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Activation of Hydrogen Peroxide through Hydrogen-Bonding Interaction with Acidic Alcohols: Epoxidation of Alkenes in Phenol

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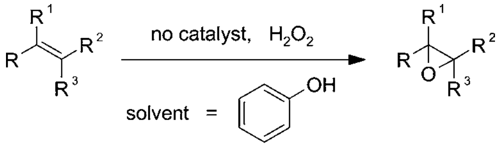
ABSTRACT



Electrophilic activation of hydrogen peroxide can be achieved in acidic alcohol solvents without the need for a metal catalyst. This concept is illustrated by the epoxidation of alkenes with H_2O_2 employing phenol as a solvent. It is proposed that intermolecular hydrogen bonding between H_2O_2 and phenol activates H_2O_2 for oxygen-atom transfer. In this interaction, the role of phenol is purely catalytic.

In the development of cost-efficient and environmentally benign oxidation processes, hydrogen peroxide holds a prominent place among other oxidants. Advantages of H_2O_2 are its low cost, high active oxygen content, high oxidation potential, and the formation of only water as a reduction product. However, a disadvantage is the high activation energy required for the oxidation of many organic compounds by H_2O_2. Therefore, catalysis is often required. Over the years, a wide range of catalysts based on metals (Ti, W, Mo, Mn, Re) or semimetals (As, Se) have been designed for the in situ activation of H_2O_2 for the epoxidation of olefins. In contrast, the number of organic, nonmetal compounds capable of activating H_2O_2 for epoxidation is rather limited, and especially catalytic cases are scarce.[1] The most prominent examples are α-halo carbonyl compounds (e.g., hexafluoroacetone), which upon reaction with H_2O_2 yield α-hydroxy hydroperoxide intermediates capable of effecting epoxidation.[2] Recently, it was shown that perfluorinated alcohol solvents such as 2,2,2-trifluoroethanol and particularly 1,1,1,3,3,3-hexafluoro-2-propanol are able to activate H_2O_2 for the epoxidation of electron-rich alkenes.[3] Moreover, significant rate enhancements were observed when classical epoxidation catalysts were employed in these "magic" fluoro alcohol solvents.[4] It was postulated that the fluoro alcohols activate H_2O_2 for oxygen-atom transfer through hydrogen bonding.

Although structurally considerably different from fluoro alcohols, phenol shows very similar physical properties, of which the high hydrogen-bond donor strength is particularly

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[1] Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499−3548.

[2] (a) Kim, L. German Patent 2 239 681, 1973. (b) Heggs, R. P.; Ganem, B. *J. Am. Chem. Soc.* **1979**, *101*, 2484−2486. (c) Ganeshpure, P. A.; Adam, W. *Synthesis* **1996**, 179−188. (d) Adam, W.; Degen, H.-G.; Saha-Möller, C. R. *J. Org. Chem.* **1999**, *64*, 1274−1277.

[3] (a) Neimann, K.; Neumann, R. *Org. Lett.* **2000**, *2*, 2861−2863. (b) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 248−250. (c) Legros, J.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *Eur. J. Org. Chem.* **2002**, 3290−3293.

[4] (a) Shryne, T. M.; Kim, L. U.S. Patent 4 024 165, 1977. (b) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Tetrahedron Lett.* **1999**, *40*, 5239−5242. (c) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 263−264. (d) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 821−822. (e) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 1305−1307. (f) ten Brink, G.-J.; Fernandes, B. C. M.; van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 224−228. (g) Berkessel, A.; Andreae, M. R. M. *Tetrahedron Lett.* **2001**, *42*, 2293−2295. (h) Iskra, J.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* **2002**, *43*, 1001−1003.

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relevant.[5] Therefore, we reasoned that under certain conditions, phenols should be capable of H_2O_2 activation. In a preliminary experiment, the oxidation of cyclooctene (5 mmol) with aqueous hydrogen peroxide (50 wt %, 5 mmol) was attempted in phenol (50 mmol) at 40 °C (Scheme 1).

Scheme 1

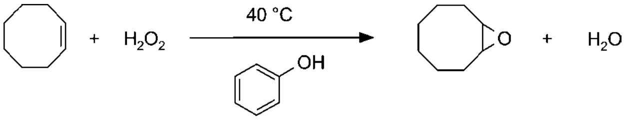


Figure 1 shows the concentration of epoxide and H_2O_2 as a function of time. After 45 h, the yield of cyclooctene oxide reached 75% (complete selectivity), while the H_2O_2 efficiency was 90%. This intriguing observation of epoxidation of alkenes promoted by phenol prompted us to investigate in greater detail the origin of this unique reactivity.[7] In addition, the present study might give better insight into the mechanism proposed for fluoro alcohol-promoted epoxidations (e.g., are the fluorine atoms essential to the catalysis?). Moreover, the use of phenol allows the study of the electronic effect of substituents on the epoxidation. From a synthetic point of view, phenol is an interesting solvent because it is available at a much lower cost than fluoro alcohols and has a high dissolving power, especially for apolar alkenes.

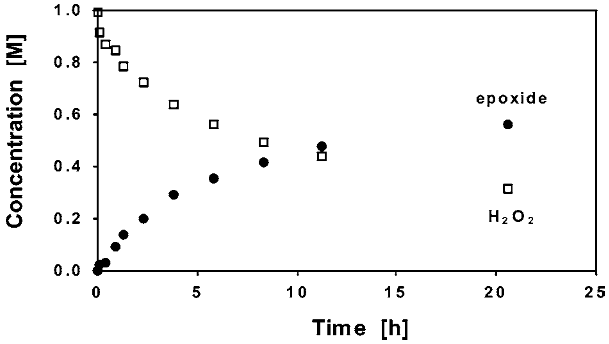
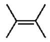
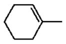
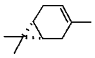
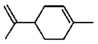
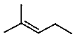
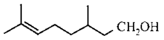
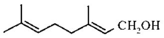
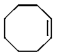
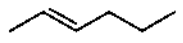
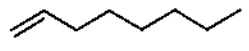


Figure 1. Plot of the concentration of epoxide (GC analysis) and H_2O_2 (iodometric titration)[6] for cyclooctene epoxidation by H_2O_2 in phenol.

To establish the essential role of phenol in the reaction, a set of control experiments was carried out. No conversion (<1%) was observed using cyclohexanol or anisole as the solvent. In benzyl alcohol, a conversion of only 5% was obtained after 24 h. Although cyclooctene is known as a reactive substrate, other alkenes could be oxidized as well (Table 1). In the oxidation of those alkenes yielding acid-sensitive epoxides, the product was mostly the epoxide, accompanied by some diol and α-hydroxy phenyl ether, arising from ring-opening of the primary epoxide product. However, higher epoxide selectivity can be achieved by buffering the reaction medium with a small amount of sodium acetate. Phosphate, borate, or carbonate bases are effective as well, proving that the added buffer is not essential to the observed activity. Moreover, the reaction is not inhibited by EDTA (5 mM), which excludes participation of metal traces.

Table 1. Epoxidation of Various Alkenes by H_2O_2 in Phenol[a]

alkene	T [°C]	t [h]	conversion [%]	selectivity [%]
	20	8	99	97
	40	22	95	84[b]
	60	12	96	95[b]
	40	22	86[c]	92[b]
	50	7	96	97
	60 60	8 2[d]	97 94	97 97
	60	8	94	97[e]
	60	12	77	89[b]
	60	22	99	99
	60	24	85	97
	60	36	25	95

[a] Reaction conditions: 5 mmol of alkene, 1 mmol of *n*-alkane (internal standard), 0.05 mmol of NaOAc, 7.5 mmol of H_2O_2 (50 wt %), 50 mmol of phenol, GC(MS) analysis.[11] [b] Diol and α-hydroxy phenyl ether were formed in 5−15%. [c] Small amounts of terminal epoxides and diepoxides were also formed. [d] *p*-Chlorophenol (50 mmol) was used. [e] 2,3-Epoxide: 6,7-epoxide = 10:90.

The intermediacy of free radicals ($O_2^{\bullet -}$, $HO_2^{\bullet}$, or $HO^{\bullet}$) or other reactive oxygen species such as $^1O_2$ is ruled out by several pieces of evidence.[8] Thus, oxidation of cyclooctene is not inhibited by the presence of 2,6-di-*tert*-butyl-*p*-cresol (50 mM), a common radical scavenger. Epoxidation of isomeric alkenes is fully stereospecific. *cis*-2-Hexene yields only *cis*-2,3-epoxyhexane, while oxidation of *trans*-2-hexene exclusively produces the *trans*-epoxide. Another indication is the absence of allylic oxidation products in the epoxidation of cyclohexene. In contrast, epoxidation via free radical intermediates also yields 2-cyclohexenyl-1-hydroperoxide,

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(5) (a) Middleton, W. J.; Lindsey, R. V., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4948−4952. (b) Filler, R.; Schure, R. M. *J. Org. Chem.* **1967**, *32*, 1217−1219. (c) Purcell, K. F.; Stikeleather, J. A.; Brunk, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 4019−4027. (d) Eberson, L.; Hartshorn, M. P.; Persson, O.; Radner, F. *Chem. Commun.* **1996**, 2105−2112.

(6) Iodometric titration was used for the determination of H_2O_2, as titration with Ce^{IV} resulted in the immediate formation of a black precipitate.

(7) Detailed literature survey revealed one report that mentions the use of phenolic compounds as cocatalysts in combination with a group Va element (e.g., As) for the epoxidation of propene with H_2O_2. In one comparative example, phenol was used in the absence of As, but only a low yield was obtained. McMullen, C. H.; Fehskens, E. E.; Plotkin, J. S. U.S. Patent 4 410 715, 1983.

2-cyclohexen-1-ol, and 2-cyclohexen-1-one. Spectroscopic evidence for the absence of radicals was obtained from ESR. The ESR spectrum of a solution of H_2O_2 (1.75 M) in phenol in the presence of the spin traps 5,5-dimethyl-1-pyrroline-*N*-oxide (80 mM) or *N*-*tert*-butyl-α-phenylnitrone (60 mM) does not show typical signals arising from adducts with $HO^\bullet$ or other radicals.[9]

Although rather large quantities of phenol are used, the phenol−H_2O_2 system is catalytic in that phenol is not consumed during the reaction. Indeed, a nearly complete mass balance is observed for phenol, and no products originating from phenol are detected by gas chromatography. However, in less optimal reaction conditions (no buffering, high temperature, poorly reactive alkenes), there seems to exist a subtle balance between epoxidation of the alkene substrate and hydroxylation of phenol itself. In such conditions, small amounts of catechol, hydroquinone, and benzoquinone are detected. In separate control experiments, catechol, hydroquinone, or benzoquinone was added to the reaction mixture, but no significant rate enhancement was observed, thus clearly demonstrating that these phenol-derived products are not responsible for the observed catalysis.[10]

Indirect information on the nature of the oxidizing species was deduced from the oxidation of differently substituted alkenes (Table 1). Whereas electron-rich tetra- and trisubstituted alkenes show high reactivity, disubstituted alkenes are reactive as well. For these substrates, high conversions (>95%) were obtained using only 1.5 equiv of H_2O_2, indicative of the efficient use of the oxidant. Geraniol, an allylic alcohol containing two trialkyl-substituted double bonds, affords a 90:10 mixture of 6,7-epoxygeraniol and 2,3-epoxygeraniol, respectively. The observed ratio reflects the preference for oxidation of the electron-rich 6,7-bond over the allylic 2,3-bond, which experiences the electron-withdrawing effect of the alcohol group. Electron-deficient terminal alkenes such as 1-octene are oxidized more slowly. The relative reactivity series for epoxidation by H_2O_2 in phenol is qualitatively similar to that expected for electrophilic oxygen-atom transfer reactions.

Electrophilic activation of H_2O_2 is further supported by the observation that electron-withdrawing substituents on phenol increase the epoxidation rate (Figure 2). Whereas phenols substituted with electron-withdrawing groups in a *meta* or *para* position show high activity, phenols bearing alkyl groups in the *para* position and *ortho*-substituted phenols show lower activity in the epoxidation of cyclooctene. Although limited to five *para*-substituted phenols, this was quantified in a Hammett-type plot, which shows that $\log(k_X/k_H)$ correlates linearly ($\rho = 0.88$, $r^2 = 0.995$) with the σ_I value of the substituents (Figure 3).[12,13] The higher epoxidation rate observed for electron-poor phenols is also illustrated in Table 1 for the epoxidation of citronellol. In *p*-chlorophenol as the solvent, about the same conversion (95%) is obtained in 2 h instead of 8 h in phenol.

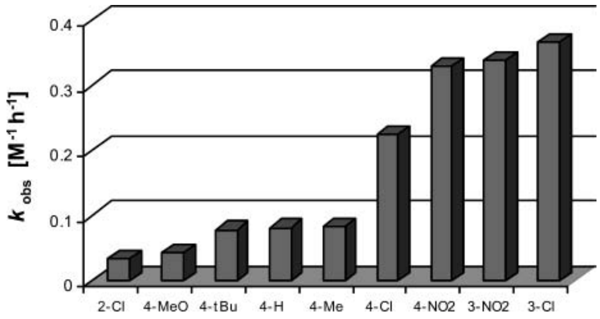

Figure 2. Second-order rate constants for the epoxidation of cyclooctene with H_2O_2 in differently substituted phenols. Reaction conditions: 10 mmol of cyclooctene, 2 mmol of *n*-decane, 0.1 mmol of NaOAc, 15 mmol of H_2O_2, 100 mmol of phenol, 16 mL of 1,2-dichloroethane, 60 °C.[14]

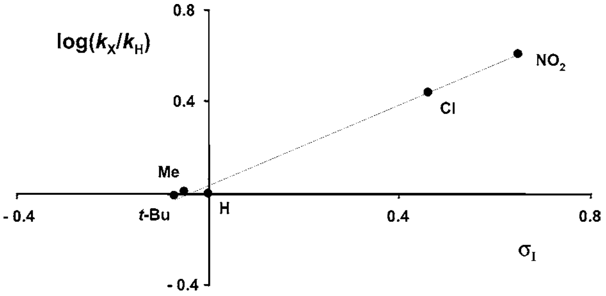

Figure 3. Hammett-type plot for cyclooctene epoxidation by H_2O_2 in *p*-substituted phenols. Reaction conditions were the same as in Figure 2.

Regarding the mechanism of oxygen-atom transfer, a tentative explanation for the activity of acidic alcohols in alkene epoxidation might be their ability to increase the electrophilic character of a peroxy oxygen atom of H_2O_2 and, at the same time, assist the leaving group (H_2O) in departing from the reactive intermediate (Scheme 2).[15,16] In these

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[8] It is well-known that small amounts of phenolic compounds play a key role in the protection of living organisms and synthetic materials against oxidative damage. In such reactions, a phenol acts as a radical scavenger by hydrogen atom transfer to a peroxyl radical. For example, see: (a) Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Green, W. H.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929−2930. (b) Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173−1183.

[9] Reference radicals were generated by Fenton's reagent: (a) Harbour, J. R.; Chow, V.; Bolton, J. R. *Can. J. Chem.* **1974**, *52*, 3549−3553. (b) Janzen, E. G.; Nutter, D. E., Jr.; Davis, E. R.; Blackburn, B. J.; Poyer, J. L.; McCay, P. B. *Can. J. Chem.* **1978**, *56*, 2237−2242.

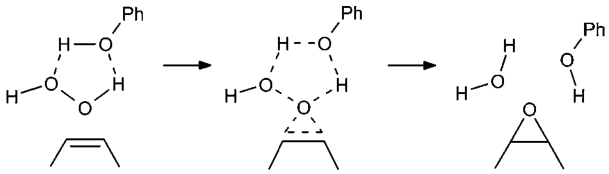
[10] Presence of benzoquinone may induce some dioxirane-like chemistry. To disprove this possibility, various sets of control experiments were carried out. Details are shown in Supporting Information.

[11] Authentic epoxides were prepared by oxidation with *m*-CPBA in $CHCl_3$.

[12] Although a Hammett correlation for substituted solvents might be regarded as nonclassical, interaction of phenol with H_2O_2 in a transition state as depicted in Scheme 2 would justify such an approach. CN and COOH substituents were excluded because these functional groups might react with H_2O_2 to form reactive peroxy species.

[13] (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195. (b) Taft, R. W., Jr.; Lewis, I. C. *J. Am. Chem. Soc.* **1958**, *80*, 2436−2443.

Scheme 2. Hypothetical Mechanism for Epoxidation of Alkenes by H_2O_2 in Phenol



interactions, hydrogen bonding plays an important role.[17,18] Moreover, aggregation of phenol molecules could be an important factor in stabilizing the transition state.

The involvement of hydrogen bonding is further illustrated by the observation that the addition of cosolvents with high hydrogen-bond acceptor strength dramatically decreases the reaction rate. In Figure 4, this is illustrated for tetrahydrofuran. Addition of an equimolar amount of tetrahydrofuran relative to phenol completely suppresses epoxidation. Also, the oxidation fails when other cosolvents such as methanol are employed.[19] It is believed that these solvents disrupt the hydrogen-bonded phenol network. The use of H_2O_2 with a higher water content (30 wt % aqueous solution) or the addition of cyclooctene oxide to the reaction mixture at the start of the reaction also has a negative effect on the rate of epoxidation. The importance of the degree of association of phenol is further demonstrated by the observation that epoxidation rates increase with increasing phenol concentration. Although a high yield of cyclooctene oxide is already obtained using only 2 mol equiv of phenol relative to cyclooctene, a higher rate is observed using 5 or 10 mol equiv. Increasing the amount of phenol beyond 10 mol equiv does not result in a further increase in the reaction rate.

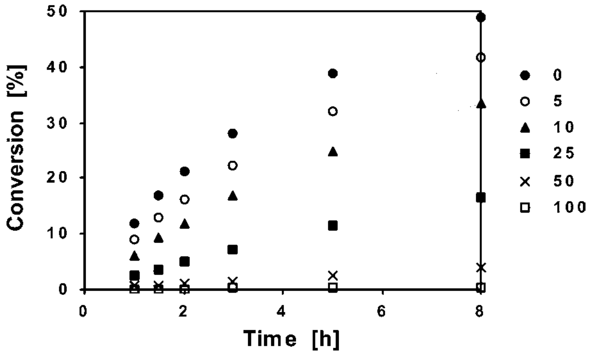


Figure 4. Epoxidation of cyclooctene with H_2O_2 in phenol in the presence of different amounts of tetrahydrofuran. Reaction conditions: 10 mmol of cyclooctene, 2 mmol of *n*-decane, 0.1 mmol of NaOAc, 10 mmol of H_2O_2, 100 mmol of phenol, 40 °C, *x* mmol of tetrahydrofuran (see legend at right of graph).

In conclusion, intermolecular hydrogen bonding between phenol and H_2O_2 yields an electrophilic peroxy species that is able to epoxidize alkenes. In these interactions, the role of phenol is purely catalytic.

Acknowledgment. This work was supported by the Belgian Federal Government in the frame of an IUAP-PAI project on Supramolecular Chemistry and Catalysis.

Supporting Information Available: Experimental procedures and detailed results of the control experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) 1,2-Dichloroethane was used as a cosolvent to dissolve the high-melting phenols. Under these conditions, but in the absence of phenol, epoxidation hardly occurred (conversion was <3% after 24 h).

(15) Similar cyclic hydrogen-bonded interactions of peroxides with alcohols have been proposed: (a) Dankleff, M. A. P.; Curci, R.; Edwards, J. O.; Pyun, H.-Y. *J. Am. Chem. Soc.* **1968**, *90*, 3209−3218. (b) Bruice, T. C.; Noar, J. B.; Ball, S. S.; Venkataram, U. V. *J. Am. Chem. Soc.* **1983**, *105*, 2452−2463. (c) Richardson, W. H. In *The Chemistry of Functional Groups, Peroxides*; Patai, S., Ed.; John Wiley & Sons: New York, 1983; Chapter 5. (d) Bach, R. D.; Su, M.-D.; Schlegel, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 5379−5391.

(16) Epoxidation of cyclooctene using *tert*-butyl hydroperoxide as the oxidant at 60 °C gave 20% conversion after 24 h.

(17) Effect of hydrogen bonding is also observed in the natural abundance ^{17}O NMR spectrum of H_2O_2 in phenol (δ 180 ppm, with H_2O as an external reference). This corresponds to a small but significant shift in comparison with H_2O_2 in other solvents (e.g., δ 176 ppm in methanol).

(18) Reduction of charge separation in transition states by intramolecular hydrogen bonding and proton transfer is a generally accepted concept, e.g., the "butterfly" transition state in epoxidations mediated by typical peracids: (a) Bartlett, P. D. *Rec. Chem. Prog.* **1950**, *11*, 47−51. (b) Bach, R. D.; Owensby, A. L.; Gonzalez, C.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1991**, *113*, 2338−2339.

(19) Chlorinated cosolvents, which are less coordinating, have a much less negative effect on the rate of epoxidation.