Stereocontrol within Confined Spaces: Enantioselective Photooxidation of Enecarbamates Inside Zeolite Supercages

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With Nature as role model, chemists have utilized confined media to achieve selectivity in chemical reactions.[1] Zeolites have been employed to control the outcome of photoreactions[2] by manipulating the spatial requirement of the excited states and reactive intermediates that are involved. Chirally modified zeolites have been shown to be effective in achieving high stereoselectivity in photoreactions.[3] Here we report the high chiral induction within confined spaces, viz. zeolite Y supercages, during the photooxidation of the enecarbamates[4] *Z/E*-**1** in zeolite Y supercages[5] (Scheme 1). One of the important features of Y-type zeolites is the presence of exchangeable cations (alkali/alkaline earth metal cations),[6] which may be readily replaced by cationic dyes[7] such as the singlet-oxygen sensitizer methylene blue.[8]

Oxazolidinone-substituted chiral enecarbamates *Z/E*-**1** are versatile substrates for the study of conformational, electronic, stereoelectronic, and steric effects on the stereoselectivity in the oxidation of the alkene functionality.[4] For example, an enantiomeric excess (ee) of 97% in the methyldesoxybenzoin (MDB) product was observed at −70 °C during the photooxidation of the *E*-**1** isomer in methanol-d_4.[9] This photooxidation in solution was shown to depend on the configuration of the double bond; the *E* diastereomer gave consistently higher stereoselectivity than the corresponding *Z* isomer. In fact, even at very low temperatures, only a modest enantioselectivity (ee) was achieved in the MDB product for the readily synthesized *Z* isomer.[4,9] Moreover, a very low conversion (<3%) and the poor mass balance (<35%) was obtained in the photooxidation of the *Z/E*-**1** diastereomers inside a cation-exchanged Y zeolite without $^1O_2$ sensitizer.[4b] Consequently, we decided to employ dye-exchanged Y zeolites[8] to enhance the efficiency of generating singlet oxygen and thereby provide bona fide photooxygenation conditions. For this purpose, we chose methylene blue as $^1O_2$ sensitizer, to probe the efficacy of asymmetric induction by the oxazolidinone chiral auxiliary in the photooxygenation of the *Z/E*-**1** diastereomers within zeolite supercages.

The *Z*-4(*R*)-3′(*R/S*)-**1** (or *Z*-4(*S*)-3′(*R/S*)-**1**) diastereomeric pair was irradiated (<500 nm cutoff) in the methylene blue (MB) exchanged NaY zeolite (NaY-MB) under oxygen-saturated atmosphere to give the chiral MDB product in good yield and high stereoselectivity[10] (cf. Table 1 and Figure 1). At room temperature an ee value of 80% for the *R*-MDB product (entry 3) was observed upon irradiation of *Z*-4(*S*)-3′(*R/S*)-**1** inside NaY-MB, compared to only 11% ee in CDCl₃ solvent (entry 1). The optical antipodes (*R* and *S*) at the C4 position of the oxazolidinone chiral auxiliary gave the opposite enantiomer of MDB (entries 3 and 4) with nearly the

Scheme 1. The Enantioselective Formation of Methyl-desoxybenzoin (MDB) in the Photooxidation of the Enecarbamates *Z/E*-**1** Inside Methylene-Blue-Exchanged MY Zeolites
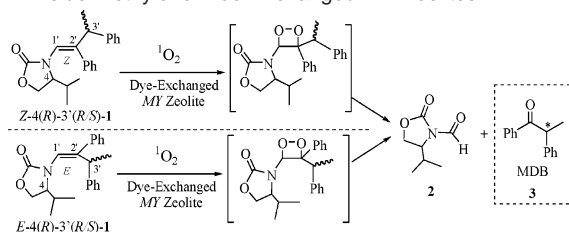

Table 1. Enantioselective Photooxygenation of *Z/E*-**1** Inside Zeolite

medium[a]	enecarbamate[b]	*hν* (time, min)	% convn[c]	% mass balance[c,d]	MDB-**3** % ee[e]
CDCl₃	*Z*-4(*S*)-3′(*R/S*)	20	47	96	11(*S*)
CDCl₃	*Z*-4(*R*)-3′(*R/S*)	20	49	94	27(*R*)
NaY-MB	*Z*-4(*S*)-3′(*R/S*)	10	41	86	80(*R*)
NaY-MB	*Z*-4(*R*)-3′(*R/S*)	10	49	89	71(*S*)
CDCl₃	*E*-4(*S*)-3′(*R/S*)	20	50	95	40(*S*)
CDCl₃	*E*-4(*R*)-3′(*R/S*)	20	47	92	55(*R*)
NaY-MB	*E*-4(*S*)-3′(*R/S*)	10	31	75	62(*S*)
NaY-MB	*E*-4(*R*)-3′(*R/S*)	10	33	71	63(*R*)

[a] Entries 3, 4, 7, and 8 are methylene-blue-exchanged MY zeolite, prepared as reported in ref 8; the methylene blue loading is one molecule per 150 supercages. [b] The enecarbamates **1** were loaded as a 50:50 mixture of 3′(*R/S*) diastereomers, one molecule per 15 supercages (low loading level of enecarbamates ∼3 mg was kept to establish the concept. Higher loading levels (gram scale, possible in preparative scale irradiations)).[13] [c] Conversion and mass balance were determined by using 4,4′-di-*tert*-butylbiphenyl as calibration standard on an achiral stationary phase (Varian GC 3900; Varian Factor-4 VG-1ms column); values are averages of three runs, the error is within ±5%. [d] The mass balance without irradiation (thermal control) in NaY is 90% for *Z*-**1** and 83% for *E*-**1**. [e] Analyzed by GC on a chiral stationary phase (Varian GC 3900; Varian CP-Chirasil-DEX CB); values are within ±5% error.

same extent of asymmetric induction, indication that the system is well behaved inside zeolites.

The time-dependent irradiation of *Z*-4(*R*)-3′(*R/S*)-**1** inside NaY-MB showed that the enantioselectivity was independent, but the mass balance was dependent on the irradiation time (cf. Table S-1, ref 10). High mass balance was observed for short irradiation times (<10 min), but on prolonged irradiation, the mass balance decreased, presumably due to side reactions.[10,11]

To investigate the influence of the *Z/E* alkene geometry, the corresponding *E*-**1** isomer was examined, since in solution[9] (entries 5 and 6, Table 1), it gave a higher enantioselectivity than the *Z*-**1** isomer. Photooxygenation of *E*-4(*R*)-3′(*R/S*)-**1** within NaY-MB gave 63% ee *R*-MDB (entry 8); as expected, the *E*-4(*S*)-3′(*R/S*) dia-

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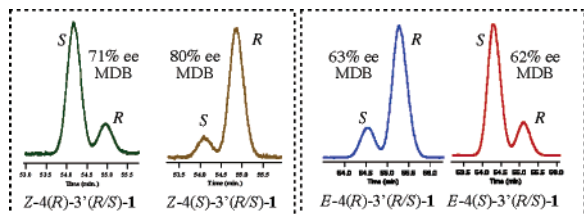[§] University of Puerto Rico and Universität Würzburg.

Figure 1. GC traces of the methyldesoxybenzoin (MDB) product, obtained in the photooxygenation of the *Z*-**1** (left) and *E*-**1** (right) within methylene-blue-exchanged NaY zeolite.

stereomer (optical antipode at the C4 position of the oxazolidinone chiral auxiliary) gave the opposite isomer *S*-MDB (entry 7). As anticipated,[10] this shows that the presence of the chiral center at position C4 is critical for achieving the high enantioselectivity. Replacement of the isopropyl group with hydrogen at the C4 position in the oxazolidinone ring gave racemic MDB.[10]

The effect of the cation[3] in the photooxygenation of the *E/Z*-**1** was examined with the MB-exchanged LiY zeolite (LiY-MB). The same enantiomer of the MDB product, the one preferred inside NaY-MB, was enhanced within LiY-MB;[10] an ee value of 35% was determined (Figure S6; ref 10).[12] The decrease of the ee value inside LiY-MB may be due to a combination of larger available volume within the supercage[5,6] and the residual water molecules present inside LiY in view of its high charge density. (Decomposition of organic dyes at high temperatures prevents complete removal of water from dye loaded-MY zeolite.)[8a]

Our unprecedented results (Table 1, Figure 1) definitively demonstrate that the sense of the stereoselectivity in the MDB formation (*R* or *S*) depends on the configuration (4*R* or 4*S*) of the oxazolidinone chiral auxiliary, whereas the extent of asymmetric induction is controlled by the *Z/E* alkene geometry. For example, the *Z*-4(*S*)-3′(*R/S*) diastereomeric pair affords the *R*-MDB product in 80% ee, whereas the corresponding *E*-4(*S*)-3′(*R/S*)-**1** leads to *S*-MDB in 62% ee. Mechanistically more revealing is the fact that in the solution versus zeolite medium, the extent of stereocontrol is substantially more differentiated for the *Z* isomers than for the *E* isomers. Previously, we had recognized the higher stereochemical steering in the oxidation of the *E*- versus the *Z*-configured enecarbamates **1**, which presumably rests on the higher conformational flexibility of the *E* diastereomers in isotropic media.[4c,9] We suspect that the more rigid structural features of the *Z* isomer are beneficially utilized in the confined space of the zeolite to align the substrate for enhanced π-facial-selective attack by the $^1O_2$ on the C=C double bond. Such favorable alignment derives presumably from the long-range binding interaction between the cationic sites in the alkali metal ion exchanged Y zeolite and/or the carbonyl and phenyl functionalities[3] of the enecarbamate molecule, which provides sterically favored trajectories for the approach of the $^1O_2$ onto the substrate double bond inside the zeolite. As conjectured in Figure 2, only the substrate-inherent (internal) steric features determine the preferred conformation in solution, whereas external factors (most likely, the cationic interactions between the carbonyl and phenyl groups) dictate the favored conformation of the *Z* diastereomer inside the zeolite. We suspect that the chirality center at the C3′ position of the alkenyl side chain in the structures **B** and **C** plays a significant role in the stereochemical outcome of the photooxygenation. High-level computations, solid-state NMR, and IR spectroscopy will be essential to substantiate these mechanistic speculations. Effort toward this goal is underway in our laboratory. As a further demonstration of the versatility of the enecarbamate system, we have explored successfully another variable, namely solution versus zeolite media, to manipulate the efficacy of stereoselective photooxygenations.
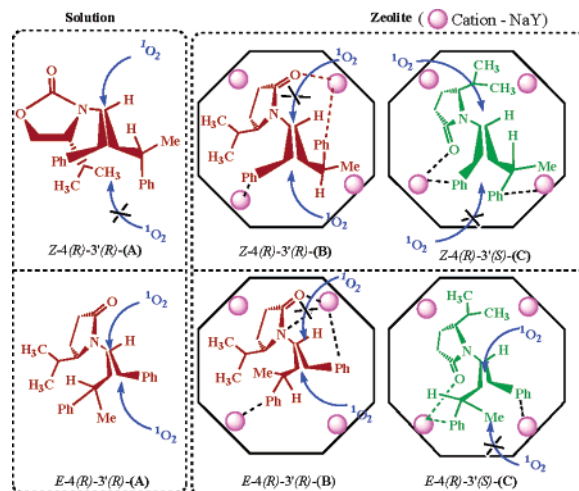

Figure 2. Transition structures proposed for the $^1O_2$ attack in the photooxygenation of the *Z/E*-**1** enecarbamates in solution [*Z/E*(**A**)] and inside MB-exchanged NaY zeolite [*Z/E*(**B,C**)].

Supporting Information Available: Experimental conditions, analysis procedures, GC traces, table for time dependence and control study with the 4-H-oxazolidinone derivative and the studies within LiY-MB. This material is available free of charge at http://pubs.acs.org.

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(10) See Supporting Information for details.
(11) Photobleaching of the singlet-oxygen sensitizers, as well as the decrease of the mass balance due to decomposition of the photoproducts, was noticed during the prolonged photooxidation of alkenes within zeolites (ref 8).
(12) Large cation-exchanged zeolites such as KY, RbY, and CsY were not examined as there was poor loading of the enecarbamates *Z/E*-**1**.
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