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The Effect of Iodine on the Peroxidation of Carbonyl Compounds

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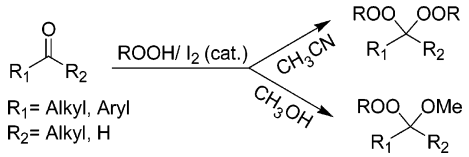

Peroxidation of ketones and aldehydes with iodine as a catalyst was studied. Ketones reacted with 30% aq hydrogen peroxide in the presence of 10 mol % of iodine to yield *gem*-dihydroperoxides in acetonitrile and hydroperoxyketals in methanol. The yield of hydroperoxidation of various cyclic ketones was 60−98%, including androstane-3,17-dione, while acyclic ketones were converted with a similar efficiency. Aromatic aldehydes were also converted to *gem*-dihydroperoxides with hydrogen peroxide and iodine as catalyst in acetonitrile and to hydroperoxyacetal in methanol, while the reactivity of aliphatic ones remained the same as in noncatalyzed reactions. *tert*-Butylhydroperoxide reacted in a similar manner, giving the corresponding perether derivatives. A study was also made of the relative kinetics of dihydroperoxidation from which the Hammet equation gave a reaction constant (ρ) of −2.76, indicating the strong positive charge development in the transition state and the important role of rehybridization in the conversion of hydroperoxyhemiketal to *gem*-dihydroperoxide. In acetonitrile, the iodine catalyst is apparently able to discriminate between the elimination of a hydroxy, methoxy, and hydroperoxy group and addition of water, methanol, and H_2O_2 to a carbonyl group.

Introduction

The increasing resistance of malaria parasites to commonly used alkaloidal drugs and the discovery of the antimalarial properties of artemisinin[1] have boosted interest into organic peroxides as potential antimalarials.[2] Monoperoxyketals and dihydroperoxides are key intermediates in the synthesis of many classes of peroxides, such as trioxanes,[3] tetraoxanes,[4] endoperoxides,[5] and acyclic analogues with a variety of functional groups.[5a] Organic peroxides are also valuable radical initiators and oxidants.[6]

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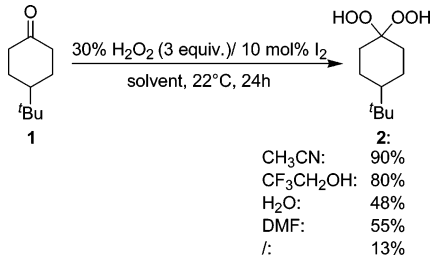
The major synthetic route to monoperoxyketals[7] and *gem*-dihydroperoxides[5d,e] is ozonolysis of ketone enol ethers or α-olefins in the presence of hydrogen peroxide, which happens to be the only general procedure for synthesis of primary *gem*-dihydroperoxides. In addition, dihydroperoxides can be synthesized from ketones or ketals with H_2O_2 under acidic conditions (tungstic acid,[8] $BF_3{\cdot}Et_2O$,[9] HCl,[10] or AcOH as solvent),[11] while methyltrioxorhenium ($MeReO_3$) in trifluoroethanol enables the synthesis of 4-*tert*-butylcyclohexyl-1,1-dihydroperoxide under neutral conditions.[4a] Dihydroperoxides can be further transformed into *gem*-bisperethers by alkylation with olefins or alkyl iodides in the presence of silver oxide or cesium hydroxide.[5a,c] Alternative methods for alkylation include the acid-catalyzed reaction of the carbonyl compound with alkylhydroperoxides in the presence of desiccants[12] and a recently published method involving the condensation of acetals and enol ethers with hydroperoxides catalyzed by protic or Lewis acids.[13] The drawbacks of these peroxidation reactions are the need for the prior synthesis of the starting substrates, the use of highly concentrated H_2O_2, the need for excess acid, moderate yields, and a restricted substrate range. The selectivity of ozonolysis is also poor and cannot be used for substrates containing ozone-sensitive groups. Because of these limitations, new, more efficient, and broad spectrum methods for synthesis of monoperoxyketals, dihydroperoxides, and also *gem*-bisperethers are sought.

Since molecular iodine is a proven Lewis acid catalyst for the activation of carbonyl compounds, including acetalization reactions,[14] we envisage that iodine could catalyze the peroxidation reactions of such compounds. We present our research on the use of iodine as a catalyst for conversion of ketones and aldehydes into dihydroperoxides, peroxyketal derivatives, and their perethers with 30% aq hydrogen peroxide or *tert*-butylhydroperoxide under neutral reaction conditions.[15] We also describe the reaction mechanism and the effect of iodine on the transformation of carbonyl compounds.

SCHEME 1



Results

Dihydroperoxides from Ketones. First we studied the effect of iodine (10 mol %) on the conversion of 4-*tert*-butylcyclohexanone **1** with 30% aq H_2O_2 (3 equiv) in different solvents. The reaction in acetonitrile (24 h at 22 °C) resulted in a 90% yield of the *gem*-dihydroperoxide, DHP (4-*tert*-butylcyclohexane-1,1-diyl dihydroperoxide **2**), as determined by NMR spectroscopy of the crude reaction mixture (Scheme 1). Trifluoroethanol also proved to be a good solvent, resulting in a high yield (80%) of DHP **2**, whereas reactions in water in *N*,*N*-dimethylformamide and without a solvent had lower selectivity and yielded lower amounts of **2** together with a mixture of various hydroperoxides. Consequently, we deemed acetonitrile to be the optimal solvent for the synthesis of DHPs, and so all further optimization of the reaction was made in this solvent. Interestingly, I_2 is able to discriminate between hydroxy and hydroperoxy as leaving groups and H_2O_2 versus H_2O as nucleophiles in addition to the ketone **1**.

Since the synthesis of acyclic DHPs is more problematic than cyclohexyl DHPs, we chose 3-decanone **3** as a test compound for the optimization of the reaction conditions. The reaction under above-mentioned conditions resulted in a low conversion of the 3-decanone **3** to DHP **4** (22%). Optimum results were obtained using 4 equiv of H_2O_2 at 22 °C, while the amount of iodine and the concentration of the reaction mixture had a marked effect (Figure 1); with 1 mol % of iodine, the conversion was below 40% at each concentration studied. Increasing the amount of iodine to 5 mol %, however, resulted in a significant improvement in conversion in the 0.1 and 0.5 M solutions of

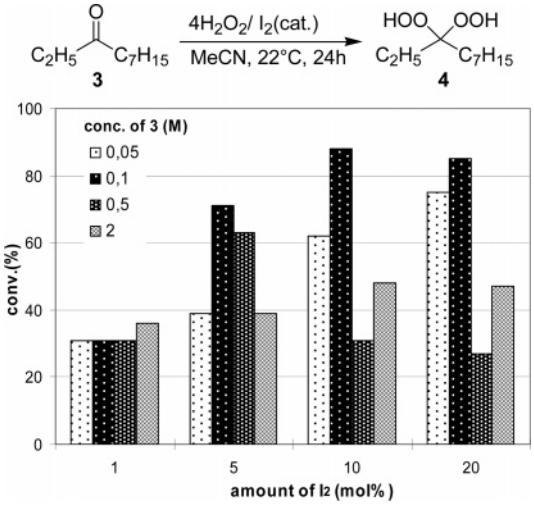


FIGURE 1. The effect of I_2 and reactant concentration on the conversion of 3-decanone **3** to DHP **4** using 30% H_2O_2 (conversion determined by NMR spectroscopy).

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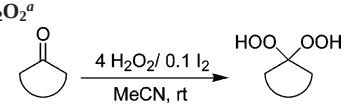
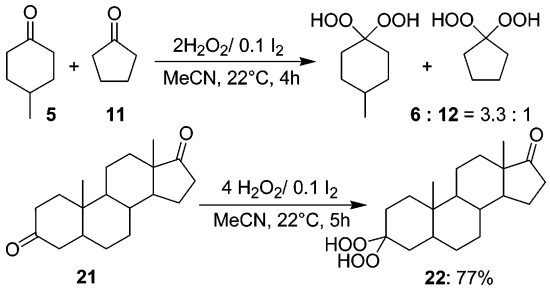
TABLE 1. Synthesis of Dihydroperoxides from Cycloalkanones with I_2/30% H_2O_2[a]



substrate		*t* (h)	yield (%)[b]
4-^{t}Bu-cyclohexanone	**1**	5	**2**: 91
4-Me-cyclohexanone	**5**	5	**6**: 98[d]
3-Me-cyclohexanone	**7**	5	**8**: 93
2-Me-cyclohexanone	**9**	5	**10**: 80
cyclopentanone	**11**	24[c]	**12**: 70
cycloheptanone	**13**	24	**14**: 90
cyclododecanone	**15**	24	**16**: 60
2-adamantanone	**17**	24[c]	**18**: 92
tetrahydro-4*H*-pyran-4-one	**19**	4	**20**: 89[e]

[a] Conditions: 1 mmol of ketone, 4 mmol of 30% H_2O_2, 0.1 mmol of I_2, 10 mL of MeCN, 22 °C. [b] Yield after column chromatography. [c] 2 mL of MeCN. [d] DHP **6** was synthesized on a few gram scale without any apparent complication. [e] Determined from the NMR spectra of the crude product and based on the starting compound.

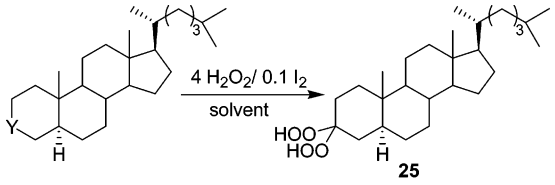
SCHEME 2. Iodine-Catalyzed Hydroperoxidation of Androstane-3,17-dione



3, although in the 0.05 and 2.0 M solutions, the effect was less pronounced. With the exception of the 0.5 M mixture, using 10 mol % of I_2 improved conversion still further with the best conversion occurring in a 0.1 M concentration of **3**. We observed a similar pattern in reactions with 20 mol % of iodine, although optimum conversion (0.1 M mixture) was lower than that in the case of 10 mol % of I_2.

From our results, we chose the best reaction conditions (a 0.1 M solution of ketone in acetonitrile, 4 equiv of 30% aq H_2O_2 and 10 mol % of I_2 at 22 °C) to synthesize DHPs from cyclic ketones (Table 1). Cyclohexanone derivatives had the highest reactivity, requiring only 5 h for an efficient conversion to DHPs, while the reactivity of the carbonyl group was sensitive to steric effects, as evidenced by a decrease in yield from 98% for 4-Me-cyclohexyl DHP **5** to 93% for 3-Me **7** and to 80% for 2-Me **9**. Cycloheptanone **13** and cyclododecanone **15** were also converted to their corresponding DHPs in good yields, while the formation of cyclopentyl **12** and 2-adamantyl dihydroperoxide **18** in sufficient amounts required a higher reaction concentration. Tetrahydro-4-pyranone **19** was efficiently transformed into DHP **20** as determined by the NMR spectroscopy of the crude reaction mixture, albeit the DHP **20** gradually decomposes during isolation into the starting ketone. To investigate the selectivity of dihydroperoxidation of cyclic ketones, we set up an experiment using typical reaction conditions with equimolar amounts of cyclopentanone **11** and 4-methylcyclohexanone **5**. According to NMR analysis of reaction mixture, the six-membered ring was 3.3 times more reactive (Scheme 2). To investigate how steric effects influence selectivity, we chose androstane-3,17-dione **21** since it incorporates both structures in a more complex steric environment. Reaction of **21** showed complete selectivity for the carbonyl group on the six-membered ring over the five-membered one, giving 3,3-dihydroperoxyandrostan-17-on **22** in a yield of 77% after column chromatography (Scheme 2).

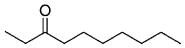
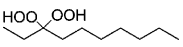
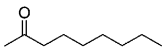
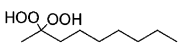
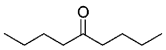
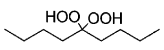
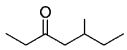
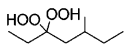
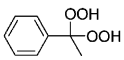
SCHEME 3



23, Y: C=O: MeCN, 5 h: 29%; MeCN, 24 h: 51%; MeCN/CH_2Cl_2 (9:1), 5 h: 42%

24, Y: $C(OMe)_2$: MeCN, 5 h: 44%

TABLE 2. Synthesis of Dihydroperoxides with I_2/30% H_2O_2

substrate		product	yield (%)[a,b]
	**3**		**4**: 91
	**26**		**27**: 96
	**28**		**29**: 78
	**30**		**31**: 50
	**32**		**33**: 16

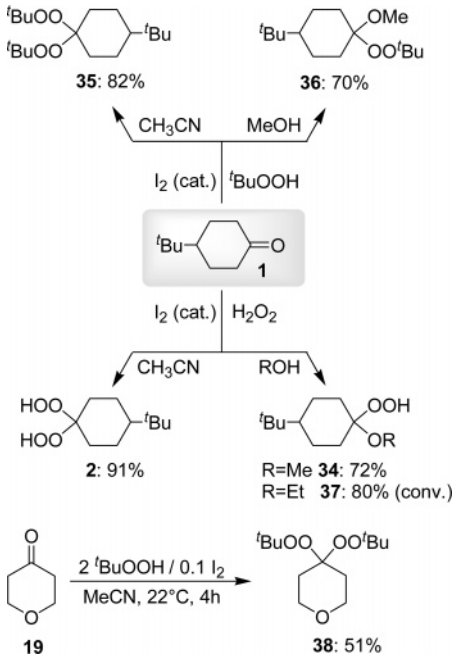
[a] Isolated yield after column chromatography. [b] Conditions: 1 mmol of ketone, 4 mmol of 30% H_2O_2, 0.1 mmol of I_2, 10 mL of MeCN, 22 °C, 24 h.

Conversion of cholestan-3-one **23** into its dihydroperoxide **25** was noticeably lower (29%) as determined by ^{1}H NMR of the crude reaction mixture. Considering the similarity of the reaction site to that in androstane-3,17-dione **21**, it is likely that this low conversion originated from cholestanone's poor solubility in acetonitrile. We were able to improve conversion by increasing the reaction time, by adding CH_2Cl_2 to improve solubility (Scheme 3), or alternatively by using a more soluble ketal derivative **24**. The result was a similar conversion in a shorter reaction time.

I_2-catalyzed hydroperoxidation with 30% H_2O_2 was also effective for acyclic ketones (Table 2), but again steric effects are important as seen from the lower yield of DHP **31**. Furthermore, *tert*-butyl methyl ketone was unreactive and gave only trace amount of its *gem*-dihydroperoxide. Acetophenone **32** was also converted to its DHP; to our knowledge, this is the first report of the dihydroperoxidation of acetophenone derivatives.

Miscellaneous Peroxides from Ketones. Since iodine proved to be a good catalyst for the reaction of ketones with hydrogen peroxide and able to discriminate between the hydroxy and hydroperoxy group and the two nucleophiles, H_2O_2 versus H_2O, we wanted to investigate its effect on peroxidation in a nucleophilic solvent and with alkylhydroperoxide (^{t}BuOOH) as a source of the peroxide unit. When using methanol as a solvent for iodine-catalyzed peroxidation of ketone with 30% aq H_2O_2, the major reaction product was monoperoxyketal **34**. Optimum

SCHEME 4



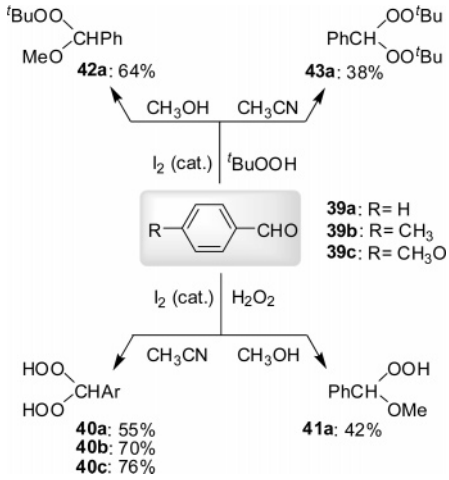
selectivity was obtained using a 0.5 M solution of ketone **1** in methanol, 1 equiv of 30% aq H_2O_2, and 5 mol % of I_2. After 20 h at 22 °C, product **34** was isolated in 72% yield (Scheme 4). Next, we performed reactions in ethanol, *n*-propanol, and *i*-propanol. Reaction of ketone **1** and H_2O_2 in ethanol resulted in a 64% conversion, while selectivity decreased and dihydroperoxide **2** and monoperoxyketal **37** were formed in a ratio of 1:1.6. Changing the amount of I_2 to 10 mol % and the concentration of **1** to 0.25 M solution in ethanol yielded the monoperoxyketal **37** selectively in a yield of 80% based on starting compound as determined from ^{1}H NMR spectra of the crude reaction mixture (Scheme 4). However, **37** was unstable and it decomposed to the starting ketone and dihydroperoxide during isolation, but it was possible to determine its structure from the crude reaction mixture by comparing spectroscopic data with its stable analogue **34**. In less nucleophilic *n*-propanol and sterically hindered *i*-propanol, selectivity for the monoperoxyketal formation was lost.

We also wanted to investigate whether or not iodine could catalyze reactions of ketones with *tert*-butylhydroperoxide, as this would open up a route to producing the *gem*-bisperethers. Seventy percent aqueous and 60% decane solutions of *tert*-butylhydroperoxide were tested as a substitute for hydrogen peroxide under the same reaction conditions used for the synthesis of DHPs. Our results revealed the conversion to *gem*-bisperether with decane solution of oxidant to be greater than that with the aqueous solution. The best result was obtained using a 1.0 M solution of ketone **1** in acetonitrile, 2 equiv of ^{t}BuOOH (60% in decane), and 10 mol % of I_2, and after 24 h reaction at 22 °C, 4-*tert*-butyl-1,1-bis-*tert*-butylperoxycyclohexane **35** was isolated in a yield of 82% (Scheme 4).

By analogy to reactions with hydrogen peroxide, we expected the formation of *tert*-butylperoxyketal when using ^{t}BuOOH in methanol. Starting from 4-*tert*-butylcyclohexanone **1** as a substrate, we were able to isolate *tert*-butylperoxyketal **36** in a 70% yield (Scheme 4).

Since bisperoxyethers are more stable than DHPs, we used ^{t}BuOOH for the peroxidation of tetrahydro-4*H*-pyran-4-one **19** since isolation of its DHP **20** failed due to its high polarity and instability. We did succeed in transforming **19** to its bisperoxyether **38** with 68% conversion and isolating it using column chromatography with a yield of 51% (Scheme 4).

SCHEME 5



Peroxidation of Aldehydes. There are, to our knowledge, also no reports concerning the direct dihydroperoxidation of aldehydes with hydrogen peroxide. To address this, we tested iodine-catalyzed hydroperoxidation with 30% aq H_2O_2 on benzaldehyde **39a** and found that it selectively converts **39a** into the *gem*-dihydroperoxide **40a** in a yield of 66 and 55% after column chromatography. The effect of the electron-donating substituent on the phenyl ring on the conversion to the DHP proved remarkable (Scheme 5) as DHP with a *p*-methyl group was isolated with 70% yield and 76% with a *p*-methoxy group. Iodine is clearly critical for good conversion of **39a** since the absence of I_2 resulted in only a 15% conversion under equivalent reaction conditions.

Next, we performed the reaction of **39a** with H_2O_2 in methanol, and we isolated hydroperoxyketal **41a** in 42% yield. We observed a similar reactivity using ^{t}BuOOH, where *tert*-butylperoxyacetal **42a** was formed in methanol, while the reaction in acetonitrile yielded di-*tert*-butylperoxide **43a**.

Simple, nonaromatic aldehydes, which easily undergo hydration,[16] have different reactivities than ketones and benzaldehydes. Using the reaction conditions under which benzaldehyde was transformed into DHP, both alkyl aldehydes—dihydrocinnamaldehyde **44a** and octanal **44b**—were not converted into their corresponding DHPs but instead into hydroxyhydroperoxides **45a** and **45b** (Scheme 6). In fact, the products are the same as in the noncatalyzed reaction. In methanol, **44b** yields a mixture of peroxyacetal **46b** and hydroxyhydroperoxide **45b** (Scheme 6). The reaction with ^{t}BuOOH was also tested, and as anticipated, the *tert*-butylperoxy hemiacetal **47a** was formed (Scheme 6).

Discussion

A major aim of ours was to achieve a better insight into the mechanism of iodine-catalyzed dihydroperoxidation of carbonyl compounds. The reaction follows the route of acid-catalyzed addition to the carbon−oxygen multiple bond, where iodine acts

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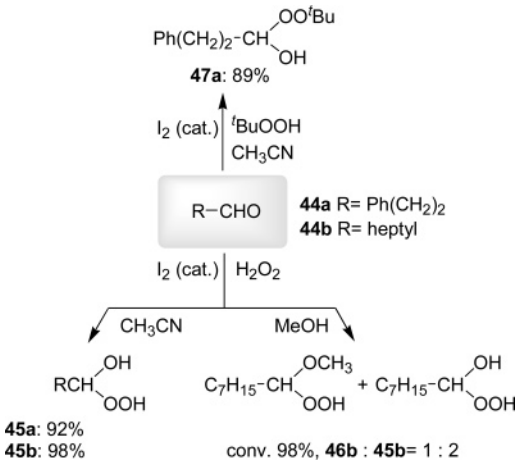
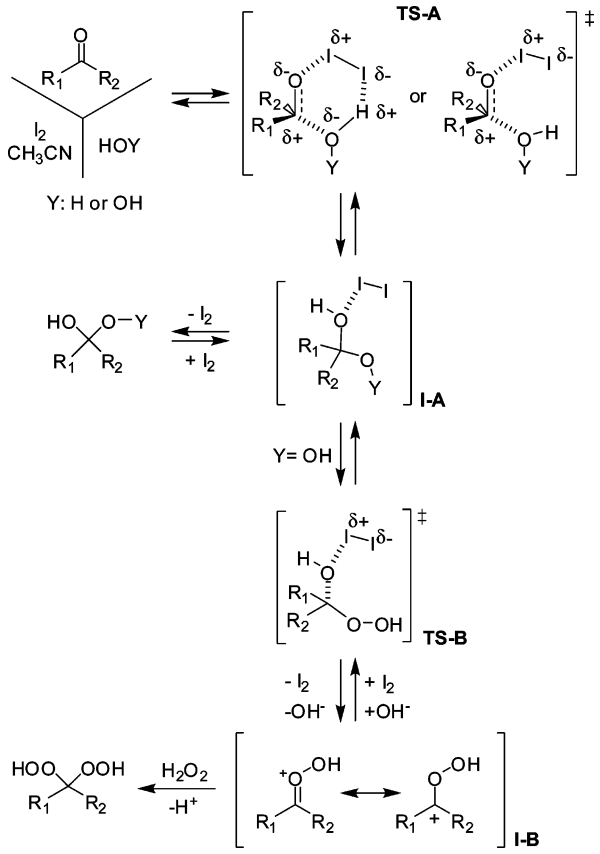
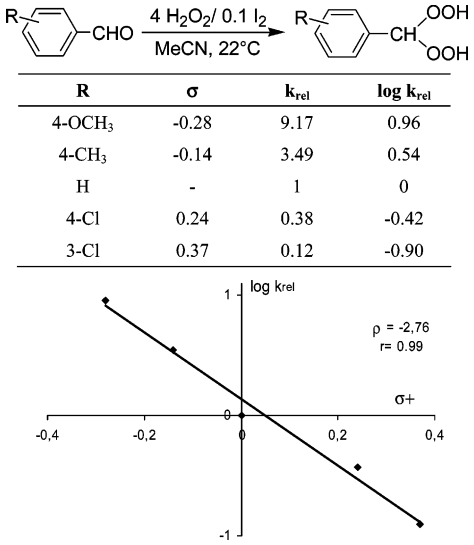
SCHEME 6



SCHEME 7



as a Lewis acid (Scheme 7).[17] Initially, a multicomponent system exists, where each component—carbonyl compound, iodine, hydrogen peroxide, water, and acetonitrile—plays an important role. The reaction begins with an interaction between iodine, the oxygen atom of a carbonyl group, and a nucleophile (H_2O_2 or H_2O) to produce a transition state TS-A (at present, we have insufficient evidence to say whether or not it is open or cyclic). Proton migration in the first intermediate (not stated in Scheme 7) leads to the sp^3 intermediate I-A, which is transformed into either the hydrate or the peroxyhydrate. Iodine once again acts as a catalyst for the elimination of the hydroxy group and leads via the TS-B to form the intermediate peroxycarbenium ion I-B. In the case of DHPs, it is trapped by another H_2O_2 molecule to give the product.



R	σ	k_{rel}	log k_{rel}
4-OCH_3	-0.28	9.17	0.96
4-CH_3	-0.14	3.49	0.54
H	-	1	0
4-Cl	0.24	0.38	-0.42
3-Cl	0.37	0.12	-0.90

FIGURE 2. Relative kinetics of iodine-catalyzed reaction of benzaldehydes with 30% H_2O_2.

It is evident that I_2 plays an essential role in the reaction. We found that the absence of I_2 results in a loss of selectivity in the formation of DHP in the case of the reaction of cyclohexanones, while the reaction of 3-decanone **3** and other less reactive substrates did not proceed at all. Similarly, the reaction of *tert*-butylcyclohexanone **1** with hydrogen peroxide in methanol without iodine did not lead to the selective formation of hydroperoxyketal **34**, instead conversion was low and the reaction was nonselective. We also observed a marked effect of the substituent on the aromatic ring of benzaldehyde on the formation of DHP. To quantify this effect by linear free-energy relationships (LFER), relative reactivities for I_2-catalyzed dihydroperoxidation of benzaldehydes with electron-donating (4-MeO, 4-Me) and electron-accepting groups (3-Cl, 4-Cl) were determined by comparison with unsubstituted benzaldehyde. Thus we obtained the relative reaction rates with a Hammett correlation with very good linearity (Figure 2). The negative reaction constant suggests the electrophilic activation of the carbonyl group, with iodine acting as a Lewis acid, while its high value ($\rho = -2.76$) suggests a transition state with a more developed charge in the rate-determining step. This is similar to the value obtained for the acid-catalyzed hydrolysis of benzaldehyde hydrates.[16]

We also wanted to determine whether or not the role of iodine is crucial in the second reaction step. Dussault et al. have proposed for the reaction of perketals with carbon nucleophiles the formation of a peroxycarbenium ion as an intermediate.[18] We believe that the rehybridization of the sp^3 C atom in I-A into a sp^2 one in I-B (Scheme 7) is important in the second reaction step. The reactions involving aliphatic aldehydes stop after the first step (yielding hydroxyhydroperoxides **45**), in contrast to benzaldehydes, where resonance stabilization of the sp^2 intermediate can occur and supposedly favors the formation of DHP. To determine the role of iodine in this step, we chose methoxyhydroperoxide **34** as our model for the intermediate

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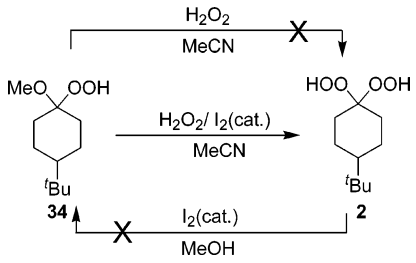
SCHEME 8



product I-A. From Scheme 8, the importance of iodine in this reaction step is evidenced by the fact that methoxyhydroperoxide **34** conversion to DHP **2** occurs only in the presence of iodine. Further, we believe that iodine activates the substitution of the OCH_3 group with OOH, while it does not activate the reverse reaction from DHP **2** to **34** (Scheme 8), which can be attributed to iodine's ability to interact with the methoxy O atom as a Lewis acid and to facilitate its release. Therefore, I_2 assists in the rehybridization of the sp^3 C atom in I-A by enabling the addition of the second nucleophile. Also, iodine does not facilitate rehybridization through interactions with the OOH group, and this is possibly due to an interaction with the O atom attached to the H and consequently does not enhance the leaving group ability of the hydroperoxo substituent.

The solvent used also had a marked effect on the iodine-catalyzed hydroperoxidation of carbonyl compounds. Acetonitrile is a good partner for iodine because it does not strongly coordinate the catalyst. Conversely, methanol is known to interact strongly with iodine, and the reaction in methanol does not lead to the formation of DHP but instead to peroxyketals. This points to the important role that solvation has on iodine and on its strength since methanol deactivates iodine to the point where it is incapable of catalyzing the second step of reaction.

Conclusion

Iodine-catalyzed hydroperoxidation of cyclic and acyclic ketones as well as aromatic aldehydes with aqueous H_2O_2 in acetonitrile is a straightforward and efficient method for the synthesis of *gem*-dihydroperoxides. An analogous reaction in methanol yields hydroperoxyacetals, while *tert*-butylhydroperoxide produces the corresponding perether derivatives.

I_2-catalyzed reaction of ketones and H_2O_2 is a two-step reaction, and iodine is essential in each step, possibly playing a double role as a catalyst by enhancing the electrophilic character of the carbonyl C atom (high negative value for the Hammet reaction constant) and enhancing the nucleophilic character of hydrogen peroxide. Iodine also assists in the rehybridization of the sp^3 C atom into the sp^2 one in the second step, which enables the further addition of a nucleophile. Iodine is able to discriminate between the hydroxy and hydroperoxy group and between two nucleophiles (H_2O_2 vs H_2O) in an addition to the ketone.

Experimental Section

Synthesis of *gem*-Dihydroperoxides. General Procedure for the Synthesis of DHPs from Ketones and Aromatic Aldehydes: To a solution of 0.1 mmol of I_2 (25.4 mg) and 4 mmol of 30% H_2O_2 (0.45 mL) in 10 mL of acetonitrile was added 1 mmol (154 mg) of 4-*tert*-butylcyclohexanone **1**, and the solution was stirred at 22 °C for 5 h. The reaction mixture was concentrated under reduced pressure (ca. 20 mmHg), dichloromethane (10 mL) added, and the solution dried over Na_2SO_4. The solvent was evaporated and product **2** isolated by column chromatography (SiO_2, CH_2Cl_2/EtOAc = 8:2).

(4-Methylphenyl)methylene Dihydroperoxide 40b: 40b was made from aldehyde **39b** according to the general procedure, with reaction time of 24 h: white solid (70%); mp 55−56 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 6.28 (s, 1H), 7.16 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 9.72 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 110.0, 126.9, 129.1, 129.5, 139.7; IR ν 3250, 1306, 1183, 1042, 983, 805, 777 cm^{-1}. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.60; H, 6.18.

Synthesis of Hydroperoxyketals. Methoxy(phenyl)methyl Hydroperoxide 41a:[19] To a solution of 0.05 mmol of I_2 (12.7 mg) and 1 mmol of 30% H_2O_2 (0.12 mL) in 2 mL of methanol was added 1 mmol (120 mg) of 4-methylbenzaldehyde **39a**, and the solution was stirred at 22 °C for 24 h. The reaction mixture was then concentrated under reduced pressure (ca. 20 mmHg), dichloromethane (10 mL) added, and the solution dried over Na_2SO_4. The solvent was evaporated and the product isolated by column chromatography (SiO_2, CH_2Cl_2/EtOAc = 9:1), and 65 mg (42%) of colorless oil was obtained: ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H), 5.73 (s, 1H), 7.30−7.68 (m, 5H), 8.82 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.0, 107.6, 126.9, 128.3, 129.2, 135.3.

Synthesis of Bisperethers. 4-*tert*-Butyl-1,1-bis(*tert*-butylperoxy)cyclohexane 35: To a solution of 0.1 mmol of I_2 (25.4 mg) and 2 mmol of 60% ^{t}BuOOH decane (0.72 mL) in 1 mL of acetonitrile was added 1 mmol (154 mg) of 4-*tert*-butylcyclohexanone **1**, and the solution was stirred at 22 °C for 24 h. The reaction mixture was concentrated under reduced pressure (ca. 20 mmHg), and the product was isolated by column chromatography (SiO_2, petrolether/ether = 95:5); 235 mg (82%), mp 49.5−50.5 °C, mp (lit)[20] 48−49 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 9H), 0.93−1.08 (m, 1H), 1.23 (s, 9H), 1.27 (s, 9H), 1.20−1.46 (m, 4H), 1.55−1.69 (m, 2H), 2.24−2.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.4, 26.7, 26.9, 27.6, 30.9, 32.4, 47.4, 78.9, 79.1, 106.8.

Synthesis of Peroxyketals. *tert*-Butyl 4-*tert*-Butyl-1-methoxycyclohexyl Peroxide 36: To a solution of 0.05 mmol of I_2 (12.7 mg) and 2 mmol of 60% ^{t}BuOOH (0.72 mL) in 1 mL of methanol was added 1 mmol (154 mg) of 4-*tert*-butylcyclohexanone **1**, and the solution was stirred at 22 °C for 24 h. The reaction mixture was then concentrated under reduced pressure (ca. 20 mmHg) and product isolated by column chromatography (SiO_2, petrolether/ether = 95:5). Its structure was determined by comparing the NMR spectroscopic data with its hydroperoxy analogue **34**: 182 mg (70%, mixture of diastereomers 1.7:1) of colorless oil; IR ν 1364, 1194, 1103, 889 cm^{-1}. Active oxygen content calcd 0.124, by iodometric titration 0.123.

Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 9H), 1.29 (s, 9H), 0.95−1.55 (m, 5H), 1.55−1.70 (m, 2H), 2.20−2.35 (m, 2H), 3.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 23.6, 26.7, 27.5, 32.0, 32.3, 47.1, 48.1, 78.8, 103.0.

Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 9H), 1.24 (s, 9H), 0.95−1.40 (m, 5H), 1.55−1.70 (m, 2H), 2.06−2.17 (m, 2H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 23.4, 26.6, 27.6, 31.7, 32.3, 47.8, 48.0, 78.75, 103.4.

Synthesis of Peroxyacetals. *tert*-Butyl Methoxy(phenyl)methyl Peroxide 42a:[21] To a solution of 0.05 mmol of I_2 (12.7 mg) and 1 mmol of 60% ^{t}BuOOH decane solution (0.36 mL) in 2 mL of methanol was added 1 mmol (120 mg) of benzaldehyde **39a**, and the solution was stirred at 22 °C for 24 h. The reaction mixture was concentrated under reduced pressure (ca. 20 mmHg), and the

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product was isolated by column chromatography (SiO_2, petrolether/ether = 95:5). Obtained was 135 mg (64%) of colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 3.59 (s, 3H), 5.76 (s, 1H), 7.25−7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.4, 56.2, 80.8, 106.86, 126.8, 128.1, 128.8, 136.2.

Synthesis of Hydroperoxyhemiacetals. To a solution of 0.1 mmol of I_2 (25.4 mg) and 4 mmol of 30% H_2O_2 (0.45 mL) in 10 mL of acetonitrile was added 1 mmol (134 mg) of 3-phenylpropionaldehyde **44a**, and the solution stirred at 22 °C for 24 h. The reaction mixture was concentrated under reduced pressure (ca. 20 mmHg), dichloromethane (10 mL) added, and the solution dried over Na_2SO_4. The solvent was evaporated to leave 153 mg (91%) of colorless oil **45a**. Its structure was deduced by comparing NMR spectroscopic data with its *tert*-butylperoxy methoxy analogue,[22] and active oxygen content was determined by iodometric titration after isolation. Further characterization failed as it is not stable, decomposing to the starting aldehyde although refrigerated.

1-Hydroperoxy-3-phenylpropan-1-ol 45a: colorless oil, 153 mg (91%); ^{1}H NMR ($CDCl_3$) δ 1.67−2.05 (m, 2H), 2.65 (t, J = 8 Hz, 2H), 5.10 (br s, 1H), 5.10 (t, J = 6 Hz, 1H), 7.00−7.30 (m, 5H), 9.25 (br s, 0.5H), 9.98 (br s, 0.5H); ^{13}C NMR ($CDCl_3$) δ 30.5, 34.2, 101.0, 126.1, 128.3, 128.4, 140.7; IR ν 3347, 1346, 1177, 1098, 1031, 925, 746, 700 cm^{-1}. Active oxygen content calcd 0.190, by iodometric titration 0.187.

Synthesis of Peroxyhemiacetal. 1-(*tert*-Butylperoxy)-3-phenylpropan-1-ol 47a: To a solution of 0.05 mmol of I_2 (12.7 mg) and 4 mmol of 60% ^{t}BuOOH decane solution (1.44 mL) in 2 mL of acetonitrile was added 1 mmol (134 mg) of 3-phenylpropionaldehyde **44a**, and the solution was stirred at 22 °C for 24 h. The reaction mixture was concentrated under reduced pressure (ca. 20 mmHg) and the product isolated by column chromatography (SiO_2, petrolether/ether = 95:5), and 199 mg (89%) of a colorless oil was obtained. Its structure was deduced by comparing NMR spectroscopic data with its methoxy analogue,[22] and active oxygen content was determined by iodometric titration straight after isolation. Further characterization failed as the product was unstable, decomposing to starting aldehyde although refrigerated: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 1.87−2.00 (m, 2H), 2.76 (t, J = 8 Hz, 2H), 3.60 (br s, 1H), 5.17 (dd, J_1 = 5.4 Hz, J_2 = 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.4, 30.6, 34.4, 99.4, 125.9, 128.2, 128.27, 128.32, 141.2; IR ν 3429, 1364, 1244, 1194, 1095, 1030, 927, 878, 748, 700 cm^{-1}. Active oxygen content calcd 0.143, by iodometric titration 0.143.

Hammet Correlation. The relative reactivities of benzaldehydes were determined by competitive reactions, carried out as follows. To a solution of 0.05 mmol of I_2 (12.7 mg) and 2 mmol of 30% H_2O_2 (0.22 mL) in 5 mL of acetonitrile were added 0.5 mmol (53 mg) of benzaldehyde and 0.5 mmol of substituted benzaldehyde, and the solution was stirred at 22 °C for 15 h. The reaction mixture was concentrated under reduced pressure (ca. 20 mmHg), dichloromethane (10 mL) added, dried over Na_2SO_4, and the solvent evaporated. The amounts of reacted benzaldehydes were determined from ^{1}H NMR spectra of the crude reaction mixture using 1,1-diphenylethylene as an internal standard. Applying this known competitive technique, relative reactivities expressed by relative rate factors (k_{rel}) were calculated from the equation[23] $k_{rel} = k_A/k_B = \log((A - X)/A)/\log((B - X)/B)$, derived from the Ingold−Shaw[24] relation where A and B are the amounts (in mmol) of starting material and X and Y are the amounts of product derived from them.

Acknowledgment. This research has been supported by the Ministry of Higher Education, Science and Technology of the Republic of Slovenia, the Young Researcher program (K.Ž.) of the Republic of Slovenia. The authors are grateful to I. Pravst, the staff of the National NMR Centre at the National Institute of Chemistry in Ljubljana (A. Gačeša and J. Plavec), and the staff of Mass Spectroscopy Centre at the JSI (B. Kralj, D. Žigon), to T. Stipanovič and Prof. B. Stanovnik for some elemental combustion analysis.

Supporting Information Available: General synthetic procedures for DHP and characterization of substances are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0708745

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