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ABNORMAL PHOTOOXYGENATION OF CYCLOHEPTATRIENE. EVIDENCE FOR 6π+ 2π CYCLOADDITION BY SINGLET OXYGEN.

Andrew S. Kende and Joseph Y.-C. Chu

Dept. of Chemistry, University of Rochester, Rochester, N.Y. 14627
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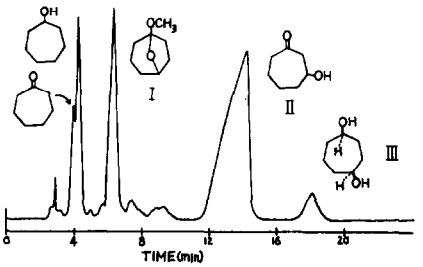
The addition of photochemically generated $^1\Delta_g$ singlet oxygen to unsaturated carbocyclic and heterocyclic systems has recently developed into a sophisticated synthetic method of wide scope.[1] In the great majority of such reactions singlet oxygen acts as a high energy dienophile which adds in the normal 4π+ 2π manner to an appropriately reactive diene or heterodiene portion of the acceptor molecule. On this basis we have examined the behavior of singlet oxygen toward cycloheptatriene as a model reaction for the total synthesis of the antitumor compound crotepoxide.[2] We now report evidence that, contrary to the above generalization and earlier results in this series,[3] the main pathway in photooxygenation of cycloheptatriene proceeds through an unprecented 6π+ 2π cycloaddition of singlet oxygen to the polyene system.

When oxygen was slowly passed at 20° into a 2% solution of redistilled cycloheptatriene in 160 ml methanol containing 60 mg methylene blue and the reaction mixture was irradiated by visible light, over 95% of the triene was consumed (glpc) within 32 hours. Evaporation of solvent below 20° and removal of product from sensitizer by extraction with ether gave 90% (based on $C_7H_8O_2$) of a yellow liquid having strong ir bands at 3450 and 1665 cm^{-1} and a broad uv maximum centered at 275 nm, log ε 3.4. While both the nmr spectrum and glpc characterization showed this crude product to be a complex mixture, the absence of aldehydic protons as well as cyclopropane CH_2 protons could be inferred from the lack of nmr signals in the regions 9-12 δ and -1 to +2 δ. All attempts to fractionate

the mixture led to decomposition; in particular, treatment with acids or passage through silica or alumina columns generated variable amounts (10-25%) of tropone[4] as the only identifiable product.

Valuable information was obtained, however, by hydrogenation of the total reaction product over 10% Pd-C in methanol. This procedure gave in high yield a distillable mixture of five discrete substances characterized by analytical glpc (Fig. I) in order of appearance as cycloheptanone , cycloheptanol, 1-methoxy-1,4-epoxycycloheptane (I), 3-hydroxycycloheptanone (II) and cis - 1,4 - cycloheptanediol (III). The five components were collected from glpc runs and unambiguously identified by comparison mass, infrared and nmr spectra as well as by coninjection on three different glpc columns[5] using authentic samples synthesized as discussed below.

FIG. I. GLPC ANALYSIS OF HYDROGENATION PRODUCTS.
(6' x 1/8" of UCON-98 on Chromosorb W, 100°)



The base-catalyzed conjugate addition of benzyl alcohol to 2-cycloheptenone gave 3-benzyloxycycloheptanone which on hydrogenolysis (Pd-C, 1 atm) gave in 76% overall yield authentic 3-hydroxycycloheptanone II (bp 83-84° at 0.3 mm; ir, 3350 and 1696 cm^{-1}; nmr in $CDCl_3$, δ 1.35-2.10, 6H, m; 2.50, 2H at C-7, m; 2.82, 2H at C-2, d, J=4.5 Hz; 3.56, 1H of OH, s; 4.11, 1H at C-3, m; mass spectrum, parent m/e=128).[6,7] Hydrogenation of the crystalline 1,4-epidioxy-2-cycloheptene[8] over 10% Pd-C in methanol produced in turn 61% of 1-methoxy-1,4-epoxycycloheptane I (bp 65-66° at 5 mm; ir, no OH or CO; nmr in $CDCl_3$, δ 1.28-1.96, 10H, m; 3.37, 3H of OCH_3, s; 4.45, 1H at C-4, m; mass spectrum, parent m/e=142)[9] and as minor product[10] 19% of cis-1,4-cycloheptanediol (mp 67-69°; lit mp 68-69°; ir, broad OH near 3300 cm^{-1} but no CO; nmr, δ 1.2-2.0, 10H, m; 3.61, 2H of OH, exch. D_2O; 3.86, 2H of C-1 and C-4, m).

When the crude photooxygenation product from cycloheptatriene was hydrogenated in ethyl acetate rather than methanol none of the methoxy compound I was detected; there was formed instead a comparable yield of 4-hydroxycycloheptanone (IV).[11] Thus the methoxyl group enters as an artefact of reduction

rather than during the photooxygenation step. Solvent variations during the photooxygenation, on the other hand, cause changes in product ratios but do not alter product identities (Table I). Controls show that the observed products were unlikely to have arisen from two successive oxidations since product ratios were the same at 20% triene conversion as at 95% conversion. The addition of di-t-butylcresol to suppress radical chain autoxidation did not change product distribution.[12] Photooxygenation was negligible in the absence of sensitizer.

TABLE I. SOLVENT EFFECTS ON PHOTOOXYGENATION OF CYCLOHEPTATRIENE

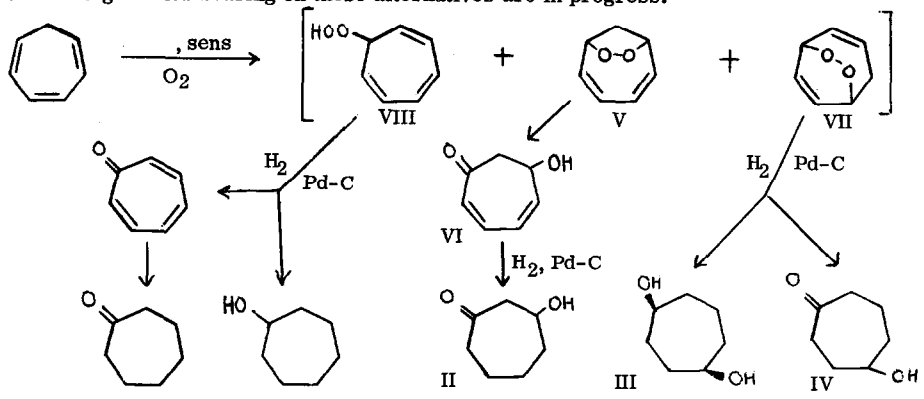
Solvent	Relative Yields of Oxygenation Products After Hydrogenation over Pd-C					
	Cycloheptanone	Cycloheptanol	I	II	III	IV
CH_3OH[a]	6 %	12 %	18 %	59 %	6 %	-
CH_3OH[b]	6	11	-	57	6	20 %
CH_2Cl_2[b]	9	19	-	26	14	31
THF-H_2O[b] (4:1)	10	12	-	57	trace	22

[a] Catalytic hydrogenation carried out in methanol
[b] Catalytic hydrogenation carried out in ethyl acetate

The most direct explanation of the experimental data is outlined in the reaction scheme below. The main path is believed to proceed through initial $6\pi + 2\pi$ cycloaddition to form the epidioxide V which may undergo appreciable thermal rearrangement during the oxygenation to the hydroxydienone VI, since no cis 1,3-cycloheptanediol was detected as one might expect from reduction of intact V. A second path involves $4\pi + 2\pi$ addition of the oxygen to the triene to yield the less strained epidioxide VII from which hydrogenation products I, III and IV would arise. It is remarkable that no adducts derived from the norcaradiene tautomer of the cycloheptatriene were observed. The intermediacy of some hydroperoxide (VIII) as suggested by von Gustorf[4] may be invoked (but is not required) to explain formation of cycloheptanone and cycloheptanol as significant components of the hydrogenation mixture.

Recently Kearns[13] has predicted on the basis of orbital correlation diagrams that singlet oxygen addition to conjugated trienes may well deviate from the "normal" $4\pi + 2\pi$ mode. The equilibrium conformation of cycloheptatriene[14] is especially suited for concerted $6\pi + 2\pi$ cycloaddition and would appear to

offer a favorable substrate for the demonstration of the Kearns prediction. It is noted, however, that other albeit less likely mechanisms to VI exist. Thus VI could arise by multiple rearrangement of VII through an allylic diepoxide intermediate[15] or, alternatively, via S_N2' hydrolysis of VII to 6-hydroperoxycyclohepta-2,4-dien-1-ol.[16] Labeling studies bearing on these alternatives are in progress.



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2. S. M. Kupchan et al., J. Am. Chem. Soc., 90, 2982 (1968).
3. G. O. Schenck and H. Ziegler, Naturwiss., 38, 356 (1951). The structures of the photooxygenation products in this reference are under reinvestigation (Dr. H. Ritter, private communication).
4. Tropone was analyzed by glpc and at 310 nm in the ultraviolet. Tropone as a minor secondary product in cycloheptatriene photooxygenation has been observed earlier by E. K. von Gustorf (Ph. D. Dissert., Gottingen, 1957). We acknowledge with pleasure valuable discussions with Prof. von Gustorf.
5. Glpc columns employed were: 6' x 1/8" of 10% UCON 98 on Chromosorb W, 6' x 1/8" of 10% Apiezon on Chromosorb G, and 8' x 1/8" of 3% polyphenyl ether on Chromosorb W.
6. Authentic samples of I, II, III and IV gave satisfactory carbon and hydrogen analyses.
7. Physical data on II were in agreement with those of H. Nozaki, M. Kurita and R. Noyori, Tetrahed. Letters, 2025 (1968) on II obtained in low yield from photohydration of 2-cycloheptenone.
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9. Ether I gave 4-hydroxycycloheptanone in high yield on mild acid hydrolysis.
10. Reduction of 1,4-epidioxy-2-cycloheptene in ethyl acetate gave 65% of the cis 1,4-diol III.
11. Authentic IV was prepared by the method of W. von E. Doering and A. A. Sayigh, J. Org. Chem., 26, 1365 (1961).
12. We thank Profs. C. Foote and L. Friedrich for valuable suggestions on control experiments.
13. D. R. Kearns, J. Am. Chem. Soc., 91, 6554 (1969).
14. F. A. Anet, J. Am. Chem. Soc., 86, 458 (1964); F. R. Jensen and L. A. Smith, ibid., 86, 958 (1964).
15. Cf. H. H. Wasserman and R. Kitzing, Tetrahed. Letters, 5315 (1969).
16. For a similar mechanism see D. L. Pavia, Ph. D. Dissert., Yale University, 1968. We are indebted to Prof. H. H. Wasserman for calling to our attention the alternative mechanisms cited in references 15 and 16 of this communication.