of selenium dioxide oxidations can now be adequately explained for the first time. With the exception of Wiberg's mechanism,[13] a common fault in all previously proposed mechanisms[14] was that they considered the oxygen end of the >Se=O dipole to be the electrophile; whereas, it is clearly the selenium atom which is the most electron deficient center in species such as **1**.

Acknowledgment. We are indebted to Dr. Daniel D. Troficante for obtaining a Fourier transform pmr spectrum of **8**. We are grateful to the National Science Foundation (GP-30485X), Hoffmann-La Roche Inc., and the Mobil Foundation for support of this research at M.I.T. and to Sandoz AG, Basel for financial assistance at the ETH.

(13) K. B. Wiberg and S. D. Nielsen, *J. Org. Chem.*, **29**, 3353 (1964).
(14) For a recent review of selenium dioxide oxidations see R. A. Jerussi in "Selective Organic Transformations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, Chapter 6, p 301.
(15) NSF Predoctoral Fellow, 1970–1973.

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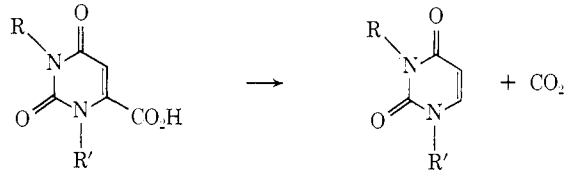
Mechanism of Decarboxylation of 1,3-Dimethylorotic Acid. A Possible Role for Orotate Decarboxylase

Sir:

The efficient enzymatic decarboxylation of orotidine 5′-phosphate (**1**) to uridylic acid (**2**), a central metabolic

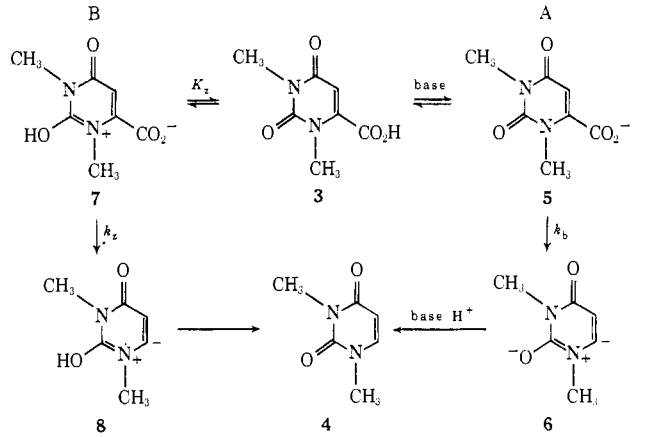


1, R = H; R′ = ribose 5′-phosphate
3, R = R′ = CH_3
2, R = H; R′ = ribose 5′-phosphate
4, R = R′ = CH_3

reaction in pyrimidine biosynthesis,[1] is mechanistically interesting because the types of stabilization usually associated with biochemically facile decarboxylations are not apparent for the pyrimidone ring of **1**.[2,3] We wish to report a study of the mechanism of decarboxylation of 1,3-dimethylorotic acid (**3**) which provides evidence that decarboxylation of this model compound can proceed *via* a zwitterionic intermediate and thereby to suggest a specific chemical role for orotate decarboxylase.

The conversion of 0.05 *M* **3** to 1,3-dimethyluracil (**4**) proceeds efficiently in sulfolane at 206°. The rate of evolution of carbon dioxide can be studied as a function of added base, concentration, and isotopic substitution. With added diethylaniline the observed pseudo-first order rate constant smoothly increases from 0.76×10^{-3} to 3.1×10^{-3} sec^{-1} as the base is increased from 0 to 0.7 *M*. The latter rate constant represents a plateau which is invariant up to 2 *M* base. The degree of ionization of the carboxylic acid, measured by the relative conductance of these solutions extrapolated to 206° from measurements at 50, 100, and 150°, also rises from essentially zero to a maximum over the same range of base concentrations.[4] These data imply that the carboxylate anion is chiefly responsible for decarboxylation in the presence of base while the low conductance in the absence of base suggests that the formally neutral acid undergoes decarboxylation in neat sulfolane.[5] Decarboxylation of an undissociated species is further required by the invariance of the first-order rate constant for CO_2 evolution from **3** as its initial concentration is varied between 0.01 and 0.25 *M*[6] in neat sulfolane. The fact that the formally neutral form of **3** which undergoes decarboxylation probably does not involve a transition state with simultaneous carbon–carbon and oxygen–hydrogen bond cleavage is revealed by the decarboxylation of carboxydeuterio **3**, which proceeds at the same rate (0.78×10^{-3} $sec^{-1} \pm 0.06 \times 10^{-3}$ sec^{-1}) as the protio species.[7]

A dual pathway process consistent with these observations is shown below. In basic solution (path A) the

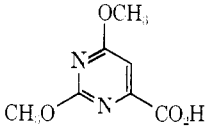


carboxylate anion undergoes decarboxylation to the dipole-stabilized carbanion **6**, an intermediate which

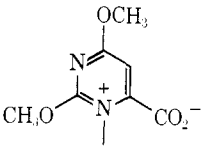
(1) P. Reichard, *Advan. Enzymol.*, **2**, 263 (1959); C. C. Cheng and B. Roth, *Progr. Med. Chem.*, **7**, 285 (1970); G. Schmidt, *Annu. Rev. Biochem.*, **33**, 667 (1969); G. Crosbie, "The Nucleic Acids, III," J. Davidson and E. Charaguff, Ed., Academic Press, New York, N. Y., 1960, p 327.
(2) Stabilization in most biochemically important decarboxylations is considered to be provided by π delocalization of the residual electron pair or by bond making concerted with bond breaking, often in an electrocyclic process.[3]
(3) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, pp 188–194; M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," Wiley-Interscience, New York, N. Y., 1971, pp 165–175, 586–594.
(4) A slight decrease observed in the conductivity as the concentration of base is further increased is attributed to the decrease in dielectric constant of the medium.
(5) Moreover, if only the carboxylate anion were reacting in neat sulfolane, the observed rate constant would necessitate an unprecedented degree of ionization (25%) in that solvent: J. Coetzee and R. Bertozzi, *Anal. Chem.*, **45**, 1064 (1973).
(6) Since the equilibrium constant (K) for acid ionization = $[\alpha/(1-\alpha)]c$, if c, the total concentration of the acid plus its carboxylate anion, decreases, the fraction of ionization, α, will increase if K is significantly different from zero.
(7) F. Westheimer, *Chem. Rev.*, **61**, 265 (1961); for some decarboxylations in which deuterium isotope effects are observed see D. Bigley and J. Thurman, *J. Chem. Soc. B*, 436 (1968).

has precedent.[8] In path B under neutral conditions **3** is considered to be in equilibrium with the zwitterion **7**[9] which is the active species giving the ylide **8** in this route to **4**. Decarboxylations by such a route have considerable analogy for other heteroaromatic acids, and **6** and **8** have been suggested earlier as possible intermediates.[10]

Comparison of the rates of decarboxylation of **9** and **10**[11] provides a semiquantitative estimate of a zwitterionic pathway. In contrast to the smooth decarboxylation of the carboxylate anion of **3** in isoquinoline at 206°, the carboxylate anion of **9**, which cannot give a dipole-stabilized carbanion, does not decarboxylate under those conditions. Accordingly, the neutral carboxylic acid in the form of **9** is also considered to be unreactive[9a] and the facile decarboxylation of this acid with a first-order rate constant of 1.3×10^{-2} sec^{-1} in the neutral solvent sulfolane at 206° is attributed solely to a zwitterionic pathway involving **11**. If the



9



10, R = CH_3
11, R = H

rate constant for the decarboxylation of **11** is estimated to be 5×10^4 sec^{-1} by extrapolation from the reaction of **10** at lower temperatures, the equilibrium constant for zwitterion formation required by the observed rate of decarboxylation of **9** is 2.6×10^{-7}.

The above study of **9** may be used in an assessment of the decarboxylation of **3** *via* **7** by the kinetic model method which was successfully used earlier to distinguish neutral and zwitterionic processes in hydrogen–deuterium exchange of pyrimidones.[10] The value of K_z for **3** may be estimated by attenuating the equilibrium constant for **9** by the ratio of base ionization constants of *N*-methyl-2-pyridone to 2-methoxypyridine.[12] Not unexpectedly this approximation yields a value of K_z for **3** (3×10^{-10}) about three orders of magnitude smaller than that for **9**. As before, using k_z estimated at 5×10^4 sec^{-1} gives $K_z k_z$, the calculated rate constant for path B, equal to 0.2×10^{-4} sec^{-1}, which is in reasonable agreement with the experimentally observed rate constant 7.6×10^{-4} sec^{-1}. Accordingly, pathway B *via* the zwitterion is the preferred mechanism for the decarboxylation of formally neutral 1,3-dimethylorotic acid.

To the extent that **3** is a valid model for the enzymatic decarboxylation of **1**, an obvious role, which could account for several powers of ten of the effectiveness of the enzyme, for orotate decarboxylase is to increase the effective zwitterion concentration by reaction of one of the carbonyl oxygens in the pyrimidone with a proton or other suitable electron-deficient center either prior to or in the transition state for decarboxylation. Further studies are in progress.

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(9) (a) B. R. Brown and D. Hammick, *J. Chem. Soc.*, 659 (1959); (b) L. Clark, "The Chemistry of Carboxylic Acids and Esters," S. Patai, Ed., Wiley-Interscience, New York, N. Y. 1969, p 589; (c) B. R. Brown, *Quart. Rev., Chem. Soc.*, **5**, 131 (1951); (d) P. Haake and T. Mantecon, *J. Amer. Chem. Soc.*, **86**, 5230 (1964); (e) G. Dunn, G. Lee, and H. Thimm, *Can. J. Chem.*, **50**, 3017 (1972).

(10) P. Beak and R. Watson, *Tetrahedron*, **27**, 953 (1971), and references cited therein. An alternative to **7** and **8** which has the proton on O-4 is clearly possible.

(11) The zwitterion **10** is prepared in mixture with a neutral ester by hydrolysis of the corresponding pyrimidinium ester. The zwitterion has been characterized by nmr spectroscopy and hydrolysis to 1-methylorotic acid.

(12) E. J. Cohn and J. T. Edsall, Ed., "Proteins, Amino Acids, and Peptides As Ions and Dipolar Ions," Hafner Publishing Co., New York, N. Y., 1943; A. R. Katritzky, Ed., "Physical Methods in Heterocyclic Chemistry," Vol. I, Academic Press, New York, N. Y., 1963; E. Arnett and C. Douty, *J. Amer. Chem. Soc.*, **86**, 409 (1964).

Designed Syntheses of the $Mo_2Cl_9^{3-}$ Anion and the New $Mo_2Cl_9^{2-}$ Anion

Sir:

Although the structures,[1] chemistry,[2] and properties[3] of the bioctahedral anions, $M_2Cl_9^{3-}$ (M = Mo or W), have received considerable attention, the synthetic methods used in the formation of these anions from mononuclear reactants remain rather haphazard and are not entirely rational by any means. The basic difficulty in any rational approach starting with mononuclear reactants is the stereospecific formation of the face-shared polyhedron having three chlorine bridges. Our current strategy for the solution of this problem employs the notion that MCl_6^{n-} (n = 0, 1, and 2) can serve as an easily reduced tridentate ligand which can displace CO ligands on a trigonal face of a metal carbonyl halide, such as $M(CO)_5Cl^-$ or $M(CO)_4Cl_3^-$. The displacement of CO, which accompanies bridge formation, should be facilitated by concomitant electron transfer. Any additional CO ligands which remain after bridge formation should be readily lost because of the rather high formal oxidation state of the metal to which they are attached. Thus, the scheme which we envision is an oxidation–reduction reaction which proceeds by an inner sphere or bridging mechanism. If $M(CO)_4Cl_3^-$ is used as a reducing agent, the scheme is

$$MCl_6^{n-} + M(CO)_4Cl_3^- \xrightarrow[-3CO]{} Cl_3MCl_3M(CO)Cl_3^{(n+1)-} \xrightarrow[-CO]{} Cl_3MCl_3MCl_3^{(n+1)-}$$

(1) (a) W. H. Watson and J. Waser, *Acta Crystallogr.*, 11, 689 (1958); (b) R. Saillant, R. B. Jackson, W. E. Streib, K. Folting, and R. A. D. Wentworth, *Inorg. Chem.*, 10, 1453 (1971).

(2) (a) R. Saillant, J. L. Hayden, and R. A. D. Wentworth, *Inorg. Chem.*, **6**, 1497 (1967); (b) J. L. Hayden and R. A. D. Wentworth, *J. Amer. Chem. Soc.*, **90**, 5291 (1968); (c) R. Saillant and R. A. D. Wentworth, *ibid.*, **91**, 2174 (1969).

(3) (a) R. Saillant and R. A. D. Wentworth, *Inorg. Chem.*, 7, 1606 (1968); (b) R. Saillant and R. A. D. Wentworth, *ibid.*, **8**, 1226 (1969); (c) J. Lewis, R. S. Nyholm, and P. W. Smith, *J. Chem. Soc. A*, 57 (1969); (d) I. E. Grey and P. W. Smith, *Aust. J. Chem.*, **22**, 121 (1969); (e) P. D. W. Boyd, P. W. Smith, and A. G. Wedd, *ibid.*, **22**, 653 (1969); (f) I. E. Grey and P. W. Smith, *ibid.*, **22**, 1627 (1969).