylic hydrogen abstraction from the more substituted side of the alkene. © 2003 Elsevier Science Ltd. All rights reserved.

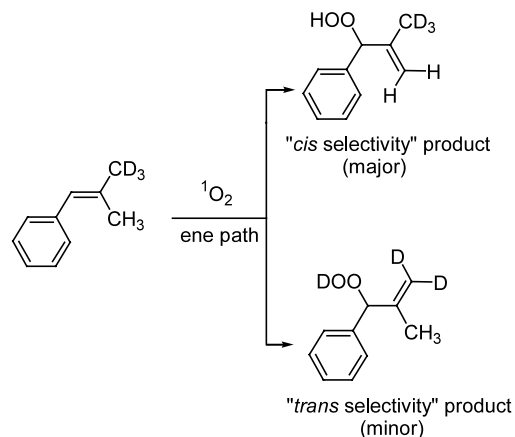
Regioselectivity studies of the ene reaction of singlet oxygen with trisubstituted alkenes have established that the more substituted side of the olefin is the more reactive ('*cis* effect' selectivity).¹ Anti '*cis* effect' selectivity² has been recognized in a few cases of trisubstituted alkenes where simultaneous interaction of the singlet oxygen with two perpendicularly aligned allylic hydrogens in the more substituted side of the alkene is not available. Previously, it was reported that the ene pathway in the reaction of ¹O₂ with β,β-dimethylstyrene³ exhibited an unexpected large *cis* selectivity (Scheme 1). Taking into account that *cis*/*trans* methyl groups (Scheme 1) do not compete in the rate determining step⁴ the preference for allylic hydrogen atom abstraction from the more crowded methyl group was attributed to a favorable electrostatic interaction between the aryl group of the olefin and the oxygen atom of the enophile in the transition state for the formation of the perepoxide intermediate in which oxygen is directed towards the more substituted side of the styrene.

In this paper, we report the electronic effect of *para*-substituted β,β-dimethylstyrenes on the site selectivity of the singlet oxygen ene reaction. In the light of these results we discuss the formation of possible transition

states (TS) which dictate the regioselectivity of the reaction.

The synthesis of deuterium-labeled, *para* substituted, β,β-dimethylstyrenes was accomplished with 92–98% geometrical purity for the *E*-isomer, following a known literature procedure.⁵

The photooxygenation of the labeled isobutenylarenes in dichloromethane gave complex mixtures of oxygenated adducts. The major products arose from double [4+2] cycloaddition⁶ of singlet oxygen to the



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Scheme 1. Regioselectivity for the ene pathway in the reaction of ¹O₂ with β,β-dimethylstyrene.

styrenes affording diendoperoxides. We isolated the minor (relative yields between 10–25%) ene adducts⁷ by column chromatography using CHCl_3 as eluent, and determined the ratio of the *cis/trans* selectivity by ^1H NMR spectroscopy. These results are summarized in Table 1. For comparison, the *cis/trans* selectivity was also determined for the ene reaction of the same array of alkenylarenes with 4-methyl-1,2,4-triazoline-3,5-dione (MTAD). In this case, the relative yields of the ene adducts were more than >95%. Although MTAD shows no substantial geminal selectivity for simple alkenes,⁸ in this case, the triazolinedione adducts⁹ were cleanly formed with >97% chemoselectivity (Table 1). The only exception to this behavior was the *p*-methoxy-substituted styrene substrate which, apart from the ene product, is known to give three other cycloadducts.¹⁰

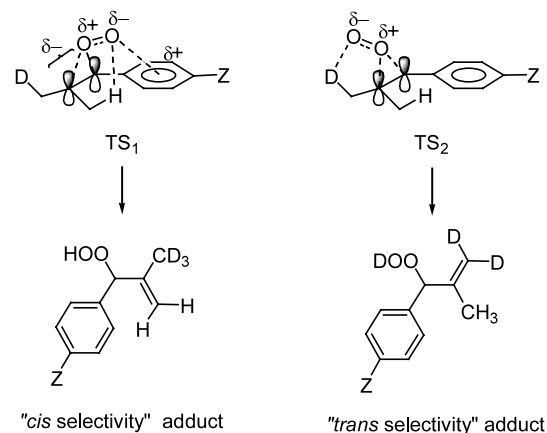
For the singlet oxygen ene reaction, there is an obvious trend. Electron-withdrawing substituents, such as $-\text{CF}_3$ or $-\text{F}$, favor increased reactivity of the allylic hydrogen atoms from the *cis* methyl group, compared to electron-donating substituents, such as $-\text{MeO}$, where the reactivity of the *trans* methyl group increases significantly. To explain these results, we considered the mechanistic rationalization invoked to explain the *cis* selectivity in the photooxygenation of β,β -dimethylstyrene. According to that postulate, interaction of singlet oxygen with the aryl ring stabilizes the transition state for the formation of the perepoxide intermediate in which the oxygen is directed towards the more substituted side of the alkene (Scheme 2). More specifically, in the transition state, a partial positive charge (δ^+) is developed on the benzylic carbon atom. Resonance stabilization of the positive charge reduces the electron density of the aryl ring, making more efficient the interaction of the negatively charged oxygen of the perepoxide with the arene.

In the case of electron donating substituents at the *para*-position (Me and MeO), the electron density of the aryl group increases and the interaction of the

oxygen with the aryl ring becomes less favorable. On the other hand, electron withdrawing substituents, such as $-\text{F}$ or $-\text{CF}_3$, decrease the electron density of the aryl group, thus the stabilizing interaction of the negatively charged oxygen with the arene is more efficient, leading to up to 74% *cis* selectivity. Therefore, the relative stability of transition state TS_1 (Scheme 2), as controlled by the electron density of the aryl ring, affects the *cis/trans* selectivity in the ene products.

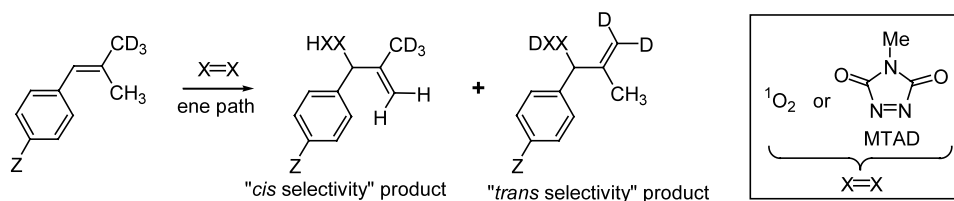
For the corresponding MTAD ene reactions, a similar stabilizing interaction is invoked during the formation of the *cis* aziridinium imide intermediate (Scheme 3). In the aziridinium imide intermediate, the partial positive charge (δ^+) on the benzylic carbon is more pronounced compared to the perepoxide.¹¹ Therefore, the resonance stabilization from the aryl group decreases significantly the electron density of the arene, making the MTAD-aryl ring interaction important for all styrenes.

In conclusion, we have found that electronic effects control the *cis/trans* selectivity in the ene reaction of



Scheme 2. Possible transition states for the formation of the '*cis* and *trans* selectivity' ene products.

Table 1. Ene regioselectivity for the ene reaction of $^1\text{O}_2$ and MTAD with the deuterium-labeled isobutenylarenes^a



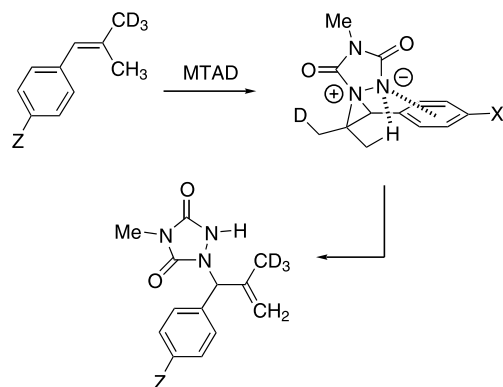
Entry	Substituent (Z)	<i>cis/trans</i> Selectivity ^b (with $^1\text{O}_2$)	<i>cis/trans</i> Selectivity ^b (with MTAD)
1	<i>p</i> -MeO	46/54	>97/3 ^c
2	<i>p</i> -Me	55/45	>97/3
3	H	63/37 ^c	>97/3 ^d
4	<i>p</i> -F	68/32	>97/3
5	<i>p</i> -CF ₃	74/26	>97/3

^a Relative yields of ene adducts with $^1\text{O}_2$ and PTAD: 10–25% and >95%, respectively.

^b Determined by ^1H NMR integration of the proper hydrogen signals. The error was $\pm 4\%$.

^c Ref. 10.

^d Ref. 3.



Scheme 3. The preferred transition state for the formation of the ‘cis selectivity’ ene adduct with MTAD.

several deuterium-labeled 1-aryl-2-methylpropenes. For the reaction of triazolinodiones, the reaction is highly chemoselective in favor of the ‘cis selectivity’ ene product with >97% ‘cis selectivity’.

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- ^1H NMR data of the allylic hydroperoxides. Z = -OMe: 7.99 (s, 1H, OOH), 7.29 (d, $J=8.5$ Hz, 2H), 6.90 (d, $J=8.5$ Hz, 2H), 5.33 (s, 1H), 5.14 (br. s, 1H), 5.08 (br. s, 1H), 3.81 (s, 3H), 1.70 (s, 3H). Z = -Me: 7.98 (s, 1H, OOH), 7.25 (d, 2H, $J=7.9$ Hz), 7.18 (d, 2H, $J=7.9$ Hz), 5.35 (s, 1H), 5.13 (br. s, 1H), 5.07 (br. s, 1H), 2.36 (s, 3H), 1.70 (s, 3H). Z = -F: 8.05 (s, 1H, OOH), 7.33 (dd, $J_{\text{H-H}}=8.0$ Hz, $J_{\text{H-F}}=5.5$ Hz, 2H), 7.06 (dd, $J_{\text{H-H}}=8.0$ Hz, $J_{\text{H-F}}=8.0$ Hz, 2H), 5.36 (s, 1H), 5.13 (br. s, 1H), 5.10 (br. s, 1H), 1.69 (s, 3H). Z = -CF₃: 8.09 (s, 1H, OOH), 7.64 (d, $J=8.1$ Hz, 2H), 7.49 (d, $J=8.1$ Hz, 2H), 5.44 (s, 1H), 5.12 (br. s, 1H), 5.11 (br. s, 1H), 1.70 (s, 3H).
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