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Enhanced Enantio- and Diastereoselectivities via Confinement: Photorearrangement of 2,4-Cyclohexadienones Included in Zeolites

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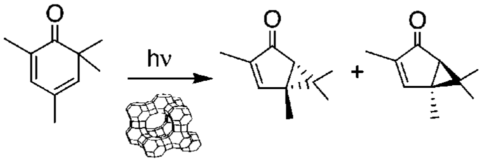
ABSTRACT



Employing zeolite as the reaction medium, it is possible to change the enantio (from achiral dienones) and diastereo (from chiral dienones) selectivities during the oxa-di-π-methane rearrangement of 2,4-cyclohexadienones.

Photochemistry of substituted 2,4-cyclohexadienones is dependent on the polarity of the reaction medium (Scheme 1).[1,2] For instance, in nonpolar solvents such as hexane the reaction occurs from the nπ^* state which results in a ketene, trappable by ethanol or diethylamine. In highly polar solvents such as trifluoroethanol, the reaction occurs from the $\pi\pi^*$ excited state and results in product **2** via the oxa-di-π-methane rearrangement.[3] We have already established that the nature of the lowest excited triplet state of aryl alkyl ketones and α,β-enones is switched to a $\pi\pi^*$ state within alkali ion exchanged Y zeolites.[4] This suggested to us that 2,4-cyclohexadienones would undergo the oxa-di-π-methane rearrangement from the $\pi\pi^*$ state within an alkali ion exchanged Y zeolite.

As expected, irradiation of compound **1a** included in zeolite NaY (hexane slurry) gave **2a** as the sole product, not surprisingly, as a 1:1 enantiomeric mixture.[5] Irradiation of **1a** in solution in the presence of optically pure ephedrine gave only a racemic product mixture. However, irradiation of a hexane slurry of compound **1a** included in dry (−)-ephedrine-modified NaY gave product **2a** enantiomerically enriched to the extent of 30 ± 3% (1 molecule of the reactant per 10 supercages and 1 molecule of the chiral inductor per 1 supercage). As expected, the optical antipode (+)-ephedrine gave the opposite enantiomer in 28 ± 3% excess. Among the various chiral inductors examined, pseudoephedrine gave respectable ee ((+) isomer 26% and (−) isomer 24%),

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[1] (a) Barton, D. H. R.; Quinkert, G. *J. Chem. Soc.* **1960**, 1. (b) Quinkert, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 211. (c) Quinkert, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1072. (d) Quinkert, G. *Pure Appl. Chem.* **1973**, *33*, 285. (e) Quinkert, G.; Bronstert, B.; Schmieder, K. R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 637.

[2] (a) Hart, H.; Warring, A. J. *Tetrahedron Lett.* **1965**, 325. (b) Collins, P. M.; Hart, H. *J. Chem. Soc. C* **1967**, 895. (c) Griffiths, J.; Hart, H. *J. Am. Chem. Soc.* **1968**, *90*, 3297. (d) Griffiths, J.; Hart, H. *J. Am. Chem. Soc.* **1968**, *90*, 5296. (e) Morris, M. R.; Warring, A. J. *J. Chem. Soc. C* **1971**, 3269.

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[5] See Supporting Information for experimental procedures, analysis conditions, sample GC and HPLC traces, and a table of data in the case of **1a** and **1b** with several chiral inductors.

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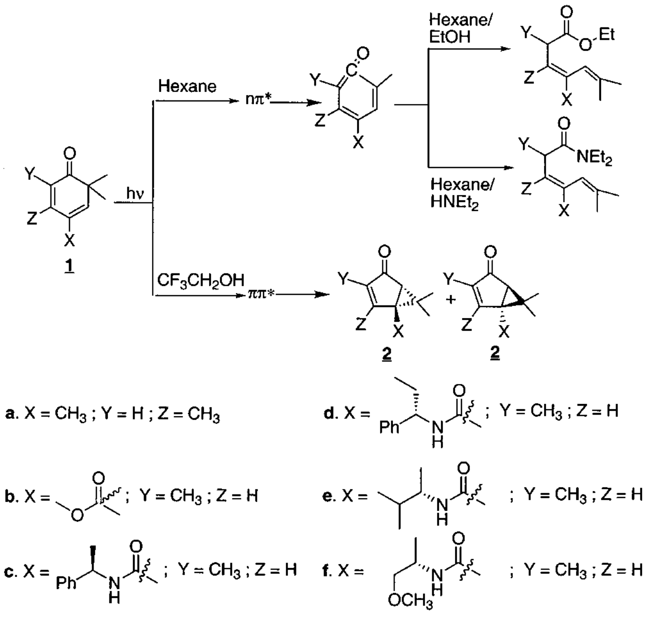
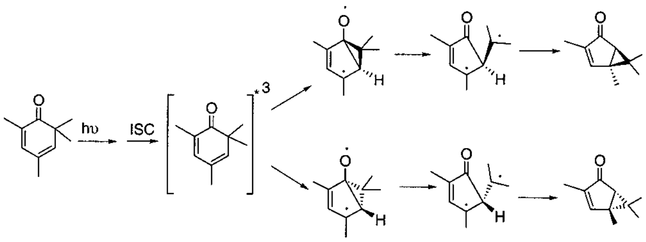
Scheme 1



whereas all others (menthol, valinol, methylbenzylamine, norephedrine, diethyltartrate) yielded the product **2** in less than 20% ee.[5] Variation of the irradiation temperature had a distinct effect on ee: with (−)-ephedrine as the chiral inductor the ee, at −55 °C it was 49% while at 100 °C it was 7%.[5] The importance of zeolite cation is revealed by the ee obtained in various (−)-ephedrine-modified alkali ion exchanged Y zeolites: LiY (0%), NaY (32%), KY 26%), RbY (5%), and CsY (0%). Consistent with the suggestion that interaction between the cation, the chiral inductor and the reactant molecules plays a crucial role, inclusion of water molecules into (−)-ephedrine-modified NaY zeolite decreased the ee to 0. Behavior similar to the dienone **1a** was observed with the methyl ester of 2,6,6-trimethylcyclohexa-2,4-diene-1-one-4-carboxylic acid **1b**. In this case, the chiral inductor camphorquinone-3-oxime gave a respectable ee within NaY (25%) while all other chiral inductors (ephedrine, isopinocamphenol, ethyl mandelate, menthol, valinol, bornylamine, norephedrine, and methylbenzylamine) gave less than 15% ee.[5] At present we do not have sufficient data to provide a model for the observed enantioselectivity except to point out that the asymmetric induction, as illustrated in Scheme 2, must be decided at the first step of the rearrangement. Considering that the ee obtained upon irradiation of **1a** in solution and as adsorbed on silica gel and Y-Sil (no cation) is zero, the observed asymmetric induction within chirally modified zeolites, although moderate, is significant. Since zeolites can include a large number of different types of molecules, with the only limitation being that the dimensions of the guest must be less than the pore dimensions of the zeolite, the above method based on zeolites as media has a potential for a long-range general applicability. Until we initiated a program on zeolite-based asymmetric induction in photochemical reactions, the most popular approaches for achieving asymmetric induction during photoreactions had been the use of crystalline materials, either the reactant alone or the reactant included in chiral hosts.[6] These methodologies are limited to crystallizable molecules. The zeolite-based approach, once standardized, is likely to compete with the above two methods.

Scheme 2



We reasoned that the observed moderate ee by chiral inductor strategy is due to lack of control in placing a chiral inductor next to a reactant molecule within the supercages of the Y zeolite. When two different molecules are included within a zeolite, the distributions are expected to follow the pattern shown in Figure 1a. The six possible distributions of guest molecules are represented by cages labeled A−F. A and C can give only racemic mixtures of products. B can induce chiral induction to a certain extent, depending on the interaction between the chiral inductor and the achiral molecule. The rest of the cages will not participate in the desired reaction, as they do not contain the achiral reactant.

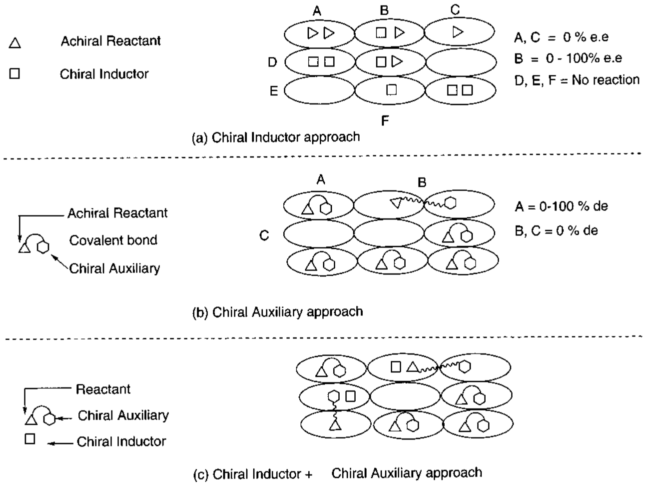


Figure 1. Probable distribution of reactants and chiral inductors within the supercages of Y zeolite.

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(6) (a) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203. (b) Leibovitch, M.; Olovsson, G.; Scheffer, J. R.; Trotter, J. *Pure Appl. Chem.* **1997**, *69*, 815. (c) Scheffer, J. R. *Can. J. Chem.* **2001**, *79*, 349. (d) F. Toda *Acc. Chem. Res.* **1995**, *28*, 480. (e) Toda, F.; Tanaka K.; Miyamoto, H. In *Molecular and Supramolecular Photochemistry*, Vol. 8; Ramamurthy V., Schanze, K. S., Eds.; Marcell Dekker: New York, 2001; p 385.

Unless a strategy to place every reactant molecule next to a chiral inductor within a zeolite is developed, high stereoselectivity is unlikely by the above chiral inductor approach. This led us to explore the chiral auxiliary approach.[7] In this approach, the chiral inductor is connected to the reactant via a covalent bond. This forces the chiral perturber and reactant center to be in close proximity most of the time (Figure 1b). Auxiliaries used were chiral amines that were covalently attached to substrates as amide linkages. Results with four chiral amides of 2,4-cyclohexadienone-5-carboxylic acid (**1c**−**f**, Scheme 1) are presented in Table 1. Similar to **1a**, only in trifluoroethanol solution, the amides **1c**−**f** rearranged to bicyclo[3.1.0] products **2c**−**f**. During solution irradiation the products were obtained in less than 5% diastereomeric excess (de). These amides when irradiated as adsorbed within achiral MY zeolites gave **2c**−**f** with respectable diastereoselectivities (Table 1).

Table 1. Photolysis of Chiral Amides **1c**−**f**: Diastereomeric Excess on the Photoproducts **2c**−**f**[a−c]

medium	% de (**1c** to **2c**)	% de (**1d** to **2d**)	% de (**1e** to **2e**)	% de (**1f** to **2f**)
TFE[d]	5 (B)	2 (B)	4 (A)	0
LiY	17 (A)	34 (A)	4 (A)	40 (A)
NaY	59 (A)	41 (A)	2 (A)	73 (A)
KY	53 (B)	34 (B)	9 (B)	1 (A)
RbY	39 (B)	13 (B)	38 (B)	25 (B)
CsY	9 (B)	8 (B)	31 (B)	20 (B)

[a] The first of the two diastereomeric peaks in the GC or HPLC trace is labled as A. [b] Loading levels of the reactants were maintained at 1 molecule per 20 supercages. [c] Reported des (±3%) are independent of conversion. [d] TFE = trifluroethanol.

As shown in Table 1 and Figure 2, the cation plays a very important role in determining the extent of diastereoselectivity as well as the nature of the diastereomer favored. For example, in the case of photoproducts from **1c**−**e**, the A isomer is favored in LiY and NaY and the B isomer in KY, RbY, and CsY (in the case of **1f**, the A isomer in LiY, NaY, and KY and the B isomer in RbY and CsY).[8] Another point to note is that the cation, which brings the maximum effect, depends on the structure of the chiral auxiliary. The importance of the cation is also evident when one recognizes that the de obtained in the case of photoproducts from **1e** on silica gel surface, Y-Sil (Y zeolite with no cation) and wet NaY is <5%. The ability to improve the diastereoselectivity from zero in solution to 73% (**1f** in NaY) using an achiral zeolite as a reaction medium is significant.

The most likely factor responsible for the change in de between solution and zeolite is the difference in conformational preference of the reactant molecule in these two media. When the dienones **1c**−**f** are included within the zeolites, the cations are expected to interact with the chromophores and thus influence the nature of the conformation of the molecule. The structures of **1c**, as calculated by RHF-3-21G (Gaussian 98),[9] in the presence and absence of Na^+ ion, are shown in Figure 3. At least two structures were identified for the Na^+−**1c** complex, one in which the Na^+ is coordinated to both the amide carbonyl and the adjacent phenyl (B) and the other in which the cation is bound to the dienone carbonyl (C). As shown in Figure 3, the former is more stable. Since the zeolite cage contains more than one cation, two cations binding to the dienone was also considered (structure D). The point that is of importance to the current discussion is the fact that the conformation of the chiral auxiliary in cation-bound forms B and D and cation-free form A is not the same. Since the cation is anchored to the surface of the zeolite, the conformational mobility of the chiral auxiliary would also be restricted. We believe that the cation−chiral auxiliary interaction resulting in a change of conformation and restriction of mobility plays a crucial role in the asymmetric induction process during the photorearrangement of dienones within zeolites. Support for this comes from the difference in de between **1e** and **1f**. While **1f** gives 73%, **1e** gives only 38%. The chiral auxiliary in **1f** would be expected to bind to the cation better than in **1e**, where there is no secondary group (OCH_3) to interact with the cation.

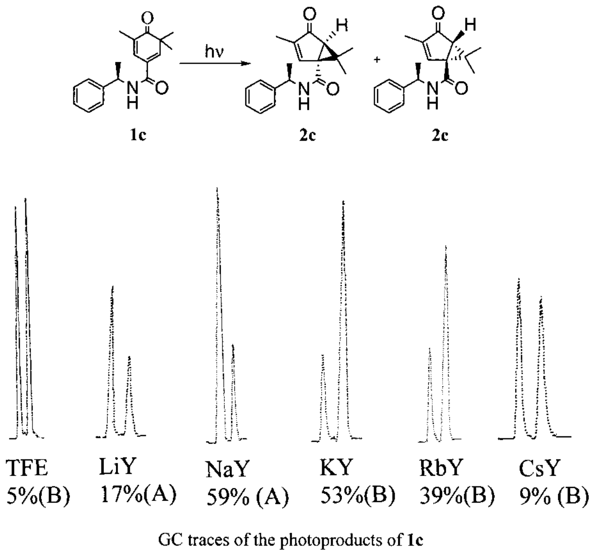

Figure 2. GC traces of photoproducts upon irradiation of **1c** included within MY zeolites: dependence of enantiomeric excess on the cation. The first diastereomeric product is labeled as A.

As shown in Figure 1b, even when the chiral inductor is covalently attached to the reactant there is a possibility that the two may remain in different cages (type B in Figure 1b). These types of cages could be the source of less than 100% de. To improve this situation, we examined the influence of chiral inductors in systems that also contain a chiral auxiliary (Figure 1c). When **1c** and **1f** were included within either

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[7] Buschmann, H.; Scharf, H. D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477.

[8] The first of the two diastereomers that elutes on the GC or HPLC is assigned as A.

[9] Gaussian 98, Revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

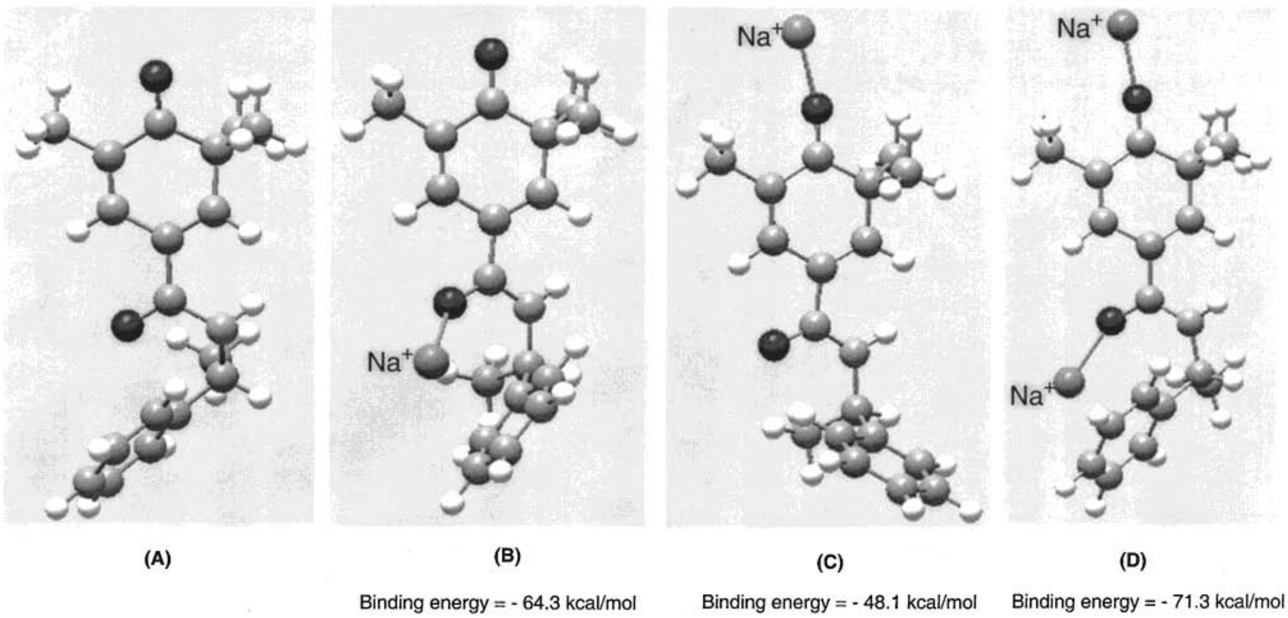

Figure 3. Structures of **1c** in the absence of Na^+ (A), **1c** complexed with one Na^+ (B) and (C), and **1c** complexed with two Na^+ (D) as calculated by RHF-3-21G (Gaussian 98).

(+)- or (−)-ephedrine-modified NaY zeolite and irradiated, the products were obtained with de lower than when they were included in achiral NaY. For example, the de in the case of **1c** changed from 56% to 3% when ephedrine was included at a loading level of 1 molecule per 3 supercages in NaY. Even the inclusion of 1 ephedrine molecule per 10 cages reduced the de to 36%. Similarly, the de in the case of **1f** decreased from 73% to 16% when ephedrine was added 1 molecule per 2 supercages. Similar observations were made with **1e** in RbY (38% to 2% with 1 ephedrine molecule per 3 supercages). The fact that the technique that worked so nicely in the case of (*S*)-tropolone 2-methylbutyl ether (de: 53% in NaY and 90% in (−)-ephedrine-modified NaY)[10] did not yield the desired result in the present case suggests that we have yet to fully understand the nature of intermolecular interactions within zeolites.

The examples presented here demonstrate convincingly that the confined space of a zeolite could serve as a useful medium to achieve asymmetric induction during a photoreaction. Consistently a higher ee or de has been obtained within zeolites than in solution. The confined space and the cations present within zeolites are believed to be responsible for the asymmetric induction within zeolites. Currently a model that can predict the outcome of asymmetric induction with zeolites as a reaction media is lacking. Experiments are underway along this direction.

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Supporting Information Available: Experimental details, separation conditions (GC and HPLC), representative HPLC and GC traces (two figures), and a table of results with chiral inductors in the case of dienones **1a** and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] (a) Joy, A.; Uppili, S.; Netherton, M. R.; Scheffer, J. R.; Ramamurthy, V. *J. Am. Chem. Soc.* **2000**, *122*, 728. (b) Joy A.; Ramamurthy, V. *Chem. Eur. J.* **2000**, *6*, 1287.