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Stereoselective Photooxidation of Enecarbamates: Reactivity of Ozone vs Singlet Oxygen

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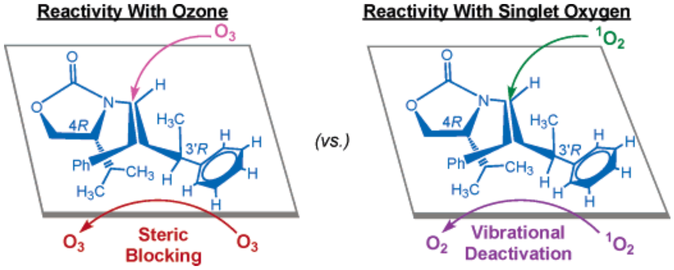
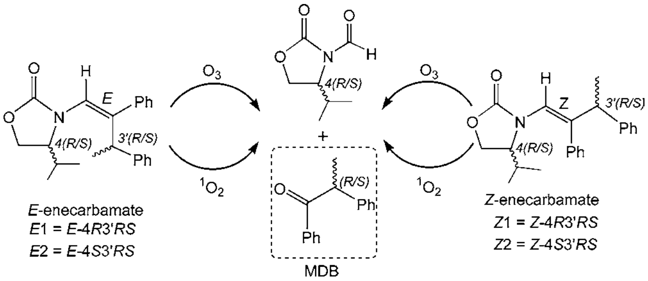
ABSTRACT



Oxazolidinone-functionalized enecarbamates show contrasting behavior upon oxidation by singlet oxygen and by ozone. The observed stereoselectivity difference indicates that the oxidation with ozone is subject to classic steric effects, whereas the very high selectivity in the photooxidation with singlet oxygen is derived from vibrational deactivation.

Scheme 1. Oxidation of (*E*)-/(*Z*)-Enecarbamates by $^1O_2/O_3$



Understanding the mechanisms of organic reactions has led to vast advances in the area of asymmetric processes.[1] Unfortunately, asymmetric photoreactions[2] have not enjoyed the same level of attention as asymmetric thermal reactions. Recently, we reported a very high stereoselectivity in the photooxidation[3,4] of oxazolidinone-derived enecarbamates (Scheme 1) with singlet oxygen[5] ($^1O_2$), both in solution[3] and in organized media.[4] To elucidate the factors responsible for the high stereocontrol in this photooxidation, we have

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investigated the reactivity of ozone[6] (O_3) with oxazolidinone-functionalized enecarbamates. The selectivity during photooxidation by $^1O_2$ was shown to depend on the alkene geometry;[3,4] the (*E*)-isomer gives higher selectivity than the corresponding (*Z*)-isomer in isotropic media.[3] By investigating the reactivity of O_3 with oxazolidinone-derived enecarbamates, we expected to gain insight into the high stereoselectivity observed with $^1O_2$, in view of the facts that (i) O_3 and $^1O_2$ are electrophilically similar in nature,[5−7] (ii) the products upon oxidation with $^1O_2$ and O_3 are the same (Scheme 1), and (iii) the importance of *radiationless deactivation (physical quenching)* may be assessed during the oxidation process because O_3 is a reactive ground-state species compared to $^1O_2$, an excited-state molecule.

$$\ln(k_R/k_S) = \ln[(100 + \%\ \mathrm{ee})/(100 - \%\ \mathrm{ee})] \qquad (1)$$

$$\ln(k_R/k_S) = \Delta\Delta S^{\ddagger}{}_{R-S}/R - \Delta\Delta H^{\ddagger}{}_{R-S}/RT \qquad (2)$$

$$\mathrm{s} = \frac{k_R}{k_S} = \frac{\ln[1 - C(1 + \mathrm{ee}_{MDB})]}{\ln[1 - C(1 - \mathrm{ee}_{MDB})]} \qquad (3)$$

where C in eq 3 is the conversion and ee_{MDB} is the ee value of the MDB product.

The epimeric pairs of oxazolidinone-derived (*E*)- and (*Z*)-enecarbamates were oxidized with O_3 in three different solvents (CD_2Cl_2, $CDCl_3$, and CD_3OD) at various temperatures (Table 1). The conversion was kept low to avoid side reactions,[6] and the enantiomeric excess (ee) was obtained by GC analysis of the methyldesoxybenzoin (MDB) product on a chiral stationary phase (Scheme 1). Inspection of Table 1 reveals the following features: (i) The same enantiomer of the MDB is enhanced upon varying the solvent, but a noticeable change in the ee values is observed at the same temperature for both (*E*)- and (*Z*)-enecarbamates; for example, at −70 °C, the ee values for O_3 oxidation of *E***1** in CD_3OD is 4%; in CD_2Cl_2, 18%; and in $CDCl_3$, 29%. (ii) The sense of the enhanced MDB enantiomer depends on the configuration at the *C*-4 position of the oxazolidinone ring as well as the alkene geometry; for example, *E***1** gave the (*S*)-MDB in excess, whereas the corresponding (*Z*)-isomer (*Z***1**) gave (*R*)-MDB in excess. (iii) The observed ee value depends on the extent of conversion, i.e., ee values were moderate at low conversions and small at high conversions. (iv) The same MDB enantiomer is enhanced upon varying the temperature. (v) The change of the configuration at the *C*-4 position of the oxazolidinone reverses the sense of the MDB enantiomer to the same extent (Figure 1).

Table 1. Oxidation of the (*E*)- and (*Z*)-Enecarbamates[a] by O_3[b]

substrate[a]	solvent	T (°C)	% ee MDB[c]	% conversion[d]	s[e]	$\Delta\Delta H^{\ddagger}$[f]	$\Delta\Delta S^{\ddagger}$[f]
*E***1**	CD_2Cl_2	20	22 (*S*)	6	1.6	0.16	1.49
		−15	24 (*S*)	15	1.7		
		−45	16 (*S*)	18	1.4		
		−70	18 (*S*)	27	1.5		
*E***1**	$CDCl_3$	20	18 (*S*)	12	1.5	−0.48	−0.97
		−15	20 (*S*)	17	1.6		
		−70	29 (*S*)	25	2.0		
*E***1**	CD_3OD	20	4 (*S*)	4	1.1	0.12	0.16
		−15	2 (*S*)	6	1.1		
		−45	0	4	1.0		
		−70	4 (*S*)	5	1.1		
*Z***1**	CD_2Cl_2	20	31 (*R*)	10	2.0	−0.14	0.79
		−15	30 (*R*)	12	1.9		
		−78	36 (*R*)	9	2.2		
*Z***2**	CD_2Cl_2	20	33 (*S*)	6	2.0	0.6	2.98
		20	27 (*S*)	9	1.8		
		−15	38 (*S*)	7	2.3		
		−15	12 (*S*)	20	1.3		
		−45	6 (*S*)	27	1.2		
		−70	36 (*S*)	9	2.2		
		−70	4 (*S*)	36	1.1		
*Z***2**	$CDCl_3$	20	20 (*S*)	16	1.6	0.08	1.03
		−15	16 (*S*)	17	1.4		
		−70	18 (*S*)	14	1.5		
*Z***2**	CD_3OD	20	20 (*S*)	3	1.5	−0.05	0.62
		−15	21 (*S*)	4	1.5		
		−45	22 (*S*)	16	1.6		
		−70	22 (*S*)	7	1.6		

[a] A ca. 50/50 mixture of diastereomers (total concentration of 2.3×10^{-3} M) was used. [b] Procedure given in Supporting Information. [c] Average of three runs; error ±6%. [d] Conversion monitored by ^1H NMR spectroscopy (see Supporting Information); the conversion was kept low to prevent side reactions (ref 6). [e] From eq 3. [f] From eqs 1 and 2. $\Delta\Delta H^{\ddagger}$ given in (kcal mol^{-1}); $\Delta\Delta S^{\ddagger}$ given in (cal mol^{-1} K^{-1}).

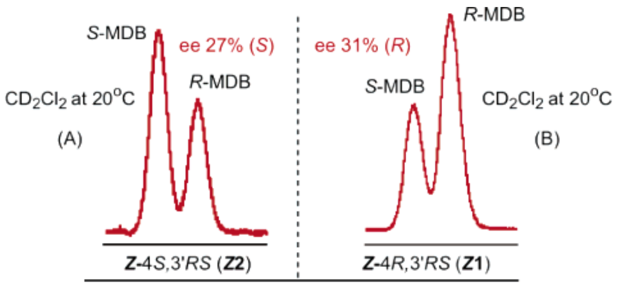

Figure 1. GC traces of product MDB. Opposite senses of ee were observed in the ozonolysis of *Z***1** (B) and *Z***2** (A) due to the opposite configuration at the *C*-4 position of the oxazolidinone.

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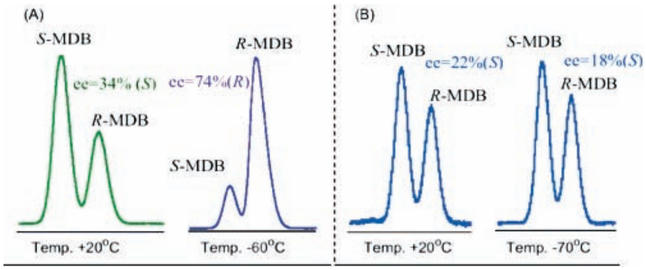

Figure 2. Representative GC traces of product MDB for the oxidation of *E***1** by $^1O_2$ (A) and O_3 (B) in CD_2Cl_2.

It is evident from Table 1 that there is no solvent or temperature dependence of the ee values for (*E*)-enecarbamates upon oxidation with O_3, which is in sharp contrast to the photooxidation[3] with $^1O_2$ (Table 2; Figure 2). Clearly, the extent of stereoselectivity in the oxidation of *E***1** with O_3 (Table 1) differs from that of $^1O_2$ (Table 2). Further, the (*Z*)-enecarbamates do not show any solvent or temperature dependence upon oxidation with O_3, a result similar to the $^1O_2$ oxidation.[3] To understand the difference in the behavior of the oxazolidinone-functionalized enecarbamates toward the oxidation of O_3 and $^1O_2$, we computed the differential activation enthalpy ($\Delta\Delta H^{\ddagger}$) and entropy ($\Delta\Delta S^{\ddagger}$) values, which are directly related to the ee values through eqs 1 and 2.[8] These data are listed in Tables 1 and 2, which reveal that there is no significant difference in the activation parameters for the oxidation of the (*E*)- and (*Z*)-enecarbamates with O_3. The sharp contrast in the differential activation parameters for the oxidation of *E***1** by O_3 and $^1O_2$ is revealing (Tables 1 and 2); for example, in the oxidation of *E***1** in CD_2Cl_2, the $\Delta\Delta S^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ values for O_3 are 1.49 cal mol^{-1} K^{-1} and 0.16 kcal mol^{-1}, respectively, compared to -15 cal mol^{-1} K^{-1} and -4.0 kcal mol^{-1} for $^1O_2$. Thus, the ee value of the MDB product is a critical balance of the enthalpy (*molecular*) and entropy (*environmental*) terms, which are interrelated by eqs 1 and 2.[8] Consequently, the large contribution from the differential activation parameters for the $^1O_2$ oxidation (Table 2) suggests that the transition state is conformationally flexible and its solvation−desolvation behavior is crucial. Expectedly, the temperature and solvent variations influence the stereodifferentiating step.[8] Enthalpic control applies when the stereoselectivity is enhanced upon decreasing the temperature, a phenomenon common to many thermal asymmetric reactions.[9] In contrast, the low contribution from the differential activation parameters for the O_3 oxidation indicates that the transition state is more rigid and is not influenced by the variation of the external factors (solvent/temperature) of the system. Expectedly, there is no noticeable change in the extent of the ee values, and the sense of the enhanced enantiomer remains the same upon oxidation by O_3.

Table 2. Photooxidation of the (*E*)-Enecarbamate by $^1O_2$[3]

substrate[a]	solvent	T (°C)	% ee MDB[b]	% conversion[b,c]	s[d]	$\Delta\Delta H^{\ddagger}$ [e]	$\Delta\Delta S^{\ddagger}$ [e]
*E***1**	CD_2Cl_2	20	34 (*S*)	25	2.3	−4.0	−15
		−20	27 (*R*)	65	2.7		
		−60	74 (*R*)	31	9.2		
*E***1**	$CDCl_3$	50	8 (*S*)	5	1.2	−4.5	−14
		18	63 (*R*)	17	5.0		
		−15	78 (*R*)	37	13		
		−40	88 (*R*)	43	31		
*E***1**	CD_3OD	50	70 (*R*)	30	7.6	−2.8	−4.9
		18	85 (*R*)	34	19		
		−15	90 (*R*)	17	23		
		−40	94 (*R*)	12	37		
		−70	97 (*R*)	8	72		

[a] A ca. 50/50 mixture of diastereomers (total concentration 3.0×10^{-3} M) in an NMR tube under O_2 pressure was used, with methylene blue (3.7×10^{-4} M) as a sensitizer. [b] Determined by GC analysis. [c] Determined by ^1H NMR spectroscopy. [d] From eq 3. [e] From eqs 1 and 2. $\Delta\Delta H^{\ddagger}$ given in (kcal mol^{-1}); $\Delta\Delta S^{\ddagger}$ given in (cal mol^{-1} K^{-1}).

As mentioned above, the ee value depends on the extent of conversion. The ratio of the rates of formation (relative rates) of the enantiomeric products may be computed from the observed ee value at a given conversion by means of eq 3, where k_R/k_S is **s**, the stereoselectivity factor.[10] Inspection of Table 1 shows that the **s** factor at best is about 2 for oxidation of enecarbamates by O_3. The low **s** factor will lead to a wide variation in the ee values at different converisons,[10] as observed for the O_3 oxidation, for which the ee values are moderate at low and small at high conversions. For example, 36% ee was observed at 9% conversion and only 4% ee at 36% conversion for the oxidation of *Z***2** by O_3 in CD_2Cl_2 at −70 °C. The consequence of the difference in the **s** factors in the oxidation by O_3 and $^1O_2$ is best illustrated in Figure 3.[10] Under identical conditions, the ee value is 97% for the $^1O_2$ oxidation (**s** factor of 72) compared to only 4% for the O_3 oxidation (**s** factor of about 1.1).

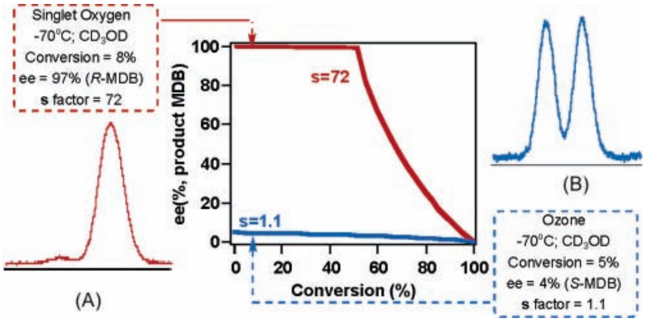

Figure 3. GC traces of product MDB for the oxidation of *E***1** by O_3 and $^1O_2$ at −70 °C in CD_3OD and the plot of % ee versus % conversion (simulated from eq 3; ref 10d) to illustrate the consequence of the difference in the **s** factors.

It is evident from Table 1 that both (*E*)- and (*Z*)-enecarbamates give only moderate ee values in the O_3 oxidation. In general, the (*Z*)-isomers display comparable or higher

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stereoselectivity than the corresponding *E* isomers, which is in contrast to the observed trend of $^1O_2$, for which the *E* isomer exhibits a very high stereoselectivity (ee >97%) compared to the (*Z*)-isomer.[3] We speculate that the steric hindrance experienced by O_3 is reflected in the observed selectivity. As shown in Figure 4B,[11] the approach of O_3 onto the double bond from the bottom is hindered by the isopropyl group, such that O_3 is forced to come in from the top. Moreover, enrichment of the MDB enantiomer depends on the configuration at the *C*-3′ position (Figure 4).[12] For example, in the case of *Z***1**, the (4*R*,3′*R*)-(*Z*)-isomer is more reactive than the (4*R*,3′*S*)-(*Z*)-diastereomer, which affords (*R*)-MDB in excess (Figure 4).

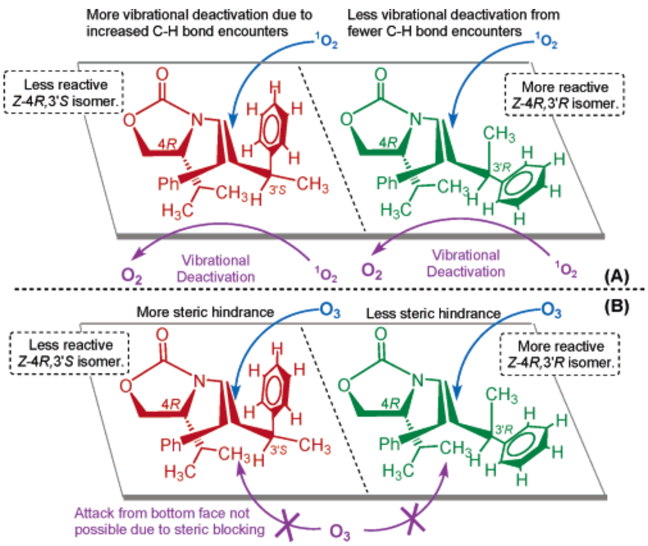
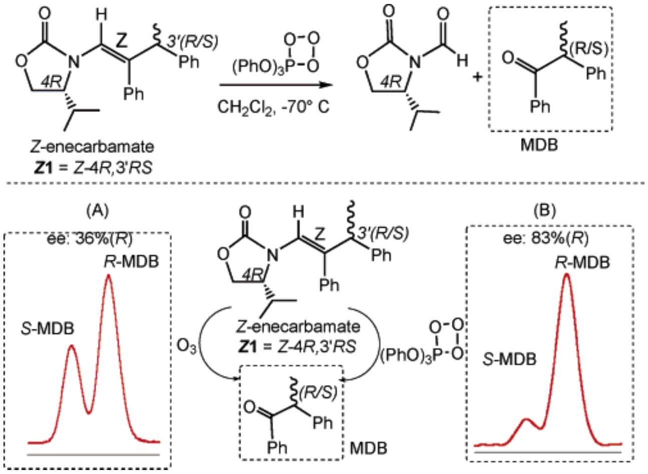


Figure 4. Control of the oxidant approach through deactivation and steric effects for $^1O_2$ (A) and O_3 (B).

If steric effects play a dominant role in the O_3 oxidation, then the observed ee values should be higher when a bulky oxidant is employed. This exception was tested with triphenyl phosphite ozonide (Scheme 2), which is reported to undergo direct addition to alkenes through a perepoxide-like transition state at −70 °C.[13] As shown in Scheme 2, an ee value of 83% ((*R*)-MDB) was observed with *Z***1** upon triphenyl phosphite ozonide [$P(OPh)_3O_3$] oxidation,[13] compared to an ee value of only 36% ((*R*)-MDB) with O_3. Besides steric effects, dipole-induced interactions of the oxidizing species with the enecarbamates may significantly differ to result in a different stereoselectivity.

Scheme 2. Oxidation of *Z***1** by with Triphenyl Phosphite Ozonide and GC Traces Comparison of (Chiral Stationary Phase) O_3 (A) and by $P(OPh)_3O_3$ (B) Oxidation of *Z***1**.



The high stereoselectivity observed for $^1O_2$ (∼97% ee at −70 °C; CD_3OD; Table 2), relates presumably to its electronically excited nature, since it may be vibrationally deactivated on encountering C−H bonds.[3,5,12] Thus, the productive chemical pathway is in competition with the unproductive physical quenching process through deactivation by C−H bonds. The oxidation efficiency of $^1O_2$ is, therefore, determined by which of the two processes dominates. In previous quenching studies on oxazolidinone-derived enecarbamates, we demonstrated that the major pathway is unproductive physical quenching rather than the useful chemical mode.[12] The isopropyl group at the *C*-4 position of the oxazolidinone chiral auxiliary is apparently responsible for the vibrational deactivation of $^1O_2$, since it abundantly furnishes C−H bonds. Evidently, a process that leads to a high stereoselectivity in the product formation must be void of such vibrational deactivation. We are currently examining the deuteration of the substrates at the *C*-4 and *C*-3′ stereogenic centers to better understand the high stereoselectivity displayed by $^1O_2$.

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Supporting Information Available: Reaction procedure, analysis conditions, and calculation of differential activation parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Structure of the (*Z*)-isomer was obtained by crystallography; see: Adam, W.; Bosio, S. G.; Turro, N. J.; Wolff, B. T. *J. Org. Chem.* **2004**, *69*, 1704.

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