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Facial Selective Photoreduction of Steroids: Role of Zeolites

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Feasibility of regio- and stereoselective photoreactions within zeolites has been reported earlier.[1] Results presented below demonstrate that, with zeolite as a reaction medium, facial selectivity during a photoreaction can be achieved in systems that possess distinctly different faces.[2] Steroids used in this study (testosterone acetate (**1**), cholestenone (**2**), and androstenedione (**3**))[3] are small enough (width $\sim$8.8 Å and length $\sim$14 Å) to be included within faujasite-type zeolites and mesoporous silica MCM-41.[4,5] Steroids **1**−**3** were included within a zeolite by stirring a 10-mL hexane solution of the steroid ($\sim$5 mg) with about 300 mg of activated zeolite (heating in air at $\sim$500 °C) for about 12 h. The zeolite thus included with steroid was washed with hexane until the GC analysis indicated the absence of steroid in the wash. On the basis of the GC analysis, we estimate that about 3 mg of steroid was included within 300 mg of NaY (1 molecule per 2 supercages). The above zeolite sample was irradiated (450-W medium-pressure mercury lamp with Pyrex filter) as a slurry in 5 mL of hexane. Following 2−4 h of irradiation, the zeolite was extracted with a tetrahydrofuran−water (95:5) mixture, and the products were analyzed by GC.[6] Products isolated by combining five irradiations were characterized by their NMR and mass spectral data and by comparison with authentic commercial/synthetic samples.[3,7] The total isolated yield (reactant and products) under such conditions (5 × 3 mg steroid in 1.5 g of zeolite) was in the range of 80−90%.

Testosterone acetate (**1**) and cholestenone (**2**) have earlier been established to exhibit a solvent-dependent photobehavior.[8,9] The reaction that is relevant to this report is photoreduction of the enone $C{=}C$ double bond. Irradiation of **1** and **2** in 2-propanol yields reduction products ($\sim$15% conversion in 2 h) shown in Scheme 1.[10,11] In 2-propanol, addition of hydrogen to carbon-5 of the A ring occurs predominantly from the less-hindered α-face of the molecule. Reduction of the enone chromophore does not take place in hexane as solvent. An unexpected result was obtained when irradiation of **1** and **2** included in NaY−hexane slurry was carried out. Under such conditions, the main reaction observed was photoreduction and the major product was the addition from the more-hindered *β*-face of the molecule (5-*β*).[10,12] The hydrogen source for the reduction was established to be solvent hexane by using perdeuterated solvent. The role played by the cation became evident when the irradiation was conducted in cation-free high silica Y and MCM-41.[13] In these zeolites, no reduction occurred. Trace amounts of products of enone rearrangement alone were seen by GC, but the amounts were too low to be isolated and characterized.

In isotropic solution, androstenedione (**3**) has been established to react mainly from the cyclopentanone D ring.[14] As illustrated in Scheme 2, the epimerization to yield 13-α-androstenedione is the major reaction in most solvents; only in 2-propanol reduction of the cyclohexenone A ring is able to compete with the epimerization process.[15] Irradiation of **3** included in NaY gave only reduction product (Scheme 2); careful analysis at the initial stages of irradiation did not show the presence of epimer **4**. Consistent with the observations made with **1** and **2**, the reduction of **3** occurred from the more-hindered *β*-face and the photobehavior of **3** within cation-free materials (high silica Y zeolite and mesoporous MCM-41) was similar to that in hexane solution (Scheme 2).

The observations made above with steroids **1**−**3** relate both to reactivity and selectivity. Hydrogen abstraction ability of the enone chromophore is clearly enhanced within NaY. The reactivity of enone (A ring) in steroid **3** is enhanced to such an extent that products from normally active cyclopentanone (D ring)

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(1) (a) Robbins, R.; Ramamurthy, V. *J. Chem. Soc. Chem. Commun*. **1997**, 1071. (b) Li, X.; Ramamurthy, V. *J. Am. Chem. Soc*. **1996**, *118*, 10666. (c) Leibovitch, M.; Olovsson, G.; Sundarababu, G.; Ramamurthy, V.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1996**, *118*, 1219. (d) Sundarababu, G.; Leibovitch, M.; Corbin, D. R.; Scheffer, J. R.; Ramamurthy, V. *J. Chem. Soc., Chem. Commun*. **1996**, 2159.

(2) An elegant approach to control the photoaddition of olefins to steroidal enones making use of silica surface has been reported by de Mayo and coworkers: (a) Farwaha, R.; de Mayo, P.; Schauble, J. H.; Toong, Y. C. *J. Org. Chem*. **1985**, *50*, 245. (b) Dave, V.; Farwaha, R.; de Mayo, P.; Stothers, J. B. *Can. J. Chem*. **1984**, *63*, 2401.

(3) All steroids used for photochemical studies and for product identification were purchased from Steraloids Inc., Wilton, NH.

(4) For background information on zeolites, see: (a) Breck, D. W. *Zeolite Molecular Sieves: Structure, Chemistry and Use*; John Wiley and Sons: New York, 1974. (b) Dyer, A. *An Introduction to Zeolite Molecular Sieves*; John Wiley and Sons: New York, 1988. (c) Supercages of Y zeolites have an entrance diameter of $\sim$8.5 Å and a cage diameter of $\sim$12 Å.

(5) (a) Beck, J. S.; Vartuli, J. C.; Roth, W. J.; Leonowicz, M. E.; Kresge, C. T.; Schmitt, K. D.; Chu, C. T.-W.; Olson, D. H.; Sheppard, E. W.; McCullen, S. B.; Higgins, J. B.; Schlenker, J. L. *J. Am. Chem. Soc*. **1992**, *114*, 10834. (b) The sample we have used does not contain aluminum in the walls; it is a pure silica MCM-41. (c) The sample that is used in this study has a pore diameter of $\sim$41 Å.

(6) Without the use of 5% water, the products could not be completely extracted. In our previous studies, we had used THF, dichloromethane, and diethyl ether to extract the zeolite-included reactants and products. We have recently found a THF−water mixture (95:5) to be a best solvent mixture to extract the included organic molecules from NaY. Under such conditions, the recovery is >85%.

(7) (a) Nishimura, S.; Shimahara, M.; Shiota, M. *J. Org. Chem*. **1966**, *31*, 2394. (b) Tsuji, Suzuki, J.; Shiota, M.; Takahashi, I.; Nishimura, S. *J. Org. Chem*. **1980**, *45*, 2729. (c) Mancera, O.; Ringold, H. J.; Djerassi, C.; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem. Soc*. **1953**, *75*, 1286.

(8) For comprehensive reviews on enone photochemistry, see: (a) Schuster, D. I. *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 3, p 167. (b) Schuster, D. I. CRC *Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: Boca Raton, FL, 1995; p 579.

(9) For a description of the photochemistry of **1** and **2** in solution, see: (a) Chapman, O. L.; Rettig, T. A.; Griswold, A. A.; Dutton, A. I.; Fitton, P. *Tetrahedron Lett*. **1963**, 2049. (b) Nann, B.; Gravel, D.; Schorta, R.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1963**, *46*, 2473. (c) Cornell, D. G.; Avram, E.; Filipescu, N. *Steroids* **1979**, *33*, 485. (d) Shoulders, B. A.; Kwie, W. W.; Klyne, W.; Gardner, P. D. *Tetrahedron* **1965**, *21*, 2973. (e) Bellus, D.; Kearns, D. R.; Schaffner, K. *Helv. Chim. Acta* **1969**, *52*, 971.

(10) For a mechanistic study of the photoreduction of a rigid cyclohexenone, see: (a) Schuster, D. I.; Woning, J.; Kaprinidis, N. A.; Pan, Y.; Cai, B.; Barra, M.; Rhodes, C. A. *J. Am. Chem. Soc*. **1992**, *114*, 7029. (b) Chan, A. C.; Schuster, D. I. *J. Am. Chem. Soc*. **1986**, *108*, 4561.

(11) Product yields shown in Scheme 1 are based on reacted material. The yield of products did not depend on the conversion in the range of 15−75%.

(12) Both isomers (α and *β*) of the reduction process were independently synthesized and introduced into the zeolite either as pure isomers or as a mixture of known ratio. Extraction of the included materials following the procedure identical to the one employed to extract products of photoreaction established that none of the isomers were selectively retained within a zeolite. This suggests that the observed selectivity is not due to selective extraction of one of the two possible products.

(13) (a) High silica Y is a silica-rich Y zeolite. The sample used had a Si/Al ratio of 285. (b) Samples were prepared using the following report: Grobet, P. J.; Jacobs, P. A.; Beyer, H. K. *Zeolites* **1986**, *6*, 47.

(14) For photochemical studies on molecules related to androstenedione, see: (a) Wehrli, H.; Schaffner, K. *Helv. Chim. Acta* **1962**, *45*, 385. (b) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Smith, L. C. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1159. (c) Wu, Z.-Z.; Morrison, H. *J. Am. Chem. Soc*. **1992**, *114*, 4119. (d) Jiang, S. A.; Xiao, C.; Morrison, H. *J. Org. Chem*. **1996**, *61*, 7045. (e) Schaffner, K. *Tetrahedron* **1974**, *30*, 1891.

(15) Since androstenedione establishes a photoequilibrium with its epimer **4**, in all media except NaY, the yields shown in Scheme 2 includes the amount of unreacted **3** after 5 h of irradiation. For this reason, unlike in Scheme 1, the total yield does not add up to 100% in Scheme 2. In NaY, total conversion was achieved within 5 h.

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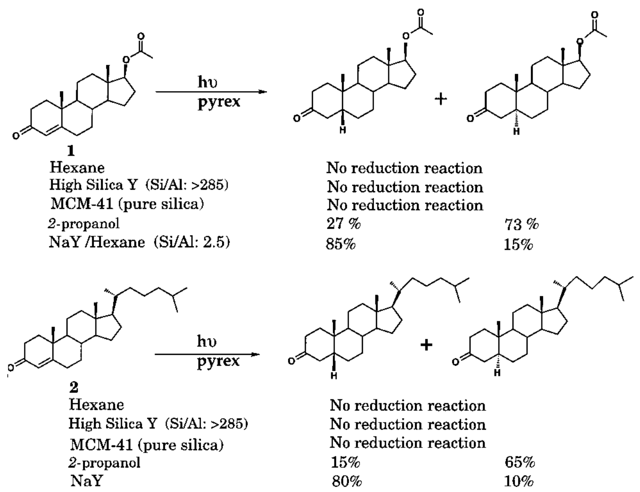
Scheme 1



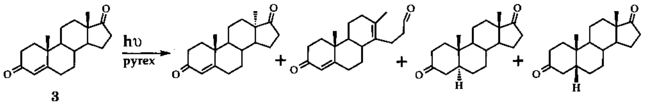
1

Hexane	No reduction reaction	
High Silica Y (Si/Al: >285)	No reduction reaction	
MCM-41 (pure silica)	No reduction reaction	
2-propanol	27 %	73 %
NaY /Hexane (Si/Al: 2.5)	85%	15%

2

Hexane	No reduction reaction	
High Silica Y (Si/Al: >285)	No reduction reaction	
MCM-41 (pure silica)	No reduction reaction	
2-propanol	15%	65%
NaY	80%	10%

Scheme 2



3

Hexane	40%	4%	–	–
2-propanol	18%	2%	14%	–
MCM-41 (Pure silica)	50%	–	–	–
High Silica Y (Si/Al: >285)	30%	–	–	–
NaY (Si/Al: ~2. 5)	–	–	25%	75%

is not seen in NaY. More importantly, there is selectivity in the reduction process. Within NaY the photoreduction occurs from the less-expected but more-hindered β-face of the steroid.

Steroids **1** and **2**, in the absence of NaY, are inert toward solvent hexane (Scheme 1). The importance of cations in the enhancement of reactivity is evident when the behavior of **1** and **2** within NaY is compared to that in cation-free materials such as high silica Y and MCM-41. No reduction of the enone chromophore takes place in the latter two zeolites (Scheme 1). Enhanced reactivity of the cyclohexenone A ring in **1** and **2**, we believe, can be understood on the basis of a change in the electronic characteristics of the lowest reactive state. Remarkable effect of changes in reactivity is seen in the case of **3**. While this molecule reacts only from the cyclopentanone D ring in hexane, no products due to reactions from the D ring are seen when it is included within NaY. This, we believe, is a reflection of the lowering of the energetics of the enone chromophore well below that of the cyclopentanone D ring. While interaction between zeolitic cation and the cyclopentanone is likely, this is not the primary cause for the enhanced reactivity of the A ring enone. Examination of model systems revealed that the reactivity of the cyclopentanone D ring is not affected within NaY.[16] This suggests to us that lowering of the $\pi\pi^*$ excited state of the A ring is responsible for the changes in reactivity of **1**−**3** included within NaY.

β-Selectivity during the reduction process can be understood on the basis of two independent models. As per one model, the selectivity is controlled by the nature of the reactive excited state; this has literature precedence.[8,10] Chan and Schuster have established in the case of 4a-methyl-4,4a,9,10-tetrahydro-2(3*H*)-phenanthrone, a molecule closely analogous to the systems investigated here, that reduction occurs stereospecifically from $\pi\pi^*$ excited triplet to yield a cis-fused bicyclic ketone. This would correspond to β-addition in our examples. On the basis of this analogy, one would suggest that the changes in the characteristics of the lowest excited triplet state of the enone chromophore discussed above is responsible for the observed selectivity. According to the second model, the facial selectivity is a result of preference for a particular mode of adsorption by steroids on the surface of a zeolite. On the basis of established interactions between aromatic molecules and cations, we suggest that the mode of adsorption will be controlled by the cation.[17] Since the cations that interact with the enone chromophore are embedded on the walls of a zeolite, the steroid will be drawn closer to the wall. Such a process would favor an adsorption mode in which the least-hindered face (α-face) of the steroid is closer to the wall of a zeolite exposing the more-hindered β-face for the reduction. A simulated model shown in Figure 1 helps to visualize the arrangement within a supercage of NaY.[18] It should be noted that despite the steroid molecule lying along a plane passing through the center of the supercage, in this mode of adsorption the steroid's olefinic functionality is available to hexane only via a narrow angle of trajectories (β-face) through the neighboring channel. It is likely that both the factors—state switching and mode of adsorption—play roles in the observed selectivity.

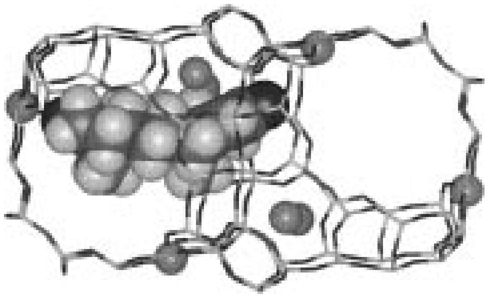


Figure 1. Androstenedione included within NaY. Dark circles represent Na^+. Steroid methyl groups face bottom of the page.

We have shown above that the photochemical behavior of steroidal enones can be altered with the use of a zeolite as a reaction medium. We recognize that the models used to rationalize the observations are rudimentary. To develop a better model that would help us predict product selectivity, we need to have a better understanding of the orientation of the steroid molecules within a zeolite. Facial selectivity discussed above and regioselectivity presented earlier[1] are controlled by a selective adsorption process steered by cations present within zeolites. Considerable amount of effort in our laboratory is directed toward understanding the cation−organic guest interactions within zeolites.

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(16) Three model ketones (3-β-acetoxy-5-androsten-17-one, 5-α-androstan-3,17-dione, and 3-α-hydroxy-5-α-androstan-17one acetate) were investigated and their behavior within zeolites was compared to that in solution. Epimerization occurred in all three ketones both in solution and within zeolites indicating that the absence of epimerization for **3** within zeolites may be related to the enhancement of the reactivity of the cyclohexenone A ring rather than to the decrease in the reactivity of the cyclopentanone D ring.

(17) (a) Czjek, M.; Fuess, H.; Vogt, T. *J. Phys. Chem.* **1991**, *95*, 5255. (b) Kirschock, C.; Fuess, H. *Zeolites* **1996**, *17*, 381. (c) Grey, C. P.; Poshmi, F. I.; Gualtieri, A. F.; Norby, P.; Hanson, J. C.; Corbin, D. R. *J. Am. Chem. Soc.* **1997**, *119*, 1981. (d) Renouprez, A. J.; Jobic, H.; Oberthur, R. C. *Zeolites* **1985**, *5*, 222. (e) Bull, L. M.; Cheetham, A. K.; Powell, B. M.; Ripmeester, J. A.; Ratcliff, C. I. *J. Am. Chem. Soc.* **1995**, *117*, 4328.

(18) Atomistic models were created for both the androstenedione and faujasite zeolite. The steroid model was constructed and optimized using the InsightII/Discover classical molecular mechanics software with the PCFF2 force field. The faujasite model was created from experimental coordinates, and sodium cations were placed at their equilibrium positions within the center of the six-membered rings. Distance−geometry calculations were performed by placing the steroid model within the space of the zeolite framework. The distance between sodium cations within a supercage is ca. 11 Å. The next nearest interaction distance is ca. 16 Å which corresponds to the sodium from one end of a supercage to the closest cations in the opposite supercage. The steroid easily spans this distance without high-energy contacts with the van der Waals envelope surrounding the zeolite framework. For the configuration illustrated in Figure 1, the distances between the associating sodium cation and carbonyl oxygen are just over 3 Å. This configuration permits a typical carbonyl−cation binding association.