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ON THE REACTIONS OF SUPEROXIDE WITH KETO ENOLS, ACI-REDUCTONES AND ASCORBIC ACID DERIVATIVES

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The superoxide-mediated base catalyzed autoxidation of α-oxo enols is initiated by the deprotonation of the labile hydoxyl group. Thus, the reaction of $O_2^{-\cdot}$ (generated from KO_2/crown ether in aprotic media) with 3-hydroxycoumarin (**1**), followed by a CH_3I-workup, generates products **2–4** via a deprotonation-oxidation sequence complicated by a competing saponification of the lactone linkage. The related coumarin reductone (α-oxo enediol) **8** is rapidly oxidized by $O_2^{-\cdot}$, HO^- and t-butoxide to the corresponding triketone, which in turn undergoes further oxidation and rearrangement ultimately yielding (upon methyl iodide workup) products **9-14**. When the $O_2^{-\cdot}$ mediated oxidation is carried out under argon in completely degassed solutions, large amounts (> 20%) of monodeprotonation product (detected as **9**) accumulate. These results are discussed in light of the differing mechanisms proposed by Sawyer and Afanas'ev for the interaction of $O_2^{-\cdot}$ with the reductone ascorbic acid.

KEY WORDS: Superoxide mediated oxidation, ascorbic acid derivatives, 3-hydroxcoumarin, keto enols, reductones.

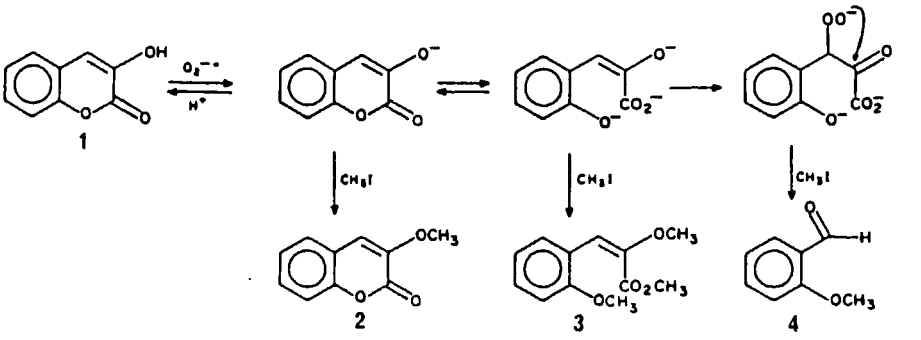
Over the past decade, the international scientific community has become increasingly aware of the crucial role superoxide anion radical ($O_2^{-\cdot}$) plays in a vast spectrum of metabolic processes.[1] Recent research on the organic chemistry of $O_2^{-\cdot}$ has revealed that, in aprotic media, this anion radical reacts with organic substrates via deprotonation, nucleophilic attack, electron transfer, and, in some isolated instances, perhaps by hydrogen atom abstraction.[2]

The first mode of action tends to predominate whenever mildly acidic protons are available. Thus, hydroperoxides, phenols and alcohols induce the disproportionation of $O_2^{-\cdot}$ to dioxygen and hydrogen peroxide (equations (1) and (2)) generating the corresponding peroxy anions, phenoxides and alkoxides, respectively.[2]

$$ROH + O_2^{-\cdot} \rightarrow RO^- + HO_2^{\cdot} \quad (1)$$

$$HO_2^{\cdot} + O_2^{-\cdot} \rightarrow HOO^- + O_2 \quad (2)$$

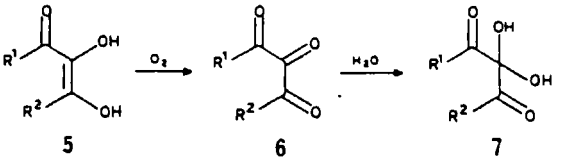
We have observed that enols, too, undergo facile proton removal by $O_2^{-\cdot}$ (generated from KO_2/18-crown-6 in inert non-polar aprotic media such as toluene at room temperature).[3] Unlike alkoxy or peroxy anions, however, the resulting enolate systems generally undergo further C-oxygenation generating a variety of interesting oxidation products. For example, in the case of the α-keto enol 3-hydroxycoumarin **(1)**, this deprotonation-oxygenation sequence is complicated by a competing superoxide-mediated saponification of the lactone linkage.[3a] As shown in equation 3, the course of this reaction could be conveniently followed and various intermediary oxy-anions trapped by quenching the reaction mixture with CH_3I at different reaction times.



(3)

β-Keto enols, too, undergo facile deprotonation with $O_2^{-\cdot}$; however, the carbanion formed is situated α to two stabilizing carbonyl groups and resists any further oxygenation,[2a,b,d,3a]

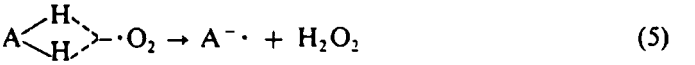
An important group of enols are the aci-reductones (**5**, equation (4)),[4] of which ascorbic acid (Vitamin C) is the most extensively studied example. These α-oxo enediols are simultaneously α- and β-keto enols and undergo facile autoxidation to the corresponding triketones (**6**) or the related hydration product (**7**).



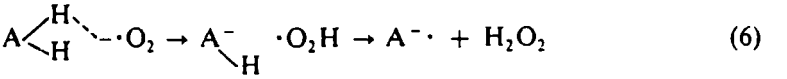
(4)

Mechanistic studies of this process have been carried out extensively and almost exclusively on Vitamin C. These have shown that, in aqueous media, $O_2^{-\cdot}$ is generated,[5] indicating that the role of molecular dioxygen is not to oxygenate the active imtermediates, but rather to serve as an electron acceptor. Furthermore, the $O_2^{-\cdot}$ once formed mediates the further autoxidation of ascorbic acid and ascorbate.[6]

Two groups have explored the autoxidation of ascorbic acid (H_2A) to dehydroascorbic acid (A) in aprotic media mediated by electrogenerated superoxide. Sawyer and coworkers[7] find that the stoichiometry of this reaction when carried out in DMF requires three molecules of ascorbic acid and two molecules of superoxide. In addition, $O_2^{-\cdot}$ mediates this process with the formation of ascorbate anion radical ($A^{-\cdot}$) and without the generation of molecular oxygen. As a result of these and related observations, Sawyer has suggested that the initial rate determining step is a concerted (equation (5)) or rapid sequential (equation (6)) transfer of a proton and a hydrogen atom to superoxide generating ascorbate anion radical ($A^{-\cdot}$) and H_2O_2. Subsequent reactions involve the proton-induced disproportionation of $A^{-\cdot}$ (equation (7)) and oxidation of the resulting HA^- by H_2O_2 to A (equation (8)). The sum total of these processes (equation (9)) indeed has the proper stoichiometry.



(5)



(6)

$$2A^{-\cdot} + H_2A \rightarrow A + 2HA^- \quad (7)$$

$$HA^- + H_2O_2 \rightarrow A + H_2O_2 \rightarrow A + H_2O_2 + HO^- \quad (8)$$

$$3H_2A + 2O_2^{-\cdot} \rightarrow 3A + 3H_2O + 2HO^- \quad (9)$$

Afanas'ev and colleagues[6] have taken issue with Sawyer's mechanism. They observe only the formation of a 50–70% yield of ascorbate anion when the same reaction is carried out in acetonitrile. The Russian group posits that such a high yield of ascorbate can only be explained by a simple deprotonation of H_2A by $O_2^{-\cdot}$. They believe, therefore, that deprotonation (equation (10)) is the main if not sole pathway of interaction between ascorbic acid and superoxide. Any oxygen generated from the disproportionation of superoxide (equation (11)) is presumably rapidly converted back to $O_2^{-\cdot}$ upon interaction with ascorbate (equation (12)). However, disproportionation is prevented by a series of rapid competing processes (equations (13–16)).

$$O_2^{-\cdot} + AH_2 \rightarrow HO_2^{\cdot} + AH^- \quad (10)$$

$$HO_2^{\cdot} + O_2^{-\cdot} \rightarrow HO_2^- + O_2 \quad (11)$$

$$AH^- + O_2 \rightarrow AH^{\cdot} + O_2^{-\cdot} \quad (12)$$

$$HO_2^{\cdot} + AH_2 \rightarrow H_2O_2 + AH^{\cdot} \quad (13)$$

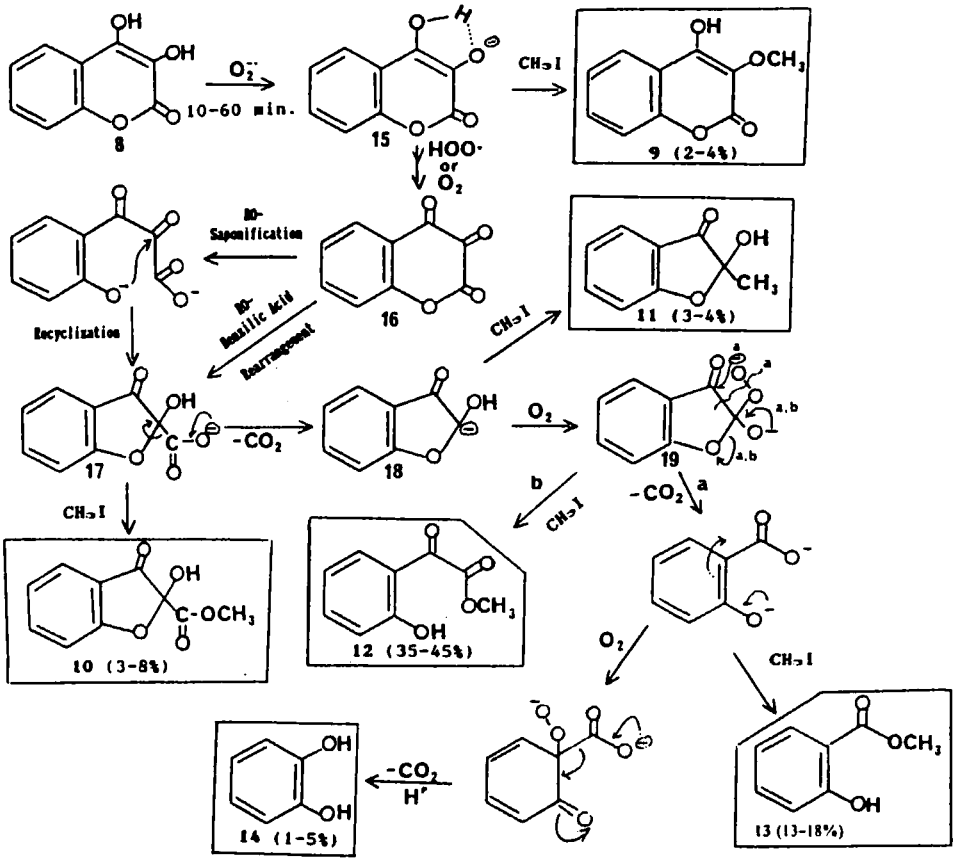
$$HO_2^{\cdot} + AH^- \rightarrow H_2O_2 + A^{-\cdot} \quad (14)$$

$$HO_2^{\cdot} + AH^{\cdot} \rightarrow H_2O_2 + A \quad (15)$$

$$HO_2^{\cdot} + A^{-\cdot} \rightarrow HO_2^- + A \quad (16)$$

This discrepancy may perhaps be resolved by invoking three separate solvent-dependent considerations. Firstly, the conflicting data may result from the substantial viscosity difference between the two solvents, DMF (0.802 cp at 25° C)[8a] and acetonitrile (0.345 cp).[8b,c] As the viscosity increases, so does the likelihood of solvent cage reactions, such as equation (6). With less viscous solvents, such as acetonitrile, HA^- may well escape the cage before being oxidized by $HOO^{\cdot}$. Alternatively, the pK_a of the substrate is expected to differ in these two solvents, and this may well have an affect on the mode of action of $O_2^{-\cdot}$. Finally, Sawyer and coworkers[9] have found that, because CH_3CN is difficult to dry, all their attempts to electrochemically prepare superoxide in this solvent generally result in the generation of high yields of hydroxide in addition to the described superoxide; hence, HO^-, not $O_2^{-\cdot}$, may be active species in Afanas'ev's system.

In our own laboratories, we have explored the reactions of various aci-reductones and ascorbic acid derivatives with superoxide (generated from KO_2/18-crown-6 in aprotic non-polar media at room temperature; for general experimental procedures see reference 3). For example, as outlined in Scheme I, coumarin reductone **8** reacts rapidly (< 10 minutes) with a mole-equivalent of $O_2^{-\cdot}$ in P_2O_5-dried THF (0.46 cp)[6c] generating products **9–14** upon CH_3I workup.[2d] Essentially the same product distribution is obtained when the oxidation is mediated by other bases (hydroxide and t-butoxide). Interestingly, when the reaction is carried out under argon (after thoroughly degassing the reaction mixture by 6 freeze-thaw cycles), there is an accumulation of substantial amounts (> 20%) of the monoanion, trapped by CH_3I as the corresponding enol ether 9, even after reaction times of 1 hour. Assuming that the



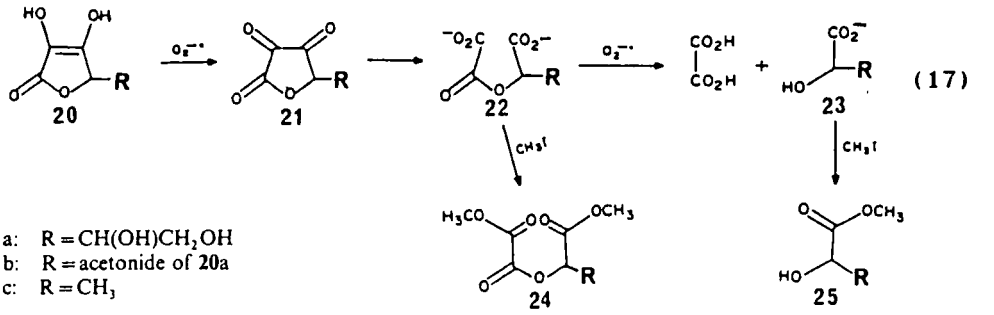
SCHEME I: Mechanism of product formation in the superoxide mediated oxidation of coumarin reductone **8**.

active species in this KO_2/crown/THF system is indeed $O_2^{\cdot-}$, these results correspond to Afanas'ev's suggestion that $O_2^{\cdot-}$ reacts with reductones primarily, if not solely, as a base.

A possible mechanism for the production of **9–14** is outlined in Scheme I. For reasons cited above, this mechanism invokes the initial formation of reductone monoanion **15** which undergoes further oxidation to coumarin triketone **16**. The latter is converted to carboxylate **17** (trapped by CH_3I as ester **10**) either via a benzylic acid rearrangement[2d] and/or a saponification-recyclization sequence (as observed with coumarin **1**[3a]). As an α-keto ester, **17** is expected to undergo facile decarboxylation to enolate **18** (isolated after CH_3I treatment as lactol **11**), which upon oxygenation generates lactolate **19** (methylated in its open form [path b] yielding α-keto ester **12**). Oxidative cleavage (path a) of α-keto hydroperoxide **19**,[2d] followed by decarboxylation and methylation lead to the observed products **13** and **14**.

It should be noted that in the corresponding ascorbic acid reaction, Sawyer has argued that the triketone (diketo ester) dehydroascorbic acid (**21a**, equation (17)) reacts further with $O_2^{\cdot-}$ via oxidative cleavage between the C_3 and C_4 carbonyls

presumably producing keto ester **22a** which undergoes saponification yielding the observed oxalate and (by inference) threonate **23a.** This suggestion has been verified by us in the case of the superoxide reaction of ascorbic acid derivatives **20b** and **20c,** in which we have actually succeeded in isolating methyl esters **24** and **25** of the proposed keto ester and threonate respectively, with the aid of a CH_3I workup of the reaction (equation (17)).



(17)

a: R = $CH(OH)CH_2OH$
b: R = acetonide of **20a**
c: R = CH_3

However, in the above case of coumarin reductone **8**, the isolation of compounds **10–12** indicates that such an oxidative cleavage of the diketo ester intermediate does not occur and that the latter proceeds by other mechanisms (see Scheme I).

Further work on related aci-reductones and ascorbic acid derivatives is presently in progress.

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