Remarkable Change of the Diastereoselection in the Dye-Sensitized Ene Hydroperoxidation of Chiral Alkenes by Zeolite Confinement

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ABSTRACT

The ene reaction of singlet oxygen with chiral trisubstituted alkenes bearing an alkyl and a phenyl group at the stereogenic center is erythro diastereoselective in solution and threo diastereoselective if carried out within zeolite Na−Y. The change of the diastereoselection trend by zeolite confinement is attributed to a synergism of steric effects and cation−π interactions.

Dye-exchanged zeolite Na−Y is a unique medium for carrying out large-scale singlet oxygen (1O2) ene reactions,1 with significant enhancement of product regioselectivity2 and chemoselectivity.3 The diastereoselectivity for the intrazeolite photooxygenation of chiral alkenes has received little attention so far. We have reported that 2-methyl-5-phenyl-2-hexene,4 a chiral alkene that bears a stereogenic center at the β-position with respect to the double bond, gives enhanced regioselectivity and diastereoselectivity, for the secondary allylic hydroperoxides, by zeolite confinement. In addition, intrazeolite photooxygenation of (R)-(−)−α-phellandrene5 affords enhanced regioselectivity and diastereoselectivity among the ene products, with predominant formation of (1S,5R)-5-(1-methylethyl)-2-methylidene-3-cyclohexen-1-yl hydroperoxide, a precursor of the naturally occurring trans-yabunikkeol.

The reaction of 1O2 with chiral alkenes, bearing a stereogenic center at the α-position with respect to the double bond, has been extensively studied in solution.6 For the majority of the chiral alkenes, the reaction is erythro diastereoselective. This trend was attributed to steric and electronic repulsions between the incoming oxygen and the substituents on the stereogenic carbon atom and to a preferable conformational arrangement to minimize the 1,3-allylic strain as well. Only the photooxygenation of chiral allylic alcohols and amines6 is threo diastereoselective due to an oxygen−hydroxy/amine steering effect.

In this paper, we present our results on the regioselectivity and diastereoselectivity in the photooxygenation of chiral alkenes 1−3, in solution and by confinement within zeolite Na−Y. Alkenes 1−3 possess a phenyl group and an alkyl group that may vary in size on the stereogenic carbon atom

(methyl, 1; ethyl, 2; and cyclohexyl, 3). The reaction of $^1$O$_2$ with 1–3 in dichloromethane (methylene blue as a sensitizer) is regioselective with preferential formation of the secondary allylic hydroperoxides. Among the secondary hydroperoxides, the erythro isomer prevails (Scheme 1).

The (Z)-stereochemistry for the minor tertiary allylic hydroperoxides 1a–3a was established by NOE experiments. Upon irradiation of the olefinic hydrogen absorption, the allylic hydrogen(s) of the R chain exhibited signal enhancement, indicative of a cis arrangement between the olefinic H and the R group. The predominant formation of the erythro isomers among the secondary allylic hydroperoxides ($b > c$) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$. The hydroperoxides were isomers among the secondary allylic hydroperoxides ($b > c$). The predominant formation of the erythro isomers among the secondary allylic hydroperoxides ($b > c$) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$. The hydroperoxides were isomers among the secondary allylic hydroperoxides ($b > c$). The predominant formation of the erythro isomers among the secondary allylic hydroperoxides ($b > c$) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$. The hydroperoxides were isomers among the secondary allylic hydroperoxides ($b > c$). The predominant formation of the erythro isomers among the secondary allylic hydroperoxides ($b > c$) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$. The hydroperoxides were isomers among the secondary allylic hydroperoxides ($b > c$). The predominant formation of the erythro isomers among the secondary allylic hydroperoxides ($b > c$) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$. The hydroperoxides were isomers among the secondary allylic hydroperoxides ($b > c$). The predominant formation of the erythro isomers among the secondary allylic hydroperoxides ($b > c$) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$. The hydroperoxides were isomers among the secondary allylic hydroperoxides ($b > c$). The predominant formation of the erythro isomers among the secondary allylic hydroperoxides ($b > c$) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$. The hydroperoxides were isomers among the secondary allylic hydroperoxides ($b > c$). The predominant formation of the erythro isomers among the secondary allylic hydroperoxides ($b > c$) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$. The hydroperoxides were isomers among the secondary allylic hydroperoxides ($b > c$). The predominant formation of the erythro isomers among the secondary allylic hydroperoxides ($b > c$) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$. The hydroperoxides were isomers among the secondary allylic hydroperoxides ($b > c$).

The preferential formation of the erythro isomer in the photooxygenation of 1–3 in solution can be explained considering the approach of singlet oxygen to the double bond as shown in transition state TS$_1$ of Scheme 2. The phenyl group is placed to the opposite plane of the double bond with respect to the attacking oxygen, due to unfavorable oxygen–arene electronic repulsions. In addition, for TS$_1$, a minimum 1,3-allylic strain between the tertiary allylic hydrogen and the twix allylic methyl group is in operation. For this conformation, singlet oxygen interacts to the tertiary allylic hydrogen, whose abstraction can lead to the formation of the (Z)-allylic hydroperoxides 1a–3a. Transition state TS$_1$ can also nicely explain the high degree of erythro diastereoselection in the photooxygenation of alkene 3 (erythro/threo = 82/18), where the substituents on the stereogenic carbon atom (phenyl and cyclohexyl) have similar steric demands. It is worth mentioning here that for the case of 2,4,5,5-tetramethyl-2-hexene, the diastereoselection in the singlet oxygen ene reaction arises from the size difference between a methyl and a tert-butyl group, the selectivity is lower (erythro/threo = 71/29). Transition states TS$_2$ and TS$_3$ (Scheme 2) which lead to the threo diastereomer are expected to be less stable compared to TS$_1$, due to substantial 1,3-allylic strain between the R group and the twix allylic methyl group for TS$_2$ and to unfavorable oxygen–phenyl electronic repulsion for the case of TS$_3$.

The thionin-sensitized photooxygenation of 1–3 adsorbed within zeolite Na–Y is highly regioselective, since only the secondary allylic hydroperoxides are formed, however, with an inverse diastereoselection trend (Scheme 3). The threo

<table>
<thead>
<tr>
<th>Alkene</th>
<th>a (%)</th>
<th>b (%)</th>
<th>c (%)</th>
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<tbody>
<tr>
<td>1$^{(7)}$</td>
<td>6</td>
<td>72</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>70</td>
<td>20</td>
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<td>3</td>
<td>14</td>
<td>71</td>
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diastereomer is now predominant, and the ratio of threo/erythro increases by increasing the size of the R group. For example, while the photooxygenation of 3 in solution gives a ratio of erythro/threo = 82/18, by zeolite confinement, the ratio of erythro/threo = 09/91. The intrazeolite photooxygenation experiments were accomplished as described in ref 2b. Control experiments revealed that the phenyl-substituted alkenes were completely adsorbed within Na-Y after 2-3 min of mixing, in accordance with the observation of Ramamurthy and co-workers10 for the higher adsorption ability of arylalkenes relative to simple alkenes. The ratio of the ene products was very reproducible (the error of three measurements for each substrate was ±3%), and the mass balance for all reactions was always higher than 80%. To ensure the accuracy of our intrazeolite results, the mixtures of the allylic hydroperoxides obtained from the photooxygenation of each alkene 1-3 in solution were adsorbed within the thionin/Na-Y and then irradiated under a constant flow of O2 gas for 3 min. After extraction with moistened tetrahydrofuran, it was found that the ratio of the hydroperoxides was almost the same (before and after the zeolite treatment).

The remarkable change of the diastereoselection on going from the solution to the confined environment of the zeolite can be explained by considering the electrostatic interaction of the phenyl ring to the Na+ present within the supercages.11 Most probably, due to the strong cation-phenyl interaction,12 the alkene adopts the conformation shown in Scheme 4. In that conformation, preferential attack of singlet oxygen from the less hindered top phase leads to the formation of the threo allylic hydroperoxide as the major adduct. As the size of the R group increases, the energy difference between the threo- and erythro-forming transition states is expected to increase, in favor of the threo isomer. A possible singlet oxygen–cation coordination leading preferably to the threo allylic hydroperoxide, as shown in TS4, which has a minimum 1,3-allylic strain, cannot be excluded.

To determine the ratio of the threo/erythro diastereoselection induced by abstraction of an allylic hydrogen atom from the twix methyl group or the less (twin CH3) substituted side of the double bond, we prepared stereoselectively the chiral alkenes d1-d3 labeled with deuterium at the twin position. The synthesis of the labeled alkenes was accomplished in >95% geometrical purity for the (E)-isomer following a procedure reported2b earlier by our group (see Supporting Information). The ratio of H-threo/H-erythro allylic hydroperoxides (Scheme 5) formed by abstraction of either from the more (twix CH3) or the less (twin CH3) substituted side of the double bond can be assessed by integration of the terminal olefinic hydrogen atoms in the region of 5 ppm. On the other hand, the D-threo/D-erythro ratio formed by abstraction of an allylic deuterium atom from the twin methyl group (CD3 in our case) can be assessed by integration of the diastereotopic allylic methyls.

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\text{Scheme 3. Diastereoselectivity for the Intrazeolite Photooxygenation of 1–3}
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\text{Scheme 4. Possible Phenyl–Na+ Coordination within Na–Y Directing O2 Attack}
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\text{Scheme 5. Products from the Photooxygenation of d1–d3 within Zeolite Na–Y}
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\begin{align*}
\text{Alkene} & \quad \text{twix/twin (\%)} & \quad \text{H-threo/H-erythro} & \quad \text{D-threo/D-erythro} \\
1d_3 & \quad 62/38 & \quad 48/52 & \quad 56/44 \\
2d_3 & \quad 60/40 & \quad 77/23 & \quad 78/22 \\
3d_3 & \quad 55/45 & \quad 89/11 & \quad 92/08
\end{align*}
\]


or extrapolated, taking into account the total ratio of threo/erythro hydroperoxides and the ratio H-threo/H-erythro as well.

While photooxygenation of 1d3–3d3 in solution gave the typical twin/twix ratio of approximately 5/95 (‘‘cis effect’’ selectivity13), by zeolite confinement, the twin/twix regioselectivity changes to approximately 60/40. The substantial increase in the reactivity of the twin methyl group is in accordance with earlier observations in the intrazeolite photooxygenation of trisubstituted alkenes.2b,c Also, the threo/erythro ratio either from H or from D abstraction is very similar within experimental error. This result indicates that within Na–Y, 1O2 forms preferentially a threo-peroxide intermediate oriented either toward the more or the less substituted side of the double bond.

In conclusion, we have shown that the erythro diastereo-selectivity trend in the photooxygenation of chiral alkenes bearing a phenyl and an alkyl group at the stereogenic center can be reversed to threo by confinement within zeolite Na–Y. A similar change in the π facial photoreduction of steroids14 has been observed on going from a homogeneous environment to the zeolite Na–Y confinement and has been postulated to be the result of Na+-π interactions. Intrazeolite photooxygenation studies of other chiral alkenes are in progress to explore novel and selective oxyfunctionalization pathways.

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Supporting Information Available: Full experimental details for the synthesis of 1d3–3d3 and 1H NMR spectra of 1d3–3d3 and their photooxygenation reactions in solution or within Na–Y. This material is available free of charge via the Internet at http://pubs.acs.org.

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