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Electrophilic Activation of Hydrogen Peroxide: Selective Oxidation Reactions in Perfluorinated Alcohol Solvents

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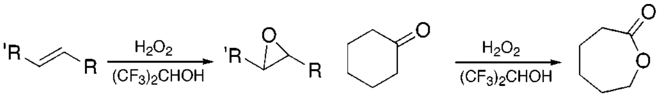
ABSTRACT



The catalytic electrophilic activation of hydrogen peroxide with transition metal compounds toward reaction with nucleophiles is a matter of very significant research and practical interest. We have now found that use of perfluorinated alcoholic solvents such as 1,1,1,3,3,3-hexafluoro-2-propanol in *the absence* of catalysts allowed electrophilic activation of hydrogen peroxide toward epoxidation of alkenes and the Baeyer–Villiger oxidation of ketones.

The activation of aqueous hydrogen peroxide has captivated researchers interested in the use of this high oxygen content, relatively inexpensive, and environmentally friendly oxidant for oxidation transformations in synthetic chemistry. Mechanistically, hydrogen peroxide may be basically activated in three ways. First, hydroxy and hydroperoxy radicals may be formed by a Haber−Weiss mechanistic scheme in the presence of many metal compounds. These radicals usually lead to nonselective transformations of organic substrates. Second, under basic conditions, the strong HOO^- nucleophile is formed which is active for epoxidation of electrophilic alkenes such as β-unsaturated ketones or carboxylic acid derivatives. The third and probably most important synthetic application of hydrogen peroxide has been in the area of heterolytic oxidation as in the epoxidation of alkenes. Very often, hydrogen peroxide was and is still used for the separate and in situ formation of percarboxylic acids, which are active for example in epoxidation, oxidation of sulfides, and the Baeyer−Villiger oxidation of ketones to esters. Mostly, environmental and safety concerns associated with the use of peracids[1] has led over the past generation to the research into catalytic alternatives based on the use of high valent (d_o), mostly on Ti, V, Mo, W, and Re, metal complexes. Some very notable effective catalysts are titanium silicates,[2] peroxophosphotungstates,[3] manganese triazocyclononane,[4] and methylrhenium trioxide.[5] From a mechanistic point of view, both the carboxy group in the peracid and the high valent metal centers in the transition metal compounds lead to the formation of electrophilic oxygen atom. It is believed by many that subsequent oxygen transfer to a nuclephile such as an alkene takes place via a butterfly type transition state.[6]

More succinctly it seems clear that any compound that will reduce the electron density at the oxygen atom of

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[1] Recently, peroxomonocarbonate has been suggested as an environmentally attractive anionic peracid. (a) Yao, H.; Richardson, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 3220. (b) Richardson, D. E.; Yao, H.; Frank, K. M.; Bennett, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 1729.

[2] Clerici, M. G.; Bellussi, G.; Romano, U. *J. Catal.* **1991**, *129*, 159.

[3] Venturello, C.; Alneri, E.; Ricci, M. *J. Org. Chem.* **1983**, *48*, 3831.

[4] De Vos, D. E.; Sels, B. F.; Reynaers, M.; Rao, Y. V. S.; Jacobs, P. A. *Tetrahedron Lett.* **1998**, *39*, 3221.

[5] Herrmann, W. A.; Fischer, R. W.; Rauch, M. U.; Scherer, W. *J. Mol. Catal.* **1994**, *86*, 243.

[6] (a) Bartlett, P. D.; Leffler, J. E. *J. Am. Chem. Soc.* **1950**, *72*, 3030. (b) Chong, A. O.; Sharpless, K. B. *J. Org. Chem.* **1977**, *42*, 1587.

[7] There are recent reports of trifluoroethanol as a "magic" solvent for *catalytic* epoxidation reactions. (a) van Viliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 821. (b) van Viliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 263. (c) Shryne, T. M.; Kim, L. US Patent 4024165, 1977.

[8] Reactions were carried out in 5 mL vials by mixing the organic substrate, hydrogen peroxide, and solvent in the quantities given in the tables. The vials were magnetically stirred at ambient temperature, ~22 °C, or in a thermostated bath at 60 °C. The mixtures were analyzed by GC (HP 5890) and GC-MS (HP 5973) using a 30 m 5% phenyl methyl silicone column (ID 0.32 mm, coating 0.25 μm).

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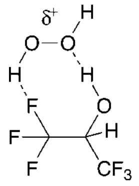
hydrogen peroxide will lead to a facilitated nucleophilic attack and heterolytic oxygen transfer. We have now found, that one can simply carry out oxidation reactions with hydrogen peroxide in inert and easy to recycle, low boiling point, perfluorinated alcohols as solvents *without* the addition of any metal or nonmetal catalyst.[7] Selective epoxidation of alkenes and the Baeyer−Villiger oxidation of ketones is shown. From the ^1H and ^{17}O NMR spectra, we deduce that the strong electron-withdrawing properties of fluorine along with the hydrogen bonding properties of the O−H hydrogen atom lead to formation of an electrophilically activated hydrogen peroxide intermediate, roughly delineated in Scheme 1. As expected reactivity is increased as a function of fluorine substitution; $CF_3CHOHCF_3$ (1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) is more active than CF_3CH_2OH (2,2,2-trifluoroethanol, TFE).

Scheme 1



First, alkenes were reacted with a slight excess of 30% or 60% H_2O_2 in both TFE and HFIP as solvents. A preliminary survey of the reactivity of the alkenes is presented in Table 1.[8] Epoxidation of an exemplary difficult to epoxidize terminal, aliphatic, acyclic alkene, 1-octene, clearly showed that activity in HFIP was greater than in TFE. Use of non-fluorine-containing alcohols as solvents such as ethanol and 2-propanol showed no activity. Raising the temperature and/or using more concentrated hydrogen peroxide easily increased the conversion. This was possible without comprising the absolute selectivity to the epoxide product. Other terminal alkenes such as 1-heptene and 1-decene reacted in a practically identical manner. As expected the more nucleophilic 2-octene was more reactive, and there was no loss of selectivity. With a yet more nucleophilic and reactive alkene, 2,3-dimethyl-2-butene, reactivity increased significantly; however, the product epoxide reacted further in acid-catalyzed type reactions to yield the ring-opened diol and the rearranged pinocolone (3,3-dimethyl-2-butanone). For cyclic alkenes, the reactivity was cyclopentene ∼ cyclooctene > cyclododecene ∼ cyclohexene. Except for cyclohexene oxide, which proved to be sensitive to further acid-type-catalyzed reactions, the epoxides were stable under the reaction conditions. The oxidation of styrene yielded mostly the carbon−carbon bond cleaved product, benzaldehyde, and products attributable to acid-catalyzed ring opening of the epoxide, α-hexafluoropropyloxy-β-hydroxyethylbenzene, and the rearranged phenylacetaldehyde. Interestingly, *meta* substitution with an electron-withdrawing, deactivating nitro moiety led to selective formation of 3-nitrobenzaldehyde. Three further observations are worth pointing out. First, the addition of buffers or basic amines in order to prevent undesired reactions of acid sensitive compounds led to deactivation and no reaction. Second, the use of perfluoro-*tert*-butyl alcohol, $(CF_3)_3COH$, as solvent gave virtually the same results in terms of both reactivity and selectivity as HFIP. Finally, no oxidation products of the perfluorinated alcohols such as 1,1,1,3,3,3-hexafluoracetone were obtained under the reaction conditions as measured by GC-MS.[9]

The activation of hydrogen peroxide in HFIP was also very successfully used for the Baeyer−Villiger oxidation of ketones, Table 2.[8] Thus, cyclic ketones were cleanly converted to lactones in high yield. As is typical for this reaction, acyclic ketones were much less reactive. Finally, although the oxidation of sulfides to sulfoxides with H_2O_2 in HFIP has already been disclosed,[10] it is valuable to state that in TFE reactions are slower and slightly less selective than those

Table 1. Alkene Epoxidation in Perfluorinated Alcohols[a]

	conversion, mol %, selectivity, mol epoxide/total products					
	TFE at 60 °C		HFIP at 22 °C		HFIP at 60 °C	
substrate	30% H_2O_2	60% H_2O_2	30% H_2O_2	60% H_2O_2	30% H_2O_2	60% H_2O_2
cyclopentene	56 (100)	99 (100)	44 (100)	93 (100)	99 (90)[f]	−
cyclohexene	37 (53)[c]	65 (48)[e]	25 (100)	91 (61)[g]	82 (26)[h]	−
cyclooctene	66 (100)	98 (100)	61 (100)	100 (100)	99 (100)	−
cyclododecene[b]	7 (100)	39 (100)	40 (100)	80 (100)	85 (100)	−
1-octene	0	14 (100)	4 (100)	21 (100)	30 (100)	59 (100)
2-octene	37 (100)	77 (100)	33 (100)	73 (100)	74 (100)	97 (100)
2,3-diMe-2-butene	96 (11)[d]	−	100 (57)[f]	−	−	−
styrene	−	−	−	−	74[j]	100[l]
3-nitrostyrene	−	−	−	−	13[k]	39[k]

[a] Reaction conditions: 1.2 mmol of substrate, 2 mmol of H_2O_2, 1 mL of perfluoro alcohol, 20 h. [b]The given mixture of 80:20 cis/trans cyclododecane gave the same epoxide ratio. [c]23% 1-(2,2,2-trifluoroethyloxy)-2-hydroxycyclohexane, 24% 1,2-cyclohexanediol. [d]89% 2,3-dimethyl-2,3-butanediol. [e] 31% 1-(2,2,2-trifluoroethyloxy)-2-hydroxycyclohexane, 21% 1,2-cyclohexanediol. [f]34% 2,3-dimethyl-2,3-butanediol, 9% pinocolone. [g]39% 1-(1,1,1,3,3,3-hexafluoroprop-2-yloxy)-2-hydroxycyclohexane. [h]10% cyclopentanediol. [i]89% cyclohexanediol. [j]47% benzaldehyde, 15% phenylacetaldehyde, 32% α-(1,1,1,3,3,3-hexafluoroprop-2-yloxy)-β-hydroxyethylbenzene, 6% phenol. [k]100% 3-nitrobenzaldehdye. [l]53% benzaldehyde, 29% phenylacetaldehyde, 13% α-(1,1,1,3,3,3-hexafluoroprop-2-yloxy)-β-hydroxyethylbenzene, 9% phenol.

Table 2. Baeyer–Villigar Oxidations of Ketones[a]

substrate	conversion, mol %
cyclopentanone	88[b]
cyclohexanone	82[b]
cycloheptanone	68[b]
cyclooctanone	60[b]
2-octanone	6.5[c]
acetophenone	0

[a] Reaction conditions: 1.2 mmol of substrate, 2 mmol of 60% H_2O_2, 1 mL of HFIP, 60 °C, 20 h. [b]Only lactones were obtained. [c]Hexyl acetate was the only product.

in HFIP. Typically, reaction selectivity is 100% to sulfoxide in HFIP and 97 ± 2% in TFE for a wide range of sulfides.

^{1}H NMR and natural abundance ^{17}O NMR were both used to investigate the interaction of hydrogen peroxide with the perfluorinated alcohol solvents.[11] Thus, the shift attributable to H_2O_2 in the ^{1}H NMR of 60% H_2O_2 in solvent varied from 9.91 ppm in 2-propanol, 9.18 ppm in TFE, and 8.08 ppm in HFIP. Similarly, in the ^{17}O NMR there is a shift for H_2O_2 from 182.2 ppm in 2-propanol to 177.5 ppm in HFIP.[12] Both results are interpreted by realizing that according as hypothesized in Scheme 1 the electron-density is reduced on the oxygen atom upon dissolution in the perfluorinated alcohol. This leads to an expected upfield shift in both the ^{1}H and ^{17}O NMR. The effect is stronger for HFIP compared to TFE.

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(9) Formation of perfluoroacetone could lead to subsequent formation of the α-hydroxy hydroperoxides and epoxidation of alkenes. cf. Ganeshpure, P. A.; Adam, W. *Synthesis* **1996**, 179.

(10) Ravikumar, K. S.; Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron Lett.* **1998**, *39*, 3141. (b) Ravikumar, K. S.; Zhang, Y. M.; Begue, J. P.; Bonnet-Delpon, D. *Eur. J. Org. Chem.* **1998**, 2937.

(11) ^{1}H NMR (250 MHz) spectra were carried out on solutions containing 12 μL of 60% H_2O_2, 0.1 mL of solvent in 0.6 mL of $CDCl_3$. ^{17}O NMR (54.25 MHz) were carried out on solutions of 120 μL of 60% H_2O_2 in 1 mL of solvent. The spectra were referenced externally to H_2O without locking.

(12) The ^{17}O shifts assigned to the hydroxyl oxygen are at 40.5 ppm for 2-propanol and at −11.7 ppm for HFIP.