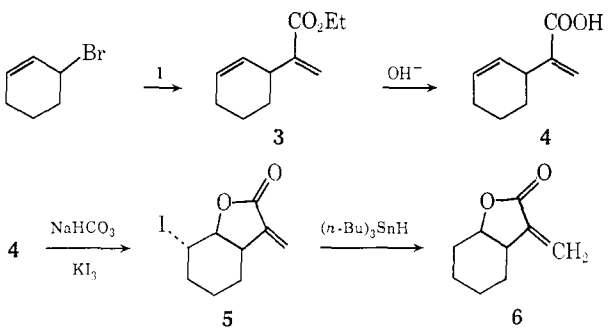
an ether solution of freshly distilled ethyl α-bromoacrylate (2 mmol) was added at −78°; this caused an immediate precipitation of a yellow solid. After 1 hr at −78°, the allylic bromide (1.33 mmol) was added, and the reaction mixture turned red-orange in color. The reaction mixture was stirred overnight at −78°, quenched with a 10% ammonium chloride solution, and then allowed to come to room temperature, at which time a standard extraction work-up was employed.

To illustrate one of the unique synthetic applications of this novel reagent, we have developed a new route to α-methylene lactones from allyl halides. The product **3** from 3-bromocyclohexene possesses all the necessary functionality for α-methylenebutyrolactones. Thus, **3** was cleanly converted to the acrylic acid derivative **4** upon base hydrolysis (10% sodium hydroxide at 70° overnight). The unsaturated acid **4** was cyclized to the crystalline iodolactone **5** (mp 78.5–80°)[13] in high yield; subsequent reduction of the iodine yielded pure *cis*-α-methylenebutyrolactone (**6**).[14] Further developments in α-methylenebutyrolactone synthesis utilizing our copper reagent **1** will be published shortly.



In summarizing the synthetic features of this new α-carbethoxyvinyl cuprate **1**, we wish to point out: (a) the completely selective transfer of only the vinyl moiety to introduce a three carbon unit, (b) the near ideal 1:1 stoichiometry of the cuprate **1** to allyl halide, (c) the high degree of specificity for only allyl halides,[15] and (d) the convenience of a one-flask sequence to form a new carbon–carbon bond at an sp^2 center under extremely mild conditions. Further work is in progress to explore the full range of reactivity of this useful, nonterminal vinyl cuprate with other electrophiles and to gain some insight into the mechanistic details of the above coupling reactions.

(13) To our knowledge, this is the first instance of direct iodolactonization of an acrylic acid derivative such as **4**. For an example of a cyclohexene acetic acid, see H. O. House, R. G. Carlson, and H. Babad, *J. Org. Chem.*, **28**, 3359 (1963).

(14) The overall yield of α-methylene lactone **6** from compound **3** is high and does not necessitate purification of any intermediates. Final confirmation of structure **6** was made by spectral comparison with an authentic sample kindly provided by Professor R. G. Lawton.

(15) Less pronounced selectivity has been noted in a few "stabilized" organocopper(I) systems: (a) E. J. Corey and M. Jautelet, *Tetrahedron Lett.*, 5187 (1968); (b) I. Kuwajima and Y. Doi, *ibid.*, 1163 (1972); (c) K. Oshima, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, **95**, 7926 (1973).

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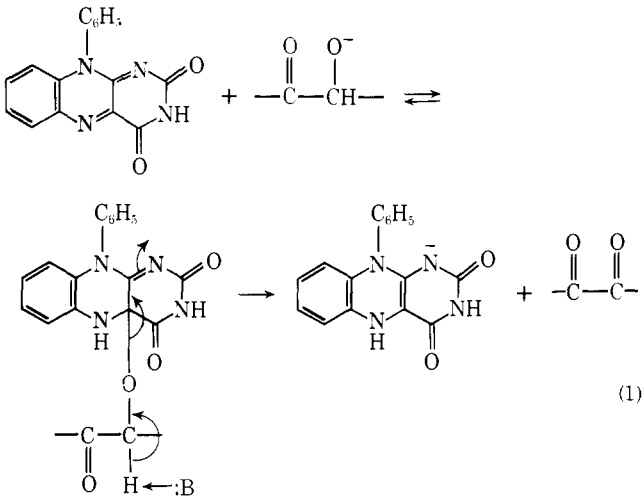
The Importance of 1,2-Enediols in the Reduction of Lumiflavin by α-Ketols

Sir:

We consider herein the mechanism of α-ketol oxidation by oxidized flavin. Brown and Hamilton[1] examined (as a representative α-ketol) the oxidation of methyl mandelate by 10-phenylisoalloxazine. Though no intermediate species could be detected, they suggested 4a addition of the alkoxide species of the substrate followed by base-catalyzed elimination of ketoester (eq 1). An electron transfer from the base generated



(1)

1,2-enediolate has been suggested as a preferred alternative to the mechanism of eq 1.[2,3] A 1,2-enediolate ion would have much appeal as an intermediate since it would serve as a π-donor toward oxidized flavin forming a charge transfer complex[4] in a preequilibrium step to electron transfer. The intermediacy of an enediol intermediate would also be consistent with the observation that chloride ion is eliminated competitively, by α-proton ionization, in the enzymatic oxidations of β-chloro-α-amino acids.[5]

α-Ketols are oxidized to the corresponding diketones by molecular oxygen.[6] The rates of this reaction and of the oxidation of α-ketols by Fehling solution are proportional to $[HO^-]$ and are identical at identical pH. These results imply rate determining enolization of ketol to the 1,2-enediolate ion followed by rapid oxidation of the latter so that the observed rate constants are independent of the nature of the oxidizing agent. In this study the rates of oxidation of furoin and benzoin by lumiflavin (LF), 2,6-dichlorophenolindophenol (DCI) (anerobic, dark), and O_2 are compared. DCI, known as Tillman's reagent, quickly traps enediols and is frequently employed for their quantitative determination.[7] Reactions were followed at λ_{max} 443

(1) L. E. Brown and G. A. Hamilton, *J. Amer. Chem. Soc.*, **92**, 7225 (1970).

(2) S. Shinkai and T. C. Bruce, *J. Amer. Chem. Soc.*, **95**, 7526 (1973).

(3) S. Ghisla, U. Hartmann, P. Hemmerich, and F. Müller, *Justus Liebigs Ann. Chem.*, 1388 (1973).

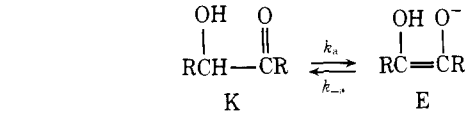
(4) M. A. Slifkin, "Charge Transfer Interactions of Biomolecules," Academic Press, New York, N. Y., 1971.

(5) C. T. Walsh, A. Schronbrunn, and R. H. Abeles, *J. Biol. Chem.*, **246**, 6855 (1971); C. T. Walsh, A. Schronbrunn, O. Lockbridge, V. Massey, and R. H. Abeles, *ibid.*, **247**, 6004 (1972); C. T. Walsh, E. Krodel, V. Massey, and R. H. Abeles, *J. Biol. Chem.*, **248**, 1946 (1973).

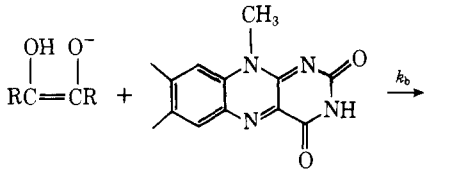
(6) A. Weissberger, W. Schwarze, and H. Mainz, *Ann.*, **481**, 68 (1930).

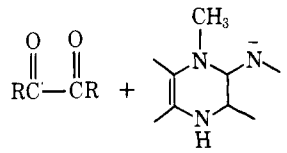
(7) B. Eistert, "Methodin. der Organishen Chemie," Vol. II, 4th ed, George Thieme Verlag, Stuttgart, 1952, p 395.

nm for LF disappearance and λ_{max} 606 nm for DCI disappearance. The reaction of O_2 with furoin was followed at 310 nm where the $\Delta\epsilon$ of furoin and furil is maximum. The disappearance of LF and DCI was found to be zero order to 75% and almost 100%, respectively, the zero order rate constants being dependent on the concentrations of ketone employed. With both LF and DCI, the appearance of furil at 310 nm was found to satisfy the first-order rate law. In the reactions with O_2, the oxidation rates were found to be independent of $[O_2]$. These results establish the reactions to be zero order in the various oxidizing agents and first order in α-ketol in accord with the mechanism of eq 2 and 3 and the kinetic expressions



(2)





(3)

of eq 4 and 5. The same kinetic observations have

$$\frac{-d[OX]}{dt} = \frac{k_a k_b[K][OX]}{k_{-a}[E] + k_b[OX]} \quad (4)$$

$$k_b[OX] \gg k_{-a}[E]$$

$$\frac{-d[OX]}{dt} = k_a[K] \quad (5)$$

been seen in the oxidation of the carbanion species derived from *trans*-dimethyl dihydrophthalate by isoalloxazines.[8]

Representative first-order rate constants for disappearance of furoin and benzoin are collected in Table I. Examination of Table I reveals the near identity of the constants for a given ketone and the lack of dependence upon the nature of the oxidizing agent. It therefore appears that the common rate-determining step among three different oxidation reactions is the enolization of α-ketol to provide 1,2-enediol. These results dictate that the true reactive species in the reduction of flavins by α-ketols is the slowly generated 1,2-enediol anion.

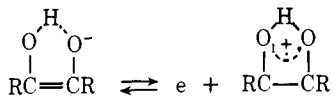
Table I. Oxidation of Furoin and Benzoin[a]

Oxidizing agent	Ketal (10^{-4} *M*)	k_a for furoin (min^{-1})	k_a for benzoin (min^{-1})
O_2, saturated	0.470	0.0666	
2,6-Dichlorophenol indophenol[b]	1.00	0.0709	0.00151
	5.00	0.0712	0.00152
Lumiflavin[c]	2.00	0.0500	
	5.00	0.0484	0.00150

[a] At pH 10.33, 0.02 *M* carbonate buffer, μ = 0.10 with KCl. For the oxidation of benzoin 20 vol % of acetonitrile was employed. [b] 5.79×10^{-5} *M*. [c] 3.00×10^{-5} *M*.

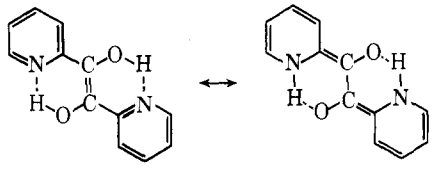
(8) L. Main, G. J. Kasperek, and T. C. Bruice, *Biochemistry*, 11, 3991 (1972).

The ability of an enediolate to donate an electron to an oxidant is a property of the E_0' value for the half reaction of eq 6.[1] In this regard, it is of interest to note



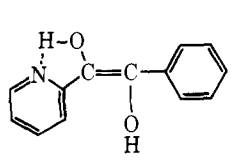
(6)

that the stable 1,2-di(2-pyridyl)-1,2-enediol (I) does not

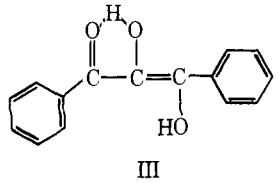


I

reduce LF under the conditions of this study. Both α-ketols from benzoin and furoin possess almost the same fraction of the enediol species in 0.1 *N* NaOH solution;[9] however, furoin is 30–50 times more reactive than benzoin. The enediols II and III, which contain



II



III

a single internal hydrogen bond, were found to reduce LF as has been noted in a separate study for the similarly internally hydrogen bonded ascorbic acid.[10]

The mechanism of the oxidation of enediols by molecular oxygen has been studied[11,12] and the existence of the semiquinone radical intermediate is well established in the case of the oxidation of benzoin, ascorbic acid, etc., in alkaline solution.[11-13] It may be inferred that the reduction of flavins by enediols also involves radical species as suggested for the oxidation of 1,5-dihydroflavins by carbonyl compounds.[1]

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(11) L. Michaelis and E. S. Fletcher, Jr., *J. Amer. Chem. Soc.*, **59**, 1246 (1937).
(12) A. Weissberger, J. E. Luvalle, and D. S. Thomas, Jr., *J. Amer. Chem. Soc.*, **65**, 1934 (1943).
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