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Dye-sensitized intrazeolite photooxygenation of 4-substituted cyclohexenes. Remote substituent effects in regioselectivity and diastereoselectivity

Manolis Stratakis,* Nikoletta Sofikiti, Constantinos Baskakis and Christos Raptis

Department of Chemistry, University of Crete, 71409 Iraklion, Greece

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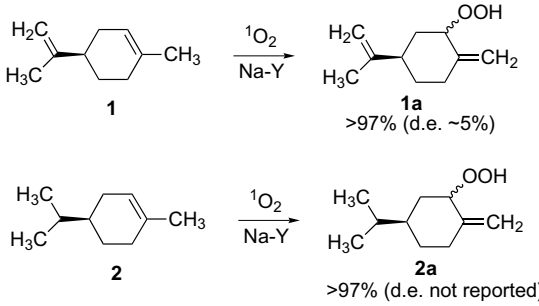
Abstract—The product distribution in the dye-sensitized photooxygenation of α-terpinyl acetate and terpinen-4-ol is quite similar in solution, however, by zeolite Y confinement, is substantially influenced by the position of the remote polar substituents relative to the reacting double bond. The intrazeolite results were rationalized in terms of Na^+-substrate and Na^+-singlet oxygen interactions.

The reaction of singlet oxygen ($^1O_2$) with alkenes with zeolite Y confinement is a promising methodology for their selective oxyfunctionalization.[1] It has been shown that the intrazeolite photooxygenation of trisubstituted alkenes is regioselective with exclusive or predominant formation of the secondary allylic hydroperoxides.[2] In addition, enhanced twin regioselectivity was found for the case of *gem*-dimethyl trisubstituted alkenes.[3] Alkenylarenes afford within NaY the ene products in a highly chemoselective manner,[4] while for chiral alkenes bearing a phenyl group on the stereogenic carbon atom, the diastereoselectivity trend changes from *threo* in solution to *erythro* within NaY.[5]

In this letter we report that polar substituents at a remote position with respect to the reacting double bond can substantially influence the photooxygenation products of 4-substituted-1-methyl-1-cyclohexenes, on going from the reaction in solution to the confined environment of zeolite Y. The thionin-sensitized intrazeolite photooxygenation of limonene (**1**) and *p*-menth-1-ene (**2**) has been reported by Ramamurthy and co-workers[6] to give exclusively the exocyclic ene allylic hydroperoxides **1a** and **2a**, respectively, in accordance with the general regioselectivity trend found in 1-methylcycloalkenes,[7] however, with negligible diastereoselectivity (Scheme 1). We examined the effect of zeolite Y confinement in the photooxygenation of the natural products terpinen-4-ol (**3**) and α-terpinyl acetate (**4**). Compounds **3**–**4** have the carbon skeleton of *p*-menth-1-ene (**2**), and possess remote polar substituents relative to the reacting double bond. Photooxygenation of **3** and **4** in solution gives quite reproducible ratios of the three regoisomeric allylic hydroperoxides, taking into account the product distribution from the photooxygenation of limonene.[8] The allylic hydroperoxides **3a**–**f** and **4a**–**f** (Table 1) were isolated by flash column chromatography using chloroform/diethyl ether = 5:1 as eluent.[9] The presence of the remote polar functionalities (–OH and –OAc, respectively) do not affect significantly, as expected, the product selectivity. However, in their intrazeolite photooxygenation, quite significant changes were



Scheme 1. Intrazeolite photooxygenation of limonene (**1**) and *p*-menth-1-ene (**2**).

Keywords: Singlet oxygen; Hydroperoxides; Diastereoselection; Zeolite NaY; Terpenes.

* Corresponding author. Tel.: +30-2810-393687; fax: +30-2810-3936-01; e-mail: stratakis@chemistry.uoc.gr

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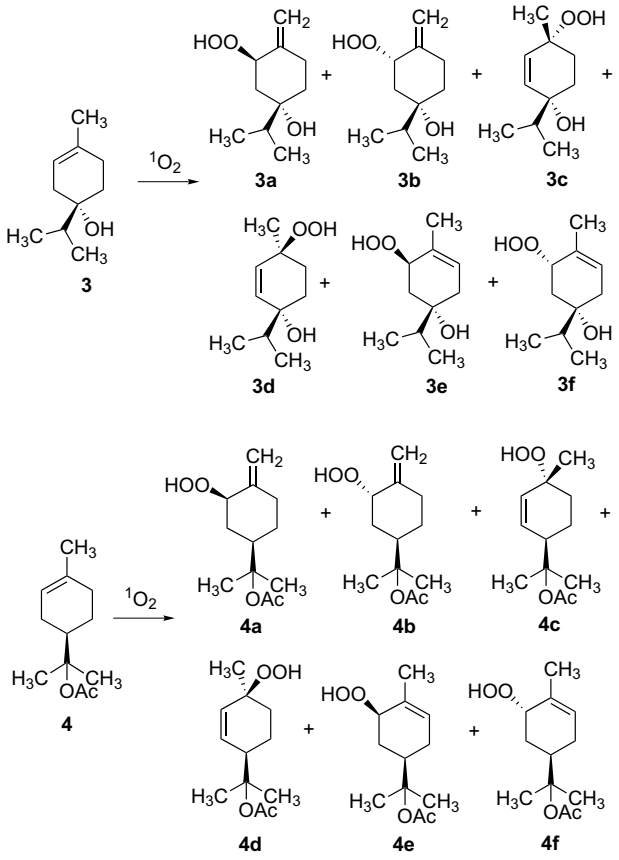
Table 1. Photooxygenation of terpinen-4-ol (**3**) and α-terpinyl acetate (**4**) in solution[a] and within NaY[b]



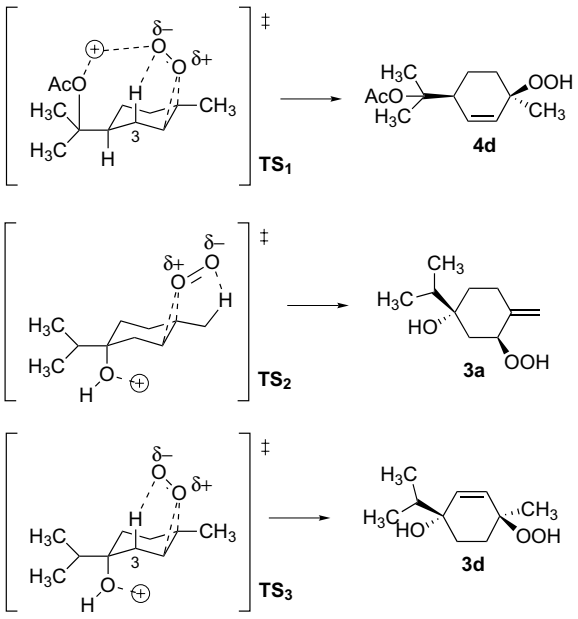
Substrate	a	b	c	d	e + f[c]
3	**67** (21)	5 (15)	9 (44)	16 (8)	3 (12)
4	5 (27)	4 (17)	2 (7)	**87** (40)	2 (9)

[a] The values in parentheses indicate the product distribution for the photooxygenation in solution (dichloromethane/methylene blue).
[b] The intrazeolite photooxygenation experiments were carried out as described in Ref. 3b.
[c] The relative stereochemistry for the minor hydroperoxides **3**–**4e** and **3**–**4f** was not assigned.

found, not only between them, but also compared to the intrazeolite photooxygenation of limonene (**1**) and *p*-menth-1-ene (**2**). The results are summarized in Table 1. The stereochemical assignment of the main products was performed as follows. DFT calculations revealed that for **3b**, the allylic hydrogen on the carbon atom bearing the hydroperoxy functionality forms, with the adjacent methylenic hydrogens, dihedral angles of 63° and 52°, respectively. Therefore, small coupling constants are expected, and this hydrogen appears as a broad triplet at 4.60 ppm with $J = 3.5$ Hz. For the diastereomer **3a**, which is more polar compared to **3b**, the analogous dihedral angles were calculated to be 55° and 172°, respectively. Thus, a large and a small coupling constant are expected, and indeed this allylic hydrogen appears as a doublet of doublets at 4.76 ppm ($J_1 = 11.5$ Hz, $J_2 = 4.0$ Hz). Compound **3c** was reduced by PPh_3 to the corresponding known *cis*-1,4-diol.[10] Finally, hydroperoxide **4c** reacted with $LiAlH_4$ in diethyl ether to afford, quantitatively, the known *trans*-*p*-menth-2-ene-1,8-diol.[11]

While the intrazeolite photooxygenation of limonene (**1**) and *p*-menth-1-ene (**2**) is highly regioselective, with exclusive formation of the ene adducts resulting from allylic hydrogen atom abstraction from the less substituted side of the endocyclic double bond, by placing an acetate functionality at the remote 8-position of the menthene carbon skeleton (α-terpinyl acetate, **4**), the reaction gives mainly one regioisomeric adduct (**4d**) in >97% diastereomeric excess, in which allylic hydrogen atom abstraction has occurred from the more substituted side of the cycloalkene. The substantial formation of the tertiary hydroperoxide **4d** for the photooxygenation of **4** within NaY is unique for an intrazeolite reaction. Generally, for the case of trisubstituted alkenes, the secondary allylic hydroperoxides are produced predominantly.[12] On the other hand, for **3**, the exocyclic ene allylic hydroperoxide is formed substantially in agreement to the intrazeolite photooxygenation results of **1** and **2**, however, in a highly diastereoselective manner (93% de).

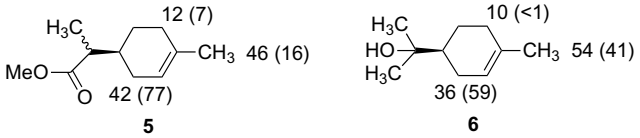
The highly regioselective and diastereoselective intrazeolite photooxygenation of **4** can be explained considering the acetate–Na^+ interaction within the zeolite cavities, which directs singlet oxygen via an electrostatic interaction towards the more substituted side of the alkene



Scheme 2. Na^+-directing regioselectivity and diastereoselection in the intrazeolite photooxygenation of α-terpinyl acetate and terpinen-4-ol.

(**TS$_1$** in Scheme 2), where it abstracts the axially oriented allylic hydrogen atom at C-3. For terpinen-4-ol (**3**), we propose that binding of the Na^+ to the hydroxy functionality places the cation on the one diastereotopic face of the double bond, thus shielding oxygen attack from that face (Scheme 2). Therefore, $^1O_2$ attacks from the opposite face, mainly oriented towards the less substituted side of the alkene (**TS$_2$**), to give the allylic hydroperoxide **3a** in 67% relative yield. A similar diastereoselectivity trend has been reported by us, in the intrazeolite photooxygenation of (*R*)-(−)-α-phellandrene.[13] This 'cation-shielding' assumption for the intrazeolite photooxygenation of **3** is supported by the fact that the tertiary hydroperoxide **3d** (**TS$_3$**, Scheme 2) is formed predominantly over its diastereomer **3c**. By contrast, the predominant formation of **3c** over **3d** in solution could be attributed to a $^1O_2$–hydroxyl steering effect.[14]

Photooxygenation of substrates **5** and **6** (α-terpineol)[15] supported the intrazeolite regioselectivity results for the case of **4** (Scheme 3). While in solution, the typical regiochemical outcome was found as in the case of **1**–**4**, by zeolite confinement the tertiary allylic hydroperoxides were formed in 77% and 59% relative yield, respectively. This regioselectivity trend is again consistent with cation binding to the ester or hydroxy functionality, which directs $^1O_2$ attack towards the more substituted side of the double bond, as proposed in **TS$_1$** of Scheme 2 to form the tertiary allylic hydroperoxide. The moderate selectivity in the case of **6** (59%), might be attributed to a less efficient cation–$^1O_2$ interaction within NaY, since the binding site of Na^+ to α-terpineol is different compared to **4** or **5**.



Scheme 3. Regioselectivity in the photooxygenation of **5** and **6** (the values in parentheses indicate the relative reactivity for allylic hydrogen atom abstraction within NaY).

In conclusion, we have shown that remote polar substituents with respect to the reacting double bond can substantially affect the product selectivity in the intrazeolite photooxygenation of *p*-menth-1-ene type compounds. In addition, we have presented the first examples of the predominant formation of tertiary allylic hydroperoxides in the photooxygenation of trisubstituted alkenes by zeolite confinement.

Acknowledgements

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9. Selected NMR data for the main allylic hydroperoxides in $CDCl_3$. Compound **3a** ^1H NMR: 4.95 (br s, 1H), 4.87 (br s, 1H), 4.76 (dd, 1H, $J_1 = 11.5$ Hz, $J_2 = 4.0$ Hz), 2.45 (dt, 1H, $J_1 = 13.0$ Hz, $J_2 = 4.0$ Hz), 2.27 (td, 1H, $J_1 = 13.0$ Hz, $J_2 = 4.0$ Hz), 2.13 (ddd, 1H, $J_1 = 10$ Hz, $J_2 = 5.0$ Hz, $J_3 = 2.5$ Hz), 1.65 (m, 2H), 1.48 (m, 2H), 0.94 (d, 3H, $J = 7.0$ Hz), 0.93 (d, 3H, $J = 7.0$ Hz). ^{13}C NMR: 146.92, 105.13, 82.82, 75.56, 39.57, 38.28, 35.11, 29.57, 16.78, 16.76. Compound **3b** ^1H NMR: 5.07 (br s, 1H), 5.04 (br s, 1H), 4.60 (br t, 1H, $J = 3.5$ Hz), 2.61 (m, 1H), 2.20 (m, 2H), 1.46–1.85 (m, 4H), 0.93 (d, 3H, $J = 7.0$ Hz), 0.92 (d, 3H, $J = 7.0$ Hz). ^{13}C NMR: 144.96, 114.59, 86.18, 72.84, 37.83, 37.34, 35.32, 25.85, 16.92, 16.79. Compound **3c** ^1H NMR: 5.82 (d, 1H, $J = 10.0$ Hz), 5.67 (d, 1H,

$J = 10.0$ Hz), 2.09 (td, 1H, $J_1 = 13.5$ Hz, $J_2 = 3.0$ Hz), 1.96 (dt, 1H, $J_1 = 13.5$ Hz, $J_2 = 3.0$ Hz), 1.69–1.79 (m, 2H), 1.51 (td, 1H, $J_1 = 13.5$ Hz, $J_2 = 3.0$ Hz), 1.37 (s, 3H), 0.97 (d, 3H, $J = 7.0$ Hz), 0.91 (d, 3H, $J = 7.0$ Hz). ^{13}C NMR: 137.12, 130.86, 78.86, 71.74, 37.18, 28.24, 27.22, 24.42, 17.35, 16.26. Compound **3d** ^{1}H NMR: 5.77 (d, 1H, $J = 10.5$ Hz), 5.74 (d, 1H, $J = 10.5$ Hz), 2.25 (m, 2H), 1.60–1.75 (m, 3H), 1.26 (s, 3H), 0.97 (d, 3H, $J = 7.0$ Hz), 0.90 (d, 3H, $J = 7.0$ Hz). ^{13}C NMR: 134.96, 132.96, 81.48, 71.61, 36.97, 28.45, 28.20, 22.65, 17.41, 16.30. Compound **4d** ^{1}H NMR: 5.92 (d, 1H, $J = 10.0$ Hz), 5.66 (dd, 1H, $J_1 = 10.0$ Hz, $J_2 = 2.0$ Hz), 2.81 (m, 1H), 2.20 (td, 1H, $J_1 = 13.0$ Hz, $J_2 = 3.5$ Hz), 2.00 (s, 3H), 1.97 (m, 1H), 1.55–1.62 (m, 2H), 1.45 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H). ^{13}C NMR: 170.51, 133.74, 129.89, 84.40, 78.62, 44.36, 31.67, 24.81, 23.68, 23.06, 22.47, 20.09.

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15. Substrate **5** was prepared as a mixture of the diastereomers *R*,*R*/*R*,*S* ~ 2:1 Guth, H. *Helv. Chim. Acta* **1996**, *79*, 1559–1571. Compound **6** is commercially available.