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Induced diastereoselectivity in photodecarboxylation of 2-phenylpropionic acid in faujasite zeolites

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Abstract—Irradiation of 2-phenylpropionic acid in various cation-exchanged faujasites leads to predominant formation of *dl*-2,3-diphenylbutane over the *meso*-isomer (in marked contrast to photolysis in isotropic media) and this zeolite-induced diastereoselectivity is attributed to steric and electronic factors. © 2001 Elsevier Science Ltd. All rights reserved.

2-Phenylpropionic acid (2-PPA) and its analogues are photoreactive and undergo decarboxylation on exposure to light.[1] The non-steroidal anti-inflammatory arylalkanoic acids such as ibuprofen, benoxaprofen, ketoprofen, naproxen, carprofen, suprofen and tiaprofenic acid, which are the structural analogues of 2-PPA are all labile in the presence of light and are phototoxic.[2–7] The arylethyl radical, which is the key intermediate of photodecarboxylation, is partly responsible for the photobiological activity of these drugs.[8] In order to protect these drugs from the action of light it is essential to study the photobehaviour of the simplest analogue, namely 2-PPA in detail.

The only reported study[1] on the photolysis of 2-PPA (**1**) in acetonitrile, methanol and benzene in a nitrogen atmosphere leads to the formation of mainly the *meso*- and *dl*-2,3-diphenylbutanes (**3**) and (**4**), respectively, in almost equal amounts (non-stereoselective) in addition to the formation of ethylbenzene (**2**), 1-(2-phenylethyl)-1-phenylethane (**6**) and 1-(4-phenylethyl)-1-phenylethane (**7**) in small amounts (Scheme 1). Photolysis in the presence of cyclohexane and carbon tetrachloride leads to solvent-derived products. Irradiation in solution in aerated conditions results in 100% formation of acetophenone (**5**).[1]

In the same study it was shown that the photolysis of 2-PPA in the presence of β-cyclodextrin (β-CD) results in the predominant formation of the *meso*-isomer[1] by the α,α-coupling of two long-lived α-methylbenzyl radical–CD units, in which the methyl groups are antiperiplanar. The influence of this constrained medium on the photolysis of 2-PPA prompted us to study its photochemical behaviour inside the cages of zeolites which are made up of $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$ tetrahedra resulting in a three-dimensional network of cages/channels that can accommodate organic molecules of the appropriate dimensions.

The generation of benzylic radicals in the steady state photolysis of dibenzyl ketone and its methylated derivatives inside the cavities of zeolites has been reported.[9,10] The lifetime of simple benzyl radicals generated inside the zeolite cages in the photolysis of phenylacetic acid has been studied using nanosecond diffuse reflectance spectroscopy and it has been concluded that the benzyl radical decays in a fast manner by a coupling reaction with a second benzyl radical and the mobility decreases along the series from LiY to CsY.[11]

Ghatlia and Turro[9] have reported the generation of benzyl radical and α-methylbenzyl radical (from diastereomeric dibenzyl ketone and 2,4-diphenylpentan-3-one, respectively) inside the cages of cation-exchanged faujasites X and Y. LiY and NaY have shown greater diastereoselectivity. In the case of LiY and NaY the *dl*-isomer of 2,3-diphenylbutane is the major product (the *dl*/*meso* ratio for LiY is ~1.8 and for NaY is ~1.9 and this decreases in the case of KY) compared to that of LiX and NaX. The magnitude of diastereoselectivity is a function of the substrate configuration inside the zeolite cavity and the observed zeolite-induced diastereoselection is more significant compared to other organized media such as micelles and porous glass.[9,10] It is also interesting to note that the zeolites preferentially retained the *dl*-isomer of both 2,3-diphenylbutane and 2,4-diphenylpentan-3-one.[9]

1. Results and discussion

In the present study, 2-PPA, loaded into various

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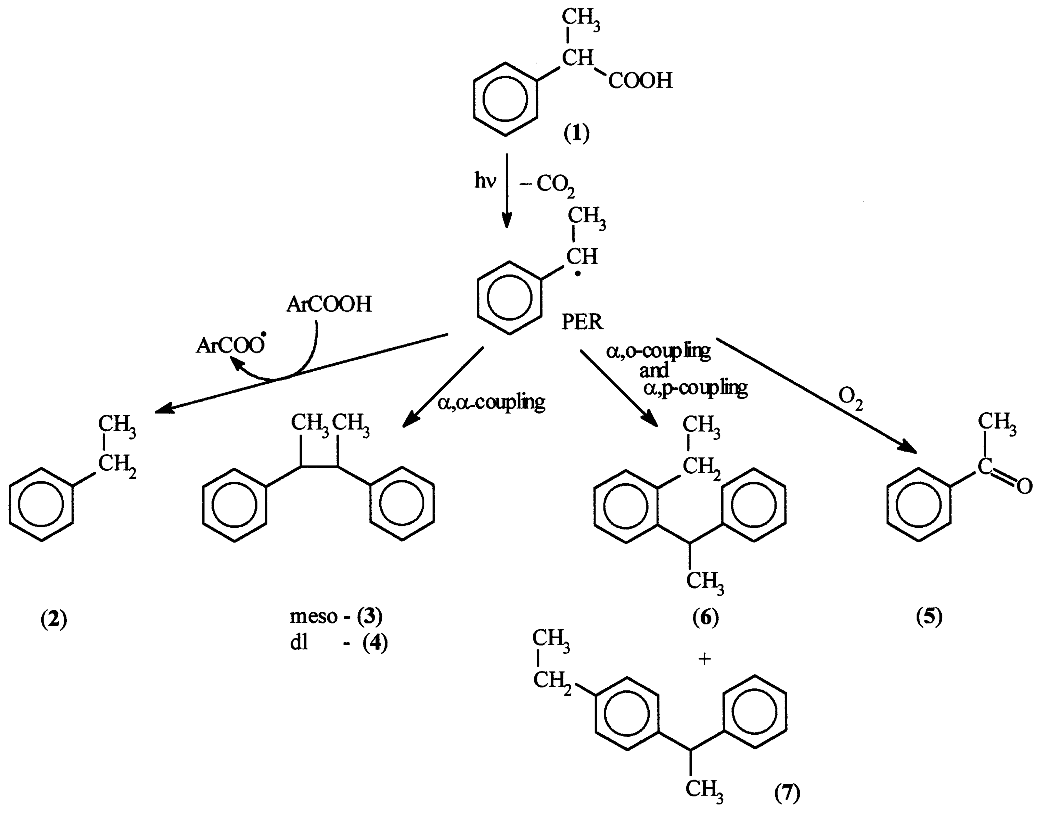

Scheme 1.

cation-exchanged Y zeolites (Si/Al ratio 2.43) was irradiated as a hexane slurry and the results are given in Table 1. In all the cation-exchanged zeolites, remarkable diastereoselectivity was observed. The *dl*-2,3-diphenylbutane was the major product with a small amount of *meso*-isomer. Ethylbenzene was also formed as one of the products and the amount of ethylbenzene increased with the increase in the cation size. A reduction in cage free volume with an increase in the cation size prevents the loading of two molecules per cage and this facilitates the unimolecular reaction pathway, namely hydrogen abstraction to yield ethylbenzene. The *ortho-* or the *para*-coupled products of the α-methylbenzyl radical were not formed in the zeolite-mediated reactions.

In the photolysis of phenylacetic acid it has been stated that the formation of toluene results from the benzyl anion formed from the decarboxylation of the carboxylate group. Likewise, here also the formation of ethylbenzene may be due to the abstraction of a proton by the α-methylbenzyl

Table 1. Product distribution (%) in the photolysis of 2-PPA (**1**) inside zeolites[a]

Medium	Loading level of 2-PPA[b] (**1**)	Conversion (%)	Ethylbenzene (**2**)	2,3-Diphenylbutane		Acetophenone (**5**)	X[c]	*dl*/*meso* ratio
				meso-(**3**)	*dl*-(**4**)			
CH_3CN	–	63	16	45	34	–	5.0	0.76
CH_3CN[d]	–	76	13	41	40	–	6.0	0.98
CH_3OH[d]	–	37	8.0	42	40	–	10	0.95
β-CD[d]	–	49	–	66	34	–	–	0.52
LiY	1.82	55	3.0	2.0	95	–	–	48
NaY	1.92	51	2.0	1.0	97	–	–	97
KY	2.02	45	5.0	3.0	92	–	–	31
RbY	1.56	39	43	5.0	52	–	–	10
CsY	1.30	36	43	5.0	52	–	–	10
NaY[e]	1.92	33	1.0	2.0	78	19	–	39
NaY[f]	1.92	47	2.0	2.0	52	44	–	26

[a] Irradiated as hexane slurry in nitrogen atm. for 6 h.; analysed by GC. Error limit ±5%. In all the experiments, retention time of 2-PPA is taken as the internal standard.

[b] Loading level refers to the number of 2-PPA molecules/cage.

[c] X: *ortho*-(**6**) and *para*-(**7**) coupled products of the α-methylbenzyl radical.

[d] Literature data[1]; (β-CD is β-cyclodextrin: irradiated in water under argon atm.).

[e] Irradiated as hexane slurry in oxygen atm.

[f] Irradiated as solid complex in oxygen atm. for 25 h.

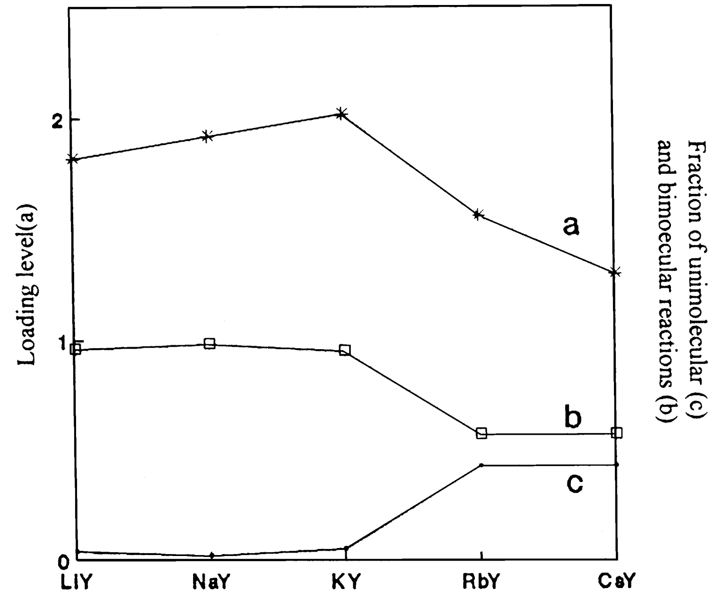

Figure 1. Dependence of unimolecular/bimolecular reactivity and loading level on zeolite size.

anion, which is likely to be formed along with the α-methylbenzyl radical.

A careful analysis of the data in Table 1 displays an interesting dependence of reactivity (unimolecular/bimolecular) on the loading level (Fig. 1). In the cases of LiY, NaY and KY about two molecules can be accommodated inside a supercage whereas in RbY and CsY the loading level decreases to 1.5 and 1.3, respectively. The mobility of the α-methylbenzyl radical inside the cages of LiY and NaY is also greater compared to RbY and CsY. This higher mobility inside the smaller LiY and NaY zeolites coupled with the higher loading level lead to a faster α,α-coupling with another radical as evident by the higher percentage conversions in LiY and NaY in relation to RbY and CsY. In the cases of larger cations, the lower loading level and decreased mobility of the α-methylbenzyl radical promotes, in addition to coupling, significant unimolecular hydrogen abstraction to give ethylbenzene and oxidation to acetophenone.

Acetophenone is the only product in the homogeneous photolysis of 2-PPA in an oxygen atmosphere due to the abstraction of oxygen by the α-methylbenzyl radical.[1] But the photolysis of 2-PPA in zeolite slurry and as a solid complex in an oxygen atmosphere gives only a minor amount of acetophenone along with considerable amounts of the *dl*-isomer (**4**). This observation is presumably due to the preassociation of the 2-PPA molecules inside the cage in such a way that the radicals are not completely free. The *dl*/*meso* ratio is very high compared to that obtained in the irradiation of 2,4-diphenylpentan-3-one (~2.0)[9] where also the same α-methylbenzyl radical is identified as the intermediate.

The predominant formation of the *dl* form of 2,3-diphenylbutane over the *meso*-isomer is explained on the basis of steric and elecronic factors. Binding to the walls of the zeolite cage takes place through the more polar carboxyl groups and this pushes the hydrocarbon part into the interior. This factor along with the higher electrostatic field present in LiY and NaY zeolites results in a hydrophobic association between the phenyl rings of adjacent 2-PPA molecules (Fig. 2). Thus, the preferred geometrical arrangement in zeolite cages is one in which the methyl groups are *anti* to each other [Fig. 2(a) and (b)]. The *syn* arrangement of methyl groups will have considerable steric hindrance [Fig. 2(c)] and hence may not be energetically favoured. Dimeric association, which is commonly encountered in carboxylic acids, may not be significant here due to:

1. the spatial constraints imposed by the cavity on the formation of the eight-membered ring in the dimer; and
2. the intrinsic polarity of the inner walls of the zeolite, which attract the carboxyl group towards them (more pronounced in a hydrocarbon solvent as in the present study).

With RbY and CsY zeolites, a combination of lower loading and decreased elecrostatic field results in a weaker preassociation (hydrophobic interaction) between the adjacent aryl rings and this leads to a decrease in diastereoselective induction.

When the results are compared with the photolysis of 2,4-diphenylbutan-3-one (which also involves the generation and subsequent coupling of a similar α-methylbenzyl radical), the induced diastereoselectivity is very high and this may be attributed to the preassociation in a preferred geometrical arrangement of the 2-PPA molecules inside the zeolite cavities (Fig. 2). The results are also remarkable in that the dramatic diastereoselectivity is achieved from a racemic mixture of 2-PPA. A closer look at Fig. 2 points to an interesting observation. Preassociation of a *d*-isomer with another *d*-isomer [Fig. 2(a)] is sterically favoured while with an *l*-isomer it leads to considerable repulsion [Fig. 2(c)]. Similarly an *l*-isomer associates only

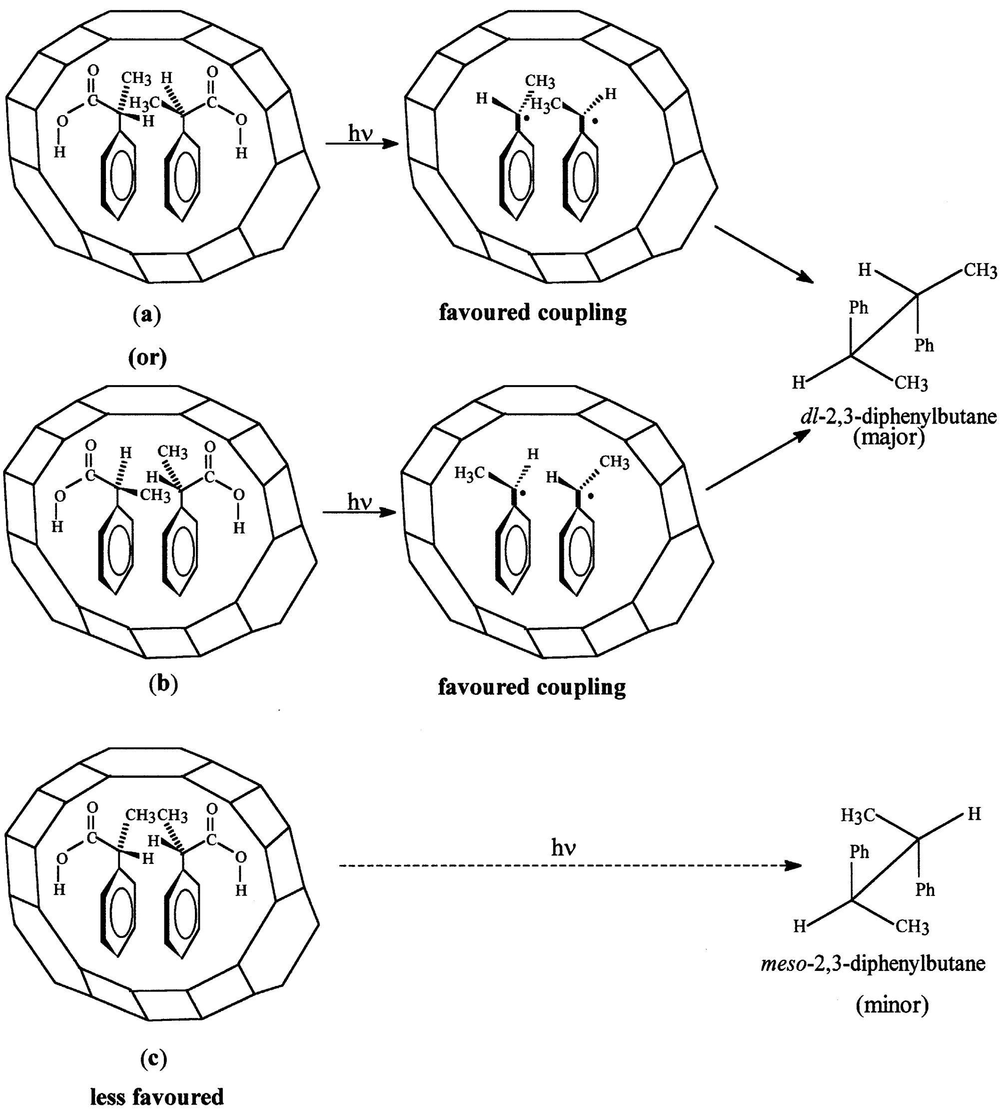

Figure 2. Packing of 2-PPA molecules inside the faujasite cage and the preferred modes of coupling of α-methylbenzyl radicals.

with another *l*-isomer [Fig. 2(b)] and this enatioselection is largely responsible for the observed zeolite-induced diastereoselectivity in decarboxylation.

It is interesting to note that while the *meso*-2,3-diphenylbutane (**3**) is the predominant product in β-cyclodextrin[1] (with a hydrophobic cavity), the corresponding *dl*-isomer (**4**) is the exclusive product in zeolite cages. This striking reversal of diasteroselectivity, in comparison to β-CD, is attributed to:

1. the polar environment inside the zeolite cage, wherein more efficient binding by the carboxyl moiety may be visualised; and
2. the larger cage size in the zeolite ensures packing of approximately two 2-PPA molecules, thereby facilitating preassociation.

Thus, it is clear that the photodecarboxylation of 2-PPA is controlled not only by the confining spaces inside the zeolite cages/cyclodextrin cavities, but also by their polarities.

The high diastereoselectivity observed with 2-PPA has prompted us to extend these studies to ibuprofen [2-(4-isobutylphenyl)propionic acid] and the methyl ester of naproxen [2-(6-methoxy-2-naphthyl)propionic acid]. These are common non-steroidal anti-inflammatory drugs and the arylethyl radicals produced from them upon irradiation are mainly responsible for their phototoxicity. In isotropic solution, cleavage products are obtained in both cases (>50% conversion). However, when irradiated in faujasites, both ibuprofen and naproxen are photostable under the conditions employed indicating that the zeolite environment offers better protection to these drugs from the action of light.

2. Experimental

2-Phenylpropionic acid was purchased from Fluka and used as such. NaY was obtained from Aldrich. The cations of interest were exchanged[12] into the NaY powder by stirring with the corresponding nitrate (10%) solution at 70°C for about 12 h. The exchange was repeated at least four times.

Each time, after exchange, the zeolite powder was washed repeatedly with distilled water and then dried. Based on an earlier literature report,[12] exchange levels are assumed to be between 62% and 84%. All these cation-exchanged zeolites were activated at 500°C for about 10 h prior to use. From the amounts of zeolite and 2-PPA taken, the loading level is calculated. (This is based on unit-cell composition of zeolite Y and hence the number of supercages present in the given amount of zeolite.)

To a solution of the substrate (50 mg) in hexane, 300 mg of the activated zeolite was added and stirred overnight. The solid complex was filtered, washed with hexane to remove the substrate present on the surface and then made into a slurry with about 5 ml of hexane which was irradiated using a 400 W medium pressure mercury vapour lamp with stirring. After completion of irradiation, the hexane portion was filtered. The zeolite was dissolved by stirring with ~4N HCl for 5–10 min and the acidic solution was extracted with diethyl ether.[9] After drying over anhydrous sodium sulphate, the ether was removed. The hexane portion and the zeolite portions were combined and analysed by gas chromatography (Netel Chromatographs) using an OV-1 (10% phenylmethylsilicone) column and flame ionization detector. In all the analyses, the retention time of the starting material was taken as an internal reference. The bulk amount of 2-PPA was irradiated in solution and the *dl* and *meso* isomers of 2,3-diphenylbutane were separated by column chromatography and were identified by their characteristic NMR spectra.[13] The NMR for *dl* δ are 1.26 (m, 6, $2CH_3$—), 3.14 (m, 2, 2CH—), 7.27 (m, 10, $2C_6H_5$) and for *meso* δ 1.05 (m, 6, $2CH_3$—), 2.80 (m, 2, 2CH—), 7.25 (m, 10, $2C_6H_5$).

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