Intrazeolite Photooxidations of Electron-Poor Alkenes

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Abstract: The inability of the intrazeolite environment to influence the regiochemistry of addition of singlet oxygen to electron-poor olefins is reported. This divergent behavior with respect to electron-rich alkenes is rationalized with a multicomplexation model that emphasizes the importance of intrazeolite substrate-cation binding.

The plethora of natural products containing the peroxide linkage and their unique biological activity imparts a sense of urgency to the development of new stereo- and regiospecific routes to these unusual materials.¹ Singlet oxygen provides an elegant approach for the introduction of the peroxide linkage. However, despite the promise of this protocol, the small size of singlet oxygen is a significant obstacle to its implementation since many of the traditional techniques used to control stereo- and regioselectivity do not work.² Nevertheless, the recent introduction of zeolites as reaction media for photooxidations provides a potential solution for this enigma.³ These supramolecular systems have the very attractive feature of being able to impart an "enzyme-like" organization to the encapsulated activated complexes.

Previous studies in our laboratory and in other laboratories have demonstrated that intrazeolite singlet oxygen ene reactions exhibit a unique regioselectivity for hydrogen abstraction from the least substituted side and the most substituted end of trialkyl-substituted alkenes.⁴⁻⁷ This phenomenon is illustrated for (*E*)-1,1,1-trideutero-2-methyl-2-pentene in Scheme 1.8 In this case, the selectivity for hydrogen abstraction from the most substituted end increases from 56 to 94% and that for the least substituted side increases from 8 to 33% as the photooxidation is moved from CD₃CN to the interior of the zeolite NaMBY.

To provide an explanation for the unique regiochemical influence of the zeolite supercage, the model depicted in Scheme 2 was proposed.⁸ This model suggests that the zeolite-induced regiochemical change is determined to a

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Scheme 1. Comparison between the Intrazeolite and Solution Photooxidations of (E)-1,1,1-Trideutero-2-methyl-2-pentene



Scheme 2. Mechanistic Model for the Intrazeolite Photooxidations of Alkenes



large extent by the relative stabilities of the diastereomeric sodium complexed perepoxides A and B. Other factors, however, such as the charge distribution on the carbon framework and the alignment of allylic substituents induced by π -complexation of the alkene also play regiochemical-defining roles. For example, the preference for perepoxide intermediate **B** to abstract a proton from the gem-dimethyl end of the alkene reflects the preferential stabilization of the positive charge on the more substituted end of the alkene and the inaccessibility of the methylene hydrogens from the face of the olefin approached by singlet oxygen.

We report here the first examples of the intrazeolite photooxidations of electron-poor alkenes 1, 4, and 5 (Scheme 3). These alkenes do not exhibit the same dramatic regiochemical enhancements observed with electron-rich systems⁸ but do provide new insight into the unique environment of the zeolite supercage.

The photooxidations of alkenes 1, 4, and 5, and for comparison carbonyl-substituted but electron-rich alkenes, 8 and 11, were conducted in NaMBY/hexane slurries as described previously.8 Gas chromatographic

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Scheme 3. Products from Intrazeolite Photooxidations of Electron-Poor Alkenes



analysis of the hexane as a function of time prior to irradiation demonstrated that 100% of the alkenes 1, 4, and 5 intercalated into the zeolite within 15 min. 2-Methyl-2-heptene, for comparison, achieved an equilibrium distribution (80% hexane)/(20% zeolite supercage) after approximately 30 min.9 Despite the greater intrazeolite affinity of the carbonyl-containing substrates, the photooxidations were sluggish and required both extended irradiation times and larger doping levels of the sensitizer Methylene Blue (MB) ($\langle S \rangle_{MB} = 0.01$ molecules of MB per supercage) to achieve comparable percent conversions. Over-photooxidation and/or peroxide decomposition was absent in all cases. In addition, the products were extracted from the zeolite with excellent mass balances in excess of 94%. The products were identified by comparison to authentic materials, and their ratios were determined by proton NMR spectroscopy. Each product ratio represents the average of at least two independent determinations.

The intrazeolite product distributions for **1**, **4**, **5**, **8**, and **11** are compared to the solution results in Scheme 3. The allylic hydroperoxide, **6**, formed in the photooxidation of **5** is very susceptible to zeolite-catalyzed closure to the α -methylene- β -peroxylactone, **14** (Scheme 4). The extent of cyclization is a sensitive function of the residence time in the zeolite. We were unable to completely eliminate



the formation of **14** in the zeolite even at very short contact times, and as a result, the 71% of **6** reported in Scheme 3 really represents the sum of **6** and **14**. In contrast, the peroxy-lactone **14** was not formed during photooxidations of **5** in solution. This provided us with the opportunity to verify the ability of NaMBY to catalyze cyclization. An 87/13 mixture of **6** and **7** formed in solution was added to a hexane slurry of NaMBY ($\langle S \rangle_{MB} = 0.01$) and allowed to stir for 1 h. The peroxide mixture was then recovered with a high-mass balance by continuous extraction with diethyl ether to give 60% of **6**, 31% of **14**, and 9% of **7**.

The peroxy-lactones analogous to **14** were not formed at all in the intrazeolite reaction of **1** and only as a trace product during intrazeolite photooxidation of **4**. We attribute the unique ability of **6** to form substantial amounts of the peroxy-lactone to the *gem*-dimethyl (Thorpe–Ingold) effect, which promotes ring formation.¹⁰ The acid-catalyzed cyclization of a β -hydroperoxy acid similar to **6** that formed during photooxidation of tiglic acid has previously been observed.¹¹ This suggests that residual acid sites in the zeolite might be responsible for the cyclization.¹²

Alkenes 1, 4, 5, 8, and 11 exhibited a wide spectrum of behavior. The carbonyl compounds, 8 and 11, react with a dramatic change in regiochemistry as the photooxidation is moved from solution into the zeolite reminiscent of the behavior exhibited by the electron-rich trialkyl-substituted alkenes previously investigated. (Scheme 1) At the other end of the spectrum, the product distributions during photooxidations of 1 and 4 were nearly identical in solution and in the zeolite. Finally, alkene 5 exhibited intermediate behavior producing an easily measurable shift in ene regiochemistry to give an enhanced intrazeolite yield of the allylic hydroperoxide formed by hydrogen abstraction from the *gem*-dimethyl group.

To account for these observations we suggest the multicomplexation mechanism depicted in Scheme 5. In this model, we postulate that several species are in dynamic equilibrium in the zeolite supercage. The uncomplexed species, **C**, is in a solutionlike homogeneous environment floating free in the supercage void. The cation-complexed species can either be bound through their olefinic linkages, **D**, or through their carbonyl linkages, **E**.¹³ We do not include in this mechanism any substrate bound to the external surface or outside the zeolite in the hexane slurry because we have previously demonstrated that singlet oxygen does not diffuse out, and **1**, **4**, and **5** exist exclusively in the zeolite supercage.¹⁴

⁽⁹⁾ The affinity for the interior of the zeolite appears to be in part a function of the cation–substrate interaction. For leading references to cation- π interactions, see: Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324.

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⁽¹³⁾ This does not imply that complexes **D** or **E** exist at unique sites since it is well established that the cations (Na⁺) accessible for complexation in NaY occupy two distinct sites. Barthomeuf, D. *Catal. Rev.* **1996**, *38*, 521–612.



In theory substrates in all three complexation modes depicted in Scheme 5 can react with singlet oxygen. Since interconversion between these complexes is expected to be a rapid process,¹⁵ the Curtin Hammett Principle/Winstein-Holness Equation applies.¹⁶ The observed rate constant for reaction will be a weighted average as given by eq 1 where n_i is the mole fraction of the *i*th complexation mode and k_i is the rate constant for reaction of singlet oxygen with that complex. Consequently, the products derived from each complex will be a function of the population of that complex and the magnitude of k_i .

$$k_{\rm obs} = \sum_{i} n_{\rm i} k_{\rm i} \tag{1}$$

The population distribution is expected to be complex **E** > complex **D** > **C**. This conclusion is based on limited binding energy data that suggest that binding is thermodynamically favorable and that binding to a carbonyl group is more favorable than binding to an olefinic linkage. For example, the interaction of Li⁺ with ethylene (24.3 kcal/mol) is approximately 21 kcal/mol less favorable than with acetone.^{17,18}

The reaction rate constants k_2 and k_3 are expected to be smaller than k_1 for **1**, **4**, and **5** since complexation is

Scheme 6. Perepoxides from Intrazeolite Photooxidation of 5



expected to decrease the nucleophilicity of the alkene. The rate constants k_1 and k_3 for substrates **8** and **11**, which have methylene groups as insulators between the carbonyl and olefinic linkage, are expected to be comparable and both larger than k_2 .

The absence of any regiochemical influence of the zeolite during photooxidations of the very electron-poor α,β -unsaturated carbonyl compounds **1** and **4** can be rationalized using two alternative explanations. (1) All three species, **C**, **D**, and **E**, are populated, and $k_3[\mathbf{E}]$ is smaller than the dominant $k_1[\mathbf{C}]$ process despite the larger population of **E**. This analysis is based on the suggestion that reaction of **C** will give "solutionlike" regiochemistry,²⁰ while reaction of complex **D** or **E** will give "zeolite-unique"²¹ regiochemistry (vide infra). (2)¹⁹ Only complexes **D** and **E** are significantly populated with $k_3[\mathbf{E}] > k_2[\mathbf{D}]$ (i.e., $k_1[\mathbf{C}]$ is too small to have any influence); complex **D** gives zeolite-unique regiochemistry since the cation is not associated with the double bond.

On the other hand, the real and measurable regiochemical influence of the zeolite environment on the photooxidation of tetrasubstituted alkene **5** suggests that $k_2[\mathbf{D}]$ is large enough relative to $k_1[\mathbf{C}]$ and $k_3[\mathbf{E}]$ to affect the product distribution. This can be attributed to an increase in the population of complex **D** for the more nucleophilic tetrasubstituted alkene **5** in comparison to the less nucleophilic trisubstituted alkenes **1** and **4**.

Addition of singlet oxygen to **D** during photooxidation of **5** is expected to give both perepoxides **F** and **G**. (Scheme 6) Both of these perepoxides are expected to decompose by cleavage of the C_1 –O bond because the C_2 –O bond is shorter and stronger in order to minimize the ability of the carbonyl group to electrostatically destabilize the incipient positive charge on the carbon framework. This will result in enhanced hydrogen abstraction from the *gem*-dimethyl group to give the experimentally observed results (Scheme 3).

As pointed out earlier, the regiochemical effect of the zeolite environment on the photooxidations of **8** and **11** is reminiscent of the behavior of electron-rich trisubstituted alkenes where complexation to the olefinic linkage has been invoked (Scheme 3). This observation along with the preferred population of site **E** (Scheme 5) suggests

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⁽²⁰⁾ Reactions of singlet oxygen with "**C**" in the photooxidations of unfunctionalized alkyl-substituted alkenes⁸ might also be responsible for the less than perfect regiochemistries observed in their reactions.

⁽²¹⁾ We suggest that the zeolite-unique regiochemistry associated with site **E** would be an increase in geminal hydrogen abstraction to give more **2** rather than less **2** as observed. This is based upon the suggestion of Stratakis and Orfanopoulos (Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595–1615) that geminal hyrogen abstraction in α , β -unsaturated carbonyl compounds is enhanced by the incipient conjugation in the ene product. This incipient conjugation should have an even greater effect when sodium is complexed to the carbonyl group.





that **8** and **11** have enough flexibility to allow complexation of the cation to the carbonyl and simultaneous stabilization of the incipient perepoxide (Scheme 7). Examination of molecular models verifies that the length of the tether is sufficient for this bidentate complexation of sodium. It is not clear, however, if substrates **8** and **11** serve as bidentate ligands for sodium or if, as the perepoxide begins to develop, the sodium migrates to the position that ensures the most thermodynamically favorable perepoxide cation complex. Stratakis and Froudakis⁷ have suggested that prior association of sodium to the alkene is necessary to observe unique regiochemistry of intrazeolite photooxidations. Unfortunately, no experimental data allowing a choice between these alternatives are available.

These results indicate that the role of the interstitial cation of preorganizing the alkene and the relative rates of reaction at the various intrazeolite complexes are both important in determining the regiochemical outcome of these reactions.²² These results provide important information for the design of zeolitic environments to control the regio- and stereochemistry of organic reactions.

Experimental Section

Alkenes 1,²³ 5,²³ and 8^{24} were prepared and purified as reported in the literature. The allylic hydroperoxides, 2, 3, 6, and 7, were too sensitive for isolation; however, their ¹H NMR spectra are consistent with their structures and with the data reported in the literature.²³ Compounds 4 and 11 were purchased commercially and used without further purification. (*E*)-4-Hydroperoxy-4-methyl-2-pentenyl Acetate (9): ¹H NMR (CDCl₃) δ 1.36 (s, 6H), 2.09 (s, 3H), 4.59 (d, J = 6 Hz, 2H), 5.78 (dt, J = 6, 16 Hz, 1H), 5.88 (d, J = 16 Hz, 1H), 7.51(s, 1H).

3-Hydroperoxy-4-methyl-4-pentenyl Acetate (10): ¹H NMR (CDCl₃) δ 1.76 (s, 3H), 1.84–1.95 (m, 2H), 2.06 (s, 3H), 4.11–4.18 (m, 2H), 4.44 (t, J = 6 Hz, 1H), 5.05 (bs, 2H), 8.03 (s, 1H).

(*E*)-6-Hydroperoxy-6-methyl-4-hepten-2-one (12): ¹H NMR (CDCl₃) δ 1.35 (s, 6H), 2.18 (s, 3H), 3.17 (d, J = 7 Hz, 2H), 5.65 (d, J = 16 Hz, 1H), 5.80 (dt, J = 7, 16 Hz, 1H), 9.34 (s, 1H).

5-Hydroperoxy-6-methyl-6-hepten-2-one (13): ¹H NMR (CDCl₃) δ 1.66–1.77 (m, 4H), 1.79 (s, 3H), 2.13 (s, 3H), 4.46–4.44 (m, 1H), 4.97 (s, 1H), 5.00 (s, 1H), 8.84 (s, 1H).

Doping of NaY with Methylene Blue. NaY was added to distilled water containing Methylene Blue. The occupancy ($\langle S \rangle = 0.01$; number of methylene blue molecules per supercage) was calculated assuming a composition of the unit cell of Na₅₆-(AlO₂)₅₆(SiO₂)₁₃₆·253H₂O with eight supercages per unit cell. The mixture was stirred overnight in the dark. The water was decanted, and the colored zeolite was filtered and washed with water and then air-dried. The NaMBY was dried at 100–120 °C for 8–10 h at 10⁻⁴ Torr on a vacuum line and then stored in a desiccator prior to use.

Solution Photooxidations. CD₃CN or (CD₃)₂CO solutions 0.05 M in alkenes **1**, **4**, **5**, **8**, or **11** and 2×10^{-4} M in Methylene Blue were presaturated with oxygen for 15 min and then irradiated for 30 min with a 600 W tungsten–halogen lamp through 1 cm of a 12 M NaNO₂ filter solution (cutoff 400 nm) under continuous oxygen flow. The reactions were monitored by proton NMR, and the product ratios were determined by integration of appropriate peaks. The product ratios are reproducible within $\pm 5\%$.

Intrazeolite Photooxidations. A 300 mg sample of NaMBY was added to 5 mL of hexane followed by the addition of sufficient alkene to bring its concentration to between 0.012 and 0.018 M. This mixture was then stirred under a constant stream of oxygen for 15 min followed by irradiation for 60 min through a 400 nm solution cutoff filter. The reaction mixtures were then centrifuged to separate the zeolite. The hexane wet zeolite powder was then placed in a Soxhlett cup and extracted for a minimum of 2 h with diethyl ether. The product ratios were determined by proton NMR after careful removal of the diethyl ether immediately following the Soxhlett extraction.

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