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# Stereochemical Features of the Physical and Chemical Interactions of Singlet Oxygen with Enecarbamates

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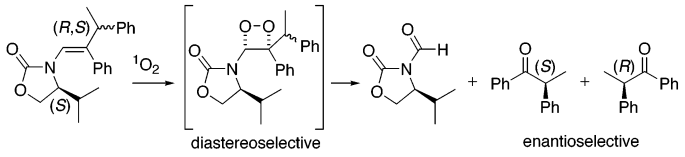
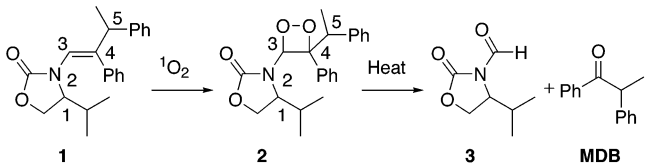
## ABSTRACT




**Oxazolidinone-substituted enecarbamates represent a mechanistically rich system for the study of stereoelectronic, steric, and conformational effects on stereoselectivity and mode selectivity in $^1O_2$ [2 + 2] and ene reactions. Photooxygenation of these enecarbamates with $^1O_2$ leads to diastereomerically pure dioxetanes that decompose to yield an oxazolidinone carbaldehyde and one of the two enantiomers of methyldesoxybenzoin in enantiomeric excess. Stereoselectivity originates at the allylic stereocenter, a result supported by quenching studies, computational analysis, and deuterium solvent isotope effects.**

Reaction[1] of the enecarbamate **1** with singlet oxygen ($^1O_2$) results in the formation of dioxetane **2** with >95% diastereoselectivity (Scheme 1). The dioxetane **2** is derived from attack of $^1O_2$ from the face anti to the isopropyl substituent at the oxazolidinone stereocenter-1 (C-1). This diastereoselectivity is consistent with classical steric $\pi$-facial shielding of attack of $^1O_2$ by the isopropyl group at C-1. Enecarbamate **1** also possesses a second stereogenic center at C-5. Since C-1 and C-5 are both in proximity of the reactive C=C double bond being attacked by $^1O_2$, both C-1 and C-5 are expected to influence the stereochemical outcome of dioxetane formation. The results of the reported reactions[1] of **1** with $^1O_2$ established that an alkyl substitutent at C-1 produces a high diastereoselectivity of dioxetane formation. However, because the reactions were run to 100% completion, the results were silent as to the role of the influence of the stereochemistry at C-5 on the stereoselectivity of dioxetane formation and in particular the possible *enantioselectivity of formation of MDB at partial conversion* (Scheme 1).

**Scheme 1**

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(1) (a) Adam, W.; Bosio, S. G.; Turro, N. J. *J. Am. Chem. Soc.* **2002**, *124*, 8814. (b) Adam, W.; Bosio, S. G.; Turro, N. J. *J. Am. Chem. Soc.* **2002**, *124*, 14004.

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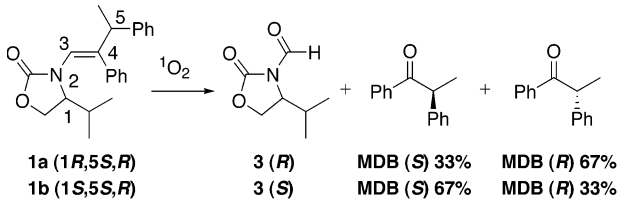
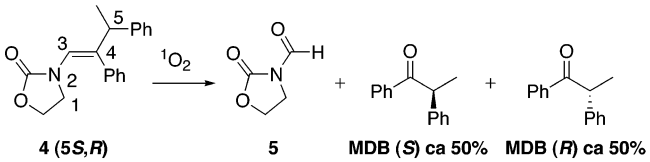
**Scheme 2**




To elucidate the mechanistic details of the reaction of the enecarbamate **1** and $^1O_2$ and to determine the role of the stereocenter at C-5 on the stereoselectivity of attack of $^1O_2$ on the double bond of **1**, we have investigated (1) the rate constant for quenching of $^1O_2$ by two diastereomers of **1** (**1a** and **1b**), by the oxazolidinone **3**, and by the enecarbamate **4**; (2) the efficiency of chemical reaction of $^1O_2$ with the two diastereomers of **1** (**1a** and **1b**); and (3) the enantiomeric excess (ee) of the ketone MDB formed from decomposition of the dioxetane after reaction of **1** with $^1O_2$ at low conversion (Schemes 2 and 3).

**Scheme 3**




**1a** and **1b** react with $^1O_2$ to form the dioxetane **2**, arising from stereoselective attack anti to the isopropyl group at C-1.[1] Subsequent decomposition of the dioxetanes at complete conversion results in the formation of nearly equal yields of (*R*)-MDB and (*S*)-MDB.[2] We report that after low (<30%) conversions of **1a** and **1b**, followed by decomposition of the dioxetane, **2**, the MDB produced is significantly enriched (ee ca. 33%) in (*S*)-MDB or (*R*)-MDB, respectively (Scheme 2). At low conversion, the reaction of $^1O_2$ with the enecarbamate **4** (which possesses no stereocenter at position 1) results in only a slight ee (ca 4%) in the MDB produced by decomposition of the precursor dioxetanes (Scheme 3).

The rates of quenching of $^1O_2$ by **1a** and **1b** were determined by monitoring the quenching of $^1O_2$ phosphorescence at 1270 nm.[3] $^1O_2$ was produced by both the thermal decomposition of 1,4-dimethylnaphthalene endoperoxide (**6**)[4] or by photosensitization with 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (**7**).[5] Stern−Volmer analysis (Figure 1) of the data yielded an indistinguishable quenching rate constant of $1.0 \pm 0.2 \times 10^5$ $M^{-1}$ $s^{-1}$ for **1a** and **1b**.

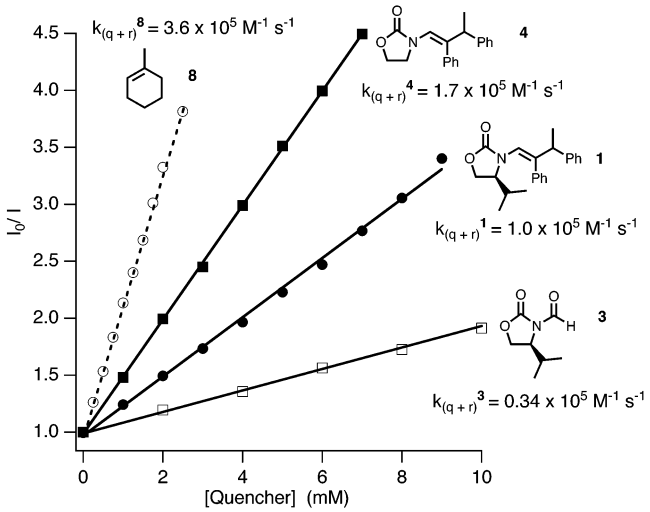



**Figure 1.** Stern−Volmer plot to determine the total quenching rate constants, $k_{(q+r)}$, where $I_0$ is the intensity of the chemiluminescence of $^1O_2$ at 1270 nm in the absence of quencher and $I$ is the intensity in the presence of quencher **1**, **3**, **4**, or **8**. For experimental details, see ref 3b.

Due to the longer lifetime of $^1O_2$ in $CDCl_3$ (7 ms)[5] compared to $CHCl_3$ (0.23 ms),[5] the conversions are expected, and found, to be higher in $CDCl_3$ (30%) relative to $CHCl_3$ (15%), for the same amount of endoperoxide decomposition. Also as expected, the increase in conversion was accompanied by a lower ee of MDB (30% ee in $CHCl_3$ compared to 10% ee in $CDCl_3$). Similar results were found when $^1O_2$ was generated with **7** as a photosensitizer. The oxazolidinone **3**, which does not possess a reactive C=C bond, was found to be a poorer quencher (Figure 1) of $^1O_2$ ($0.34 \times 10^5$ $M^{-1}$ $s^{-1}$), and the unsubstituted enecarbamate **4** was found to be a better quencher ($1.7 \times 10^5$ $M^{-1}$ $s^{-1}$) than the isopropyl-substituted enecarbamate, **1** ($1.0 \times 10^5$ $M^{-1}$ $s^{-1}$).

The quenching of $^1O_2$ by any substrate can proceed via two pathways: (1) a chemically productive "reactive" pathway with a rate constant, $k_r$, and (2) a chemically unproductive, net physical "quenching" pathway with a rate constant, $k_q$. The relative efficiency of the reaction of **1** with $^1O_2$ was determined by comparison of the chemical reaction of $^1O_2$ with **1** and with 1-methylcyclohexene (**8**)[6] as a standard. The rate of disappearance of **8** in $CCl_4$ was ca. 10 times faster than the rate of disappearance of **1** under comparable conditions (Supporting Information). Since the maximum efficiency of reaction of **8** with $^1O_2$ is 1.0, the maximum efficiency of reaction of **1** with $^1O_2$ is 0.1. This result demonstrates clearly that the *major path of interaction of* ***1*** *with* $^1O_2$ *is a quenching mode rather than a reactive mode*.

(2) (a) That the relative yields are not exactly 50:50 is attributed to the observed small excess of one of the diastereomers of **1** after purification by column chromatography. (b) An authentic sample of (*S*)-MDB was synthesized using a literature procedure (McKenzie, A.; Roger, R.; Wills, G. O. *J. Chem. Soc.* **1926**, 779). Thus, the stereochemical assignments in Scheme 2 are absolute.

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(6) Monroe, B. M. *J. Am. Chem. Soc.* **1981**, *103*, 7253.

The substituent at C-1 of **1b** controls[1] the facial direction of *reactive* $^1O_2$ attack, which occurs exclusively from the face opposite to the isopropyl group. Thus, the mechanistic analysis needs to consider only the influence of C-5 on the trajectories of $^1O_2$ toward the double bond from the top face. In Figure 2, the lowest energy conformations at C-5 for (1*R*, 5*R*)- and (1*R*, 5*S*)-**1b** can be used as a working structural basis to analyze the enantiomeric selectivity of reaction with $^1O_2$.

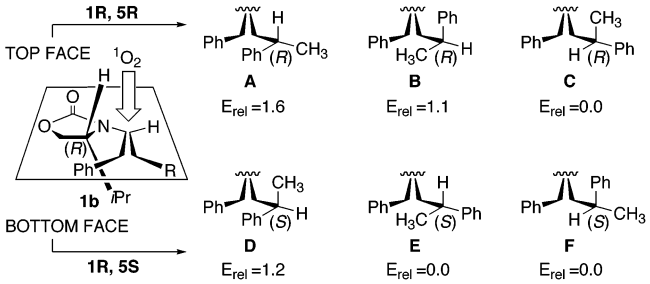


**Figure 2.** Isopropyl group shields the bottom face of the alkene in **1b**. **A**−**C** are the lowest energy conformations for the (1*R*,*5R*)-isomer. **D**−**F** are the lowest energy conformations for the (1*R*,*5S*)-isomer. Energies were computed at the PM3 level and are in kcal/mol.

The energies of the three lowest energy conformations shown in Figure 2 at C-5 for **1a** and **1b** were calculated at the PM3 level of theory.[7] For the (1*R*,*5R*)-**1b** conformations, the lowest energy conformation is **C** where the hydrogen eclipses the double bond. This conformation places the methyl group over the top face of the alkene. For the (1*R*,*5R*)-**1b** conformations, the two lowest energy conformations are (**F**) with the hydrogen and (**E**) with the methyl eclipsed to the double bond. Both **E** and **F** were found to be of the same energy by both PM3 and MM2[8] (not shown) computations. In **F**, the phenyl group is positioned over the top face of the alkene, clearly providing a steric barrier to attack by $^1O_2$. The experimental observation (Scheme 2) is that (1*R*,*5R*)-**1b** reacts with $^1O_2$ faster than (1*R*,*5S*)-**1b**. Thus, we can conclude that although **E** and **F** have nearly identical energies computationally, to be consistent with the experimental results, **F** probably exists as the major conformer at equilibrium.

In conclusion, the reaction of $^1O_2$ with enecarbamates has proven to be rich in testable aspects of stereoselectivity at the two stereogenic centers of these molecules. The results are remarkable in that $^1O_2$, a sterically undemanding and simple diatomic molecule, is still subject to significant stereochemical effects on its chemical reactivity and quenching, as well as its diastereomeric and enantiomeric selectivity. Our results demonstrate that the isopropyl group at C-1 completely controls the diastereofacial attack on the double bond of **1**, and the absolute configuration at C-5 exerts a significant control on the enantioselectivity of attack from the face opposite to the isopropyl group. It has been well established that $^1O_2$ is quenched by X−H vibronic interactions.[9] It is possible that the remarkable stereoselectivity is due to vibronic physical quenching of the sterically blocking group rather than, or in addition to, classic steric effects. This possibility can be tested by replacing the hydrogens of the isopropyl group at C-1 and the hydrogens of the methyl group at C-5 with deuteria.

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**Supporting Information Available:** Experimental details and a comparison of the efficiency of reaction of **1** and **8** with $^1O_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) As implemented in *SPARTAN* version 5.0 (Wavefunction, Inc.: Irvine, CA).

(8) As implemented in *Macromodel*: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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