J|A|C|S ARTICLES

Published on Web 02/02/2010

Hydrolytic Decarboxylation of Carboxylic Acids and the Formation of Protonated Carbonic Acid

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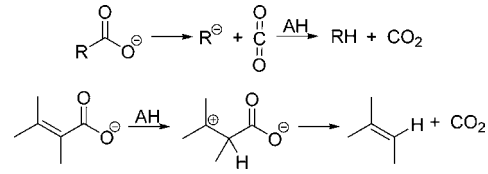
Abstract: Acid-catalyzed decarboxylation reactions of carboxylic acids should avoid formation of protonated carbon dioxide, a very high energy species. A potential alternative route parallels ester hydrolysis, with addition of water to the carboxyl group followed by protonation of the unsaturated leaving group and formation of protonated carbonic acid, a species that had been predicted to be a viable reaction intermediate. The hydrolytic mechanism for the decarboxylation of pyrrole-2-carboxylic acid is consistent with observed $^{12}C/^{13}C$ kinetic isotope effects (1.010 ± 0.001 at $H_0 = -0.01$ and 1.043 ± 0.001 at $H_0 = -2.6$), solvent kinetic isotope effects ($k_{H_2O}/k_{D_2O} = 2$ at $H_0 = 0.9$; $k_{H_2O}/k_{D_2O} = 1$ at $H_0 = -2.9$), and activation parameters [$\Delta H^{\ddagger} = 23.5$ kcal·mol^{-1} and $\Delta S^{\ddagger} = 5.5$ cal·deg^{-1}·mol^{-1} at $H_0 = -2.9$]. Thus, the specific route for a decarboxylation process is a consequence of the nature of the potential carbanion (or its conjugate acid), the acidity of the medium and avoidance of formation of protonated carbon dioxide.

Introduction

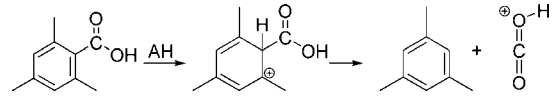
Decarboxylation, formally the replacement of a carboxyl group by a proton, is the source of carbon dioxide from organic compounds in diverse oxidative processes. The loss of a carboxyl group is normally portrayed as the direct conversion of its conjugate base, a carboxylate, to carbon dioxide and a carbanion, followed by protonation of the carbanion. In the case of a derivative with appropriate unsaturation, protonation at an adjacent site can precede the cleavage of the carbon−carbon bond from the carboxylate that leads to formation of carbon dioxide (Scheme 1).

Acid-catalyzed decarboxylation reactions of carboxylic acid derivatives of aromatic compounds appear to be notable exceptions to these patterns. In the 19th century, Klages and Lickroth[1] noted that mesitoic acid (2,4,6-trimethylbenzoic acid) and related materials undergo decarboxylation in acidic solutions. In 1949, Schubert[2] reported a detailed investigation of that reaction, in which he noted that the rate of the acid-catalyzed decarboxylation process is proportional to solution acidity. He also proposed the involvement of a molar equivalent of water, as evidenced by the reaction rate leveling in highly acidic media where water activity is reduced. In order to account for these observations, Schubert[2] proposed a mechanism that involves the formation of protonated carbon dioxide, with water serving to shuttle a proton to the carbanion (Scheme 2). However, subsequent determination of the high energy of protonated carbon dioxide (proton affinity for $CO_2 = 128$ kcal mol^{-1}, p$K_a = -39$) makes it clear that this route is energetically prohibitive.[3,4]

Scheme 1. General Mechanisms of Decarboxylation Reactions of Carboxylates



Scheme 2. Decarboxylation of Mesitoic Acid via Protonated Carbon Dioxide



We recently reported[5] that the kinetic patterns for acid-catalyzed decarboxylation of pyrrole-2-carboxylic acid are consistent with an alternative acid-catalyzed decarboxylation route that involves addition of water to the conjugate acid of the carboxyl group (Scheme 3). Upon tautomerization to a ring-protonated species, cleavage of the bond to the carboxyl group leads to formation of protonated carbonic acid.[6]

The addition step has a precedent in observations of acid-catalyzed oxygen isotope exchange from $H_2{}^{18}O$ into the carboxyl group of benzoic acid and its extension to ester hydrolysis in acid.[7] Loss of a proton and aqueous decomposition of the resulting carbonic acid would have the overall effect of formation of carbon dioxide from a carboxyl group and its replacement by a proton.

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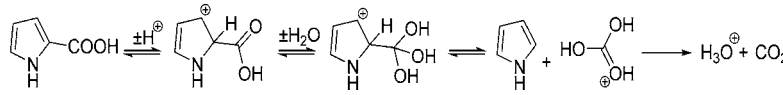
 10.1021/ja910608m

Scheme 3. Hydrolytic Decarboxylation of Pyrrole-2-carboxylic Acid



The general pattern of decarboxylation via loss of protonated carbonic acid has the following features: (1) protonation of the reactant (as a pseudoequilibrium prior to a rate-determining step or being itself rate-controlling); (2) reversible formation of the covalent hydrate of the carboxyl group; (3) carbon−carbon bond cleavage from the hydrate; and (4) decomposition of protonated carbonic acid.

In order to determine the relative kinetic significance of these steps, we have measured the magnitude of the $^{12}C/^{13}C$ kinetic isotope effect for decarboxylation of pyrrole-2-carboxylic acid as a function of the acidity of the reaction medium as well as solvent isotope effects (H_2O/D_2O). The results provide detailed resolution among various isotope-sensitive steps. The acidity dependence and rates are consistent with rapid protonation of the carboxyl group, which will be in equilibrium with the reactive ring-protonated tautomer that undergoes hydration followed by carbon−carbon bond cleavage (Scheme 3).

Experimental Section

Materials. Commercial pyrrole-2-carboxylic acid was spectroscopically characterized and then used directly. Solutions of reagent-grade concentrated acids (hydrochloric acid, perchloric acid, and sulfuric acid) were diluted to the indicated weight percentage.

Methods. Measurements of the rate of decarboxylation of pyrrole-2-carboxylic acid were conducted in acidic solutions in the cell compartment of a UV−vis spectrometer with the temperature controlled to ±0.1 °C. The reaction was followed at 262 nm. Data were collected with an interfaced computer. Observed first-order rate constants were calculated from nonlinear regression fitting to the integrated first-order rate expression. For slower reactions, the rate constants were determined by the method of initial rates. Solvent kinetic isotope effects were compared on the basis of the concentration of proton versus deuterium in hydrochloric acid and deuterium chloride.

$^{12}C/^{13}C$ Kinetic Isotope Effects. Reactions were carried out in a serum vial (40 mL) with a glass side arm connected to a digital pressure gauge. A solution of acid (20 mL, degassed) was added to the vial, and the headspace was purged with helium to remove all CO_2. Pyrrole-2-carboxylic acid (6 mg) was dissolved in dimethyl sulfoxide (100 μL, degassed) and injected into the vial. The space above the aqueous solution ("headspace") was sampled by use of a pressure-lock analytical syringe with a side-port taper needle.[8] The headspace was sampled up to 30% conversion of the reactant. Reaction progress was monitored directly by the increase in pressure in the headspace and confirmed by comparison with the peak area obtained from mass intensity scans on an isotope-ratio mass spectrometer coupled to a gas chromatograph and combustion oven (GC-IRMS).[9] Measurements of materials from complete conversion of the reactants were taken after 24 h. All reactions were maintained at 25.0 °C in a circulating water bath.

As a control, for each set of conditions, the sequence was repeated without substrate. In these cases, CO_2 was not detected in the headspace. In addition, samples were prepared and injected with CO_2 of known isotopic composition. The headspace was sampled over several days to ensure that the reaction conditions did not alter the isotopic composition of the CO_2.

$^{12}C/^{13}C$ kinetic isotope effects (CKIE) were calculated by use of Bigeleisen's derivation of the simplified Rayleigh equation ($R/R_0 = f^{\varepsilon/1000}$). This is based on the assumption that at the low natural abundance of the heavy isotope $(1 + R)/(1 + R_0) \approx 1$, where R and R_0 are the $^{13}C/^{12}C$ ratios of CO_2 at time t and time 0, respectively, and f is the fraction of CO_2 remaining, ε (per mil) is the enrichment factor, equal to $1000(\alpha - 1)$, where $\alpha = (CKIE)^{-1}$.[10] We use the variation of this equation developed by Bothner-By and Bigeleisen[11] for monitoring isotope effects in decarboxylation reactions:

$$k^{12}/k^{13} = \log (1 - f)/\log [1 - f(N_x/N_{x_0})]$$

where k^{13} and k^{12} are the observed first-order rate coefficients for reaction of the heavy and light isotopes. R and R_0 are replaced with N_x and N_{x_0} (the $^{13}C/^{12}C$ ratio reported from the IRMS are converted into abundances).

Results

The rates of decarboxylation of pyrrole-2-carboxylic acid in solutions of hydrochloric acid, perchloric acid, and sulfuric acid are consistent with those previously reported (Figure 1).[5] The rates increase with increasing acidity of the medium (H_0), independent of the counterion. This is an indication of specific acid catalysis, making it most likely that the reactive species is a conjugate acid of the reactant. At higher acidity ($H_0 < -2$) the rate becomes independent of acidity, consistent with a change in rate-determining step in a single mechanism or saturation of protonation of the reactant by the medium.

Application of the Bunnett−Olsen method[12,13] gives $w \cong 5$, which was determined from a plot of $(\log k + H_0)$ versus $\log a_{H_2O}$. This is within the range observed for typical acid-catalyzed ester hydrolysis reactions that proceed via addition of water.[14] A mechanism involving hydrolytic decarboxylation is an extension of this type of mechanism.

We approximated the value of the pK_a of the conjugate acid formed by protonation of the carboxyl group based on the definition of H_0. The pK_a that results from the fit in Figure 1 to a titration curve is −1.3. The macroscopic pK_a does not correspond to ring protonation of a pyrrole, as the pK_a of the

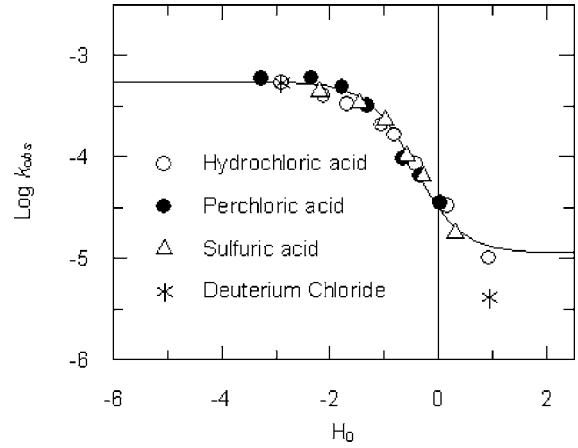


Figure 1. Logarithm of the observed first-order rate constant (k_{obs}) as a function of the Hammett acidity function (H_0) for the decarboxylation of pyrrole-2-carboxylic acid in hydrochloric acid, perchloric acid, sulfuric acid, and deuterium chloride at 25 °C as reported,[5] with the addition of the rate constants for deuterium oxide containing deuterium chloride (*).

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Table 1. $^{12}C/^{13}C$ Kinetic Isotope Effects on the Acid-Catalyzed Decarboxylation of Pyrrole-2-carboxylic Acid[a]

f	N_x	CKIE
	42 wt % $HClO_4$	
0.03	0.0103 81	1.0426
0.05	0.0103 76	1.0436
0.06	0.0103 80	1.0434
0.08	0.0103 86	1.0432
0.10	0.0103 85	1.0438
	avg CKIE 1.043 ± 0.001	
	33 wt % $HClO_4$	
0.04	0.0104 14	1.0394
0.05	0.0104 21	1.0389
0.06	0.0104 17	1.0396
0.07	0.0104 26	1.0389
0.08	0.0104 22	1.0394
0.12	0.0104 32	1.0393
0.15	0.0104 42	1.0389
0.16	0.0104 38	1.0397
0.25	0.0104 62	1.0392
0.28	0.0104 72	1.0389
0.34	0.0104 88	1.0388
	avg CKIE 1.039 ± 0.001	
	15 wt % $HClO_4$	
0.02	0.0105 41	1.0265
0.02	0.0105 36	1.0269
0.02	0.0105 34	1.0271
0.02	0.0105 37	1.0268
0.05	0.0105 44	1.0265
0.05	0.0105 47	1.0262
0.07	0.0105 43	1.0269
	avg CKIE 1.027 ± 0.001	
	5 wt % $HClO_4$	
0.02	0.0107 13	1.0098
0.05	0.0107 14	1.0099
0.05	0.0107 10	1.0103
0.13	0.0107 12	1.0105
	avg CKIE 1.010 ± 0.001	

[a] $N_{x_0} = 0.010\,816 \pm (5 \times 10^{-6})$.

C2-protonated conjugate acid of pyrrole is considerably lower (−3.8).[15] However, the proposed pK_a is consistent with that for the conjugate acid of a carboxyl group.[16] On the basis of the relative pK_a values at equilibrium, at $H_0 = -1.3$, only about one part per thousand will be protonated on the pyrrole ring. However, upon addition of water to the carboxyl group, a weaker, more localized base results. Protonation can then occur to a greater relative extent on the heterocyclic ring, with pyrrole becoming the leaving group.

The solvent kinetic isotope effect (SKIE) for decarboxylation was determined with hydrochloric acid in water and with deuterium chloride in deuterium oxide. On the basis of published solvent effects on acidity functions, the H_0 scale for hydrochloric acid solutions was adapted for deuterium chloride solutions (D_0).[17,18] The SKIE was determined at $H_0 = 0.9$ where an acid-catalyzed step is expected to be rate-determining, yielding $k_{H_2O}/k_{D_2O} = 2$. This value corresponds to the SKIE reported by Willi[19] [$k_{H_2O}/k_{D_2O} = 1.76$ (50 °C)] for the decarboxylation of 2,4-dihydroxybenzoic acid under similar conditions. The magnitudes

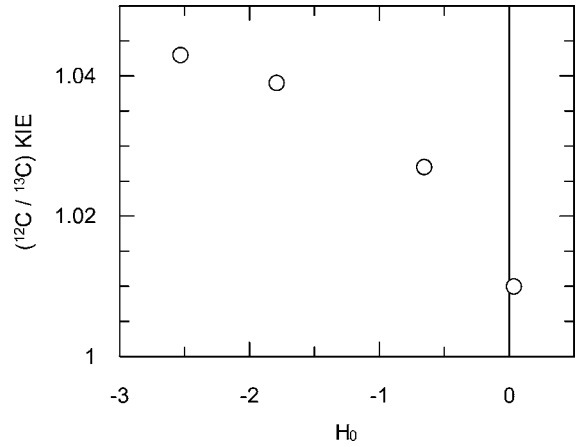

Figure 2. $^{12}C/^{13}C$ kinetic isotope effect as a function of solution acidity for the decarboxylation of pyrrole-2-carboxylic acid in perchloric acid at 25 °C.

of the SKIEs in solutions of this acidity correspond to those for the hydration of alkenes ($k_{H_2O}/k_{D_2O} \sim 2-4$), where the isotope effect arises from protonation of the double bond.[20]

Our results are consistent with protonation of the reactant being involved in the rate-controlling step under these conditions. There is no SKIE at $H_0 = -2.9$, where the rate is acidity-independent (Figure 1). The absence of a SKIE at this acidity requires that the rate-determining step does not include a proton transfer in the rate-determining transition state.

$^{12}C/^{13}C$ kinetic isotope effects (CKIE) were determined in solutions containing perchloric acid (Table 1). The observed CKIEs increase from 1.010 ± 0.001 in 5% perchloric acid to 1.043 ± 0.001 in 42% perchloric acid. The increase in CKIE also begins to level with acidity at $H_0 \sim -2$ (Figure 2), supporting the notion that there is a change in rate-determining step as the solution becomes more acidic. We were unable to measure the CKIE satisfactorily in solutions with concentrations of perchloric acid greater than 42%. At these concentrations, dimethyl sulfoxide, which is used to dissolve pyrrole-2-carboxylic acid, is oxidized by perchloric acid. The single CKIE value reported by Dunn and Lee[21] (1.028) for decarboxylation of pyrrole-2-carboxylic acid in 4 M perchloric acid was obtained via dual-inlet mass spectroscopy and purification of CO_2 on a vacuum line. This agrees with the values we obtain at comparable acidity from headspace analysis and gas chromatography, coupled to a combustion oven and isotope ratio mass spectrometer (GC-IRMS).

Rates of decarboxylation were also determined for reactions in 0.5%, 5%, and 23% hydrochloric acid. Activation parameters were obtained as a fit of a plot of the Eyring equation (Figure 3). The activation free energy ($\Delta G^{\ddagger}$), enthalpy ($\Delta H^{\ddagger}$), and entropy ($\Delta S^{\ddagger}$) are listed in Table 2. The parameters for reaction in 0.5% hydrochloric acid correspond to values previously reported for reactions at this acidity.[22] Activation parameters for the decarboxylation of pyrrole-2-carboxylic acid in 23% hydrochloric acid ($H_0 = -2.9$) and 0.5% hydrochloric acid ($H_0 = 0.9$) differ in enthalpy of activation by ~3.6 kcal·mol^{-1}. At

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(22) Hutchinson, K. M.; Bretz, S. L.; Mettee, H. D.; Smiley, J. A. *Biochem. Mol. Biol. Educ.* **2005**, *33*, 123–127.

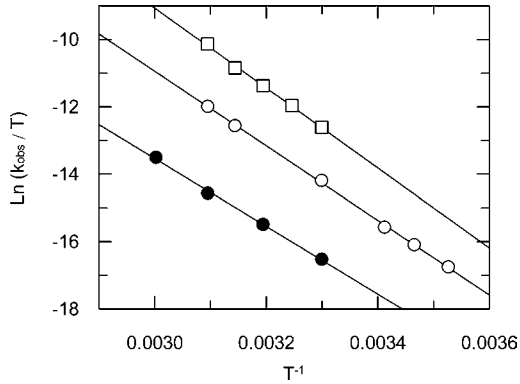

Figure 3. Eyring plot for the decarboxylation of pyrrole-2-carboxylic acid in 0.5% (●), 5% (○), and 23% (□) hydrochloric acid.

Table 2. Activation Parameters for Decarboxylation of Pyrrole-2-carboxylic Acid in Hydrochloric Acid

H_0	$\Delta G^{\ddagger}_{298K}$ (kcal·mol^{-1})	$\Delta H^{\ddagger}$ (kcal·mol^{-1})	$\Delta S^{\ddagger}$ (cal·deg^{-1}·mol^{-1})
0.9	24.2	19.9	−14.2
−0.5	22.8	21.9	−3.1
−2.9	21.9	23.5	+5.5

first glance this is surprising, as the reaction rate would be much slower based solely on this difference. However, the difference in entropy, 19.7 cal·deg^{-1}·mol^{-1}, is sufficient to change the net free energy of activation by 2.3 kcal·mol^{-1} in the opposite sense. Thus, the overall change in free energy results in the observed acceleration in more concentrated acid solutions.

Discussion

The rate of decarboxylation of **1** increases in proportion to solution acidity where $H_0 < 1$ (Figure 1). Dunn and Lee[21] reported that the decarboxylation rate is independent of acid concentration in the region $1 < H_0$, pH < 3. These authors attribute the increase in rate with acidity to a change in rate-determining step from the formation of **2** to carbon−carbon bond cleavage, leading to products from **3** (Scheme 4). They interpret the mechanism as being consistent with the negligible $^{12}C/^{13}C$ kinetic isotope effect (CKIE) in the acid-independent region that increases to 1.028 in 4 M perchloric acid. This mechanism is generally accepted for the decarboxylation of most aromatic acids; however, the products must be formed from the zwitterion **3**, a process that is expected to have a higher barrier in concentrated acid solutions. This leads to the obvious question: How can a reaction be catalyzed by acid when the concentration of the acid does not favor formation of the reactive species?

The reported result and interpretation would require formation of protonated carbon dioxide as the immediate product of C−C bond cleavage. Formation of protonated carbon dioxide was also proposed by Schubert[2] to account for the acid-catalyzed decarboxylation of mesitoic acid based on applying the Hammett−Zucker hypothesis,[23] a guideline whose criteria were later shown by Bunnett[12,24] to be unreliable. As we noted in the Introduction, protonated carbon dioxide is an impossibly high-energy species as a reaction intermediate or component of a transition state.[3] Guthrie[4] calculated that the pK_a of protonated carbon dioxide (CO_2H^+) is −39.

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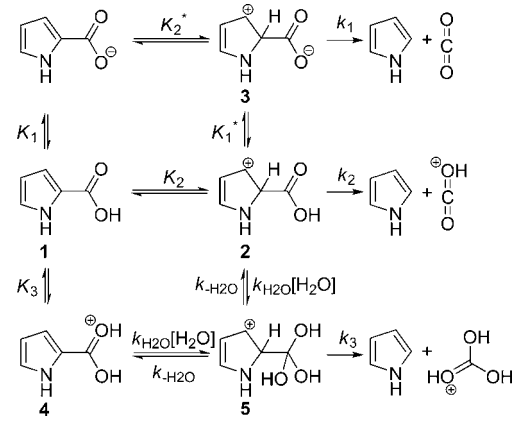
(24) Bunnett, J. F. *J. Am. Chem. Soc.* **1961**, *83*, 4956–4967.

Scheme 4. Mechanisms for Decarboxylation of Pyrrole-2-carboxylic Acid



A resolution of the problem can be drawn from the experimental observations of Olah and White,[25,26] who reported the preparation and NMR characterization of protonated carbonic acid, a cation whose structure reflects the symmetry of the formula $^{+}C(OH)_3$. The stability of this compound led the authors to propose it as a potential intermediate in biochemical processes. This also makes protonated carbonic acid a reasonable product of a decarboxylation reaction that is formed from the covalent hydrate of a carboxyl group in acid.[25,27]

An early proposal of a decarboxylation reaction proceeding via an addition mechanism comes from Warren and Williams,[6] who proposed the mechanism for phosphonoformic acid based on the acidity dependence of the rate of the reaction. A mechanism involving formation of protonated carbonic acid requires that the rate of addition of water to the carboxyl group must be consistent with the overall rate of decarboxylation. The rate of exchange of ^{18}O into carboxylic acids from $H_2{}^{18}O$ is a good measure of the rate of covalent hydrate formation. The hydrate is a kinetically competent precursor to C−C bond cleavage in a decarboxylation pathway via protonated carbonic acid.[7,28,29] We can also consider the rates of hydrolysis of thiolcarboxylic acids. These reactions involve acid-catalyzed addition of water to a carboxyl derivative. Hipkin and Satchell[30] reported rates of hydrolysis of thiolacetic acid that are comparable to those for the decarboxylation of pyrrole-2-carboxylic acid.[21]

On the basis of these observations, we had proposed that the decarboxylation of pyrrole-2-carboxylic acid involves the addition of water to the carboxyl group, followed by release of protonated carbonic acid (bottom of Scheme 4).[5] We observed a similar increase in rate in solutions of acids with concentrations of 0.1 M and higher, reaching a plateau at $H_0 \sim -2$ (Figure 1). Since the Dunn and Lee[21] mechanism cannot proceed through protonated carbon dioxide, the logical alternative is that formation of the predecarboxylation intermediate **3** is catalyzed by removal of the proton leading to the carboxylate ion by a base. At high acid concentrations, the counterion could facilitate this step. If this were the case, the observed rate should be affected by the nature of the counterion involved in proton removal. Yet

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(30) Hipkin, J.; Satchell, D. P. *Tetrahedron* **1965**, *21*, 835–842.

we find that catalysis is independent of the acid and counterion, showing that the reaction does not proceed through the carboxylate ion.

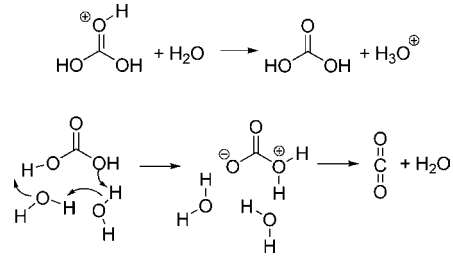
The solvent kinetic isotope effect for this reaction (k_{H_2O}/k_{D_2O} = 2 at H_0 = 0.93) is within the reported range for the decarboxylation of aromatic acids at this acidity.[31,32] The proposed mechanism involves protonation of the aromatic ring in the transition state of the rate-limiting processes. The activation parameters (Table 2), most significantly the large negative activation entropy, are consistent with the values reported by Kresge et al.[33] for ring protonation of aromatic compounds. Although formation of the zwitterion **3** is not expected to be acid-catalyzed, protonation of the ring would be facilitated at higher acidity; however, the overall reaction rate would not increase as it is counteracted by a larger concentration of the undissociated carboxyl group compared to the necessary carboxylate ion. Moreover, the CKIE is negligible, indicating that carbon−carbon bond cleavage is not part of the rate-limiting transition state.[21] Therefore, in the region $1 < H_0$, pH < 3, the mechanism of decarboxylation of **1** is likely to be that which was presented by Dunn and Lee,[21] involving rate-limiting protonation of the aromatic ring.

The solvent kinetic isotope effect at $H_0 = -2.9$ is unity. The magnitude of the values reported for other aromatic acids vary in this region.[31,32,34,35] In the present study, in highly acidic solutions, proton transfer is not involved in the rate-determining transition state. This is supported by the activation parameters (Table 2). In particular, activation entropy changes from a large negative value at $H_0 = 0.93$ to a small positive value at $H_0 = -2.9$. The value in the more acidic solution corresponds to that reported by Warren and Williams[6] for the decarboxylation of phosphonoformic acid. They suggested that the lower entropic value relative to those observed in unimolecular fragmentation results from the additional contribution of the negative entropic value expected for the hydration step. The lower entropy for pyrrole-2-carboxylic acid may arise from contributions from protonation of the ring and/or hydration of the carboxyl group; however, the absence of a solvent kinetic isotope effect suggests that contributions from steps involving a proton are not significant in this case.

The magnitude of the CKIE increases with solution acidity (Figure 2), as is observed for the decarboxylation of aromatic acids.[34–36] The increase in CKIE does not distinguish between rate-determining C−C bond cleavage from the zwitterion **3** vs the hydrated intermediate **5**. In both cases, protonation of the ring, or addition of water, can decrease the observed value from the magnitude of the intrinsic value for C−C bond cleavage.[37] However, the CKIE at $H_0 = -2.6$ of 1.043 is sufficiently large to be consistent with C−C bond breaking being a significant component of the overall process.

In our preliminary report[5] we had proposed that the plateau observed at $H_0 \sim -2$ results from a decrease in availability of water at these acidities. However, on the basis of the additional studies reported here, we conclude that the saturation of protonation of the carboxyl group is the cause. If the activity of water did control the rate, the CKIE would decrease in highly acidic solutions where the activity of water decreases.[13] As indicated earlier, the pK_a for the conjugate acid of the carboxyl is ~ -1.3. The pK_a for protonation of pyrrole is −3.8, and inductive effects should yield a lower value for pyrrole-2-carboxylic acid.[15] Therefore, the saturation in rate does not result from protonation of the ring. However, since the site of protonation is subject to tautomerism, only the pK_a of the weakest acid under these conditions (the protonated carboxyl group) will be observed.

Scheme 5. Decomposition of Protonated Carbonic Acid



Longridge and Long[32] discussed a similar issue for the decarboxylation of azulene-1-carboxylic acid. They suggested that protonation of the carboxyl group is more reasonable, based on the behavior of most aromatic acids, as protonation of the ring would not occur in the region of acidity where acid catalysis of decarboxylation is observed. However, at the time their paper was submitted, Olah and White[38] had not reported the existence of protonated carbonic acid. Longridge and Long[32] assumed that initial protonation of the carboxyl group would not lead to the products of the reaction.

The range of pK_a values of the conjugate acids of carboxyl groups of pyrrole carboxylic acids and related compounds is −2 to −0.5.[16] This suggests that the increase and plateau in the rate of decarboxylation directly follows the pK_a for protonation of the carboxyl group of pyrrole-2-carboxylic acid.[16] This clearly implicates intermediate **5** as the species leading to products, since formation of intermediate **3** is not possible from the conjugate acid of a carboxyl group. Initial protonations of the carboxyl group or the aromatic ring are kinetically equivalent. In either case, protonation will accelerate the rate of addition of water to the carboxyl group and lead to rapid formation of intermediate **5**. This is supported by rates of addition of water to a protonated carbonyl group that range from 10^2 to 10^6.[39] The observed CKIE results from C−C bond cleavage from this intermediate in a kinetically significant step.

In Scheme 4, pK_1 for removal of the proton from the carboxyl group to form the carboxylate ion is 4.39.[40] pK_2 for the conjugate acid from protonation of the α-carbon adjacent to the carboxyl group is −3.8, and pK_3 for O-protonation of the undissociated carboxylic acid is ~ -2.[15,16] Acid catalysis is observed in the region $-2 < H_0 < 1$. The pK_a obtained from the dependence on acidity of the observed rate in this region is −1.3. Where acid

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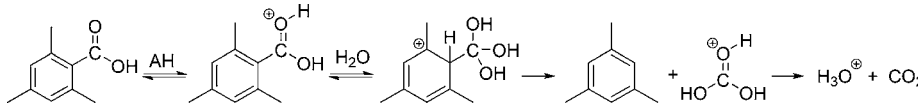
Scheme 6. Alternative Mechanism of Decarboxylation via Protonated Carbonic Acid



catalysis occurs, intermediates **2** and **4** are thermodynamically favored. These are activated for addition of water to the carboxyl group. Thus, k_{H_2O} will be large and k_3 will be rate-limiting. The observed rate constant is given by eq 1; however, at $H_0 < -2$, K_2K_3 is small, k_{H_2O} is fast, and k_{obs} approaches k_3.

$$k_{obs} = K_2K_3k_{H_2O}[H_2O]k_3 \quad (1)$$

Decomposition of Protonated Carbonic Acid. This species should readily lose a proton to water to produce neutral carbonic acid (Scheme 5). Carbonic acid cannot spontaneously decompose without migration of a proton.[41] This is achieved readily in water.

Consideration of the literature on aromatic decarboxylation reactions suggests that the hydrolytic mechanism is not limited to pyrrole-2-carboxylic acid. The decarboxylation of mesitoic acid, proposed to proceed through the loss of protonated carbon dioxide,[2] should instead proceed through addition of water and loss of protonated carbonic acid (Scheme 6). Other examples that are proposed to proceed through an acid-catalyzed mechanism involving departure of protonated carbon dioxide should be re-examined for hydrolytic decarboxylation, as well as reactions of concentrated solutions of carboxylic acids in various media with microwave heating.[42,43]

An extension of these ideas can be applied to the decarboxylation of acetoacetic acid, which is often depicted as proceeding through a concerted mechanism[44] involving C−C bond breaking and O−H bond formation. An alternative proposal based on kinetic and thermodynamic analysis involves initial tautomerization to a zwitterion,[45,46] followed by C−C bond breaking. In the concerted mechanism, C−C bond breaking and O−H bond formation occur in the same step. Therefore, the transition state necessarily derives some of its character from protonated carbon dioxide. Figure 4 is a More O'Ferrall−Jencks plot for such a process. In order to avoid the high energy required for a contribution from protonated carbon dioxide, the O−H bond must be completely broken prior to C−C bond breaking. Thus, the lowest energy pathway must pass through the carboxylate ion at the lower right corner of Figure 4, which is the tautomer-forming mechanism, rather than the concerted alternative.

Pedersen[47] reported rates for the hydrolysis of ethyl acetoacetate and the decarboxylation of acetoacetic acid in highly acidic media. The decarboxylation of acetoacetic acid is not catalyzed

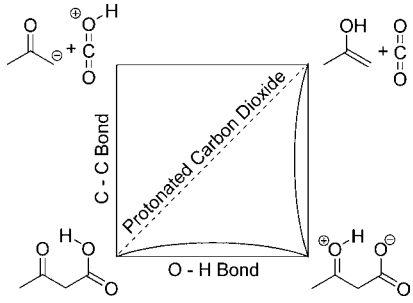
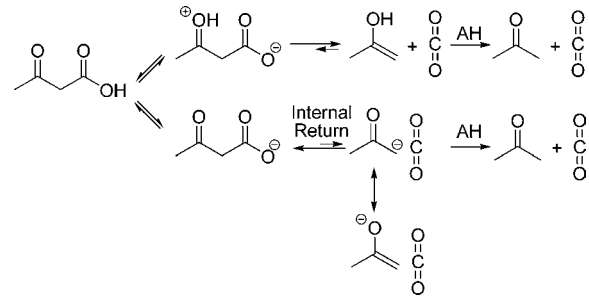


Figure 4. More O'Ferrall−Jencks plot for the decarboxylation of acetoacetic acid.

Scheme 7. Decarboxylation of Acetoacetic Acid via an Enol versus an Enolate Ion That Is Subject to Internal Return



by acid. This is expected, as zwitterion formation is not subject to acid catalysis. In more concentrated acid solutions, the rate should decrease as the concentration of the protonated ketone increases. Reaction from the undissociated carboxyl group would then lead to formation of protonated carbon dioxide, which would be too high in energy to exist. Moreover, the hydrolysis of ethyl acetate is subject to acid catalysis under the same conditions. Therefore, protonation of the carbonyl group of the ester occurs and enhances the addition of water and subsequent hydrolysis of the ester. This suggests that protonation of the carboxylic acid could occur in the analogous decarboxylation reaction. If this were the case, the decrease in rate from the neutral zwitterionic mechanism would be compensated by the route involving addition of water and formation of protonated carbonic acid. Pedersen did not evaluate reactions in sufficiently acidic solutions to realize this possibility, which deserves further investigation.

Generalized Decarboxylation Pathways. What determines the path of a decarboxylation reaction? The general scheme for decarboxylation reactions requires an adjacent "electron sink" to stabilize the carbanion generated upon loss of CO_2.[48] According to Hammond's postulate,[49] the transition state will resemble the intermediate, which will be more stable as the negative charge associated with the carbanion is stabilized. However, in the decarboxylation of acetoacetic acid, the half-life of the reaction differs where the residual product is the enol (7 h) rather than the enolate ion (430 h).[4] The adjacent carbonyl is the same group in both cases; however, the enolate ion possesses significant carbanion character that is not present in the enol.[50] Therefore, upon formation of the nascent CO_2 adjacent to a reactive carbanion (enolate ion), the forward progress of the reaction is hindered by internal return (carboxylation of the carbanion).[37,51] Formation of the tautomer, which ultimately leads to decarboxylation via the enol product, does not compete with internal return (Scheme 7).

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Conclusions

Carbon isotope effects and solvent isotope effects of acid-catalyzed decarboxylation reactions are consistent with a mechanism involving initial addition of water to the conjugate acid of the carboxyl group, followed by proton migration and C−C bond cleavage. This initially yields protonated carbonic acid. The alternative mechanism via protonated carbon dioxide is too high in energy to be considered. A variation of the addition route to decarboxylation could apply in enzyme-catalyzed reactions. For example, catalysis could proceed by addition−elimination reactions of the substrate with a serine hydroxyl in an active site as was observed with a substrate analogue in benzoylformate decarboxylase.[52] Decarboxylation by carboxyl transfer to form a hemicarbonate would facilitate CO_2 departure, thereby reducing internal return and leading to accelerated reaction rates. as reported for a substrate analogue.[37] If this were the case, the specificity of enzymes could be altered through the addition of serine residues in the active site, leading to decarboxylase activity.[53] Applications to other reactions and insights on the nature of decarboxylation reactions in general are informed by this approach.

Acknowledgment. The Natural Sciences and Research Council of Canada provided support through the Discovery Grant program. We thank Peter Guthrie and Robin Cox for helpful discussions.

JA910608M

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