

THE REACTION OF SINGLET OXYGEN WITH 1-METHOXYCYCLOHEXENE*

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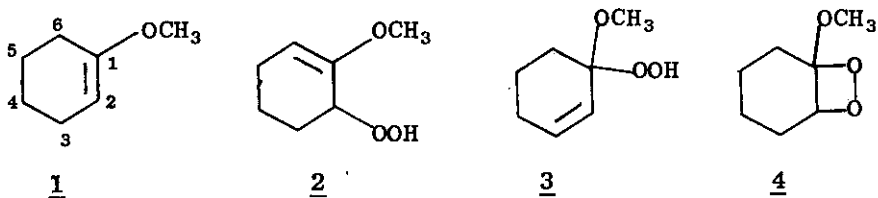
Abstract: 1-Methoxycyclohexene (1) on photosensitized oxygenation yields the two allylic hydroperoxides 2 and 3 and the dioxetane 4. In a slower reaction 2, which is still an enol ether, is further photo-oxidized. The initial oxidation products are all thermally unstable, but analytical procedures are described by which their amounts can be determined. The rate of oxygenation and the proportion of 3 are both approximately doubled in benzene compared to acetonitrile as solvent. The mechanism of the reaction is discussed in the light of this and related evidence recently developed for the 2,3-dihydro-4H-pyrans.

*Cordially dedicated to Professor Tetsuo Nozoe on the occasion of his 77th birthday.

Introduction

Open-chained and monocyclic olefins having allylic hydrogen react generally with singlet molecular oxygen to yield allylic hydroperoxides. A single alkoxy substituent imparts enough additive reactivity to the double bond to allow dioxetane formation to compete with the "ene" type reaction leading to hydroperoxide. In a recent paper³ we have reported solvent and isotope effects on the rate and product composition in the photosensitized oxidation of 4-methyl-2,3-dihydro-4H-pyran, where the immediate product consists of a mixture of dioxetane with the single allylic hydroperoxide possible in that system. The isotope effects were consistent with an intermediate perepoxide or with competing one-step processes in which the transition states deviated from the "least motion" path in each case toward an intramolecularly hydrogen-bonded perepoxide.

In 1-methoxycyclohexene (1), since the activating ether oxygen is not a part of the ring, the two directions of ene reaction leading to the hydroperoxides 2 and 3 are both possible, as well as dioxetane 4. This therefore appeared to be a favorable



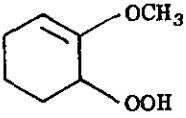
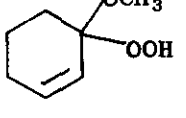
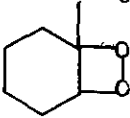
case in which to supplement the information already obtained for the dihydropyrans.

Results

1 was prepared from cyclohexanone (5) via its dimethyl ketal (6). Since the expected products of photo-oxidation, dioxetane and allylic hydroperoxides, are all thermally unstable under the conditions of vapor chromatography, the direct oxidation mixture was treated with triphenylphosphine prior to chromatography, which converts hydroperoxides quantitatively into the corresponding alcohols. In this case the dioxetane, which was never isolated, evidently decomposed by cleavage to the corresponding dicarbonyl compound, 5-carbomethoxypentanal (7), also quantitatively, at -10°C , before the triphenylphosphine was added. As shown in Table 1, the reaction product after

Table 1.

Products of Photo-oxidation of 1-Methoxycyclohexene at 10°C .

Solvent	Sensitizer	(a)  <u>2</u>	(b)  <u>3</u>	(c)  <u>4</u>
$\text{CH}_3\text{CN}^{\text{f}}$	MB^{d}	37	34	29
$\text{C}_6\text{H}_6^{\text{f}}$	TPP^{e}	27	67	6
$\text{C}_6\text{H}_6^{\text{g}}$	TPP^{e}	--	89	11

Analysis by vapor chromatography after treatment of product mixture with triphenylphosphine. (a) Analyzed as 2-methoxy-2-cyclohexen-1-ol (11). (b) Analyzed as 2-cyclohexenone (8). (c) Analyzed as 5-carbomethoxypentanal (7), (d) Methylene blue. (e) Tetraphenylporphin. (f) Conversion 60%. (g) Total conversion (1.2 moles O_2 absorbed).

absorption of 60% of a mole of oxygen could be accounted for as a mixture of dioxetane 4 and the two allylic hydroperoxides 2 and 3. The rate of oxygen uptake under identical conditions and the ratio of 3/2 in the product were both about twice as great in benzene as in acetonitrile. The amount of dioxetane, small in benzene, was almost five times as great in acetonitrile. For purposes of this analysis the reference compounds 7, 8, and 11 were prepared for comparison, as well as the allylic hydroperoxide 2, 2,3-epoxycyclohexanone (9), and 2-methoxy-2-cyclohexenone (10). As in the case of 4-methyl-2,3-dihydro-4H-pyran³, the more polar solvent, acetonitrile, favors dioxetane formation relative to benzene, in part at least because the polar solvent competes with the internal hydrogen bonding which is involved in the ene reaction. A similar effect has been observed by Ando et al.⁴ in the photo-oxidation of 1-ethoxycyclohexene in methanol vs. acetone.

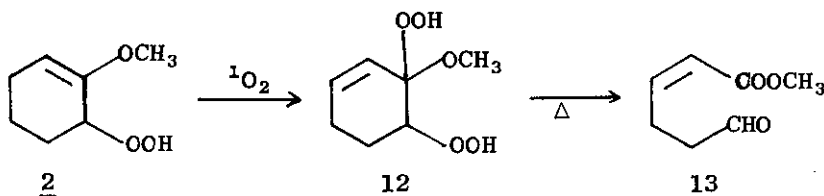
When the photo-oxidation in benzene was run until no more oxygen was absorbed, a total of about 1.2 moles of oxygen per mole of enol ether was taken up, and the product, after treatment with triphenylphosphine, showed no vpc peak corresponding to 11 coming from 2. Since there had been 27% of hydroperoxide 2 earlier in the same reaction, it appeared that this hydroperoxide, being itself an enol ether, underwent further photo-oxidation in the later stages of the reaction.

Hydroperoxide 2 was therefore synthesized⁵ and its behavior toward singlet oxygen was further investigated.

Reactions of 3-Hydroperoxy-2-Methoxycyclohexene (2). Treatment of 2 with triphenylphosphine gave a quantitative yield of the corresponding alcohol 11 and triphenylphosphine oxide.⁶

Thermolysis of 2 in the vpc injection port (200°) yielded primarily alcohol 11 and ketone 10 plus small amounts of several cleavage products.

Photo-oxidation of 2 proceeded, with the uptake of one equivalent of oxygen, approximately four times more slowly than that of 1, a deactivation observed generally for allylic hydroxy and hydroperoxy groups.⁷ The nmr spectrum of the product mixture is consistent with dihydroperoxide 12 as the major product.



Thermolysis of the oxygenation mixture in the vpc injection port gave two products in a 4:1 ratio. The major product was identified by its spectral characteristics as the aldehydoester 13, the unsaturated counterpart of 7. Thermal cleavage of either O-O bond of 12 should lead to 13 through β-fission of the initial alkoxy radical.

Although 13 never appeared as a separate vpc peak in the photo-oxidation product analyses, the nmr spectra of samples of 7 after the absorption of the maximum of O₂ in acetonitrile

showed the presence of about 30% of 13. Thus any 13 in the analyses corresponding to further oxidation of 2 would be interpreted as evidence of the dioxetane 4 in the product. This is not a serious perturbation in the analyses up to 60% oxygen absorption in benzene because of the minor importance of the peak and the relative slowness of the second oxidation of 2, but it leads us to expect an increase in the (7 + 13) peak in the analyses of the fully oxygenated samples.

In acetonitrile, where dioxetane is a more important part of the product, a series of product distributions were determined from 20% to 120% oxygen absorption, with direct vapor chromatography without prior treatment with triphenylphosphine. This affects the analysis in the known way that the concentration of 2 is represented by the sum of the peaks for 10 and 11, while the unresolved peak for (7 + 13) represents the sum of dioxetane and the doubly oxidized 2 formed in the latter part of the experiment. These results are summarized in Table 2.

In both benzene and acetonitrile there is an increase in the peak for cleavage products toward the end as expected. In benzene (Table 1) the late disappearance of 2 amounts to 27%, of which 5% appears as an increase in cleavage products (corresponding to newly formed 13 in the peak with 7), but there is an increase of 22% in the peak interpreted as coming from 3. Similarly, in acetonitrile (Table 2) at the end the 2 has gone down from its maximum of 36% to 5% of the product. Of this 31% decline, 12% is found in the peak for the cleavage products, while there is a 19% increase in the peaks attributed to 3. Thus

Table 2.

Photo-oxidation of 1-Methoxycyclohexene in Acetonitrile
with 0.001 M Methylene blue, 10°

% Reaction	Relative Amounts of Products ^a		
	(<u>7</u> + <u>13</u>)	<u>8</u> (from <u>3</u>)	(<u>10</u> + <u>11</u>) (from <u>2</u>)
20	55	9	36
40	55	11	34
60	50	14	36
80	49	16	35
100	57	25	18
120	62	33	5

^avpc peaks from untreated photo-oxidation mixture. (7 + 13) represents the sum of 4 and further oxidized 2.

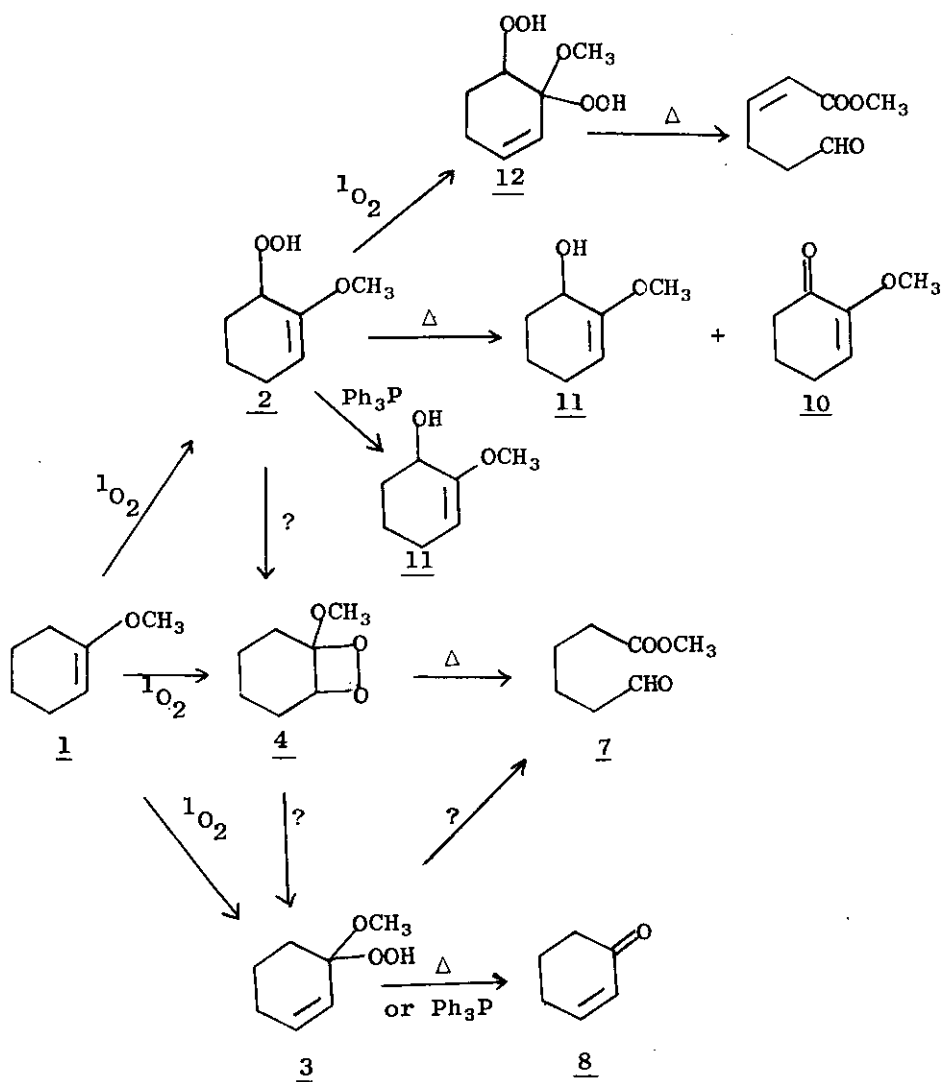
there appears to be a substantial time-dependent conversion of 2 into 3, not necessarily connected with the later oxidation. By what mechanism might 2 undergo conversion into 3? It is easy to write a mobile closure of 2 to 4 (a favored first step in Hock cleavage of allylic hydroperoxides) and then by invoking reversibility, to reopen the dioxetane 4 to the isomeric 3. Such a mobile interconversion would rationalize the interconversions during photo-oxidation seen in Tables 1 and 2, even if excited states were required to mobilize the interconversion. We have, however, no convincing evidence that such a process could occur in defiance of irreversible cleavage to 7, which prevents 4 from being a viable product even at temperatures as

low as -78° .

As to the occurrence of isomeric allylic hydroperoxides in comparable amounts, our observations are parallel to the results of Pusset, Guenard and Beugelmans,⁸ who photo-oxidized 3-acetoxy-2-cholestene and obtained upon workup 25% of 1-cholesten-3-one and 30% of 4-cholesten-3-one, traceable to the allylic hydroperoxides formed by ene reaction in the two directions. Those authors did not detect any cycloaddition of singlet oxygen, but if the missing 45% of the product was dioxetane, its ring-opening product, or a polycondensation product of the latter, there would be a rather close resemblance between the behavior of 3-acetoxy-2-cholestene and that of 1-methoxycyclohexene.

Scheme 1 summarizes the reactions reported in Tables 1 and 2 and discussed above. Scheme 1 also shows why the two reactions in which triphenylphosphine converts hydroperoxides into alcohols simplify the analysis by intercepting a number of other reactions of the hydroperoxides. The uncertain routes shown by which 2 and 3 might form 7 are less important than the suspected conversion of 2 to 3, indicated in the tables and discussed above.

Insistent as the evidence appears to be for the involvement of something resembling a perepoxide in the photo-oxidation of enol ethers, it has not yet proved possible to obtain definitive proof of a true intermediate with this structure. It may be relevant to recall an earlier unexplained observation concerning solvent effects in the competition between certain dioxetane- and hydroperoxide-forming photo-oxidations. Whereas there is as much as a 35-fold increase between benzene and acetonitrile



Scheme 1.

solutions in the ratio of cycloaddition to ene reaction in the dihydropyrans,³ there was no significant effect of this solvent change⁹ on the intermolecular competition between tetramethylethylene (which always yields ene product) and 1,2-diethoxyethylene (which yields entirely dioxetane).

This is just what would be predicted if in all cases the formation of perepoxide is rate-determining, with an "early" transition state not having developed much polarity, the solvent effect arising from the differing polarities as perepoxide goes concertedly to allylic hydroperoxide or to dioxetane. In this case there could be no solvent effect on the product composition when each reactant gave only a single product. As far as it goes, this is at least one case where the facts would not be fitted as well by two independent transition states as by a perepoxide intermediate.

Experimental

Nmr spectra were obtained on a Varian A-60 spectrometer while ir spectra were recorded with a Perkin-Elmer model 137 spectrometer. Mass spectra were run on an Associated Electrical Industries, Ltd., model MS-9 mass spectrometer. Vapor phase chromatograms were run with Hewlett-Packard F and M model 700 and a Varian Aerograph model 90-P3 and Autoprep model A-700. Peak areas were measured by disc integration or triangulation. Ozone was generated in a Welsbach Corporation ozonator model T-23 (2-4% ozone in oxygen). Singlet oxygen was generated in the photo-oxidation cell described in a previous paper.³ The

preparation of compounds 6, 9, 10, and 12 have been described elsewhere.⁵

1-Methoxycyclohexene (1).¹⁰ A three-necked, one-liter, round-bottom flask fitted with dropping funnel, reflux condenser and stopper was charged with 200 g (2.04 mol) of cyclohexanone, 200 ml of anhydrous methanol and 1.5 g of p-toluenesulfonic acid. To the magnetically stirred solution, 260 g (2.45 mol) of methyl orthoformate was added at a moderate rate from the dropping funnel. A vigorous reaction occurred which caused boiling, after which the reaction was heated under reflux overnight. An additional gram of p-toluene-sulfonic acid was then added and the solution was distilled through a 14" column packed with helices with a reflux ratio of 13:1. The distillate was analyzed by vpc.¹¹ After the methyl formate, methanol and excess methyl orthoformate had been distilled off, the desired 1-methoxycyclohexene (164.1 g, 1.46 mol, 71.7% yield) distilled in a range of 140-143°, 45% yield. The center cut (142 g) distilled at 143° (lit. 138-142°, ¹⁰ 67-68° (57 mm), ¹² 143-145° (760 mm)¹³). Vpc¹¹ analysis indicated that the product was more than 99% pure. As recommended by Lienhard and Wang¹⁴ and Wade,¹⁵ the product was stored at -20° in the dark in a serum-capped brown bottle under argon.

nmr (δ , neat): 1.57 (4H, homoallylic); 2.0 (4H, allylic); 3.40 (3H, methoxy); 3.51 (with fine splitting, 1H, olefinic).

ir (film, cm^{-1}): 2900 (s), 1658 (s), 1431 (s), 1325 (m), 1290 (w), 1256 (m), 1229 (w), 1208 (s), 1178 (s), 1158 (s), 1136 (m), 1081 (m), 1055 (m), 1029 (s), 957 (m), 930 (w), 913 (w),

858 (m), 828 (m), 784 (s), 774 (s).

Reference Compounds

2-Methoxy-2-cyclohexen-1-one (10) was prepared by the procedure of Tobias, Strong and Napier^{16,17}. Yields ranged from 25 to 35%. b.p. 115-130° (24 mm.); lit 116-118 (19 mm.)¹⁶; 100-117° (20 mm.)¹⁸ nmr (δ , CDCl₃): 2.00 (m, 2H); 2.43 (m, 4H); 3.58 (s, 3H); 5.90 (t, 1H). Mass spec.: P = 126.

2-Methoxy-2-cyclohexen-1-ol (11) was prepared by reducing 30.4 g. (0.24 mole) of 10 with diisobutylaluminum hydride¹⁹ in 600 ml. of dry benzene and 360 ml. heptane. The addition was carried out at 10° over about 30 minutes, after which the mixture was stirred at 5-10° for an hour. The aluminum salts were precipitated with the aid of methanol and sodium sulfate and filtered off; distillation gave an 88% yield of product, b.p. 92-98° (15 mm.). Nmr (CDCl₃): 1.73 (m, 4H); 2.01 (m, 2H); 3.10 (broad, 1H, hydroxyl); 3.53 (s, 3H); 4.13 (m, 1H); 4.73 (t, 1H). Mass spec.: P = 128.

Photo-oxidation of 1-Methoxycyclohexene (1). 125 μ l of 1-methoxycyclohexene (1) was dissolved in 1 ml of solvent (benzene/ 10^{-3} TPP or CH₃CN/ 10^{-3} MB) and photo-oxidized in the apparatus of ref. 3. After the desired duration of photo-oxidation (rate of oxygen uptake: 0.9 ml/min in benzene, 0.4 ml/min in acetonitrile), aliquots were removed, placed in serum-capped test tubes with molecular sieves 4A (and sometimes Ph₃P) and analyzed soon afterwards. Analytical and preparative vpc were run on an Aerograph Autoprep model A-700 using a 10' x 1/4" aluminum column packed with 20% Carbowax on Chromosorb W AW DMCS 60-80 mesh. Injector

and detector temperatures were set at 200° with a helium flow of 75 ml/min. The following temperature program was used: the initial temperature of approximately 90° was maintained until all the solvent eluted (5-6 min) at which time the oven temperature was raised to 150°. This temperature was maintained as unreacted starting material (retention time (r.t.) = 11 min), if any, a small amount of cyclohexanone (r.t. = 12 min) and cyclohexanone (r.t. = 24 min) eluted off the column. The temperature was then raised to 200°C and maintained there until compounds 11 (r.t. = 35 min), 7 (r.t. = 38 min) and 10 (r.t. = 46 min) came off. The oven was then allowed to cool and the process was repeated for the next sample.

5-Carbomethoxypentanal (7)²⁰. 3 g (0.268 mol) of 1 was dissolved in 20 ml of methylene chloride and ozonized at -79° until the solution turned blue. The system was then flushed with nitrogen to remove the excess ozone and the reaction solution was treated with 6 g (0.0229 mol) of triphenylphosphine. The reaction mixture was allowed to warm slowly to room temperature. The methylene chloride was removed under reduced pressure and the remaining yellow fluid was bulb-to-bulb distilled under high vacuum to give crude 7. Vpc revealed the presence of about 10% impurity. In addition, aldehydoesters are known to polymerize on standing.¹⁴ Hence, pure samples of 7 (~99% pure) were obtained via preparative vpc¹¹ (oven 120°, r.t. = 7.5 min) and spectra of such samples were taken immediately.

nmr (δ , neat): 1.67 (4H, β -H); 2.40 (4H, α -H); 3.67 (3H, methoxy); 9.78 (1H, aldehydic).

ir (neat, cm^{-1}): 3482 (w), 2927 (s), 2869 (m), 2729 (w), 1738 (s), 1430 (s), 1354 (m), 1195 (s), 1094 (m), 1012 (m), 886 (w).

Photo-oxidation of Hydroperoxide 2; 3,4-Dihydroperoxy-3-methoxy-cyclohexene (2); 5-Carbomethoxy-4-penten-1-al (13). Approximately 250 μl (1.7 mol. equiv.) of 2 was dissolved in 1.5 ml of $\text{C}_6\text{H}_6/10^{-3}$ M TPP solution and photo-oxidized in the usual manner until the oxygen uptake had essentially ceased. After 155 minutes approximately 38 ml of oxygen (1.7 mol. equiv) had been absorbed by the system. Nmr showed the following major absorptions (CDCl_3 , δ): 1.85 (broad multiplet, relative area 100); 3.49 (methoxy, rel. area 23); around 3.7 (3 clustered singlets, rel. area 17); 4.58 (broad singlet, rel. area ~7); 5.90 (dd, rel. area 18); 8.20 (broad singlet, rel. area 21). The data fit compound 12, assuming the presence of impurities which are hidden under the 1.85 absorption and which account for the cluster of singlets about 3.7. Based on this assumption we can make the following assignments for compound 12.

Nmr for compound 12 (CDCl_3 , δ): 1.85 (4H, allylic and homo-allylic); 3.49 (3H, methoxy); 4.58 (broad singlet, 1H, α to the 4-hydroperoxy group); 5.90 (probably two doublets at 5.7 and 6.1, 2H, olefinic); 8.20 (broad singlet, 2H hydroperoxy).

Vpc analysis²¹ of the product mixture (oven - 190°, injector and detector temp. 210°) showed two products in a 4:1 ratio (retention times: 11.5 and 17.5 min, respectively). The former was collected and spectral data indicate that it is compound 13.

Nmr for compound 13 (CDCl_3 , δ): 2.75 (4H); 3.68 (3H, methoxy); 5.76 (1H); 6.20 (1H); 9.73 (1H, aldehydic).

Mass spec. P = 142.

Ir (CCl_4 , cm^{-1}): 2938 (w), 2812 (w), 2715 (2), 1741 (s), 1648 (m), 1432 (m), 1399 (m), 1195 (s), 1171 (s), 1002 (w).

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21. 9' x 14/" aluminum column packed with 20% Carbowax 20 M on Chromosorb W AW DMCS; flow rate 85 ml/min; injector 200°, detector 250°.

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