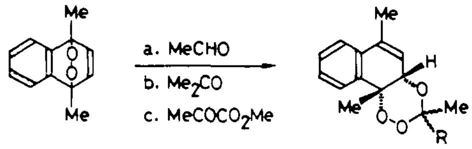
To test this mechanism, we subjected the more stable 1,4-endoperoxide[10] of 1,4-dimethylnaphthalene (**7**) to the same reaction with acetaldehyde, but at room temperature. The same result was obtained with a variety of catalysts such as amberlyst-15, trifluoroacetic acid, and even aqueous sulfuric acid, namely, the formation of the epimeric mixture of cis-fused 1,2,4-trioxanes **8** in quantitative yield.[9]

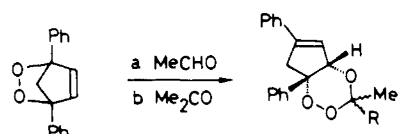
Ketones proved less reactive with **7**. Acetone gave a 30% yield after purification of the trioxane **9**, while methyl pyruvate gave a 31% yield of the two epimers **10**.[9]



7

8 R = H
9 R = Me
10 R = CO_2Me

Lastly, we tried the endoperoxide[11] of 1,4-diphenylcyclopentadiene (**11**) in dichloromethane as solvent using amberlyst-15 resin as catalyst at room temperature. It gave with acetaldehyde 89% of the epimeric product **12**; acetone furnished a 41% yield of **13**.[9]



11

12 R = H
13 R = Me

The extension of the mechanistic principle, the capture of a stable β-hydroperoxy cation by an active carbonyl compound to give 1,2,4-trioxanes, is being studied. We will show elsewhere that the structurally similar zwitterionic peroxides formed by reaction of singlet oxygen with appropriate enol ethers can also undergo the same cyclization.[12] Development of such synthetic approaches to trioxanes is feasible and desirable, especially in view of the paucity and limited scope of methods currently available[13] and because of the potent anti-malarial activity reported for the naturally occurring trioxane Qinghaosu.[14]

Acknowledgment. We thank the Swiss National Science Foundation for the support of this work (Grant 2.201-0.81).

(9) Compounds **4**, **8**, **9**, **10**, **12**, and **13** all gave satisfactory elemental analyses. The structures of **10** and **13** were elucidated by single-crystal X-ray analyses (Kennard, O., Bellard, S.; Allen, F. H. University Chemical Laboratory, Cambridge, England). The structures of **4**, **8**, **9**, and **12** were ascertained by comparison of their NMR spectra with those of **10** and **13**. Moreover, the pairs of epimers of **4**, **8**, and **12** (separated by HPLC by Dr. H. Grant) were identified by NMR spectroscopy and NOE difference experiments (Prof. U. Burger and co-workers).

(10) Wasserman, H. H.; Larsen, D. L. *J. Chem. Soc., Chem. Commun.* **1972**, 253.

(11) Schenck, G. O.; Müller, W.; Pfennig, H. *Naturwissenschaften* **1954**, *41*, 374. Coughlin, D. J.; Brown, R. S.; Salomon, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 655.

(12) For example, the exo-zwitterionic peroxide derived from 2-methoxynorbornene (Jefford, C. W.; Rimbault, C. G. *J. Am. Chem. Soc.* **1978**, *100*, 6437–6445) incorporated acetaldehyde in the expected electronic sense to give the cis-fused 1,2,4-trioxanes (Jefford, C. W.; Kohmoto, S.; Boukouvalas, J.; Burger, U. *Ibid.*, submitted for publication.

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(14) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624.

Registry No. 2, 87051-06-7; **3**, 130-15-4; **4**, 87051-07-8; **7**, 35461-84-8; **8**, 87051-08-9; **9**, 87051-09-0; **10**, 87051-10-3; **11**, 62121-84-0; **12**, 87051-11-4; **13**, 87051-12-5; MeCHO, 75-07-0; Me_2CO, 67-64-1; $MeCOCO_2Me$, 600-22-6; 2-methoxynorborn-2-ene, 17190-90-8; 2-methoxymethylideneadamantane, 72590-63-7; 2-methoxynorborn-2-ene(methyl-1,2,4-trioxane adduct), 87051-04-5; 2-methoxymethylideneadamantane(methyl-1,2,4-trioxane adduct), 87051-05-6.

Reaction of Singlet Oxygen with Enol Ethers in the Presence of Acetaldehyde. Formation of 1,2,4-Trioxanes

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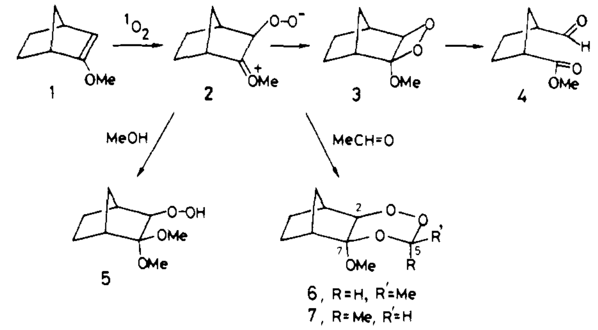
Received April 5, 1983

Electron-rich olefins, such as enol ethers, which are denied the opportunity of forming hydroperoxides, invariably react with singlet oxygen to give 1,2-dioxetanes.[1] As an alternative to concerted [2 + 2] addition,[2] two-step mechanisms involving diradicals,[3] zwitterions,[4] charge-transfer complexes,[5] and radical ion pairs[6] have been proposed to account for the course of the reaction. However, from our studies with norbornenyl ethers, unambiguous evidence for transient zwitterionic peroxides has been secured.[7] An illustration is the behavior of 2-norbornenol methyl ether (**1**), which in aprotic solvents undergoes dye-sensitized photooxidation to give the *exo*-dioxetane **3** or its cleavage product **4**. In contrast, when methanol is used as solvent, the hydroperoxy



dimethyl ketal **5** is isolated in high yield. The formation of **5** is

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(6) Foote, C. S.; Dzakpasu, A. A.; Lin, J. W. P. *Tetrahedron Lett.* **1978**, 1247.

(7) Jefford, C. W.; Rimbault, C. G. *Tetrahedron Lett.* **1977**, 2375; *J. Am. Chem. Soc.* **1978**, *100*, 295, 6437, 6515. Jefford, C. W.; Kohmoto, S. *Helv. Chim. Acta* **1982**, *65*, 133.

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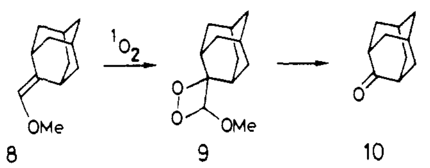
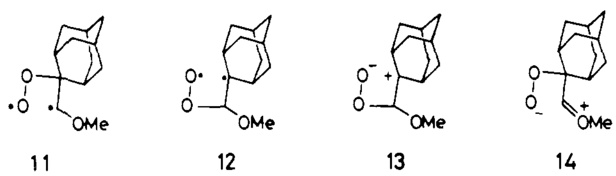
significant as it constitutes evidence for the existence of the precursive zwitterionic peroxide **2**, which instead of cyclizing to dioxetane **3** is intercepted by solvent.

We now report a new reaction of such zwitterionic peroxides by demonstrating that they can be captured by acetaldehyde to give the corresponding 1,2,4-trioxanes. Photooxygenation of **1** using rose bengal as sensitizer at −78 °C in acetaldehyde as solvent gave the same aldehyde ester **4** (31%) as before but also **6** and **7** as a mixture of isomers in a 2:3 ratio in a yield of 13%.[8]

The structure and composition of **6** and **7** was readily ascertained from their ^{1}H and ^{13}CNMR spectra. The zero coupling of the proton at C2 with the adjacent bridgehead proton attests to the exo orientation of the dioxa element in both isomers. Moreover, the similarity of the spectra of the two isomers indicates that they are epimeric at C5. Saturation of the resonance of the methoxy group of the minor epimer **6** performed in a FID difference experiment at 360 MHz produced a positive nuclear Overhauser effect (NOE)[9] of the proton at C5. Consequently, the C5 methyl group is trans to the methoxy group in **6**. Since the same experiment with the major epimer **7** showed no such effect, it can be deduced that the same groups have a cis relation.[10]

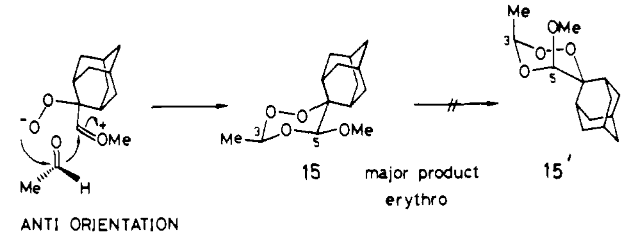
Another substrate that on photooxidation gives only 1,2-dioxetane, namely **9**, is 2-(methoxymethylene)adamantane (**8**).[11] Once again, a variety of mechanisms involving diradical and ionic species, e.g., **11**, **12**, **13**, and **14**, as well as the aforementioned alternatives, can be invoked. However, when **8** was photooxidized in a solution of acetaldehyde at −78 °C with rose bengal as sensitizer, three products were formed. The first was 2-adamantanone (**10**) obtained in 31% yield after purification. The



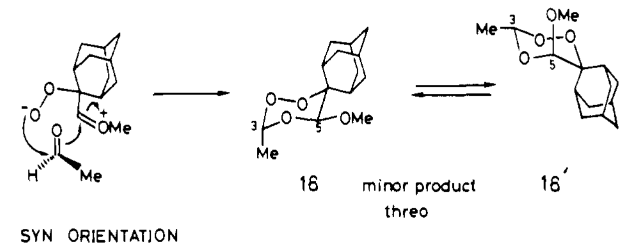


other products were the pair of isomeric 1,2,4-trioxanes **15** and **16** formed in 30 and 23% yield, respectively.

The trioxanes were separated by thin-layer chromatography over silica gel and their structures established by NMR spectroscopy.[8,10] The major product **15** was assigned to the pair of enantiomers of erythro configuration[12] by means of NOE–FID-difference experiments. Irradiation of the methoxy group at C5 had no effect on the substituents at the C3 position. However, saturation of the C5 proton caused a positive NOE of the C3 proton; thus these protons are diaxial, which means that their concomitant methyl and methoxy groups are diequatorial (**15** and not **15′**).



The minor isomer **16** was assigned the threo configuration. Saturation of the methoxy group brought about a positive NOE on the C3 proton, showing the nuclei to be contiguous, whereas irradiation of the C3 methyl group left the intensity of the C5 proton unaffected. Whence it follows that the preferred conformation is the one in which the methoxy substituent occupies the axial position (**16′** and not **16**).[13]



When dioxetane **9** was treated with excess acetaldehyde under the conditions of photooxidation, no trioxanes were formed, only 2-adamantanone (**10**). In another experiment, **8** was found to be inert when submitted to irradiation in the presence of oxygen and acetaldehyde at −78 °C, but without sensitizer. We therefore conclude that all intermediates except the zwitterionic peroxide **14** can be discarded.[14] Interception of the key intermediate **14** by acetaldehyde may occur in two ways. The acetaldehyde molecule can adopt either the anti or syn orientation with respect to the methoxonium substituent of **14**. Nucleophilic attack by the peroxide anion on the aldehyde function followed by closure then gives the trioxanes **15** and **16**, respectively.

In summary, our experiments demonstrate the capture of zwitterionic peroxides by an external carbonyl function and complement a recent result[15,16] in which the singlet oxygen reaction with an enol ester passed through a similar peroxide which attacked the carbonyl function intramolecularly. We will show elsewhere how this mechanistic principle can be applied as a general method for the synthesis of 1,2,4-trioxanes, which hitherto have not been readily accessible.

Acknowledgment. We thank the Swiss National Science Foundation for support of this work (Grant 2.201-0.81).

(8) (a) Acceptable elemental analyses were obtained for the epimeric mixture of **6** and **7** and for pure samples of **15** and **16**. (b) In special cases, with biadamantylidene for example, rose bengal can intervene chemically and bring about epoxidation (Jefford, C. W.; Boschung, A. F. *Helv. Chim. Acta* **1977**, *60*, 2673–2685). Neither **1** nor **8** under the present conditions of photooxygenation revealed any anomaly. It is worth adding that the usual chemical source of singlet oxygen, namely, the 1,4-endoperoxide of 1,4-dimethylnaphthalene reacts with acetaldehyde in the presence of acid to give 1,2,4-trioxanes (Jefford, C. W.; Jaggi, D.; Boukouvalas, J.; Kohmoto, S. *J. Am. Chem. Soc.*, accepted for publication).

(9) Noggle, J. H.; Schirmer, R. E. "The Nuclear Overhauser Effect"; Academic Press: New York, 1971. Martin, M. L.; Delpuech, J. J.; Martin, G. J. "practical NMR spectroscopy"; Heyden: London, 1980.

(10) We have good reason to believe that the conformation of the trioxane ring in **15** and **16** is that of a chair. (Unpublished work with O. Kennard and co-workers, University of Cambridge). However, inspection of models of **6** and **7** indicates that nonchair conformations are possible. Nonetheless, arguments based on contiguity of groups remain valid.

(11) Meijer, E. W.; Wynberg, H. *Tetrahedron Lett.* **1979**, 3997.

(12) Erythro designates the enantiomer having *R* and *S* configurations at C3 and C5, respectively. The pair of threo diastereoisomers has the *R*,*R*, and *S*,*S* configurations.

(13) Independently of the possible conformational effect of the ring oxygen atoms in **16**, such a preference is already displayed by *cis*-1-methyl-4-methoxycyclohexane at 193 K (96% axial OMe/4% axial Me) (Booth, H.; Josefowicz, M. L. *J. Chem. Soc., Perkin Trans. 2* **1976**, 895).

(14) (a) It is possible that an exciplex could form between the enol ether and singlet oxygen and that it could further decay to our zwitterionic peroxide (cf., ref 5). However, there is neither evidence nor precedent for such exciplexes, even if they were sufficiently long-lived to react with methanol, let alone acetaldehyde, in the regioselective manner observed. (b) The behavior of diradicals **11** and **12** together with the analogous diradical derived from **1** is problematic. However, taking the reaction of the peroxy diradical obtained from 2-phenylnorbornene as a guide (Jefford, C. W.; Boschung, A. F.; Rimbault, C. G. *Helv. Chim. Acta* **1976**, *59*, 2542–2550), trimerization by addition to the olefin precursor would be expected. Furthermore, radicals such as **11** and **12** would be expected to abstract a hydrogen atom from acetaldehyde rather than add across the carbonyl function (Kharasch, M. S.; Urry, W. H. *J. Org. Chem.* **1949**, *14*, 248–253. Patrick, T. M., Jr. *Ibid.* **1952**, *17*, 1009–1016).

(15) Wilson, S. L.; Schuster, G. B. *J. Am. Chem. Soc.* **1983**, *105*, 679.

(16) The distinction between the proposed zwitterionic peroxide and the alternative perepoxide formulation, although possible, is not made as it would not be revealed by the trapping experiments described.