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Enhanced diastereoselectivity of an ene hydroperoxidation reaction by confinement within zeolite Na-Y; a stereoisotopic study

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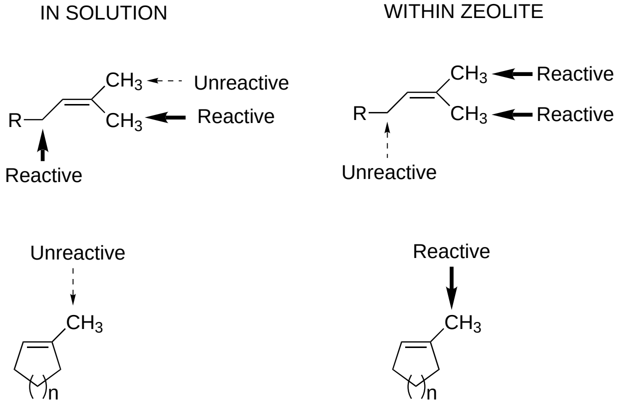
Abstract—The ene reaction of singlet oxygen with the chiral alkene 2-methyl-5-phenyl-2-hexene in solution is not regioselective and exhibits very poor diastereoselectivity (~10% d.e.). Within thionin-supported zeolite Na-Y, significant enhancement of product regioselectivity and diastereoselectivity (up to 54% d.e.) was obtained. Higher diastereoselectivity is found if the reaction occurs at the *twix* relative to the *twin* methyl group. © 2001 Elsevier Science Ltd. All rights reserved.

Dye-supported zeolites Na-Y are unique media for performing singlet oxygen ene reactions, with significant enhancement of product regioselectivity.[1] It is found that, in the intrazeolite photooxygenation of geminal dimethyl trisubstituted alkenes, formation of the new double bond in the ene adducts occurs preferentially at the methyl groups.[2] Labeling experiments have shown that the '*cis*-effect' selectivity found in solution does not operate within the zeolite.[3] Also, in the intrazeolite photooxygenation of 1-methylcycloalkenes[4] the methyl group is remarkably more reactive in contrast to the reaction in solution (Scheme 1). Despite the recent extensive studies on the regioselectivity of $^1O_2$ ene reactions within Na-Y, examination of the diastereoselectivity in the intrazeolite photooxygenation of chiral alkenes has not received any attention so far.

Due to cation–π interactions and to the confinement of the reactant alkenes within the zeolite cavities, asymmetric induction could be expected in cases where a chiral center resides at a remote position with respect to the reaction center (double bond). This aspect of enhancement of asymmetric induction by a remote stereogenic center within zeolite Na-Y has elegantly been shown by Ramamurthy and co-workers[5] in the photochemical disrotatory electrocyclic cyclization of a chiral tropolone ether.

For singlet oxygen ene reactions in solution, if a stereogenic center resides at the α- position with respect to the double bond, moderate to excellent diastereoselectivities have been reported (20–85% d.e.).[6] Alkenes that bear a stereogenic center at the β- or at a more remote position with respect to the double bond are expected to afford low or negligible diastereoselection. For example, chiral homoallylic alcohols[7] exhibit negligible diastereoselectivity upon photooxygenation in $CHCl_3$.

We report in this communication, a stereoisotopic study of the intrazeolite photooxygenation of 2-methyl-5-phenyl-2-hexene **1**, a chiral alkene that bears a stereogenic center at the β-position with respect to the double bond. Photooxygenation of **1** in solution (CH_2Cl_2/



Scheme 1. Regioselectivity trends for the $^1O_2$ ene reactions in solution and within dye-supported zeolite Na-Y.

Keywords: zeolite Na-Y; ene reactions; diastereoselection.

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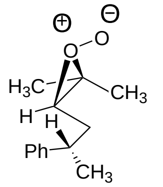
methylene blue) is, as expected, neither regioselective[8] nor significantly diastereoselective (~10% d.e.). However, reaction of **1** with $^1O_2$ within thionin-supported zeolite Na-Y affords not only mainly (94%) the regioisomeric products that result from double bond formation at the allylic methyl groups, but with significant enhancement of the diastereoselectivity compared to the reaction in solution (Scheme 2).

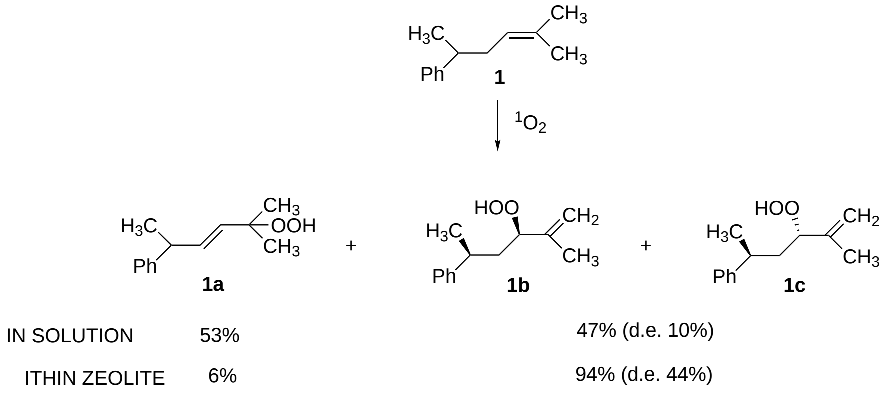
The ratio of the diastereomers **1b** and **1c** within the zeolite is 68/26 (44% d.e.), whereas in solution it is 26/21 (10% d.e.). The major diastereomer of the intrazeolite reaction is also the major product of the reaction in solution. We were unable, based on the ^{1}H NMR data, to assign the relative stereochemistry of products **1b** and **1c**. However, it is more likely that the major isomer is **1c**, taking into account the more favorable (less sterically hindered) approach of singlet oxygen to **1** to form the **pro-1c** perepoxide intermediate.



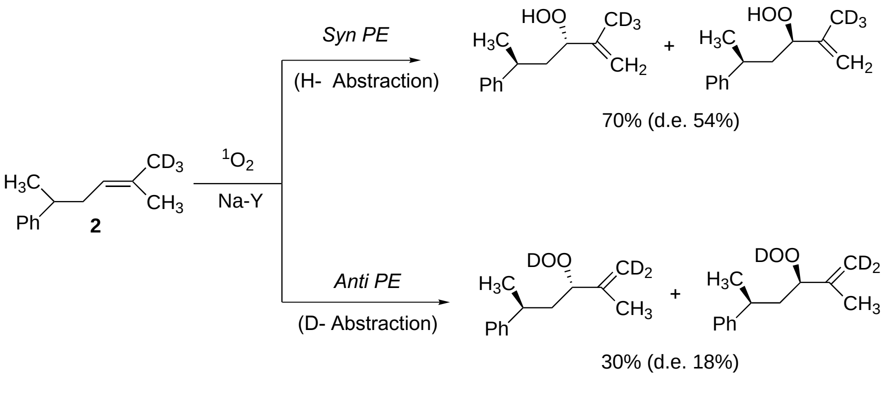
Pro-1c perepoxide

In the current experiments we used thionin-supported zeolite samples that have been vacuum dried for several hours at 120°C prior to use. The alkene loading levels were low ($n=0.2$) and the irradiation time was 3–5 min. Prolonged irradiation time selectively destroys the tertiary hydroperoxide **1a**, which is in agreement[2b,3b] with earlier observations. Generally, low loading levels ($n=0.2$) and short irradiation times (<5 min) are the optimum conditions for intrazeolite photooxidations. The percentage reactivity of the allylic hydrogens were reproducible (the error of three measurements was ± 4%). The mass balance of the reaction, as measured by using 2-phenylethanol as internal standard, was 88±4%. Additionally, by loading the mixture of the hydroperoxides produced from the photooxygenation reaction of **1** in solution, to the dye-supported Na-Y and stirring for 5 min followed by extractive workup, **1a–c** were recovered almost unchanged.

For a further study of this enhanced diastereoselectivity, we prepared[9] the specifically labeled alkene **2** in 94% geometrical purity, to determine the degree of diastereoselection induced by abstraction of an allylic hydrogen either from the more (CH_3) or the less (CD_3) substituted side of the double bond (Scheme 3). We define as *syn PE* the intermediate perepoxide where the oxygen is placed at the more substituted side of the alkene, and as *anti PE* that where the oxygen is placed on the less substituted side of the double bond. The allylic hydroperoxides from the *syn PE* and the *anti PE* intermediates were reduced to the corresponding allylic alcohols by adding triphenylphosphine, and the ^{1}H NMR was taken. The *twix/twin*[10] methyl reactivity was



Scheme 2. Photooxidation of alkene **1** in solution and within Na-Y.



Scheme 3. Photooxidation of alkene **2** within zeolite Na-Y.

found within Na-Y to be 70/30, while in solution, a typical '*cis*-effect' selectivity of *twix*/*twin* = 94/6 was found. These results are in agreement with the change of the stereoselectivity reported[3] in the solution or intrazeolite photooxygenation of other trisubstituted alkenes. Integration of the allylic methyl resonances at 1.76 (major diastereomer) and 1.69 ppm (minor diastereomer), respectively, affords the diastereomeric ratio of the products derived from the *anti PE* (D-abstraction). On the other hand, integration of the olefinic protons at 4.89 and 4.79 ppm for the major diastereomer, versus 4.87 and 4.85 ppm for the minor diastereomer, affords the diastereomeric ratio of the products formed from the *syn PE* (H- abstraction). The diastereomeric ratio from the *anti PE* intermediate was found to be 59/41 (18% d.e.), whereas from the *syn PE* intermediate it was significantly higher, 77/23 (54% d.e.). All values were corrected for the 100% geometric purity of **2**. Product distribution was also roughly estimated by GC analysis of the allylic alcohols. Using a 60 m polar capillary column and an isothermal program (110°C) the allylic alcohols formed by H or D abstraction can be slightly separated.

The enhancement of the diastereoselectivity within Na-Y could be attributed to the cation–π interactions, and to the confined environment inside the cages as well. Upon interaction of **2** to a Na^+ within the cage, the alkene probably folds in a way that both functionalities (phenyl ring and double bond) interact electrostatically to the cation. Therefore, the chirality is 'transferred' close to the reaction center (double bond) and affects significantly the distribution of the diastereomeric ene products. It is interesting that the degree of diastereoselection is higher if the reaction occurs at the *twix* (CH_3) relative to the *twin* (CD_3) methyl group. Probably, upon folding of the molecule within the cages, the stereogenic center comes closer to the more substituted side of the double bond, thus higher diastereoselectivity is found if the reaction occurs at the *twix* methyl group.

An extension of this work is currently in progress to examine whether a stereogenic center at a far more remote position could influence the diastereoselection in the photooxygenation of chiral alkenes within dye-supported zeolites.

Acknowledgements

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References

1. (a) Ramamurthy, V.; Lakshminarasimhan, P.; Grey, C. P.; Johnston, L. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2411–2418; (b) Sen, S. E.; Smith, S. M.; Sullivan, K. A. *Tetrahedron* **1999**, *55*, 12657–12698; (c) Clennan, E. L. *Tetrahedron* **2000**, *56*, 9151–9179.
2. (a) Robbins, R. J.; Ramamurthy, V. *J. Chem. Soc., Chem. Commun.* **1997**, 1071–1072; (b) Shailaja, J.; Sivaguru, J.; Robbins, R. J.; Ramamurthy, V.; Sunoj, R. B.; Chandrasekhar, J. *Tetrahedron* **2000**, *56*, 6927–6943.
3. (a) Stratakis, M.; Froudakis, G. *Org. Lett.* **2000**, *2*, 1369–1372; (b) Clennan, E. L.; Sram, J. P. *Tetrahedron* **2000**, *56*, 6945–6950.
4. Li, X.; Ramamurthy, V. *J. Am. Chem. Soc.* **1996**, *118*, 10666–10667.
5. Joy, A.; Uppili, S.; Netherthon, M. R.; Scheffer, J. R.; Ramamurthy, V. *J. Am. Chem. Soc.* **2000**, *122*, 728–729.
6. Prein, M.; Adam, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 477–494.
7. Adam, W.; Saha-Möller, C. R.; Schmid, K. S. *J. Org. Chem.* **2000**, *65*, 1431–1433.
8. Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595–15615.
9. Alkene **2** was prepared by reaction of 3-phenylpropionaldehyde with the stabilized ylide methyl(triphenylphosphoranylidene)propionate followed by sequential reduction of the ester functionality to CD_3, as described earlier.[3a]
10. For the terminology *twin* and *twix*, see: Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791–6792.