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Decarboxylation via Addition of Water to a Carboxyl Group: Acid Catalysis of Pyrrole-2-Carboxylic Acid

Scott O. C. Mundle and Ronald Kluger*

Davenport Chemical Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

Received June 24, 2009; E-mail: rkluger@chem.utoronto.ca

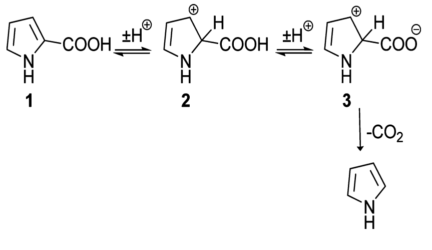
Decarboxylation, formally the conversion of a carboxyl group to a proton and carbon dioxide, is normally a dissociative process that leads directly to the formation of carbon dioxide and a stabilized carbanion.[1] This mechanism is unusual among carbonyl substitution reactions, which are commonly associative processes involving tetrahedral addition intermediates.[2] Because protonated carbon dioxide is a very high energy species,[3,4] the bond-breaking process in decarboxylation reactions occurs from the conjugate base of the carboxylic acid. However, reversible addition of water to carboxyl groups is well-known and subject to specific acid catalysis.[5] In the case where the leaving group would be a very weakly basic carbanion, the resulting decarboxylation from the hydrated carboxyl group would produce protonated carbonic acid. This is a much more stable species than protonated carbon dioxide, which would result from a dissociative acid-catalysis mechanism.[6] In accord with expectations for acid-catalyzed decarboxylation, we report observation of a reaction whose characteristics are consistent with an associative mechanism.

Pyrrole is an unusually weak base that undergoes equilibrium protonation on its α and β carbons rather than on nitrogen.[7] The neutral form of pyrrole 2-carboxylic acid (**1**) is subject to acid-catalyzed decarboxylation in strong acids but resistant to decarboxylation in less acidic solutions (Scheme 1).[8]

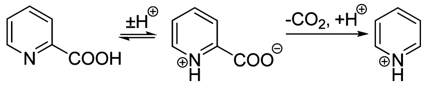
This is in contrast to the reactivity of 2-picolinic acid, the related derivative of pyridine, which is most reactive in solutions at pH 5, where its zwitterionic form is at its maximum concentration; the rate decreases in more acidic solutions.[9,10] A logical mechanism for the decarboxylation in that case involves the usual dissociative transition state (Scheme 2).

Scheme 1 shows that protonation of **1** at the α-carbon to give **2** activates the molecule toward decarboxylation only if the carboxyl group is ionized. Since equilibrium protonation of the α-position requires highly acidic solutions, the concentration of the dissociated carboxyl group is largely suppressed under those conditions, as is the rate of any process that would pass through that species.

Scheme 1. Neutral Decarboxylation of Pyrrole-2-carboxylic Acid



Scheme 2. Decarboxylation of 2-Picolinic Acid



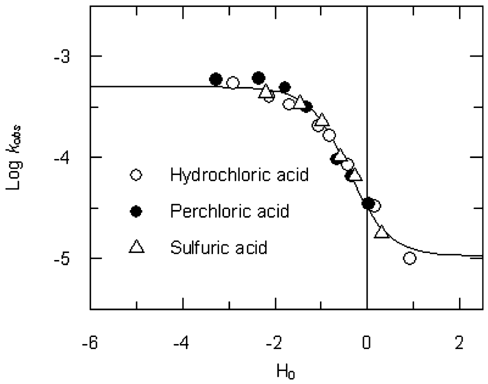


Figure 1. Logarithm of the observed first-order rate constant (k_{obs}) as a function of the Hammett acidity function (H_0) in hydrochloric acid, perchloric acid, and sulfuric acid at 25 °C.

The observed decarboxylation of **1** in acid suggests that protonation of a ring carbon is more significant in promoting the reaction than is ionization of the carboxyl group. Kinetic observations[8] are consistent with a mechanism involving at least two distinct steps: protonation of the ring and carbon−carbon bond cleavage. Dunn and Lee[8] proposed that at low acid concentrations, protonation of the ring at the α-carbon is rate-determining, while at higher acid concentrations that produce significant quantities of the protonated intermediate, C−C bond cleavage is rate-determining. Consistent with this proposition, they observed that the $^{12}C/^{13}C$ kinetic isotope effect in dilute acid is much smaller than it is in a more acidic solution. However, those authors formulated the reaction as proceeding through the neutral zwitterion, a process that would require removal of the proton from the carboxyl group in acid, which is inconsistent with the observed increase in rate with increasing acidity.

We determined the rate of decarboxylation of **1** in aqueous hydrochloric, perchloric, and sulfuric acid solutions by following the decrease in absorbance at 262 nm. A plot of the logarithm of the observed first-order rate coefficient versus the Hammett acidity function (H_0) is shown in Figure 1.[11,12] The rate was also determined at $H_0 = -7.4$ in perchloric acid ($\log k_{obs} \approx -3.0$). Rather than a decrease in rate with increasing acidity, as predicted by Dunn and Lee[8] for a mechanism involving suppression by the acid of formation of the zwitterion at very high acidity, we found an increase in the rate, indicating the involvement of a different mechanism. The data in Figure 1 show that the rate does not depend on the identity of the acid but only on the resulting H_0. It is conceivable that at high acidity, the expected decrease in rate from the unfavorable removal of the proton on the carboxylic acid could be compensated by the

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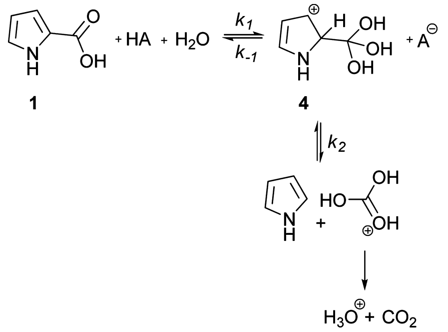
Scheme 3. Mechanism of Decarboxylation via Addition of Water to the Carboxyl Group of Pyrrole-2-carboxylic Acid



high concentration of the counterion acting as a Brønsted base in the transition state for decarboxylation. However, it is clear that variation of the medium's conjugate base has no effect on the rate, and the reaction is limited by the decreasing availability of water at high acidity.

These results clearly rule out the involvement of the zwitterionic intermediate **3** and related transition states in the acid-catalyzed reaction. Direct formation of the zwitterion by simultaneous loss of the proton from the carboxylic acid and gain of a proton on the α-carbon of the ring does not require an external source of protons. This would not be subject to acid catalysis, as in the mechanism for decarboxylation of 2-picolinic acid (Scheme 2).[10] A mechanism in which the ring nitrogen of the already protonated reactant accepts an additional proton would have a prohibitively high energy, as the initially protonated ring is cationic at nitrogen.

A mechanism that is consistent with the observed kinetic patterns involves addition of water to the carboxyl group (Scheme 3). Under strongly acidic conditions, the α-carbon of the pyrrole ring is partially protonated, and water adds to the carboxyl group to form a reactive addition intermediate, **4**, after which C−C bond cleavage occurs (there are several kinetically equivalent routes from **1** to **4**). One product resulting from C−C bond cleavage is the conjugate acid of carbonic acid, which rapidly dissociates into protonated water and carbon dioxide.[6]

The acid-catalyzed addition of water to carboxylic acids is well-established from the pioneering work of Roberts and Urey[13] on oxygen exchange from water into benzoic acid. The rate constant can be extrapolated to our reaction conditions and is kinetically competent for the proposed mechanism ($\sim 0.1\ \mathrm{s}^{-1}$). Protonation of the ring carbon of **1** as shown produces an even more electrophilic carboxyl group. A similar associative process was suggested by Warren and Williams[14] for the mechanism of decarboxylation of phosphonoformic acid, in which a phosphorus anion is the residual anionic site.

The rate law associated with Scheme 3 and the steady-state assumption give the dependence of the observed first-order rate constant on acidity and water activity (eq 1):

$$v = k_{\mathrm{obs}}[\mathbf{1}] = \frac{k_1 k_2[\mathrm{HA}][\mathrm{H_2O}]}{k_{-1}[\mathrm{A}^-] + k_2}[\mathbf{1}] \qquad (1)$$

At high acidity, the increase in the observed rate constant with additional acid is countered by the decrease in the activity of water, leading to the plateau in Figure 1.[11]

Biochemical catalysis of the reaction of **1** has been observed. Omura et al.[15] reported pyrrole 2-carboxylate decarboxylase-carboxylase, an enzyme whose activity depends on the presence of exogenous carboxylic acids. While the mechanism they formulated involves deprotonation of the pyrrole nitrogen, the evidence is more easily understood in terms of formation of a carbocation β to the carboxylate, leading to dissociative loss of carbon dioxide. However, such a process is inherently slow unless there is a way to stabilize the requisite zwitterionic intermediate. It also does not provide a clear rationale for the readily observed carboxylation. On the other hand, an associative mechanism can be subject to acid catalysis, and the reaction of carbonic acid rather than carbon dioxide is mechanistically reasonable.

Thus, we conclude that while dissociative formation of carbon dioxide is a well-established driving force in chemical reactions, direct formation of carbonic acid via an associative mechanism may be competitive in acidic solutions involving good leaving groups. This alternative pathway presents an opportunity for the existence of multiple modes of catalysis according to the reaction conditions.

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