DOI: 10.1002/chem.200800932

Reaction of Epoxyketones with Hydrogen Peroxide—Ethane-1,1-dihydroperoxide as a Surprisingly Stable Product

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Oxidation of organic compounds with hydrogen peroxide has attracted attention for a long time and has been attributed to green chemistry. We used hydrogen peroxide in reactions with cyclic alcohols and observed unusual rearrangement reactions under ring enlargement giving new hydroperoxides and peroxides.[1–3] In this way we also obtained aliphatic primary geminal dihydroperoxides.[2] We report here on reactions of cyclic epoxyketones with hydrogen peroxide. Such epoxides are usually synthesised by the Weitz–Scheffer reaction, that is, by reaction of α,β-unsaturated ketones with H_2O_2 under basic conditions.[4] We treated such products with 70% H_2O_2 in the presence of catalytic amounts of camphor sulfonic acid at room temperature.

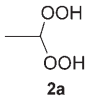
Substituted 6-ring epoxyketones **1** at the 3-position gave mixtures of products, interestingly consisting of geminal dihydroperoxides **2**, dicarboxylic acids **3**, carboxylic acids **4** and ketocarboxylic acids **5** (Table 1, Scheme 1).

Table 1. Distribution of products in the reaction of epoxy ketones **1** with H_2O_2.

Epoxyketone	*n*	R	**2**/[%][a]	**3**/[%][b]	**4** [%][b]	**5** [%][b]
1a	0	Me	**2a**/2	**3a**/38	**4a**/29	**5a**/57
1b	1	Me	**2a**/12	**3b**/53	**4a**/6	**5b**/15
1c	1	Et	**2b**/19	[c]	[c]	[c]
1d	1	Ph	**2c**/19	**3b**/18	–	**5c**/35
1e	2	Me	**2a**/4	**3c**/66	**4a**/20	–

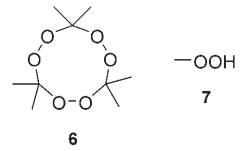
[a] Yields of isolated products. [b] Yields determined by ^{1}H NMR spectroscopy. [c] The aqueous phase consisted of a complex mixture and could not be analysed.

The geminal dihydroperoxides **2** show significant signals in the NMR spectra.[2,5–7] Thus, the hitherto unkown ethane-1,1-dihydroperoxide (**2a**) exhibits a signal at 107.9 ppm in the ^{13}C NMR spectrum and one typical hydroperoxide-H signal (intensity two protons) at 9.71 ppm in the ^{1}H NMR spectrum. In combination with the HR-ESI MS result, the structure of **2a** could be proven unambiguously. The geminal dihydroperoxide **2a** has the highest content of peroxide oxygen (68%) relative to hitherto known organic peroxides and hydroperoxides.

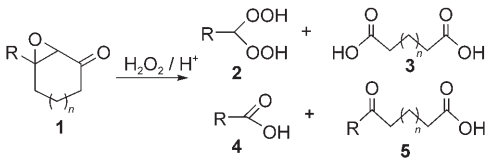


2a

The so-called triacetone triperoxide (**6**; 43% peroxidic oxygen) and methylhydroperoxide (**7**;[8] 66.7%) were reported as highly explosive compounds. Despite the very high oxygen content compound **2a** is remarkably stable. It can be kept at room temperature for several days and at −20 °C for several weeks without decomposition. Thermogravimetric investigations (see Supporting Information) showed decomposition in the temperature range 60–130 °C with the highest decomposition rate at about 105 °C. Using differently substituted epoxyketones as reactants we were also able to isolate and characterise propane-1,1-dihydroperoxide (**2b**), which is not yet described in literature, and to obtain benzylidenedihydroperoxide (**2c**). The latter was previously described by using a different method from the reaction of benzaldehyde with H_2O_2.[5] Remarkably, known syntheses of geminal dihydroperoxides based on reactions of carbonyl compounds with H_2O_2 are re-



6 **7**



1 **2** **3** **4** **5**

Scheme 1. Acid-catalysed reaction of epoxy ketones **1** with H_2O_2

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200800932.

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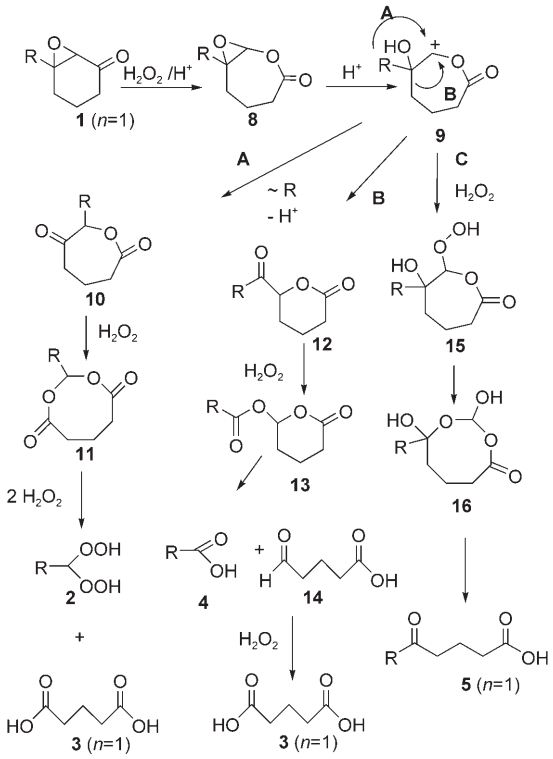
stricted mainly to ketones and aromatic aldehydes.[5,7,9] With the exception of the special case of chloral[10] and one insufficiently described reaction of pentanal,[11] primary aliphatic geminal dihydroperoxides have only been synthesised by ozonolysis of enol ethers in the presence of excess of H_2O_2.[12] Iskra et al. reported that aliphatic aldehydes form 1-hydroperoxy-1-hydroxyalkanes, that is, hemiacetal structures, in reactions with H_2O_2 in acetonitrile in the presence of iodine.[7] We checked if by the application of more highly concentrated H_2O_2 in this reaction with acetaldehyde whether the formation of the geminal dihydroperoxide could be achieved; however, we could not detect **2a**, even when using 70% H_2O_2.

As can be seen by the product spectrum of the different reactants used, the carbon skeleton of **2** is evidently derived from the substituent R and the C2 atom of the epoxyketone **1**, with the occurrence of a number of C–C bond fissions.

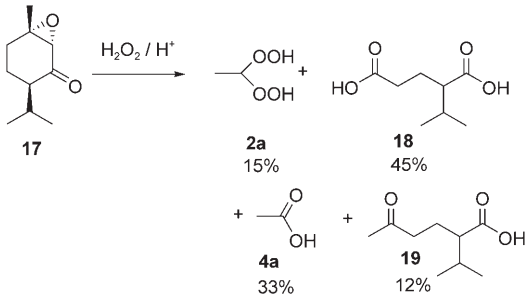
To rationalise the complex reaction pathway we propose the following mechanism as shown in Scheme 2 for 6-ring



Scheme 2. Proposed reaction mechanism of 6-ring epoxyketones with H_2O_2.

epoxyketones **1** ($n=1$). Epoxyketones can be attacked by H_2O_2 at the carbonyl C atom and/or at both epoxy C atoms as electrophilic centers. We suppose that the primary attack occurs at the carbonyl C atom causing a Baeyer–Villiger type rearrangement in which the oxirane C atom migrates, because of its higher migratory aptitude. Under acid conditions the acetal moiety of the resulting lactone **8** can be easily cleaved affording carbenium ion **9**, which can react in three different ways; Scheme 2 A, B and C. Alternatively, hydrogen peroxide could add to the C2 atom to form a 2-hydroperoxy-3-hydroxyketone, which could then by protonation and water elimination react in a Hock type reaction under ring expansion to give intermediate **9**. According to pathway A, the R substitutent migrates to give ketolactone **10**, which affords *O*,*O*-diacylacetal **11** by a further Baeyer–Villiger oxidation. The latter is ring-opened by H_2O_2 affording dihydroperoxide **2** and glutaric acid **3b**. The alternative reaction pathways B and C do not provide geminal dihydroperoxides **2**. Following pathway B the ring C atom of **9** migrates. The resulting 5-acyl-δ-lactone **12** undergoes a Baeyer–Villiger rearrangement by migration of the C5 atom of the lactone ring, which again has a high migratory aptitude because of the ring O atom. Cleavage of the acetal in the resulting intermediate **13** by H_2O_2 or water leads to the formation of the carboxylic acid **4**, while the remaining fragment **14** is oxidised to glutaric acid. Finally, the formation of ketocarboxylic acids **5** according to pathway C can be realised by the addition of H_2O_2 to the cation **9** followed by a Hock type hydroperoxide rearrangement.[1] The ring enlargement occurs by migration of an O-atom-stabilised carbenium ion. The resulting orthoester **16** is unstable and decomposes into ketoacid **5** and formic acid, which is further oxidised to carbon dioxide.

We further wondered if this unusual reaction behaviour can also be observed with structurally related epoxyketones. Initial results revealed that the acid-catalysed reaction of 5- and 7-ring homologues **1** ($n=0$, 2) with H_2O_2 runs similarily (Table 1). However, they show a lower tendency to form the geminal dihydroperoxide **2a**. We finally investigated in how far 6-ring epoxyketones with additional alkyl substituents in the ring exhibit a similar reaction behaviour. Piperitone oxide **17** forms compound **2a** to a similar level with the corresponding reaction products **4a**, **18** and **19** (Scheme 3). Although an isopropyl substituent with a relatively high migratory aptitude is found in **17**, the oxiranyl moiety still migrates, as can be seen by the exclusive formation of **18** and **19**.



Scheme 3. Reaction of piperitone oxide **17** with H_2O_2.

Interestingly, the hydroperoxylactone **21** and the acyllactone **23** were obtained in addition to **2a**[13] and **22** in the reaction of isophorone oxide **20** with H_2O_2 (Scheme 4). These types of products were not observed in the other cases. Compound **21** (see Figure 1 for X-ray crystal analysis) is the

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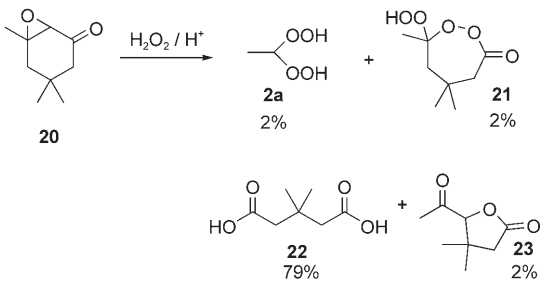

Scheme 4. Reaction of isophorone oxide **20** with H_2O_2.

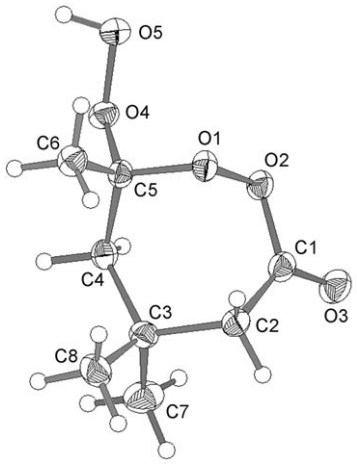

Figure 1. X-ray structure of the hydroperoxyperoxylactone **21**.

first representative in the 7-ring series. So far, only analogous 5-ring[14] and acyclic hydroperoxyperoxy esters[15] were reported. They were obtained in totally different ways.

The hydroperoxyperoxylactone **21** can be considered as a dimethyl analogue of ketoacids **5** being converted into a peracid, which cyclises and forms **5** by substitution of the hemiacetal OH group with H_2O_2. This peculiar behaviour of isophorone oxide **20** could be explained by the Thorpe–Ingold effect (geminal dialkyl effect) supporting the ring closure of the δ-oxocarboxylic acid to the hyroperoxylactone **21**. Accordingly, acid treatment of the 3,3-dimethyl-5-caproic acid with H_2O_2 gave **21** independently, while other ketoacids (e.g., **5b**) lacking the two methyl groups failed to give peroxidic products. The acyllactone **23** is likely to be formed from **21** by a ring-contracting peroxide rearrangement. Interestingly, an industrial process for the preparation of dimethylglutaric acid **22** from isophorone and H_2O_2 was claimed.[16]

In summary, we have shown that cyclic, 3-substituted epoxyketones react with H_2O_2 under acid catalysis by an unknown, complex reaction mechanism that includes several C–C bond cleavages by Baeyer–Villiger oxidation and Hock type hydroperoxide rearrangements. In this way ethane-1,1-dihydroperoxide could be obtained; this compound contains the highest peroxidic oxygen content of all hitherto known organic compounds and is remarkably stable.

Experimental Section

Warning! 70% H_2O_2 as well as peroxidic compounds are potentially explosive and should be handled with precautions.

Representative preparation of 2a: Compound **1b** (923 mg, 8.38 mmol) was dissolved in Et_2O (2 mL) and treated with 70% H_2O_2 (2 mL) and D-(+)-camphorsulfonic acid monohydrate (20 mg) under ice cooling. After stirring at room temperature overnight, the reaction mixture was diluted with water (30 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were washed with satd. aq. $NaHCO_3$ (20 mL). After drying (Na_2SO_4) the solvent was removed with a rotatory evaporator and the remainder purified by column chromatography (cyclohexane/EtOAc, 65:35) to yield **2a** (95 mg, 12%) as colourless oil. $R_f = 0.29$; ^{1}H NMR: ($CDCl_3$): $\delta = 9.71$ (s, 2H; OO*H*), 5.47 (q, $J = 5.7$ Hz, 1H; C*H*), 1.42 ppm (d, $J = 5.7$ Hz, 3H; CH_3); ^{13}C NMR: ($CDCl_3$): $\delta = 107.9$ (*C*H), 14.6 ppm (*C*H_3); HRMS(ESI): *m*/*z* calcd for $C_2H_6O_4Cl$: 128.9960 $[M+Cl]^+$; found: 128.9958.

Acknowledgements

We thank one referee for pointing out several interesting ideas and additions to our article, Dr. Burkhard Ziemer for X-ray crystal analysis and Solvay Interox GmbH, Bayer Services GmbH & Co. OHG, BASF AG and Sasol GmbH for the donation of chemicals. A. Bunge gratefully acknowledges a grant from DFG.

Keywords: epoxides · hydrogen peroxide · hydroperoxides · oxidation · rearrangement

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Received: May 15, 2008
Published online: July 4, 2008

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