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Novel regiochemistry in the aqueous singlet oxygen ene reactions of carboxylic acid salts: a comparison of substrate structure

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Abstract—The singlet oxygen ($^1\Delta_g$) photooxidations of angelic acid salt (**1**), tiglic acid salt (**2**), 2,3-dimethyl-2-butenoic acid salt (**3**), 3-ethoxycarbonyl-5,6-dihydro-2-methyl-4*H*-pyrane acid salt (**4**), *cis*-3-hexenoic acid salt (**5**), and *trans*-3-hexenoic acid salt (**6**) were conducted in deuterated water. The major and minor ene allylic hydroperoxide products were quantified and indicate that the allylic hydrogen geminal to the carboxylate group is preferentially abstracted in **1–4**, whereas the allylic hydrogen α to the carboxylate is slightly favored for **5** and **6**. We have attributed the observed regiochemistry in **1–4** to stabilizing hydrogen bonding interactions between the solvent and the perepoxide, which leads to the major ene product.
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Following the initial discovery of the singlet oxygen ($^1O_2$) ene reaction in 1943 by Schenck,[1] this fascinating reaction continues to receive considerable mechanistic attention today. In fact, recent computational studies[2] suggest that the ene reaction proceeds through a two step no intermediate process involving a transition state with the symmetry of a perepoxide rather than a discrete perepoxide intermediate. Much of the experimental mechanistic[3] evidence indicates that the reaction proceeds through an exciplex intermediate with perepoxide symmetry.[4] Clearly the structure and subsequent stabilization of the perepoxide is very important in determining the regiochemistry of the ene reaction.

Previous studies of the $^1O_2$ ene reactions of several α,β-unsaturated esters and acids[5] in hydrogen bonding solvents such as methanol and water indicate that hydrogen bonding interactions do affect the relative stabilities of the perepoxides formed and, therefore, the product distribution. Our continued interest on the effect of aqueous solvents on the singlet oxygen ene reaction led us to investigate the aqueous photooxidations of sodium salts **1–4**.[6] Scheme 1 depicts the $^1O_2$ ene reaction of angelic acid salt **1** using deuterated water as the solvent. Deuterated solvents were chosen because of the

longer singlet oxygen lifetimes and therefore decreased photooxidation times. Singlet oxygen was generated via photosensitization using either methylene blue or rose bengal as the sensitizer (2×10^{-4} M). A typical sample was irradiated with a 500 W tungsten/halogen lamp while being continuously purged with dry oxygen. Scheme 1 shows formation of two possible perepoxides, **PE**$_{major}$ and **PE**$_{minor}$, leading to the two observed ene hydroperoxide products. Each reaction involves a hydrogen abstraction ($-H_a$ for major, $-H_b$ for minor) followed by a shift in the placement of the double bond.

Table 1 shows the percentage of allylic hydrogen abstraction leading to the major and minor hydroperoxide products during the photooxidations of the angelic acid derivatives (**1**), tiglic acid derivatives (**2**), and the methyl 2,3-dimethyl-2-butenoic acid derivatives (**3**). The major products during the photooxidations of **1–3** were always the lower energy, conjugated isomers formed by abstraction of the hydrogens geminal to the carboxylate groups. This geminal selectivity has been demonstrated for many alkenes bearing an electron withdrawing group at the α position.[3c] However, we were surprised to observe that salts **1–3** displayed overwhelming geminal selectivity. In fact ≥93% major product was formed in each case. This is an unexpected result because previous studies with corresponding esters[7] and acids[5] showed a definite solvent polarity effect on the product distribution. In fact increasing the dielectric constant of the solvent also increased the amount of

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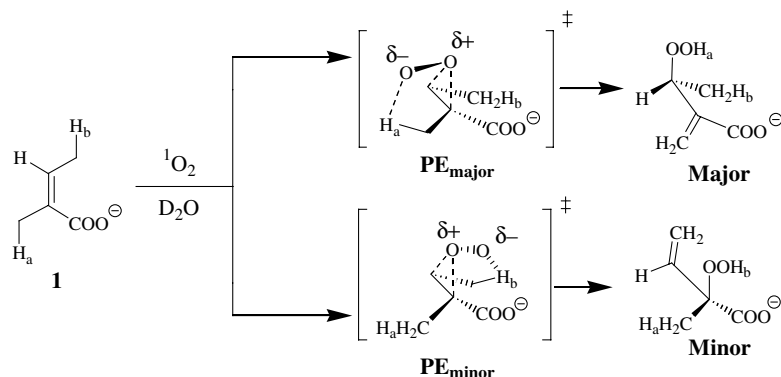
Scheme 1. Photooxidation products from $^1O_2$ reaction with **1**.

Table 1. %Hydrogen abstraction leading to major (a)/minor (b) ene product ratios[a] for substrates **1–3**[b] where X = OCH$_3$, OH, and ONa

| | | **1** | | | **2** | | | **3** | | |
| | | OCH$_3$ | OH | ONa | OCH$_3$ | OH | ONa | OCH$_3$ | OH | ONa |
Solvent	ε[c]									
C$_6$D$_6$	2.3	86/14	100/0	—	97/3	100/0	—	89/11	100/0	—
(CD$_3$)$_3$COD	12.5	—	**99/1**	—	—	—	—	—	—	—
CD$_3$OD	33.0	79/21	87/13	—	100/0	100/0	—	85/15	91/9	—
CD$_3$CN	36.6	78/22	80/20	—	—	—	—	83/17	86/14	—
90%CD$_3$OD/10%D$_2$O	51.8	70/30	81/19	—	100/0	—	—	82/18	90/10	—
D$_2$O	80.1	—	—	**93/7**	—	—	**95/5**	—	—	**94/6**

[a] Product ratios were determined by ^{1}H NMR of the allylic hydroperoxides.
[b] Except for bold-faced ratios, data taken from Ref. 5.
[c] Taken from *Handbook of Chemistry and Physics*, 81st edition.

minor product formed. Orfanopoulos attributed this result to the relative increased stability of the perepoxide, **PE$_{minor}$**, leading to the minor product because of its net higher dipole moment (Scheme 1). Furthermore, we observed[5] that the minor product increased from 14% to 30% during the photooxidation of the methyl ester of **1** when switching from C$_6$D$_6$ (ε 2.3) to a 90/10 mixture of deuterated methanol/water (ε 51.8) and from 0% to 19% with the acid of **1** (Table 1). Thus, it is surprising that increasing the solvent polarity substantially with D$_2$O (ε 80.1) actually produced much less minor product.

Simple structural changes as observed in **1–3** and placing the double bond in a cyclic system **4** failed to produce a significant change in the major to minor product ratios. Photooxidation of pyrane salt **4** produced 99% major product (Fig. 1). These results suggest that with salts **1–4** neither the polarity of the solvent nor the well-established *cis* effect[8] are major factors determining regiochemistry. We propose that the overwhelming factor is stabilizing hydrogen bonding interactions between water and perepoxide **I**, which leads to major product (Fig. 2). Perepoxide **I** is favored over **II** for both steric and electronic reasons. Strong hydrogen bonds formed between the carboxylate oxygens and water
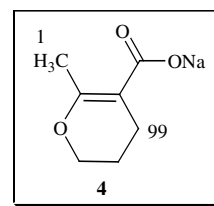

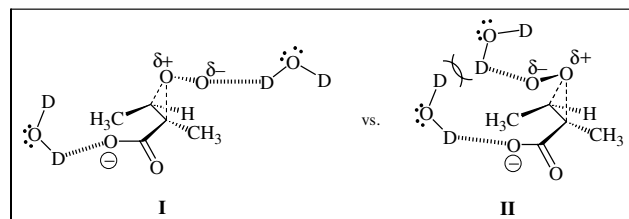**Figure 1.** %Hydrogen abstraction leading to major and minor ene products for **4**.

Figure 2. Perepoxide **I** is stabilized by hydrogen bonding.

disfavor **II** because of the steric interference between the solvated pendant oxygen and the solvent molecules hydrogen bonded to the carboxylate oxygen.

These hydrogen bonds are expected to be stronger (COO⁻ ··· DOD bond dissociation energy 14–40 kcal/mol versus 4–15 kcal/mol for COOH ··· OD₂)[9] than those formed with the corresponding acids and therefore the steric interactions incurred with **II** should be intensified. We previously[5] observed this trend with angelic acid and indeed the interaction is intensified with angelic acid salt **1**; angelic acid produced 19% minor product in a 90/10 mixture of deuterated methanol/water as compared to only 7% in deuterated water for the salt (Table 1).

Electronically **II** is expected to be higher in energy due to the interaction between the negatively charged pendant oxygen and the negatively charged carboxylate. Placing the pendant oxygen on the opposite side as in **I** minimizes electronic interactions with this electron-rich group. Therefore, even though **I** is expected to be less polar than **II**, it appears that hydrogen bonding is much more important in determining the regiochemistry with the salts than solvent polarity. Also the *cis* effect is expected to operate in substrates **2**–**4** but the effect on the product distribution is minimal; only 1–5% more major product is formed when compared to **1**. Pyrane salt **4** produced the least minor product, and it has been suggested[10] that this result is due to a type of *cis* directing effect caused by the oxygen in the ring system. The oxygen in the ring system directs the approaching electrophilic singlet oxygen so that hydrogen abstraction occurs from the allylic hydrogen *cis* to the oxygen in the ring.

In order to further compare the effect of substrate structure and in particular the placement of the carboxyl group in relation to the double bond, we photooxidized the *cis*-[11] and *trans*-3-hexenoic acids and their corresponding sodium salts (**5**, **6**). Table 2 shows that the product ratios for the hexenoic acids and their corresponding salts **5** and **6** remained around 60/40 with the allylic hydrogen α to the carboxyl group being preferentially abstracted. Neither the polarity of the solvent nor the hydrogen bonding capability of the solvent appeared to affect the product ratios for these acids. The only exception occurred utilizing deuterated *tert*-butanol, a sterically demanding solvent, which significantly increased the amount of minor product for both the hexenoic acids. The corresponding acid perepoxide for **6**major (Fig. 3) is slightly less favored in (CD₃)₃COD because of steric interactions between the solvated pendant oxygen and the carboxyl group, similar to that observed previously in Fig. 2, perepoxide **II**. It is interesting to note that angelic acid produced 99% geminal abstraction in (CD₃)₃COD (Table 1). This is indeed further evidence for the steric effect as the energy of perepoxide **II** is increased, therefore favoring perepoxide **I** (Fig. 2).

Placing the carboxylate group in a β position to the double bond greatly increases the amount of minor ene product formed as compared to functionality at the α position. Furthermore it appears that the overwhelming hydrogen bonding interactions observed with salts **1**–**4** are minimized in determining regioselectivity with salts **5** and **6**. We attribute the minimal hydrogen bonding

Table 2. %Hydrogen abstraction leading to major (a)/minor (b) ene product ratios[a] for substrates **5** and **6** where X = OH, ONa

		5		6	
Solvent	ε[b]	OH	ONa	OH	ONa
C₆D₆	2.3	63/37	—	—	—
(CD₃)₃COD	12.5	49/51	—	52/48	—
CD₃OD	33.0	61/39	—	65/35	—
CD₃CN	36.6	62/38	—	—	—
60% CD₃OD/40% D₂O	51.8	60/40	—	—	—
D₂O	80.1	—	61/39	—	59/41

[a] Product ratios were determined by ¹H NMR of the allylic hydroperoxides.
[b] Taken from *Handbook of Chemistry and Physics*, 81st edition.
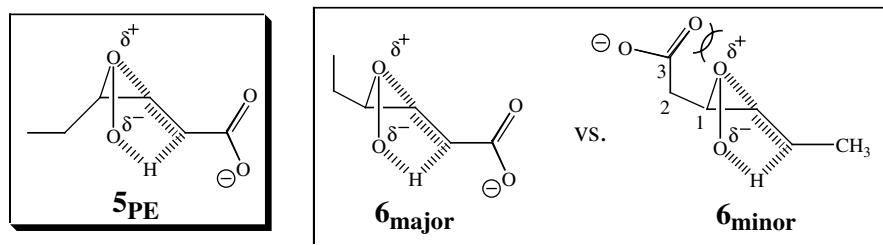

Figure 3. Possible perepoxides resulting from photooxidation of **5** and **6**.

effect in **5**, **6**, and their acids to the different steric demand that is experienced by salts **1**–**4**. Certainly inclusion of a CH_2 group between the double bond and the carboxylate group increases the distance from the perepoxide pendant oxygen, thereby reducing the steric and electronic effects of perepoxide **II**. Previous studies[12] on the regiochemistry of alkenes with a β electron withdrawing group suggest that several competing factors affect this product ratio including developing conjugation, a steric 1,3-nonbonded interaction, and electronic interactions. Inspection of the perepoxides leading to product show that **5** only has one possibility, **5$_{PE}$**, whereas **6** has two possible competing perepoxides, **6$_{major}$** and **6$_{minor}$** (Fig. 3).

The important contributing factors favoring major product in **5** appear to be the developing conjugation and the reduced 1,3-nonbonded steric interaction by placing the larger carboxylate group away from the positive perepoxide oxygen (**5$_{PE}$**, Fig. 3). These interactions appear to be nearly balanced by an opposing electronic interaction due to placement of the negatively charged pendant oxygen close to the carboxylate group, thus the approximate 60/40 ratio of products. Inspection of the two possible perepoxides, **6$_{major}$** and **6$_{minor}$**, for the *trans* salt reveals that developing conjugation again favors the major product. **6$_{minor}$** has a substantial steric 1,3-nonbonded interaction, which further favors the major perepoxide. However, the electronic interaction is removed in **6$_{minor}$** because the negatively charged pendant oxygen and carboxylate are on opposite sides of the perepoxide. Clearly removing the electronic repulsion favors formation of the minor product and is extremely influential in determining the overall regiochemistry.

In conclusion, the major factor dictating the product distribution of singlet oxygen ene reactions of α substituted alkene salts **1**–**4** in water is hydrogen bonding interactions between the solvent and substrate. However, placing the carboxylate group β to the double bond as in salts **5** and **6** produces a profound change in the observed regiochemistry due to the interplay of a number of interactions including developing conjugation, 1,3-nonbonded interactions, and electronic effects.

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