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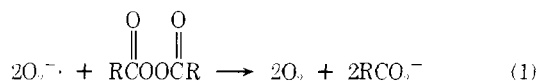
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Received February 6, 1978

Generation of Singlet Oxygen in the Reaction of Superoxide Anion Radical with Diacyl Peroxides¹

Sir:

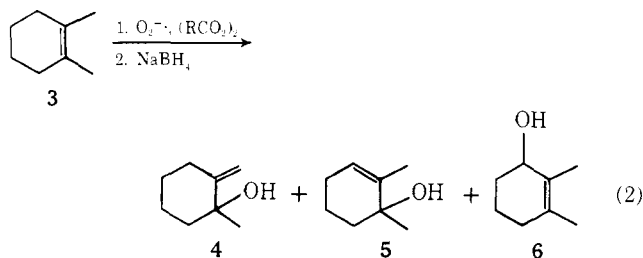
There has been considerable debate recently regarding the formation of singlet molecular oxygen from superoxide anion radical, $\text{O}_2^{\cdot-}$.² We wish to report the apparently efficient production of singlet oxygen in the reaction of $\text{O}_2^{\cdot-}$ with the oxidizing agents benzoyl peroxide and lauroyl peroxide. These experiments involved the addition of a solution of the diacyl peroxide in benzene to a slurry consisting of KO_2 and 18-crown-6 in benzene. The corresponding carboxylic acids³ were isolated in quantitative yield in accordance with the stoichiometry shown in eq 1.



The following observations suggest that a significant fraction of the oxygen generated in these systems is in the excited singlet state, presumably $^1\Delta_g$.

A. Trapping Experiments. Reaction of $\text{O}_2^{\cdot-}$ with benzoyl peroxide or lauroyl peroxide in the presence of a slight excess of the common singlet oxygen trap 1,3-diphenylisobenzofuran, **1**, was found to produce 2 equiv of *o*-dibenzoylbenzene, **2**, per equivalent of peroxide. The yields of **2** determined by ultraviolet spectroscopy were found to be >97% in both systems; isolated yields of **2** from $\text{O}_2^{\cdot-}$ benzoyl peroxide averaged 86% for three trials. Trapping experiments were also conducted with tetramethylethylene⁵ to produce 3-hydroxy-2,3-dimethyl-1-butene in low yield.

Since there is evidence^{6,7} that these commonly utilized scavengers may not be unambiguous as detectors of singlet oxygen, we investigated the reaction of $\text{O}_2^{\cdot-}$ with benzoyl peroxide or lauroyl peroxide in the presence of 1,2-dimethylcyclohexene, **3**. This compound has been shown⁵ to distinguish between oxidation by singlet oxygen and a simple free-radical autoxidation reaction on the basis of a distinctly different distribution of products for the two processes. Under our conditions in the reaction of $\text{O}_2^{\cdot-}$ and benzoyl peroxide, **4**, **5**, and **6** (eq 2) were formed in relative yields of 92, 5, and 3%, respectively, demonstrating the generation of singlet oxygen in this system. When lauroyl peroxide was used as the sub-



strate, the relative yields were found to be 77, 18, and 5%, respectively. Simple free-radical autoxidation of **3** by triplet molecular oxygen catalyzed by di-*tert*-butyl peroxide produced a ratio for **4**, **5**, and **6** of 16, 7, and 77%, respectively. The predominance of **6** in radical autoxidation but its production in low yield in the $\text{O}_2^{\cdot-}$ and peroxide experiments is indicative of the intermediacy of singlet oxygen in the latter.⁵ Control experiments indicated that **1** and **3** were unreactive toward KO_2 , benzoyl peroxide, or lauroyl peroxide separately. Likewise, controls with KOH, crown ether, and molecular oxygen demonstrated no reaction with **1** or **3**; KOH, crown ether, and dibenzoyl peroxide underwent only slow reactions with these singlet oxygen traps which could not effectively compete with the rapid reaction with KO_2 .

B. Oxygen Evolution. When reactions of $\text{O}_2^{\cdot-}$ were carried out in the presence of **1**, the amount of oxygen liberated was found to be dependent upon the amount of **1** used; oxygen evolution was suppressed completely with excess **1**. Although oxygen evolution could never be completely inhibited by less efficient singlet oxygen traps⁸ such as tetramethylethylene or **3**, a decrease in the amount of oxygen evolved was observed.

C. Quenching of Singlet Oxygen by Superoxide. The rate constant for quenching of singlet oxygen by $\text{O}_2^{\cdot-}$ has been determined^{2b} to be $1.6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. This suggests that $\text{O}_2^{\cdot-}$ should compete with even efficient singlet oxygen traps such as **1** while slower reacting olefinic and other traps should be less effective in our system compared to other methods of generating singlet oxygen. We found this to be the case with **1**, **3**, and tetramethylethylene; the latter two scavengers produced the singlet oxygen product in comparatively low yields. Additional substantiation that $\text{O}_2^{\cdot-}$ competes with **1** for singlet oxygen was obtained when experimental conditions were varied in the reaction of benzoyl peroxide with $\text{O}_2^{\cdot-}$ in the presence of **1**. It was found that the yield of **2** depended logically upon the following three factors: (i) the amount of KO_2 used, (ii) the concentration of 18-crown-6, and (iii) and concentration of **1**.⁹ Increasing the amounts of either KO_2 or crown ether resulted in lower yields of **2** while increasing the concentration of **1** produced higher yields of the singlet oxygen product.

D. Quenching of Singlet Oxygen by β -Carotene. When the reaction of benzoyl peroxide with $\text{O}_2^{\cdot-}$ was carried out in the presence of both **1** and β -carotene, the yield of **2** was found to depend upon the amount of β -carotene, a known quencher of singlet oxygen.¹⁰ Moreover, the amount of **2** produced was qualitatively in accord with the respective rate constants for trapping by **1** and quenching by β -carotene.

Our results indicate that singlet oxygen or some species mimicking singlet oxygen^{2a,11} can be efficiently produced by the reaction of $\text{O}_2^{\cdot-}$ with diacyl peroxides, although the mechanism of production is only speculative at present. It is possible that many of the deleterious effects on metabolic systems which have been attributed to $\text{O}_2^{\cdot-}$ or $\text{HO}\cdot$ may actually be due to singlet oxygen produced by oxidation of $\text{O}_2^{\cdot-}$ with biological oxidizing agents. This hypothesis is particularly attractive since there is now a consensus that the Haber-Weiss reaction between $\text{O}_2^{\cdot-}$ and H_2O_2 to generate $\text{HO}\cdot$ is too slow to be of significance in biological systems.⁷

Additional work on the reaction of $\text{O}_2^{\cdot-}$ with other oxidizing agents is in progress.

Acknowledgment. The authors gratefully acknowledge helpful discussions with G. D. Mendenhall (National Research Council of Canada) and A. Frimer (Bar-Ilan University, Israel). Financial assistance by Kansas State University is greatly appreciated.

References and Notes

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Received November 7, 1977

$\text{S}_{\text{N}}2'$ Reactions of *cis*-3,4-Dichlorocyclobutene

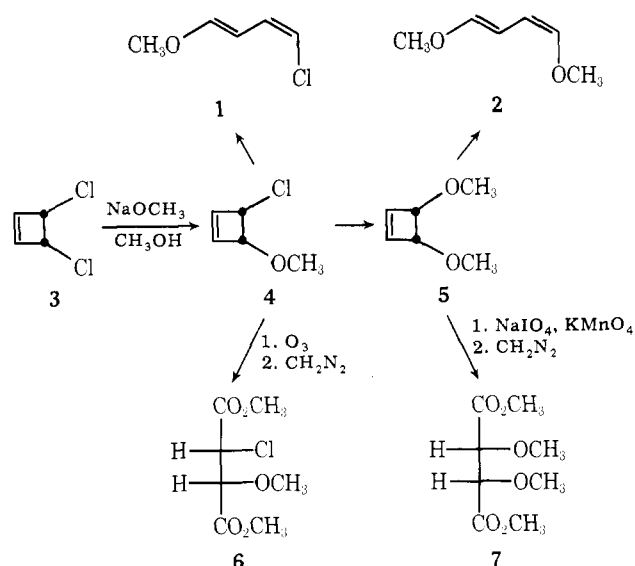
Sir:

The $\text{S}_{\text{N}}2'$ reaction (bimolecular nucleophilic substitution with allylic rearrangement) has been the subject of considerable interest as well as substantial controversy.¹ Most of the reported examples involve bulky nucleophiles and/or hindered substrates which minimize $\text{S}_{\text{N}}2$ displacement. Syn attack (in which the nucleophile and leaving group are on the same face of the allylic system) has been demonstrated with secondary amines and, in some cases, with thiolates.^{2,3} Whether this is due to hydrogen bonding or to an inherent stereoelectronic preference in $\text{S}_{\text{N}}2'$ reactions remains to be settled. Some cases of predominant anti attack by other nucleophiles are known.^{4,5} Theoretical calculations supporting both syn and anti pathways are available.⁶

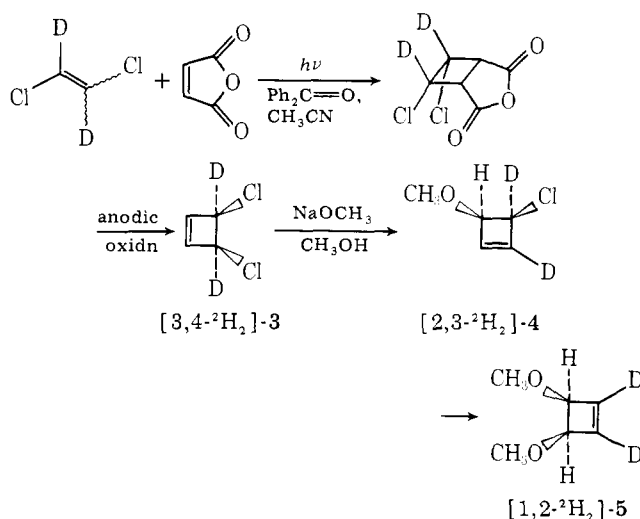
We should like to report that the reactions of *cis*-3,4-dichlorocyclobutene (**3**) with methoxide proceed exclusively with syn stereochemistry and with allylic rearrangement (see Scheme I). Treatment of **3** with 1 equiv of NaOCH_3 (4 M in methanol, 1.5 h, 80 °C) afforded a mixture containing ~25% *cis*-3-chloro-4-methoxycyclobutene (**4**), ~25% *cis*-3,4-dimethoxycyclobutene (**5**), and ~50% **3**.⁷ An excess of methoxide produced **5** quantitatively. No reaction occurred without added methoxide. When **3** reacted in $\text{CH}_3\text{OD}/\text{NaOCH}_3$, no deuterium was incorporated into **4** and **5**.

The configuration of **4** was established by ozonolysis, followed by treatment with diazomethane, to give dimethyl *erythro*-2-chloro-3-methoxysuccinate (**6**).⁸ GLC of the crude product revealed the absence of any threo isomer. Similarly, Lemieux oxidation⁹ of **5** afforded exclusively *meso*-2,3-dimethoxysuccinate (**7**).¹⁰ The thermal rearrangement of **4** and **5** to give *Z,E* dienes is also consistent with their *cis* configuration. Two products may arise from the conrotatory reaction

Scheme I



Scheme II



of **4**, but only one was actually found which we assign as (1*Z*,3*E*)-1-chloro-4-methoxybutadiene (**1**) on the basis of $J_{1,2} = 6$, $J_{3,4} = 12$ Hz. The remarkable effects of alkoxy groups on the rates and selectivities of cyclobutene rearrangements will be subject of a forthcoming paper.

The $\text{S}_{\text{N}}2'$ mechanism of the **3** → **4** + **5** transformation was established with the aid of [3,4- $^2\text{H}_2$]-**3**, synthesized as shown in Scheme II.^{11,12} In the NMR spectrum of **4**, 3-H (δ 5.0) and 4-H (4.4) are clearly resolved. The spectrum of labeled **4**, obtained from [3,4- $^2\text{H}_2$]-**3**, displayed the signals of 4-H and of one vinylic proton. No resonances due to vinylic protons were found in the NMR spectrum of labeled **5**. Obviously, the nucleophilic displacements at **3** and **4** involve allylic rearrangement.

Theoretical analyses have led to the prediction that $\text{S}_{\text{N}}2$ reactions of strained cyclic systems should proceed with retention of configuration.¹³ This postulate has not yet received experimental support. Cyclobutyl tosylates prefer the inversion pathway.¹⁴ The present work shows that the cyclobutenyl chloride **3** avoids $\text{S}_{\text{N}}2$ displacement in favor of an exceptionally clean $\text{S}_{\text{N}}2'$ reaction.

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