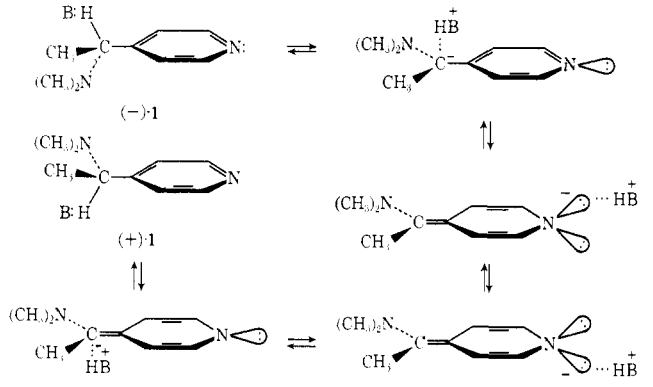
$k_e = 6.03 \pm 0.13 \times 10^{-6}$ and $k_\alpha = 8.05 \pm 0.18 \times 10^{-6}$. A second run was made similarly in 67% (by volume) hexamethylphosphoramide–33% *tert*-butyl alcohol-*O*-*d* (98% D by pmr),[4a] 0.100 *M* in (−)-**1** and 0.56 *M* in 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at 175.0 ± 0.1°. The reactions were followed with seven points through 82% racemization with controls similar to the first run. Rate constants[14] were $k_e = 1.38 \pm 0.10 \times 10^{-6}$ and $k_\alpha = 3.30 \pm 0.25 \times 10^{-6}$. A third run identical with the second except that the reaction mixture was 0.005 *M* in DBN–DI gave the same rate constants within probable error of those obtained in the second run. Control runs established that (−)-**1** was optically stable to the temperatures of runs 1–3 in the absence of the added base and to glc purification conditions.

In *tert*-butyl alcohol–potassium *tert*-butoxide, $k_e/k_\alpha = 0.75$, whereas in HMPA–*tert*-butyl alcohol–DBN, $k_e/k_\alpha = 0.42$. The contrast in behavior of (−)-**1**, which contains a 4-pyridyl group, with that of (−)-**3**, which contains a phenyl group,[4a] is striking. The system without an electronegative atom on which to distribute the negative charge of its derived carbanion gave isotopic exchange with high retention of configuration in *tert*-butyl alcohol–potassium *tert*-butoxide ($k_e/k_\alpha \simeq 7$).[4a] In the same medium, 4-biphenylmethoxyphenylmethane gave isotopic exchange with even higher retention of configuration ($k_e/k_\alpha \simeq 33$).[4b] Clearly the nitrogen of the pyridyl group is responsible for this difference between systems **1** and **3**.

The results indicate the presence of an isoinversion mechanistic component in the racemization reactions of (−)-**1**. Thus the proton abstracted from the carbon acid is transported by the base from one face of the carbanion to the other, where it is released to form inverted carbon acid. This process must compete with drowning of the proton in the deuterium pool of the surrounding medium. The ion pair is structured somewhat by a series of hydrogen-bonded intermediates. This hypothesis is strengthened by the direct observation by Hogen-Esch[15] of hydrogen-bonded carbanions that are much stabilized by charge delocalization. The conducted tour mechanism envisioned for isoinversion is formulated.



The enzymatic 1,3-proton shifts in aza allylic systems that involve imines formed from pyridoxal or pyridoxamine and amino acids or α-keto acids occur stereospecifically.[16] Our results suggest that although the 4-pyridyl moiety of these imines offers an isoinversion mechanistic option for loss of stereospecificity, the enzyme system confines the proton being transferred to the aza allylic part of the anion's total π system.

(15) T. E. Hogen-Esch, *J. Amer. Chem. Soc.*, **95**, 639 (1973).
(16) (a) J. A. Ayling, H. C. Dunathan, and E. E. Snell, *Biochemistry*, 7, 4537 (1968); (b) P. Besmer and D. Arigoni, *Chimia*, **23**, 190 (1969); (c) H. C. Dunathan, L. Davis, P. J. Kury, and M. Kaplan, *Biochemistry*, 7, 4532 (1968).

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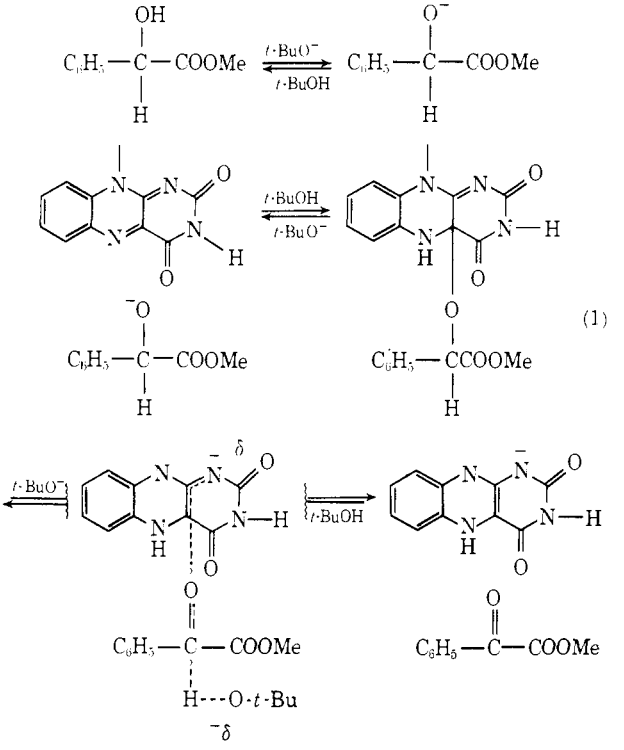
The Question of Covalent Intermediate Formation in the Flavine-Catalyzed Carbonyl to Carbinol Oxidation–Reduction Reaction

Sir:

The mechanisms by which flavoenzymes catalyze oxidation–reduction reactions are of much concern. We address ourselves herein to the interconversion of aldehydes (ketones) and alcohols coupled to the oxidation–reduction of flavine. In a study of the oxidation of 10-phenylisoalloxazine Brown and Hamilton[1] proposed 4a addition of alkoxide followed by base-catalyzed elimination of ketone (eq 1). In the forward

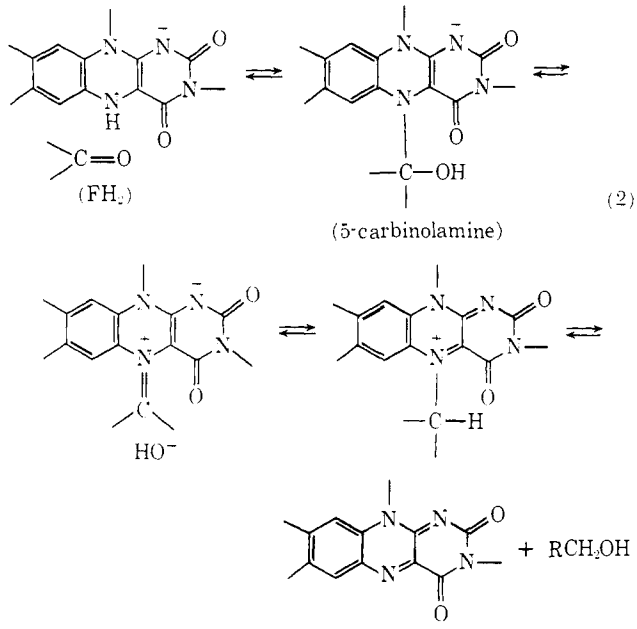


(1)

direction this mechanism has much appeal but in actuality model reactions involving oxidation of alcohol by flavine require extreme conditions. The reverse reaction requires nucleophilic attack of an enamine anion on the *carbonyl oxygen* with proton donation to the *carbonyl carbon*. No precedent for this highly unfavorable type reaction exists so that if the mechanism of eq 1 were correct the reduction of carbonyl compounds by reduced flavine should be a most difficult process. In fact, nonenzymatic flavine-catalyzed reduction of aldehydes and ketones may, depending on the carbonyl function, be quite facile in dilute aqueous

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

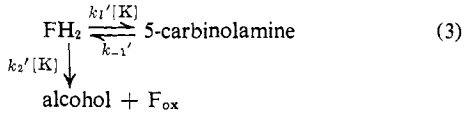
solutions at ambient temperatures.[2] This observation, in essence, eliminates the mechanism of eq 1 for reduction of carbonyl compounds by reduced flavine. Hemmerich and coworkers[2] have suggested the mecha-



(2)

nism of eq 2 which involves the formation of a 5-carbinolamine adduct. The following experimental results establish that the 5-carbinolamine adduct is not along the reaction path and that the mechanism of eq 2 has no basis.

The formation of oxidized flavine (Fl_{ox}) from 1,5-dihydrolumiflavin-3-acetic acid (FH_2) in the presence of ethyl pyruvate (ketone, K) (30°, μ = 1.0 with KCl, solvent H_2O, N_2 atmosphere) is biphasic (Figure 1) yielding ethyl lactate as the only other product. An initial first-order burst of Fl_{ox} appearance is followed by its zero-order formation to abrupt completion of reaction. At completion of the initial burst reaction the spectra of the solution exhibits λ_{max} at 345–360 nm in accord with the formation of a 5-alkyl adduct (not an imine[3]). At any constant pH the reaction sequence of eq 3 is required. The initial burst reaction (shown



(3)

to be first order in $[FH_2]$ and ketone [K]) is provided by competitive conversion of FH_2 to Fl_{ox} and to carbinolamine. The zero-order reaction, shown to be zero order in ketone, is due to trapping of FH_2 (at steady state) by ketone as it is formed from carbinolamine. These results show that carbinolamine formation does not occur along the reaction path to oxidized flavine and that reaction of ketone directly with FH_2 is a most expeditious process.[4]

(2) G. Blankenhorn, S. Ghisla, and P. Hemmerich, *Z. Naturforsch. B*, 27, 1038 (1972).

(3) An imine structure has been assigned to a "red complex" possessing a broad visible absorption [V. Massey and Q. H. Gibson, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **23**, 18 (1964); P. Hemmerich, C. Veeger, and H. C. S. Wood, *Angew. Chem.*, **4**, 671 (1965); W. R. Knappe and P. Hemmerich, *FEBS (Fed. Eur. Biochem. Soc.) Lett.*, **13**, 293 (1971)].

(4) The reactive species of reduced flavine has been shown to be the monoanion (kinetic pK_{app} = 6.61). The pH dependence of k_1', k_{-1}', and k_2' of eq 3 will be discussed in the full manuscript.

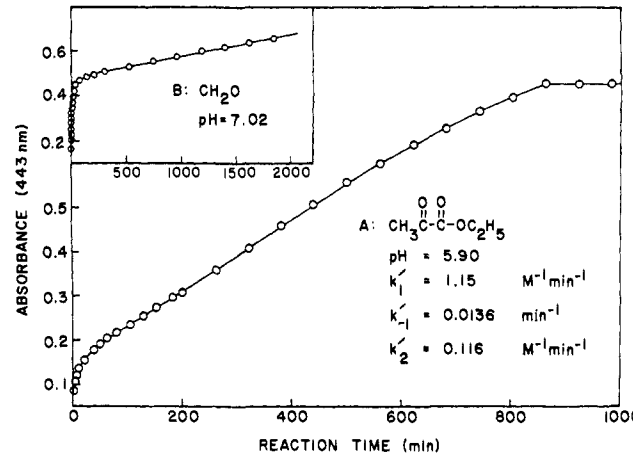
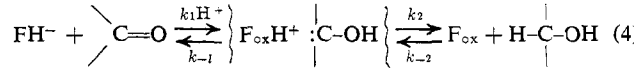


Figure 1. Time dependence of absorbance of lumiflavin-3-acetic acid (443 nm): (A) [ethyl pyruvate] = 0.10 *M*; $[FH_2] = 6 \times 10^{-5}$ *M*; (B) $[CH_2O] = 0.10$ *M*; $[FH_2] = 7 \times 10^{-5}$ *M* (30°, solvent H_2O (10 vol of CH_3OH), μ = 1.0 with KCl, N_2 atmosphere). The formalin solution was prepared by thermal depolymerization of paraformaldehyde and trapping of gaseous formaldehyde in doubly glass distilled water.

Abeles and coworkers have established the formation of intermediate carbanion species [R–Ċ(–XH)COOH] in the oxidation of β-chlorolactate and β-chloroamino acid by L-lactate and D- and L-amino acid oxidase.[5] Two mechanisms come to mind which incorporate a carbanion as an intermediate: (1) covalent intermediate formation at the 5 or 4a position of oxidized flavine (*i.e.*, similar to the mechanism of eq 1 but involving a covalent bond between flavine and the α carbon of the substrate); and (2) electron transfer from the carbanion to protonated oxidized flavine. Possibility 1 is chemically more appealing than the mechanism of eq 1 but suffers from the fact that the 4a adduct is of sufficient stability that it should have accumulated in both the initial burst and zero-order portions of the reactions reported herein.[6] Possibility 2, when approached from the direction of carbonyl compound and reduced flavine monoanion (FH^-), amounts to a "hydride transfer reaction" (eq 4, where $k_2 \gg k_{-1} \gg$



(4)

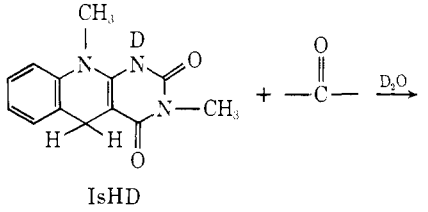
k_{-2}). Evidence for electron transfer in the case of "hydride" reduction of ketones by dihydronicotinamide has been claimed by Chipman.[7] It is of interest that we find 1,5-dihydro-5-deaza-3,10-dimethylisoalloxazine (IsHD) reduces pyridoxal in D_2O by direct transfer of a hydrogen.[8]

(5) (a) C. T. Walsh, A. Schonbrunn, and R. H. Abeles, *J. Biol. Chem.*, **246**, 6855 (1971); (b) C. T. Walsh, E. Krodel, V. Massey, and R. H. Abeles, *J. Biol. Chem.*, **248**, 1946 (1973); (c) C. T. Walsh, A. Schonbrunn, and R. H. Abeles, *J. Biol. Chem.*, in press.

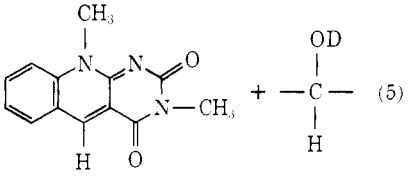
(6) Preliminary studies (D. Clerin and T. C. Bruice, unpublished results) indicate that 4a-alkyl adducts of 3-methyllumiflavine exhibit $t_{1/2}$ values (pH ~6) for conversion to reduced flavine of ~10^3–10^4 min which exceeds the time courses of the reactions of Figure 1.

(7) J. J. Stephens and D. M. Chipman, *J. Amer. Chem. Soc.*, **93**, 6694 (1971).

(8) To 289 mg of IsHD suspended in 30 ml of D_2O–methanol-d_6 (1:1) was added 40.6 mg of pyridoxal·HCl in 5 ml of D_2O. The mixture was stirred for 8 days in the dark (N_2 atmosphere, room temperature). The nmr spectrum of recovered pyridoxine showed the 4-CH_2O group at 4.83 ppm (Me_2SO-d_6). Also refer to M. Brüstlein and T. C. Bruice, *J. Amer. Chem. Soc.*, **94**, 6548 (1972).



IsHD



(5)

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(9) Postdoctoral Fellow.

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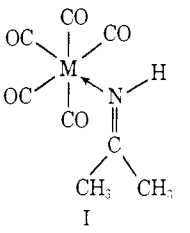
Stabilization of Dimethylketimine by Metal Complex Formation

Sir:

Ketimines, $RR'C{=}NR''$, are stable compounds only when the R, R′, and R″ groups are relatively large.[1] Thus dimethylketimine, $(CH_3)_2C{=}NH$, the imine analog of acetone, has never been isolated and is apparently too unstable for isolation. This communication describes the preparation and characterization of the first stable metal complex of dimethylketimine.

A solution of $Na_2[Cr_2(CO)_{10}]$, prepared[2] by photolysis of a tetrahydrofuran solution of $Cr(CO)_6$ in the presence of excess dilute sodium amalgam with stirring, was treated with excess of a tetrahydrofuran solution of 2-bromo-2-nitrosopropane,[3] $(CH_3)_2C(NO)Br$. Evaporation of the solvent followed by chromatography on alumina (CH_2Cl_2 solution) and sublimation at ~55° (0.01 mm) gave a 3–5% yield of yellow crystalline $(CH_3)_2C{=}N(H)Cr(CO)_5$. *Anal.* Calcd for $C_8H_7CrNO_5$: C, 38.5; H, 2.8; Cr, 20.8; N, 5.6; O, 32.1; mol wt, 249. Found: C, 38.4; H, 2.8; Cr, 20.2; N, 5.5; O, 32.3; mol wt, 279 (vapor pressure lowering), mp 45–47°. The analogous yellow tungsten compound $(CH_3)_2C{=}N(H)W(CO)_5$, mp 66–67°, was similarly prepared from $Na_2[W_2(CO)_{10}]$ and 2-bromo-2-nitrosopropane.

The spectroscopic properties of $(CH_3)_2C{=}N(H)Cr(CO)_5$ were in accord with its formulation as the dimethylketimine complex I. The infrared spectrum (CH_2Cl_2 solution) exhibited ν(CO) frequencies at 2073 (w), 1930 (vs), and 1896 (m) cm^{-1} which may be assigned to the A_1, E, and A_1 modes, respectively, of an $LM(CO)_5$ molecule. A more intense infrared spectrum (KBr pellet) exhibited a sharp band at 3317 cm^{-1} assigned to the ν(NH) frequency and an extremely weak band at ~1645 cm^{-1} which may be the ν(C=N) frequency. The proton nmr spectrum ($(CD_3)_2CO$ solution) exhibited resonances at τ 0.66 (broad, width at half-height 13 Hz) and 7.87 (sharp singlet) of approximate relative intensities ~1:6 which may be assigned to the single imine proton and the six equivalent methyl protons, respectively.



I

The formation of the compounds $(CH_3)_2C{=}N(H)M(CO)_5$ (I: M = Cr and W) from 2-bromo-2-nitrosopropane and the corresponding metal carbonyl anions $[M_2(CO)_{10}]^{2-}$ clearly must involve debromination and deoxygenation of the halonitroso compound by the strongly reducing metal carbonyl anion. Since *gem*-halonitroso alkanes of the type $RR'C(NO)X$ (X = Cl or Br) are available from the corresponding ketones $RR'C{=}O$ through halogenation of their oximes,[4] the reaction outlined in this communication should be useful for the preparation of a wide range of ketimine–metal carbonyl complexes from the corresponding ketones.

Reactions of 2-bromo-2-nitrosopropane with other metal carbonyl anions and related compounds appear to give unusual products of other types such as the yellow iron carbonyl derivative $[(CH_3)_2C{=}NFe(CO)_3]_2$ (from $Fe(CO)_4^{2-}$) and the purple cyclopentadienylmolybdenum carbonyl derivative $(CH_3)_2C{=}NOMo(CO)_2C_5H_5$ (from $C_5H_5Mo(CO)_3^-$). Details of this chemistry will be presented in future publications.

Acknowledgment. We are indebted to the National Cancer Institute for partial support of this work under Grants CA12938-01 and CA-12938-02 and to Mr. K. C. Hodges for help with the infrared spectra.

(1) S. Patai, Ed., "The Chemistry of the Carbon–Nitrogen Double Bond," Interscience, New York, N. Y., 1970.
(2) R. G. Hayter, *J. Amer. Chem. Soc.*, **88**, 4376 (1966).
(3) O. Piloty, *Ber.*, **31**, 452 (1898).
(4) J. H. Boyer in "The Chemistry of the Nitro and Nitroso Groups," H. Feuer, Ed., Interscience, New York, N. Y., 1969, pp 235–238.
(5) Postdoctoral research associate, 1971–1973.

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Detailed Stereochemistry in Solution of a Macrocyclic Complex Having Eight Chiral Centers. Observation of an Intramolecular Nuclear Overhauser Effect

Sir:

Complexes of metal chelates that contain several chiral centers exhibit intricate stereochemistries and large numbers of possible isomers.[1] Powerful techniques are required to deduce the detailed structures of individual isomers of such species in solution. We report here the use of double resonance nmr measurements, including a novel example of an intramolecular nuclear Overhauser effect (NOE), combined with stereospecific deuteration and strain energy calculations to produce an exceptionally detailed description of the

(1) See, for example, L. G. Warner and D. H. Busch, *J. Amer. Chem. Soc.*, **91**, 4092 (1969).