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A new method for the synthesis of bishydroperoxides based on a reaction of ketals with hydrogen peroxide catalyzed by boron trifluoride complexes

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Abstract—A reaction of cycloalkanone, alkanone and alkyl aryl ketone ketals with H_2O_2 catalyzed by boron trifluoride etherate and boron trifluoride–methanol complexes was studied. A new versatile method for the synthesis of bishydroperoxides and their derivatives, viz. 1,1′-dihydroperoxyperoxides and 1,2,4,5-tetraoxacyclohexanes, was developed based on this reaction.

In recent years, the interest in organic bishydroperoxides has increased sharply, due to the discovery of their pharmacological activity, in particular, the antimalarial activity of dispiro-1,2,4,5-tetraoxanes and their analogues.[1–8]

Bishydroperoxides are prepared by ozonolysis of ketone enol ethers or α-olefins in the presence of H_2O_2[6–9] and by the reaction of H_2O_2 with ketones[6–10] or ketals in the presence of tungstic acid.[11] The major drawbacks of most of these processes are moderate yields of the target products and the long reaction times required to prepare them. Consequently there is a need for the development of more efficient methods for the preparation of these compounds.

Herein, we report a new method for the synthesis of bishydroperoxides and their derivatives, viz., 1,1′-dihydroperoxyperoxides and 1,2,4,5-tetraoxacyclohexanes, which allows preparation of the products easier and faster and in good yields (70–95%). The method is based on the reaction of ketals with a solution of hydrogen peroxide in anhydrous ether catalyzed by boron trifluoride complexes. This reaction is applied to the preparation of the title products for the first time.

We have studied cycloalkanones **1a**–**i** and **2a**,**b**,**e** (Scheme 1), adamantan-2-one **3**, 4-methylpentan-2-one **4a**, pentadecan-8-one **4b**, acetophenone and α-tetralone ketals, which were obtained by known methods from the corresponding ketones.[12–14] A solution of H_2O_2 in Et_2O was prepared as described earlier.[15] Experiments were carried out at ~20°C using an excess of H_2O_2 and 0.1–0.3 equiv. of $BF_3{\cdot}OEt_2$ or $BF_3{\cdot}MeOH$. Solutions of the ketals were gradually added to a solution of H_2O_2 in anhydrous ether (Scheme 1). With a twofold excess of H_2O_2 cyclododecanone ketals **1e** and **2e** were converted exclusively into cyclododecylidenebishydroperoxide (**5e**). Other cycloalkanone ketals **1c**,**d**,**f**,**h**, adamantan-2-one ketal **3**, 4-methylpentan-2-one ketal **4a** and pentadecan-8-one ketal **4b** were converted selectively into the corresponding bishydroperoxides only with a seven- to eightfold excess of H_2O_2. The yields of bishydroperoxides **5c**–**h**, **6**, and **7a**,**b** were 48–95% (Table 1).

For all ketals **1**–**4**, except for cyclododecanone ketals **1e** and **2e**, when the excess of H_2O_2 is below 7 equivalents, bishydroperoxides were obtained as side products along with their derivatives, viz. 1,1′-dihydroperoxy dicycloalkyl peroxides **8**, 8,8′-dihydroperoxy pentadecan-8-yl peroxide **10** and tetraoxadispiroalkanes **9** and 3,3′,6,6′-tetra-*n*-heptyl-1,2,4,5-tetraoxacyclohexane **11** (Scheme 2). Thus bishydroperoxides **5a**,**b** and peroxides **8a**,**b** were formed from cyclopentanone **1a**,**b** and cyclohexanone **2a**,**b** ketals in overall yields of 73–92%, whereas cyclooctanone **1d**, 2-methylcyclohexanone **1g**, and pentadecan-8-one **4b** ketals gave 6–19% yields of

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Keywords: acetals; boron compounds; catalysts; peroxidation; peroxides.

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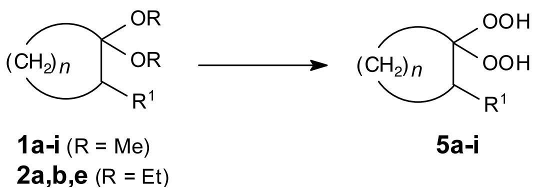
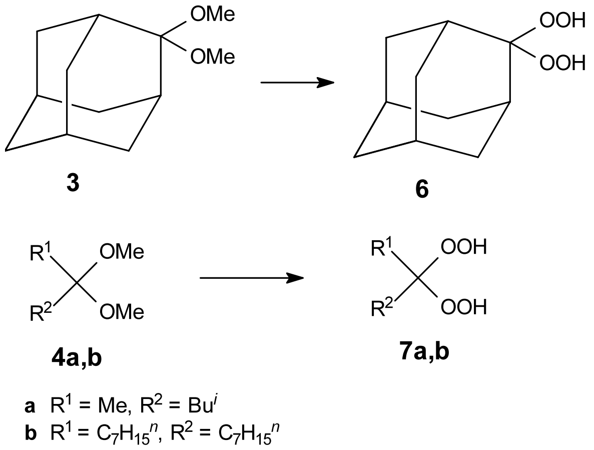


1, 2, 5	a	b	c	d	e	f	g	h	i
R^1	H	H	H	H	H	n-C_8H_{17}	Me	n-C_9H_{19}	Bn
n	3	4	5	6	10	3	4	10	10



Scheme 1. *Reagents and conditions*: Et_2O, H_2O_2 (2.5–8 equiv.), $BF_3{\cdot}OEt_2$ or $BF_3{\cdot}MeOH$ (0.2–0.4 equiv.), 1–3 h, 20–25°C.

Table 1. The products obtained in the $BF_3{\cdot}OEt_2$-catalyzed reaction of ketals **1**–**4** with H_2O_2[a]

Ketal	$BF_3{\cdot}OEt_2$ (equiv.)	Ratio ketal:H_2O_2	Method	Product[b] (yield, %)		
1a	0.2	1:2.5	*A*	**5a**[11] (60)	**8a**[11] (30)	
1b	0.2	1:3	*A*	**5b**[11,18] (62)	**8b**[19] (25)	
1b	0.3	1:3	*A*	**5b** (30)	**8b** (59)	
1b	0.2[c]	1:2.5	*A*	**5b** (61)	**8b** (29)	
1c	0.3	1:7	*B*	**5c**[8] (80)		
1d	0.2	1:2	*A*	**5d**[7,8] (9)	**8d**[11] (59)	
1d	0.3	1:3	*B*	**5d** (24)	**8d** (25)	**9d**[20,21] (12)
1d	0.3	1:7	*B*	**5d** (71)		
1e	0.2	1:2.5	*C*	**5e**[8,9,11] (95)		
1e	0.2[c]	1:2.5	*A*	**5e** (91)		
1f	0.4	1:7	*B*	**5f** (77)		
1g	0.2	1:1.5	*B*	**5g** (70)	**8g** (15)	**9g**[22] (6)
1h	0.2	1:8	*B*	**5h** (48)		
2a	0.2	1:2.5	*A*	**5a** (60)	**8a** (32)	
2b	0.2	1:2.5	*A*	**5b** (65)	**8b** (25)	
2e	0.2	1:2.5	*C*	**5e** (92)		
3	0.2	1:8	*B*	**6**[8] (84)		
4a	0.2	1:8	*B*	**7a** (78)		
4b	0.3	1:3	*A*	**7b** (44)	**10** (22)	**11** (19)
4b	0.2	1:7	*A*	**7b** (48)		

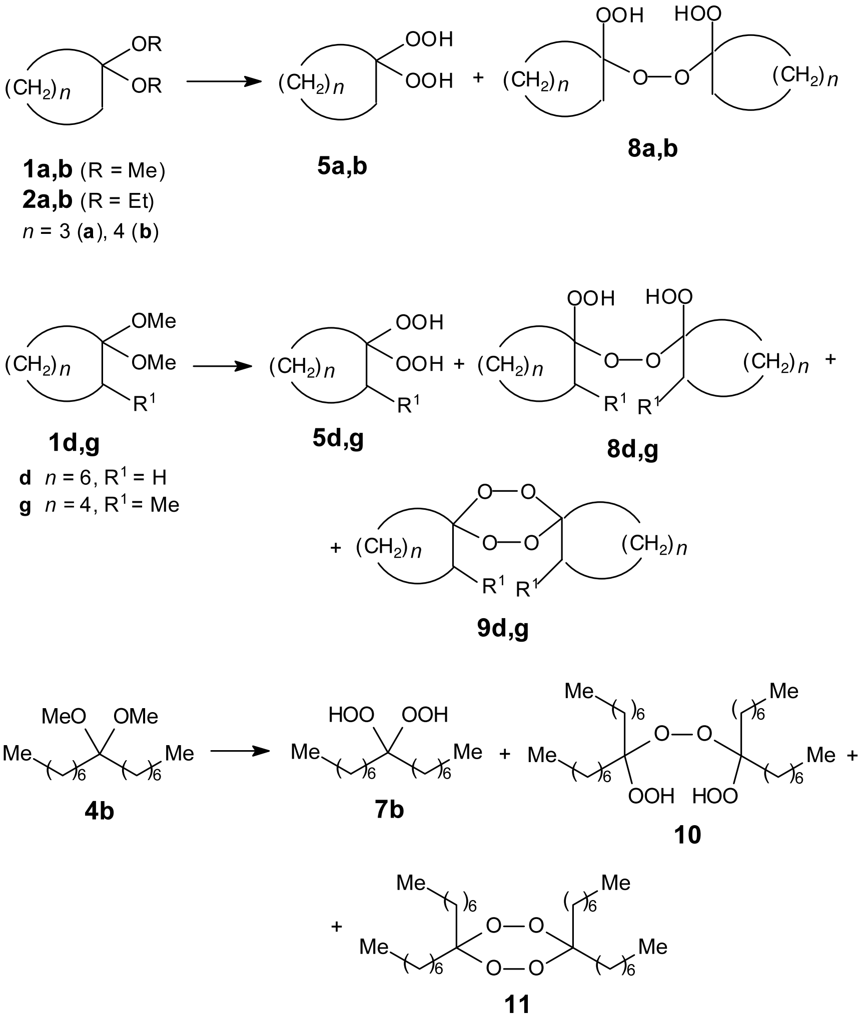
[a] Solvent–Et_2O (40–70 ml), 20–25°C, 1–3 h.

[b] Bishydroperoxides (1st column) and their derivatives, 1,1′-dihydroperoxyperoxides and tetraoxacyclohexanes (2nd and 3rd columns).

[c] $BF_3{\cdot}MeOH$.

tetraoxacyclohexanes **9d**,**g** and **11** in addition to the corresponding bishydroperoxides **5d**,**g** and **7b** and peroxides **8d**,**g** and **10**.

In addition to the excess of H_2O_2 in relation to the ketal, other factors substantially effect the ratio of the reaction products. These are the relative amounts of the catalyst, the mode of quenching of the catalyst after completion of the reaction under the action of K_2CO_3 in the presence (method *A*),† in the absence of water (method *B*),† or under the action of aqueous NaOH (method *C*),† as well as a time interval between the complete ketal conversion and the quenching of the catalyst. An increase in this interval and in the relative amounts of the catalyst, as well as the use of method *B* for quenching changed the ratio of bishydroperoxides to their derivatives in favour of the latter. This fact suggests that $BF_3{\cdot}OEt_2$ and $BF_3{\cdot}MeOH$ catalyze both the reaction of ketals with H_2O_2 and the conversion of bishydroperoxides into their derivatives. The optimal



Scheme 2. *Reagents and conditions*: Et_2O, H_2O_2 (2.5–3 equiv.), $BF_3{\cdot}OEt_2$ or $BF_3{\cdot}MeOH$ (0.2–0.3 equiv.), 1–3 h, 20–25°C.

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† *Typical procedures*: *A*. A solution of a ketal (10 mmol) in Et_2O (40 ml) was added dropwise over ca. 5 min to a stirred solution of H_2O_2 (1.5–8 equiv.) and $BF_3{\cdot}OEt_2$ or $BF_3{\cdot}MeOH$ (0.2–0.4 equiv.) in Et_2O (50 ml) at 20–25°C, the resulting mixture was stirred until the ketal was completely consumed (1–2 h, TLC monitoring). Then, K_2CO_3 (2 equiv.) and water (40–50 ml) were added and the mixture was stirred for an additional 0.5–1 h. The aqueous layer was extracted with ether (3×10 ml) and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromagraphed (SiO_2, gradient elution with light petroleum–diethyl ether mixtures with the content of the latter increasing from 30 to 70%) to provide bishydroperoxides **5**–**7** and their derivatives **8**–**11**.

B. The reaction mixture obtained according to procedure *A* after complete ketal conversion was treated with K_2CO_3 (2 equiv.), stirred for 0.5 h and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed to give bishydroperoxides **5**–**7** and their derivatives **8**–**11**.

C. The reaction mixture obtained as in *A* after complete conversion of the ketal **1e** or **2e** was treated with aqueous NaOH (2 equiv., to remove organic impurities from the water soluble Na-salt of the bishydroperoxide obtained. Then, Et_2O (50–70 ml) was added and the mixture acidified with 2–5% aqueous H_2SO_4 with cooling and stirring until pH 5–6. The ethereal layer was separated, washed with water (2×10 ml), saturated aqueous $NaHCO_3$ (2×10 ml), and again with water (10 ml), and worked-up as in *A* to provide white crystals of bishydroperoxide **5e**, which contained a small amount of water.

Analytical samples of products **5**–**11** were prepared by storing **5**–**11** in vacuo (0.1 Torr) at room temperature for 3–4 h. All of the products gave satisfactory elemental analyses.

relative amount of the catalyst is 0.2–0.3 equivalents. With lesser amounts, the reaction rate sharply decreases and the time needed for complete ketal conversion is increased accordingly (to 24 h with 0.05 equivalents of the catalyst). Both complexes catalyze the reaction with about equal efficiency and as in the oxidation of ketones with H_2O_2 (the Baeyer–Villiger reaction)[16,17] they are first transformed presumably into boron trifluoride–hydroperoxide complexes. As a result of the coordination of BF_3 with H_2O_2, the acidity of the latter and the rate of ketal transformation into bishydroperoxides are increased substantially. Attempts to prepare bishydroperoxides from 2-benzylcyclododecanone ketal **1i**, acetophenone and α-tetralone ketals failed.

The structures of bishydroperoxides **5a**–**h**, **6**, **7a**,**b** and their derivatives **8**–**11** were established on the basis of the IR, ^{1}H and ^{13}C NMR spectra.‡ Products **8g** and **9g** seem to be diastereoisomeric mixtures. Their composition was not studied in detail. Mostly, **5a**–**d**, **5f**–**h**, **6**, **7a**,**b**, **8**, **10** were obtained as colourless oils, while bishydroperoxide **5e**, dihydroperoxyperoxide **8b** and tetraoxacyclohexanes **9d**,**g** and **11** were obtained as colourless solids. Bishydroperoxides **5a**–**h** were sufficiently stable at room temperature and their stability increased with an increase in the molecular mass. Thus bishydroperoxides **5e** and **5h** can be stored without apparent decomposition at room temperature for 6 months, dihydroperoxides **5c** and **6** were stable on cooling (−5–0°C) for 3–4 months, whereas bishydroperoxide **5a** was half decomposed on cooling after a month. The stabilities of dihydroperoxyperoxides and tetraoxacyclohexanes **8**–**11** changed in a similar manner. The presence of acids as impurities sharply decreased the stabilities of both bishydroperoxides and their derivatives. **CAUTION**. Bishydroperoxides **5**–**7** and their derivatives **8**–**11** are shock and friction sensitive and consequently should be handled with care. Tetraoxacyclohexanes **9** and **11** decompose explosively on heating to 100°C and above.

Thus, as a result of our studies on the $BF_3\cdot OEt_2$ and $BF_3\cdot MeOH$-catalyzed reaction of ketals with H_2O_2, a new method for the synthesis of cycloalkylidene and alkylidene bishydroperoxides and their derivatives has been developed. The most important advantage of this method over known methods[5–11] is that it allows easier and faster preparation of the products, and in higher or comparable yields.

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‡ *Spectroscopic data of new compounds*. 2-*n*-Octylcyclopentylidene-1,1-bishydroperoxide (**5f**): clear oil; IR (NaCl) ν cm^{-1}: 3428 (OOH). ^{1}H NMR δ: 0.82–2.05 (m, 24H, CH, CH_2, CH_3), 9.63–9.70 (brs, 2H, OOH); ^{13}C NMR δ: 14.0 (CH_3), 21.9, 22.6, 28.1, 29.2, 29.3, 29.5, 29.7, 31.0, 31.8, 32.7, 46.4 (CH, CH_2), 121.2 (C). 2-Methylcyclohexylidene-1,1-bishydroperoxide (**5g**): clear oil; IR (NaCl) ν cm^{-1}: 3418 (OOH); ^{1}H NMR δ: 0.89–2.29 (m, 12H, CH, CH_2, CH_3), 8.72–8.83 (brs, 2H, OOH); ^{13}C NMR δ: 22.0 (CH_3), 29.4, 30.5, 31.5, 34.0, 37.4 (CH, CH_2), 111.5 (C). 2-*n*-Nonylcyclododecylidene-1,1-bishydroperoxide (**5h**): clear oil; IR (NaCl) ν cm^{-1}: 3415 (OOH); ^{1}H NMR δ: 0.18–1.82 (m, 40H, CH, CH_2, CH_3), 8.75–9.20 (brs, 2H, OOH); ^{13}C NMR δ: 14.2 (CH_3), 19.4, 20.0, 21.8, 22.0, 22.1, 22.2, 22.3, 22.4, 22.5, 22.8, 25.4, 26.0, 26.2, 26.5, 27.4, 29.2, 29.4, 29.8, 32.0 (CH, CH_2), 115.2 (C). 4-Methylpentan-2-ylidene-2,2-bishydroperoxide (**7a**): clear oil; IR (NaCl) ν cm^{-1}: 3340 (OOH); ^{1}H NMR δ: 0.96 (d, 6H, CH_3, $J=6.6$ Hz), 1.46 (s, 3H, CH_3), 1.66 (d, 2H, CH_2, $J=5.9$ Hz), 1.76–1.80 (m, 1H, CH), 9.19–9.31 (brs, 2H, OOH); ^{13}C NMR δ: 17.9, 23.7, 24.1, 41.3 (CH, CH_2, CH_3), 112.7 (C). Pentadecan-8-ylidene-8,8-bishydroperoxide (**7b**): IR (NaCl) ν cm^{-1}: 3405 (OOH); ^{1}H NMR δ: 0.82–1.74 (m, 30H, CH_2, CH_3), 9.60–9.80 (brs, 2H, OOH); ^{13}C NMR δ: 14.0 (CH_3), 22.6, 23.8, 29.0, 29.2, 29.6, 31.8 (CH_2), 113.4 (C). 1,1′-Dihydroperoxydi-(2-methylcyclohexyl) peroxide (**8g**): clear oil; IR (NaCl) ν cm^{-1}: 3415 (OOH); ^{1}H NMR δ: 0.83–2.31 (m, 24H, CH, CH_2, CH_3), 9.47–9.60 (brs, 2H, OOH); ^{13}C NMR δ: 22.0 (CH_3), 29.2, 30.5, 31.6, 34.0, 37.6 (CH, CH_2), 111.6 (C). 8,8′-Dihydroperoxypentadecan-8-yl peroxide (**10**): clear oil; IR (NaCl) ν cm^{-1}: 3416 (OOH); ^{1}H NMR δ: 0.83–1.80 (m, 60H, CH_2, CH_3), 9.59–9.64 (brs, 2H, OOH); ^{13}C NMR δ: 14.1 (CH_3), 22.6, 23.5, 29.0, 29.2, 29.6, 31.7 (CH_2), 114.6 (C). 3,3′,6,6′-Tetra-*n*-heptyl-1,2,4,5-teraoxacyclohexane (**11**): clear oil; ^{1}H NMR δ: 0.84–1.71 (m, 60H, CH_2, CH_3); ^{13}C NMR δ: 14.0 (CH_3), 22.6, 23.5, 29.0, 29.5, 29.6, 31.7 (CH_2), 114.7 (C). Analytical data for the other products were identical to those reported in the literature (see Table 1).

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