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Base-Catalyzed Decarboxylation of Mandelylthiamin: Direct Formation of Bicarbonate as an Alternative to Formation of CO_2

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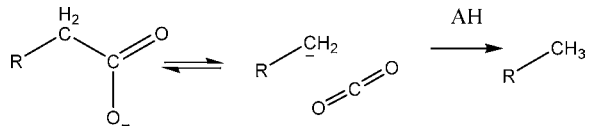
Supporting Information

ABSTRACT: The decarboxylation of mandelylthiamin is subject to general base catalysis (β = 0.26), an outcome that is inconsistent with the expected dissociative transition state in which CO_2 forms along with a residual carbanion. The results implicate a previously unrecognized associative route in which addition of water to a carboxylate followed by base-catalyzed proton transfer and C−C cleavage produces bicarbonate directly. Various reports of the presence or absence of base catalysis in decarboxylation reactions are consistent with the associative route's occurrence in cases where nucleophiles would be generated along with CO_2 in the usual dissociative route.

Decarboxylation reactions of carboxylic acids in water nominally involve the replacement of a carboxyl group by a proton.[1] Reactivity patterns suggest that the deprotonated form, the carboxylate, either directly or indirectly, is the reactive species.[2] Carbon−carbon bond cleavage from the carboxylate produces carbon dioxide and a residual electron pair in a stabilized carbanion, a carbanion equivalent, or an anionic leaving group. Evidence from catalytic patterns,[3,4] stereochemical outcomes,[5] changes in isotope effects,[6,7] and QM/MM calculations[8] suggests that in some cases the reaction may be slowed by recombination of CO_2 and the nascent nucleophile. It has been proposed that in a reaction that is slowed by recombination, a preassociated acid that quenches the carbanion (Scheme 1) increases the overall rate.[7] Recent

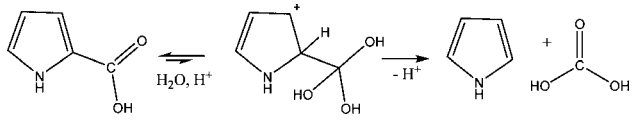
Scheme 1



reports of computational analyses dispute the possibility that the catalysis occurs by protonation in competition with recombination of CO_2.[9,10] One of those reports concludes that the catalysis arises from stabilization of the transition state through complexation rather than proton transfer.[9]

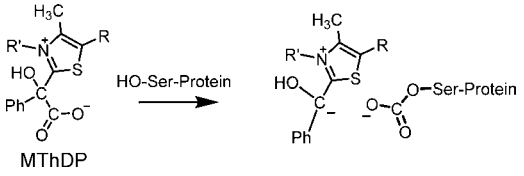
A contrasting specific acid-catalyzed route is consistent with initial addition of water and a proton to a neutral carboxyl group in an associative process. A proton shift and departure of protonated carbonic acid (rather than protonated CO_2) eventually produces CO_2.[11−13] In that process, C−C cleavage is facilitated as the residual lone pair is absorbed by the conjugated cationic center (Scheme 2). Recent computational results support this mechanism.[14,15]

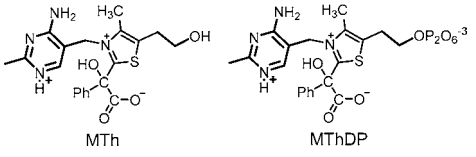
Scheme 2



Mandelylthiamin (MTh)[16] is an accurate functional model of the key covalent intermediate (MTh diphosphate, MThDP) in catalysis by benzoylformate decarboxylase.[17] However, the rate constant for decarboxylation of MThDP in the enzymatic reaction is at least 10^6 times larger than that of MTh in water.[6,16] The source of the enzyme's rate enhancement is unknown. An analogy to the proposed addition of an active-site serine hydroxyl to the carboxyl of enzyme-bound MThDP proposed for BAL A28S[18] (Scheme 3) would be a reasonable prospect.

Scheme 3





In the decarboxylation of MTh, a neutral associative pathway could occur by initial addition of water to the carboxyl. In that case, removal of a proton and C−C cleavage would produce a carbanion and bicarbonate, a weaker electrophile than CO_2 that would be less susceptible to internal return.[19] We found that consistent with such an expectation, general base catalysis facilitates the decarboxylation of MTh. Increasing concentrations of acetic acid/acetate buffers gave a linear increase in

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the observed first-order rate constant for conversion of MTh to 2-(1-hydroxybenzyl)thiamin (HBnTh) (Figure 1). We confirmed that the reaction gave the expected products of decarboxylation and that there were no inhibitory materials in solution or effects originating from ionic strength variation.

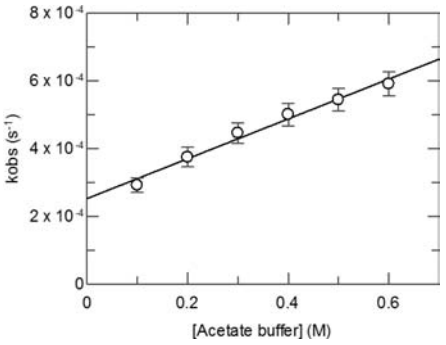


Figure 1. The observed first-order rate constant increased linearly with acetate buffer concentration at 25 °C, as observed by UV spectroscopic analysis of the product and reactant concentrations.

A plot of the observed rate constant for the buffer-dependent process as a function of the buffer component ratio indicated that only the Brønsted base is catalytic (Figure 2). The slope of the plot for a series of substituted acetates as catalysts in the decarboxylation of MTh gave β = 0.26 (Figure 3). This implicates a rate-determining transition state in which there is a very small extent of proton transfer from water to the Brønsted base.[20] This also rules out a process in which simple C−C bond cleavage alone is rate-determining with these catalysts. We also observed a solvent kinetic isotope effect of k_{H_2O}/k_{D_2O} = 1.8 in 0.4 M 1:1 acetate/acetic acid buffer. This is consistent with the conclusion that proton transfer is a component of the transition state of the rate-determining step in an associative mechanism.

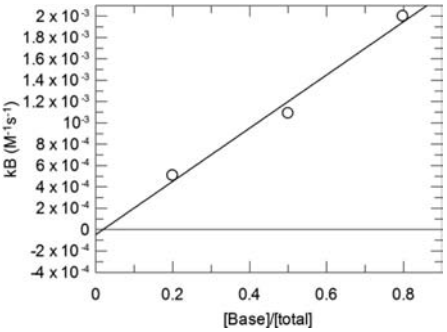


Figure 2. The observed catalysis arises from the action of the base component of the acetate buffer on protonated MTh.

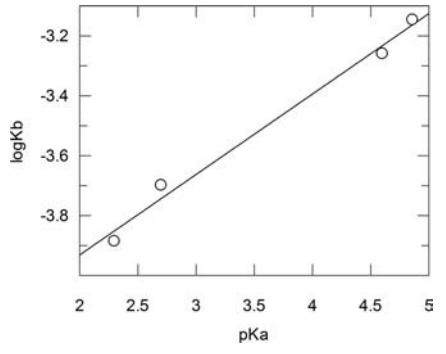
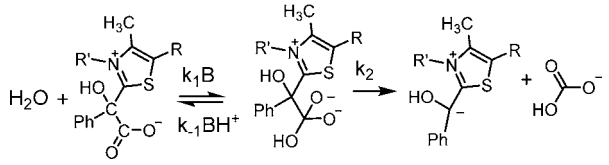


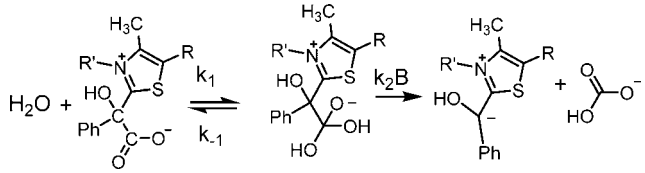
Figure 3. Brønsted plot for the decarboxylation of MTh using the following buffers: cyanoacetate (pK_a = 2.3), chloroacetate (pK_a = 2.7), acetate (pK_a = 4.6), and propanoate (pK_a = 4.9).

Since transfer of a proton from MTh cannot accelerate the unimolecular dissociative decarboxylation process, the catalytic effect of the base must be achieved by its interaction with water and MTh in combination. Base-catalyzed addition of water to the carboxyl of MTh could produce a dianionic intermediate (similar to those postulated by Hine and Koser in the reactions of aldehydes[21]) in a rate-determining process. That intermediate could release bicarbonate and the conjugate base of HBnTh (Scheme 4). However, given the high basicity of such an intermediate,[21] it is more likely that transfer of the proton would be concerted with cleavage of the C−C bond, producing bicarbonate in the same step (Scheme 5). Extrapolation of the base-catalyzed rate to that for the reaction in the absence of buffer suggests a variant on the same general mechanism in which bicarbonate is the initial product (Scheme 6).

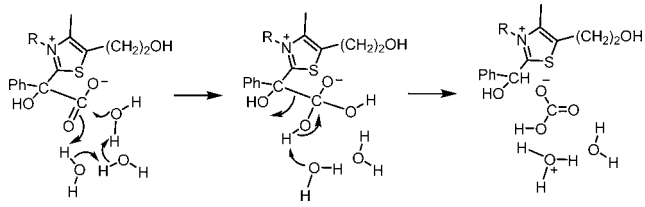
Scheme 4



Scheme 5



Scheme 6



The reaction pattern suggests that when the formation of CO_2 occurs in concert with annihilation of the negative charge (i.e., where there is no residual nucleophile), there is no route for recombination with CO_2. Therefore, base catalysis following addition of water will not be observed. The decarboxylation of carboxyisoxazoles is consistent with this hypothesis (Figure 4). Kemp and Paul reported that "a discrete carbanion [upon loss of CO_2] is excluded as a significant reactive intermediate".[22] Fragmentation of the carbanion is concerted with its formation along with CO_2, leading to stabilized products that cannot recombine. Those authors also reported that the reaction is not subject to buffer catalysis, which is consistent with the concerted loss of the leaving group and CO_2. Theoretical

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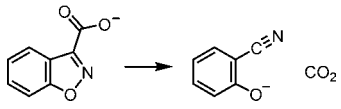

Figure 4. Decarboxylation of carboxybenzisoxazoles is irreversible, occurring in the same step as elimination to form a nitrile. With no intermediate carbanion, internal return of CO_2 cannot occur.

analysis also led to the conclusion that the reaction has a high barrier to reversal that accounts for the lack of catalysis.[23]

In a related reaction, the decarboxylation of trichloroacetate (TCA) produces the conjugate base of chloroform. The rates of deprotonation of chloroform[24] and of HBnTh[25] by hydroxide are similar. Therefore, according to our proposed mechanistic criteria, decarboxylation of TCA should also be accelerated in a base-catalyzed associative route. This is consistent with otherwise inexplicable observations that have stood for more than a century. Silbertstein reported in 1884 that aniline promotes the decarboxylation of TCA.[26] This was confirmed and investigated in greater detail by Goldschmidt and Bräuer in 1906.[27] The production of deuterochloroform from hexachloroacetone involves decarboxylation of TCA and is catalyzed by pyridine[28] and by sodium deuteroxide.[29] The carbon kinetic isotope effect in the spontaneous decarboxylation of TCA is consistent with rate-determining C−C bond cleavage.[30] However, in connection with the observation of the products of decomposition of the resulting conjugate base of chloroform, Bigeleisen and Allen noted that "alkali increases the rate of chloride production," attributing this to factors that may be interpreted as a consequence of acceleration of the decarboxylation process.[30] As we have noted, this is required in the associative route that produces bicarbonate (which then produces CO_2) but is not consistent with a dissociative process that forms CO_2 initially.

In conclusion, our results provide a basis for the development of a comprehensive view of decarboxylation that specifies a role for base catalysis. The addition of water to the carboxylate is followed by base-catalyzed loss of bicarbonate. The usual dissociative route that forms CO_2 may be slowed by reversion, while addition of water to the carboxyl group provides an opportunity for initial formation of the less reactive bicarbonate ion along with the residual carbanion. This also supports the notion that enzymes may provide active-site nucleophiles to overcome internal return of CO_2, accounting for the apparent acceleration of what is usually presented as a unimolecular dissociative process.[3,18]

■ ASSOCIATED CONTENT

Supporting Information

Materials and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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