Notes

Highly Diastereoselective Epoxidation of Cycloalkenols with Monoperoxyphthalic Acid in Water

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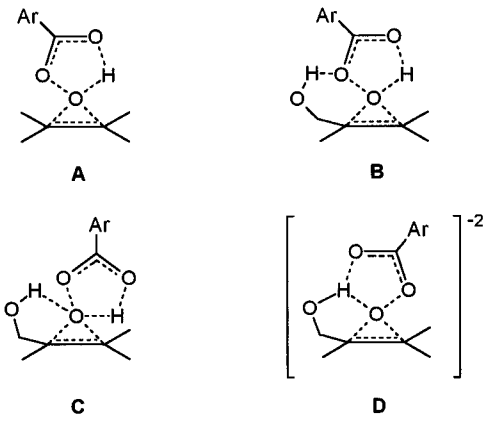
Received December 17, 1996

It is well-known[1] that carboxylic peroxy acids are useful reagents for the epoxidation of carbon−carbon double bonds and that the reaction has the characteristic of electrophilic addition of active oxygen to nucleophilic alkene.

The epoxidation of simple alkenes occurs on the less-hindered side of the double bond[2] and was first rationalized by Barlett[3] assuming a "symmetrical" transition state **A** (Scheme 1), with the intramolecular hydrogen bond of peracid acting as the driving force of the reaction.[4] We have shown[5] that a protic medium, such as water, is not an obstacle to the intramolecular association of peracid, and the reaction can be easily carried out in aqueous medium under neutral or weakly basic conditions. However a strong basic medium inhibits epoxidation because the internal hydrogen-bond structure of the peracid monomer is disrupted.[6]

The epoxidation of allylcycloalkenols by peroxy acids is stereodirected by the hydroxy group, and, in apolar solvents,[7,8] unhindered or slightly hindered five-, six-, and seven-membered compounds give prevalently (rarely exclusively) *cis*-epoxy alcohols. In protic media, such as methanol, epoxidation occurs more stereorandomly.[7a]

Scheme 1



Hembert,[9] Whitham,[10] and Sharpless[11] attribute the *syn*-stereodirecting effect of the hydroxy group to the hydrogen bond between the allylic hydroxy group of the alkenol and one of the oxygens of the peroxy group of peracid as depicted in the transition states **B** and **C**.[4]

To date the epoxidation of homoallylcycloalkenols has not been thoroughly investigated. Unlike simple alkenes, polyene alcohols react with peroxy acids in strong alkaline medium to give regioselective epoxidations.[6a,12] For example, geraniol is regioselectively epoxidized by monoperoxyphthalic acid (MPPA) at the 2,3-allylic double bond in aqueous solution of NaOH (pH 12.5 ca.) and at the more electron-rich 6,7-double bond in $NaHCO_3$ solution (pH 8.3 ca.). The remarkable regiocontrolled epoxidation in strong alkaline medium has been explained[6a] on the basis of the transition state **D** being stabilized by secondary interactions between the hydrogen of the hydroxy group and the oxygens of the peroxycarboxylate function of the peracid. This means that the hydrogen of the alcohol group is absolutely necessary for the success of the reaction,[13] and therefore, the hydroxy group of an allylic alcohol should also exert a considerable stereodirecting effect on the epoxidation of the double bond by peroxy acids in strong aqueous alkaline medium. As a continuation of our studies[5,6a,12,14] on organic reactions in aqueous medium, this paper reports the results supporting this hypothesis.

The stereochemistry of the epoxidations of a series of allylcycloalkenols and homoallylcycloalkenols with MPPA at room temperature in 0.5 M and 1 M aqueous solutions

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(1) (a) Hudlicky, M. *Oxidation in Organic Chemistry*; American Chemical Society: Washington, DC, 1990. (b) Hains, A. H. *Method for the Oxidation of Organic Compounds*; Academic Press: New York, 1985. (c) Dryuk, V. G. *Russian Chem. Rev.* **1985**, *54*, 986.

(2) Berti, G. *Top. Stereochem.* **1973**, *7*, 93.

(3) Bartlett, P. D. *Rec. Chem. Prog.* **1957**, *18*, 111.

(4) (a) A transition state involving an unsymmetrical transfer of electrophilic oxygen atom of the peracid to the carbon−carbon double bond has been suggested on the basis of kinetic deuterium isotope effect and theoretical studies.[4b−d,7a] In the epoxidation of allylic alcohols, a backside attack by the olefin along the axis of the peroxide bond[11] should be in agreement with a more extensive bond formation at the site adjacent to the heteroatom. (b) Hanzlik, R. P.; Shearer, G. O. *J. Am. Chem. Soc.* **1975**, *97*, 5231. (c) Plesnicar, B.; Tasevski. M.; Azman, A. *J. Am. Chem. Soc.* **1978**, *100*, 743. (d) Yamabe, S.; Kondon, C.; Minato; T. *J. Org. Chem.* **1996**, *61*, 616.

(5) (a) Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. *Tetrahedron Lett.* **1989**, *30*, 1427. (b) Fringuelli, F.; Pizzo, F.; Germani, R.; Savelli, G. *Org. Prep. Proced. Int.* **1989**, *21*, 757.

(6) (a) Fringuelli, F.; Germani, R.; Pizzo, F.; Santinelli, F.; Savelli, G. *J. Org. Chem.* **1992**, *57*, 1198. (b) Curci, R.; Di Prete, R. A.; Edwars, J. O.; Modena, G. *J. Org. Chem.* **1970**, *35*, 740. (c) Kavicic, R.; Plesnicar, B. *J. Org. Chem.* **1970**, *35*, 2033.

(7) (a) Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Kocovsky, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1759. (c) Ganeshpure, P. A.; Adam, W. *Synthesis* **1996**, 179. (d) Kluge, R.; Shulz, M.; Liebisch, S. *Tetrahedron* **1996**, *52*, 2957. (e) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895. (f) Hornback, J. M. *J. Org. Chem.* **1973**, 38, 4122. (g) David, F. *J. Org. Chem.* **1981**, *46*, 3512. (h) Mori, K.; Hazra, B. G.; Pfeiffer, R. J.; Gupta, A. K.; Lindgren, B. S. *Tetrahedron* **1987**, *43*, 2249. (i) Chautemps, P.; Pierre, J.-L. *Tetrahedron* **1976**, *32*, 549. (j) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159. (k) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(8) Sterically congested cycloalkenols and large-ring allylic alcohols prevalently give *trans*-epoxy alcohols.[7b]

(9) Hembert, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958.

(10) Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc.* (B) **1970**, 1374.

(11) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63.

(12) Fringuelli, F.; Pizzo, F.; Germani, R. *Synlett* **1991**, 475.

(13) Desoxygeraniol, geranyl methyl ether, cyclohexene, and 1-methoxy-2-cyclohexene are unreactive toward MPPA in NaOH solution.[6a]

(14) (a) Fringuelli, F.; Germani. R.; Pizzo, F.; Savelli, G. *Gazz. Chim. Ital.* **1989**, *119*, 249. (b) Fringuelli, F.; Pellegrino, R.; Pizzo, F. *Synth. Commun.* **1993**, *23*, 3157. (c) Fringuelli, F.; Pellegrino, R.; Piermatti, O.; Pizzo, F. *Synth. Commun.* **1994**, *24*, 2665. (d) Fringuelli, F.; Pani, G.; Piermatti, O.; Pizzo, F. *Tetrahedron* **1994**, *50*, 11499. (e) Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *43*, 1257.

S0022-3263(96)02360-2 CCC: $14.00

Table 1. Epoxidation Reactions of Cycloalkenols by Carboxylic Peroxy Acids

		Monoperoxyphtalic acid (MPPA)						Aryl Peroxyacid [a]		
Entry	Cycloalkenol	0.5 M $NaHCO_3$			1 M NaOH			Organic Solvent		
		t (h)	cis:trans	Y (%)	t (h)	cis:trans	Y (%)	t (h)	cis:trans	Y (%)
1		3	9:1	83	6	>100:1	74	24	5.2:1	80[b]
2		0.5	9:1	86	5	99:1	80	0.5	19:1	80[c]
3		3	7:1	91	18	99:1	85	-	50:1	76[d,e]
4		1	10:1	90	14	>100:1	95	0.25	>100:1	100[f]
5		1	99:1	90	15	>100:1	85	15	24:1	70[g]
6		5	1:1	80	10	1:1.6	88	24	1.6:1	95[b]
7		1	1:100	86	0.5	<1:100	90	24	<1:100	81[b]
8		2	7:1	70	2	>100:1	68	1	24:1	70[h,i]
9		0.5	1:1	89	15	>100:1	48	2	85:15	90[j,k]
10		1	1.2:1	90	16	99:1	80	2	3:1	90[l]

[a] See ref 15. [b] MCPBA, CH_2Cl_2, 0 °C; ref 7j. [c] MCPBA, CH_2Cl_2, 1−3 °C; this work. [d] CF_3CO_3H, CH_2Cl_2, −40 °C; ref 7e. [e] MPPA, CH_2Cl_2, 3 h, rt, *cis:trans* 5.6:1 (80%); this work. [f] MCPBA, CH_2Cl_2, 1−3 °C; ref 7h. [g] *p*-$NO_2C_6H_4CO_3H$, Et_2O, rt; ref 7i. [h] MPPA, CH_2Cl_2, rt, this work. [i] MCPBA, THF, 12 h, 5 °C, *cis:trans* 7:1 (40%); ref 7f,g. [j] MPPA, CH_2Cl_2, rt; this work. [k] PBA, PhH, 2.5 h, 0 °C, *cis:trans* 1.5:1 (90%); ref 7k. [l] MPPA, CH_2Cl_2, rt; this work.

of $NaHCO_3$ and NaOH, respectively, was examined. The reaction times, yields of isolated products, and the *cis*/*trans* epimer ratios of each reaction are summarized in Table 1; the data from the reactions carried out in organic solvent are also included for comparison.

The epoxidation in weak alkaline medium is usually as fast as in organic solvent with basically the same stereoselectivity, which is particularly low for homoallylcycloalkenols.

The reaction with MPPA in strong alkaline medium requires a longer reaction time but occurs with very high stereoselectivity and good yield. The *cis*-epoxy alcohol is practically the sole reaction product, except for (*Z*)-cyclooct-2-en-1-ol which gives the *trans* adduct exclusively, while cyclohept-2-en-1-ol gives it prevalently.

The five- and six-membered allylcycloalkenols (entries 1−5) are epoxidized by MPPA in 1 M NaOH solution with the same level of *syn* stereoselectivity as found[7j] when the $VO(acac)_2$-catalyzed *t*-BuOOH system is used in dry benzene at 40 °C for 24 h. The oxidation of analogous homoallylcycloalkenols (entries 8 and 9) in water proceeds with higher face-selectivity than the reaction catalyzed by transition metals in organic solvent.[7a]

MPPA in water selectively epoxidizes the (*Z*)-cyclooct-2-en-1-ol to *trans*-2,3-epoxycyclooctan-1-ol[16] similar to *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 (entry 7), but the reaction in aqueous medium is much faster especially when it is carried out under strong basic conditions.

While MCPBA in CH_2Cl_2 and the *t*-BOOH/vanadium catalyst system epoxidize[7j] cyclohept-2-en-1-ol prevalently to *cis*-2,3-epoxycycloheptan-1-ol, the MPPA in aqueous medium (entry 6) increases the amount of *trans* adduct, which is the prevalent stereoisomer when the reaction is carried out in 1 M NaOH solution.

The dissociation constants of MPPA in water at 25 °C are pK_{a1} 2.96 and pK_{a2} 8.2,[17] and the epoxidizing agent in $NaHCO_3$ solution is therefore the monocarboxylate anion of MPPA which is present in large amounts and more reactive than the corresponding bis-anion. Under these conditions, epoxidation proceeds through a **C** or **C**-like[4] transition state, and the diastereoselectivity of the reaction is similar to that found when arylperoxy acids are used in organic solvents.

In strong alkaline medium, the MPPA[18] exists largely as bis-anion, and the reaction proceeds through a **D** or **D**-like[4] transition state, with high diastereoselectivity due to the indispensable interactions of the hydrogen of the hydroxy group with the oxygens of the peroxycarboxylate function.

Molecular models and previous studies[4b,c,7a,9−11] suggest that this favorable orientation of reactants depends on various factors such as stereoelectronic requirements, the dihedral angle between the double bond and the hydroxy group,[19] and the conformation and flexibility of the ring.

cis- and *trans*-2,3-Epoxy-3-methylcyclopentan-1-ol and *cis*- and *trans*-3,4-epoxycycloheptan-1-ol were isolated for the first time, and their structure is supported by NMR data (see Experimental Section).

In summary, the epoxidation of allyl- and homoallylcycloalkenols with MPPA in strong aqueous alkaline medium occurs with high yield and high diastereoselectivity and the ease of experimental procedure should make this a useful, less polluting method in organic synthesis.

Experimental Section

MPPA was prepared from commercial magnesium monoperoxyphthalate as described.[6a,20] GLC analyses were performed with SPB-5 fused silica capillary column (30 m, 0.25 mm diameter), an "on column" injector system, a FID detector, and hydrogen as the carrier gas. GC-MS analyses were carried out on a GS-MS instrument with a 70 eV electron energy mass selective detector. Column chromatography was carried out on silica gel (0.04−0.063 mm, 230−400 mesh ASTM). ^1H- and ^{13}C-NMR spectra were recorded on a 200 MHz spectrometer in $CDCl_3$ solutions. Reaction products were identified by comparison with authentic synthetized samples. The epoxidations in organic solvent (CH_2Cl_2) were carried out by using the described procedure.[7j] The references of known epoxy alcohols are reported in Table 1. The new epoxides are described below. Elemental analyses to check the purity of the epoxides were satisfactory.

(15) Variations in the kind of peroxy acid and apolar organic solvents generally have little effect on the diastereoselectivity of the reaction.[10] The reaction time is not always optimized.

(16) The epoxidation of seven-, eight-, and nine-membered allylcycloalkenols with t-BuOOH catalyzed by $VO(acac)_2$ occurs with opposite stereoselectivity giving *cis*-2,3-epoxycycloalkan-1-ol.[7j]

(17) Jones, P.; Hagget, M. L.; Holden, D.; Robinson, P. J.; Edwards, J. O.; Bakofer, S. J.; Hayden, Y. T. *J. Chem. Soc., Perkin Trans. 2* **1989**, 443.

(18) Unlike MCPBA, MPPA is a nonhazardous chemical and a pure compound; in water it epoxidizes allylic and homoallylic alcohols with higher yields and higher selectivities.[6a] In strong alkaline medium the transition state of the epoxidation is a bis-anion or a mono-anion depending on the peroxy acid used.

(19) In the transition state, the directing effect of the OH group is more efficient when it is disposed pseudoequatorially in the allylcycloalkenols and pseudoaxially in the analogous homoallylcycloalkenols.[7a]

(20) Böhme H. *Organic Synthesis*; Wiley: New York, 1955; Coll. Vol. 3, p 619.

Epoxidation of Cycloalkenols in Water. General Procedure. Cycloalkenol (10^{-2} mol) was added at room temperature to an aqueous solution of MPPA (1.2×10^{-2} mol in 160 mL of 0.5 M $NaHCO_3$ or 2.5×10^{-2} mol in 160 mL of 1 M NaOH) and left under stirring for the time reported in Table 1. The final solution was then saturated (NaCl) and extracted (CH_2Cl_2, 4×100 mL). The extracts were washed (saturated brine), dried (Na_2SO_4), and concentrated under reduced pressure to give the crude epoxy alcohols which were purified by column chromatography (eluent *n*-hexane−diethylether 8:2). The yields of isolated products are reported in Table 1.

***cis*-2,3-Epoxy-3-methylcyclopentan-1-ol:** ^{1}H-NMR δ: 1.20−1.40 (m, 1H, C_4HH), 1.44 (s, 3H, Me), 1.50−1.70 (m, 1H, C_4HH), 1.8 (s broad, 1H, OH), 1.87−2.07 (m, 2H, C_5H_2), 3.31 (d, 1H, C_2H, $J = 1.3$ Hz), 4.27 (t broad, 1H, C_1H, $J = 7.8$ Hz). ^{13}C-NMR δ: 17.7 (Me), 28.4, 30.1 (C_4, C_5), 63.4 (C_3), 65.2 (C_2), 73.3 (C_1). Anal. Calcd for $C_6H_{10}O_2$: C, 63.12; H, 8.84. Found: C, 63.24; H, 8.86.

The *cis* configuration was confirmed by an NOE experiment. The saturation of C_1H proton frequency gives an NOE effect on the C_2H proton (6%). The saturation of C_2H proton frequency gives an NOE effect on the C_1H proton (6%) and on the protons of the Me group (8%).

***trans*-2,3-Epoxy-3-methylcyclopentan-1-ol:** ^{1}H-NMR δ: 1.20−1.40 (m, 1H, C_4HH), 1.52 (s, 3H, Me), 1.55−1.70 (m, 1H, C_4HH), 1.8 (s broad, 1H, OH), 1.90−2.05 (m, 2H, C_5H_2), 3.22 (s, 1H, C_2H), 4.32 (t broad, 1H, C_1H, $J = 5.1$ Hz). ^{13}C-NMR δ: 17.0 (Me), 28.9, 30.3 (C_4, C_5), 64.5 (C_3), 64.7 (C_2), 71.7 (C_1). Anal. Calcd for $C_6H_{10}O_2$: C, 63.12; H, 8.84. Found: C, 63.29; H, 8.80.

***cis*-3,4-Epoxycycloheptan-1-ol:** ^{1}H-NMR δ: 1.25−2.55 (m, 8H, 4 CH_2), 3.12 (d broad, 1H, OH, $J = 6.9$ Hz), 3.2 (m, 2H, C_3H, C_4H), 3.97 (q broad, 1H, C_1H, $J = 6.9$ Hz). ^{13}C-NMR δ: 17.4 (C_6), 27.8 (C_5), 34.8 (C_7), 37.7 (C_2), 54.1, 56.5 (C_3, C_4), 68.3 (C_1). Anal. Calcd for $C_7H_{12}O_2$: C, 65.58; H, 9.44. Found: C, 65.75; H, 9.41.

The *cis* configuration was confirmed by NOE experiment. The saturation of C_1H proton frequency gives a NOE effect on the C_3H and C_4H protons (7%).

***trans*-3,4-Epoxycycloheptan-1-ol:** ^{1}H-NMR δ: 1.15−2.55 (m, 9H, 4 CH_2 and OH), 3.10 (m, 2H, C_3H, C_4H), 3.80 (dddd, 1H, C_1H, $J = 9.9, 9.9, 3.0, 3.0$ Hz). ^{13}C-NMR δ: 18.6 (C_6), 27.9 (C_5), 36.8 (C_7), 39.7 (C_2), 52.8, 55.8 (C_3, C_4), 69.4 (C_1). Anal. Calcd for $C_7H_{12}O_2$: C, 65.58; H, 9.44. Found: C, 65.71; H, 9.46.

Acknowledgment. The Consiglio Nazionale delle Ricerche (CNR, Rome) and the Ministero dell'Università e della Ricerca Scientifica (MURST) are thanked for financial support.

JO9623604