Tetrahedron Letters No. 32, pp 2805 - 2808, 1976. Pergamon Press. Printed in Great Britain.

SUPEROXIDE RADICAL ANION-OXIDATIVE CLEAVAGE OF CHALCONES

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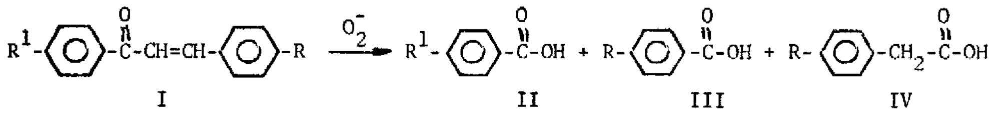
(Received in UK 14 May 1976; accepted for publication 21 June 1976)

The experimental detection of $O_2^{\bar{\cdot}}$ as a product of enzymatic reduction of molecular oxygen, as well as the recently recognized function of several "superoxide dismutases" as the enzymatic catalyst for its disproportionation,[1] have provided the motivation of a regained interest in the chemistry of this species. While a major effort has been directed to "in situ" generation and reactions of this species in aqueous media,[2] the recent observation that potassium superoxide, KO_2, can be appreciably dissolved in aprotic solvents by complexation with crown ethers,[3] has sharply promoted the use of this reagent.[4,5,6,7]

The reaction of tetracyclone with KO_2[8], to yield unexpectedly 2-hydroxy-2,4,5,-triphenylfuranone-3[9], suggested a possible nucleophilic addition of $O_2^{\bar{\cdot}}$ to an enone system. We wish to report the application of this reaction to chalcones. Thus we found that chalcones are efficiently cleaved by $O_2^{\bar{\cdot}}$ to yield carboxylic acids. The results obtained in the reactions tested are summarized in Table I.

A typical experimental procedure is as follows. A benzene (100 ml) solution containing chalcone (500 mg, 2.4 mmole) KO_2 (680 mg, 9.6 mmole) and 18-crown-6 ether (1.27 g, 4.8 mmole) was stirred protected from light for 20 hrs. During this period of time the solution turned from yellow to orange. The mixture was extracted several times with a solution of NaCl. The aqueous washings were acidified to pH=1 with 1 N HCl and extracted with benzene. After drying over Na_2SO_4, the organic layer was evaporated. The residue was chromatographed on silicagel (petroleum ether-acetone) to yield benzoic acid (526 mg) and phenylacetic acid (16 mg). No crown ether could be recovered from the mixture at the end of the reaction. It was noted that the crown ether deteriorates in the presence of KO_2. Thus in control experiment run in the absence of chalcone, virtually no crown ether could be recovered.

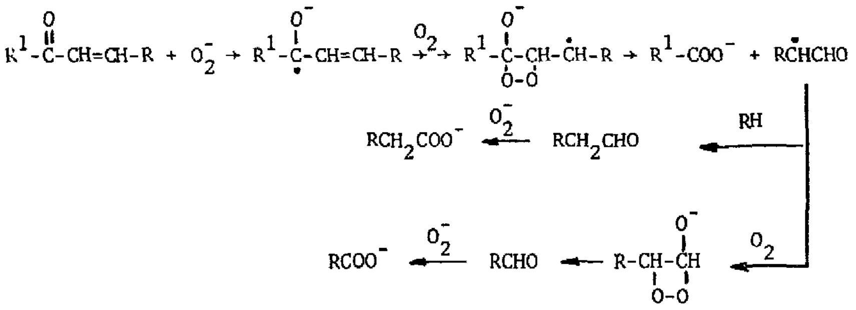
TABLE I. The Reaction of Chalcones with KO_2



Chalcone[a]		Yield[b] (%)		
R^1	R	II	III	IV
H	H	89.8		5
4'CH_3	H	62	32	6
4'CH_3O	H	72	29	5
4'Cl	H	73	35	5
4'Br	H	52	33	5
4'CH_3	4Br	64	24	
4'Br	4Me	59	43	6
H	4Br	62	40	
H	4Cl	57	39	3
H	$2NO_2$	53	35	
H	3Br	64	36	

a) The chalcones were prepared as described.[10] We are indebted to Dr. M. Luvish for kindly providing us with samples of some chalcones. b) The yields were established (after a crude column-chromatographic separation of the acids and their esterification) by GLC analysis.

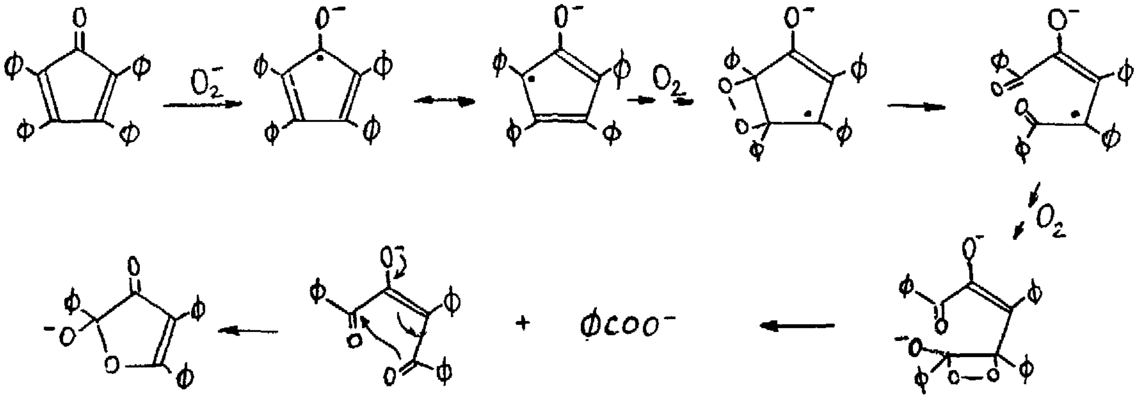
In order to clarify the reaction mechanism, 4'-methylchalcone (27 mg, 0.12 mmole), ^{18}O-enriched KO_2[11] (86% ^{18}O, 34 mg, 0.48 mmole) and 18-crown-6 ether (63 mg) were reacted in 200 ml benzene which was saturated with isotopically normal oxygen (ca. 1.8 mmole $^{16}O_2$). The mass-spectral analysis of the resulting acids showed that only 17% of 4-methylbenzoic acid and less than 10% of benzoic acid had one oxygen labelled. Control test showed that no scrambling between $K^{18}O_2$ and $^{16}O_2$ occured under reaction conditions. This result indicated that the oxygen is not incorporated in the product by direct nucleophilic attack of O_2^-. It is probable that the reaction proceeds by a preliminary electron transfer from O_2^- to the enone system of the substrate. The resulting radical anion reacts in turn with the surrounding molecular oxygen. Similar initiation steps have been suggested for the oxidation of 3,5-di-t-butylcatechol with KO_2[12]. Such a mechanism is sketched in Scheme I.



Scheme I

In support of this mechanism, control experiments have shown that both benzaldehyde and phenylacetaldehyde are readily oxidized to the corresponding acids by KO_2.[13]

A similar mechanism enables the understanding of the surprising formation of 2-hydroxy-2,4,5-triphenylfuranone-3 in the reaction of KO_2 with tetracyclone.[9] As shown in Scheme II, subsequent to electron transfer, the highest electron density is expected at a position which allows for extended conjugation as well as double allylic and benzylic stabilization of the radical. Addition of oxygen to the anion radical leads naturally to the observed product.



Scheme II

The only previous observation on the reaction of O_2^- with an enone system is the epoxidation of cyclohexen-3 one by electrolitically generated O_2^-[14]. Thus it seems that the substituents at the enone group play a crucial role in determining the reaction pathway.

Acknowledgement. We thank the Israel Commission for Basic Research for support . A.F. thanks the Weizmann Institute of Science for a Postdoctoral Fellowship.

References and Notes

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13. It was noted that while the reaction of KO_2 with benzaldehyde yields benzoic acid almost quantitatively, phenylacetaldehyde yields in addition to phenylacetic acid, benzoic acid and small amount of unidentified product. The formation of benzoic acid in this case can be explained by the abstraction of one of methylene hydrogens followed by addition of oxygen to the benzylic radical.
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