

REACTION OF SUPEROXIDE ANION RADICAL [O₂⁻] WITH CYCLOHEX-2-EN-1-ONES

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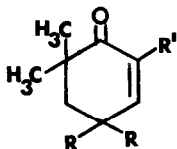
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Abstract: Cyclohex-2-en-1-ones with available acidic hydrogens undergo base catalyzed autoxidation in the presence of KO₂/18-crown-6 in benzene yielding 2-hydroxycyclohexa-2,5-dien-1-ones in the case of 4,4- and 5,5-disubstituted substrates and 2,3-epoxycyclohexanones in the case of 6,6-disubstituted analogs; 4,4,6,6-tetrasubstituted cyclohexenones are totally inert.

The pioneering work of Fridovich and others has shown that the very oxygen which supports life is metabolized producing thereby O₂⁻ and its derivatives which are highly toxic to respiring organisms. In spite of its biological importance,^{1a,b} until 1975 only a few studies had been carried out on the organic chemistry^{1c,d} of O₂⁻. The major hurdle was the problem of solubility. The observation of Valentine and Curtis² that KO₂ can be appreciably dissolved in aprotic solvents by complexation with crown ethers sharply promoted the use of this reagent and allowed for a more in depth study of the nature of superoxide reactions.

Recently we reported^{1d,3} that O₂⁻ reacts with chalcones and tetracyclone via what seems to be an initial electron transfer to the extended π-system, ultimately producing oxidative cleavage products of these enones. Dibenzyl acetone reacts in a similar fashion.^{1c} No epoxides were isolated in these cases. On the other hand, Dietz et al.⁴ reported a 30% yield of epoxyketone when cyclohex-2-en-1-one was reacted with electrolytically generated O₂⁻. Because of this discrepancy we decided to investigate the reaction of KO₂/18-crown-6 with cyclohexenones 1-4. Enones 2a,^{5a} 2b,^{5b} 3a,^{5c} 3b,^{5d} were all synthesized as previously described. Compounds 1b and 1c were prepared from 2b and 2a respectively according to the procedure of Russel and Stevenson,^{5e} with ketone 1a isolated as a sideproduct in the preparation of 1b. Finally, enone 4 was obtained from dimedone following the method of Ganon and House.^{5f}

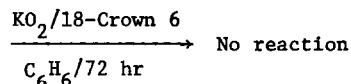
Cyclohexenones 1a-c proved totally inert to O₂⁻ even after several days of mixing. This fact indicates that the simple enone moiety per se is unreactive to O₂⁻ be it via electron transfer or Michael addition. However this moiety does labilize the adjacent hydrogens towards proton abstraction.



1a: R=R'=CH₃

1b: R=CH₃; R'=H

1c: R=C₆H₅; R'=H



Thus 4,4-disubstituted cyclohexenones 2a and 2b reacted with O₂⁻ yielding enols 5a^{6a} and 5b^{6b} respectively as the primary products.^{6c} [See Table]. Again no epoxides were formed. Considering that the reaction of 2a and 2b with KOH/18-Crown-6 gave similar results, we suggest that the enol 5 is formed via an initial base-catalyzed autoxidation⁷ process, with O₂⁻

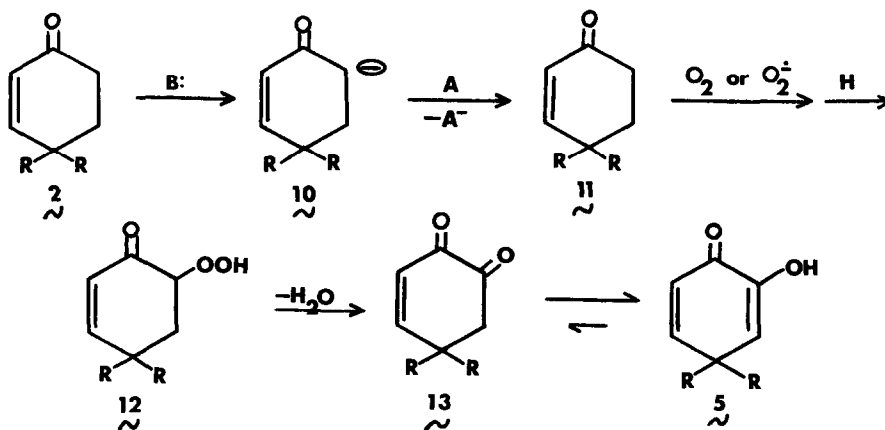
TABLE: Reaction of Selected Cyclohex-2-en-1-ones with O_2^- and HO^- in Benzene

ENONE	REACTION CONDITIONS*	PRODUCT YIELDS (%)				
		enol 5	$\overset{O}{\parallel}$ RCR 6	epoxide 7	dimer 8	trimer 9
$\overset{2a}{\sim}$ (R=Ph)	KO ₂	80	15			
	KO ₂ (Argon)	80	**			
	KOH	75	**			
$\overset{2b}{\sim}$ (R=CH ₃)	KO ₂ (5 hr)	50 ^{6c}				
	KOH	40 ^{6c}				
$\overset{3a}{\sim}$ (R=Ph)	KO ₂		20	50		
	KOH		**	36	12 ^c	
$\overset{3b}{\sim}$ (R=CH ₃)	KO ₂			20	40	
	KOH				25	
$\overset{3c}{\sim}$ (R=H)	KO ₂ (4 hr)				20	40
$\overset{4}{\sim}$ (R=CH ₃)	KO ₂ (7 hr)	78 ^{6c}				
	KOH	32 ^{6c}				

* Ratio of KX (X=OH or O₂): Crown ether: Substrate was 4:2:1 for $\overset{2a}{\sim}$ and $\overset{2b}{\sim}$, 1:1:1 for $\overset{3a-c}{\sim}$ and 2:1:1 for $\overset{4}{\sim}$. Reactions were run at ambient temperature for 16 hr under dry air unless indicated otherwise.

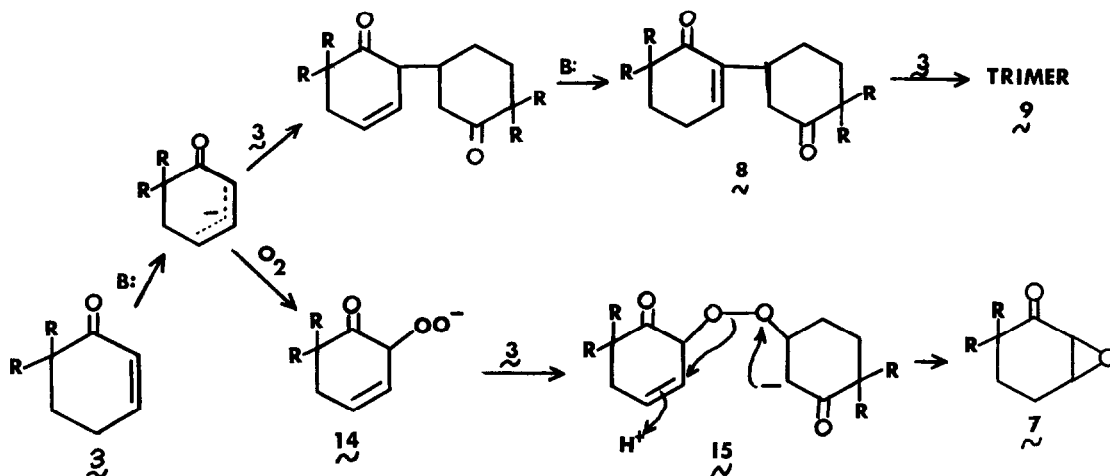
** The presence of this compound was determined by TLC.

functioning as base.⁸ The resulting α -keto hydroperoxide ($\overset{12}{\sim}$) dehydrates,⁹ probably via a DeLaMare-Kornblum¹¹ process, to α -diketone $\overset{13}{\sim}$ which tautomerizes to the more stable enol form. The Russel^{7b,c} mechanism for such autoxidations involves electron transfer from the initially formed anion to some electron acceptor (A) such as oxygen itself or HOO·,⁸ the conjugate acid of O_2^- .



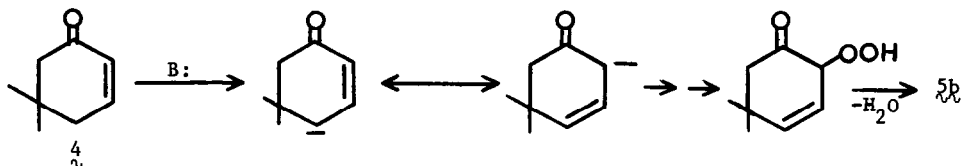
With the 4-position open as in enones $\overset{3a-c}{\sim}$, a variety of products can be formed depending on the substituent at position 6. Thus while $\overset{3a}{\sim}$ reacts to give primarily epoxyketone $\overset{7a}{\sim}$,^{12a,b} enone $\overset{3b}{\sim}$ yields some epoxyketone $\overset{7b}{\sim}$,^{12a,b} and dimer $\overset{8b}{\sim}$,^{12c}. Unsubstituted cyclohexenone, on the other hand, gives mostly trimer $\overset{9c}{\sim}$ (Parent peak at m/e 288), some dimer $\overset{8c}{\sim}$,^{12c}

but, unlike the report of Dietz *et al.*⁴, no epoxide. Here too, our control studies with KOH lead us to suggest that O_2^- is again functioning as a base with two pathways available to the resulting cyclohex-2-en-1-on-4-yl anion as outlined below. One involves dimer and trimer



formation *via* Michael type additions.^{12d} We have found that the rate of this process is quite sensitive to the size of the substituent at carbon 6.^{12e} Thus while $3c$ dimerizes with aqueous base^{12c} at room temperature, $3b$ does so only upon reflux and $3a$ not at all. We believe, therefore, that with dimerization slowed substantially for enones $3a$ and $3b$, base catalyzed autoxidation can compete favorably leading to peroxy anion 14 . The latter can then attack substrate producing anion 15 which then cleaves as shown to yield epoxide 7 . This latter process finds precedent in the work of Muckensturm¹³ on the base catalyzed autoxidative epoxidation of 9-benzylidene-flourene.

In the case of cyclohexenone 4 both the 4 and 6 positions are open but dimerization seems to be inhibited by the disubstitution at carbon 5. Interestingly, the major product is enol $5b$ most likely formed as shown below. We note that the first step involves abstraction



of a proton at position 4 which is consistent with our observation that compounds of type 3 react more rapidly than their analogs of type 2 . It is well known that the dienolate anion formed by abstraction of a γ -proton of an α,β -unsaturated ketone is more stable than its cross-conjugated isomer generated by abstraction of an α' -proton.¹⁴

While the bases O_2^- and HO^- react qualitatively in similar fashions in our system, the latter reacted somewhat more sluggishly and produced "dirtier" mixtures leading to lower product yields.¹⁵

In closing we should note that we have yet to resolve the discrepancy between our results and those of Dietz *et al.*⁴ Electrochemical experiments are called for to resolve the question as to whether the active species in both these systems are the same.

Further work on the basic organic chemistry of O_2^- , including the reactions of enols, enol ethers, and reductones will be reported shortly.

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