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# Accelerated decarboxylation of 1,3-dimethylorotic acid in ionic liquid

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## Abstract

The solvent effect of ionic liquids on the decarboxylation of 1,3-dimethylorotic acid and its analogue in ionic was investigated. The rate acceleration observed was proposed to be a result of the stabilization of the zwitterionic intermediates by the charged groups available in these special solvents.

*Keywords:* Decarboxylation; Orotic acid; Ionic liquid

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## 1. Introduction

The decarboxylation of 1,3-dimethylorotic acid (**1**) and its analogues has been studied in much detail as a model for the enzymatic decarboxylation catalyzed by orotidine-5′-monophosphate decarboxylase [1–9]. 1,3-Dimethyluracil (**2**, Scheme 1) is formed as the sole product from the decarboxylation of acid **1** at elevated temperatures. The mechanistic studies involve the investigation of the nature and stability of the intermediate as well as the effects of factors such as solvent and hydrogen bonds.

The vastly different rates observed in the decarboxylation of acids **1**, **3**, and **4** (acid **4** reacts about 3000 times faster than **1** or **3**) have provided a unique opportunity to investigate the factors important for the rate of the reactions [1,7]. Recent work has demonstrated that the stability of carbanions formed from the decarboxylation of these three acids does not play an important role in determining the rate of decarboxylation [6,7]. A two-step

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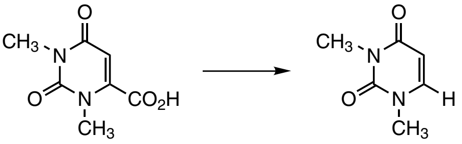
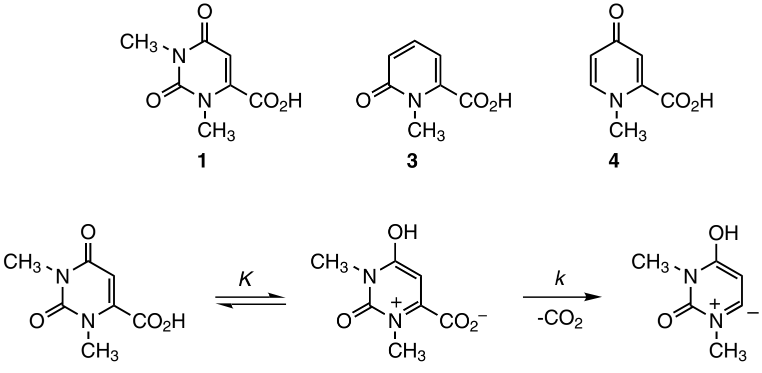


**1** **2**

Scheme 1.



**1** **3** **4**

**1** **5** **6**

$$dP/dt = Kk[\mathbf{1}]/(K+1) \quad \text{When } K << 1,\ k_{ob} = Kk$$

Scheme 2.

mechanism has been proposed to account for the large difference in rate constants measured for acids **1**, **3**, and **4** as shown in Scheme 2. In this mechanism, an equilibrium leading to the formation of a zwitterionic structure such as **5** precedes the loss of $CO_2$ and formation of the carbanion (e.g., **6**) [1,7]. When the zwitterionic structure is much less stable than the acid, i.e., equilibrium constant $K \ll 1$, the observed rate constant is simply the product of the $K$ and the rate constant $k$ for the second step, loss of $CO_2$ [1,7].

Theoretical calculations on the relative stability of the zwitterionic structures from acids **1**, **3**, and **4** have shown that the zwitterionic structure derived from acid **4** is indeed much more stable than those from acids **1** and **3**, providing support for the proposed mechanism [7]. In this report, we present kinetic results for decarboxylations in ionic liquid solvents that provide further support for the mechanism.

## 2. Materials and methods

### 2.1. Kinetic measurements

The progress of the reaction was followed by NMR spectrometry. A series of NMR tubes (each containing 7 mg of substrate and 200 mg of solvent) was heated in an oil-bath at 206 °C for time intervals of 2–20 min. DMSO-$d_6$ (1 ml) was added to the NMR tubes to form a homogeneous solution. The percentage of substrate remaining was calculated from the integration of corresponding peaks of the substrate and product. The logarithm of the fractions of substrate remaining was plotted over time and excellent first-order kinetics was

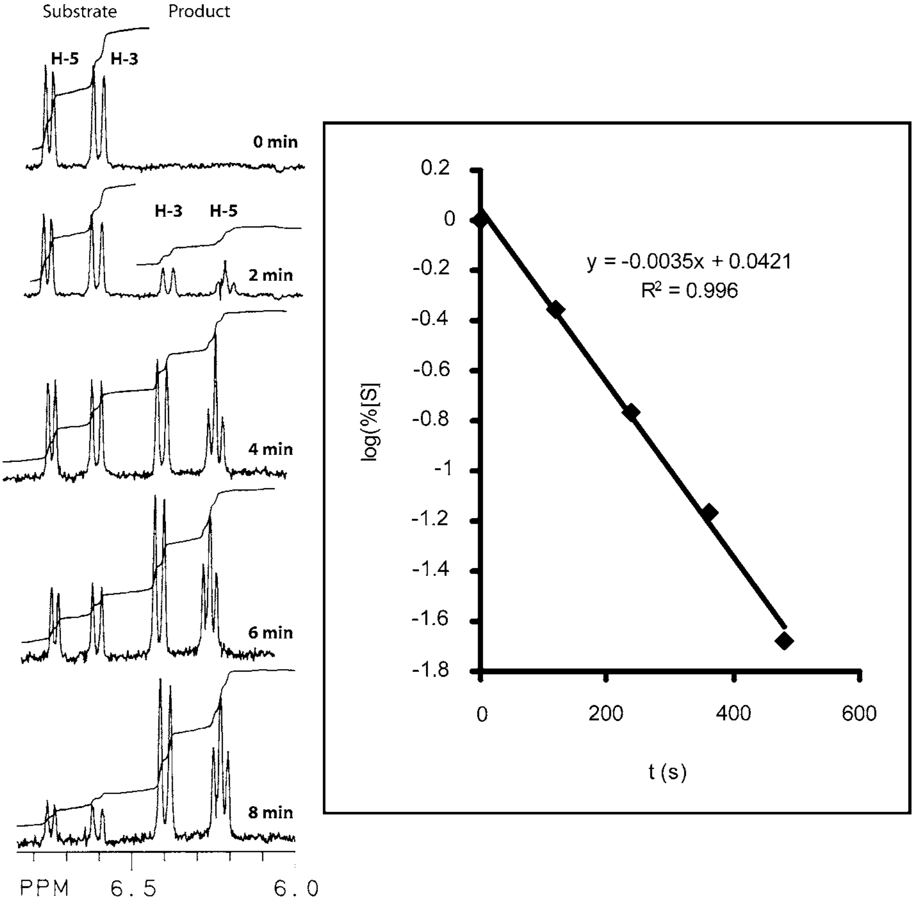


Fig. 1. NMR spectra and data analysis for the decarboxylation of acid **3**.

observed. The NMR spectra and data analysis of the decarboxylation of acid **3** in imidazolium ionic liquid was shown in Fig. 1 as an example. The reaction was monitored until there was less than 20% substrate remaining.

### *2.2. Chemicals*

Acid **1** was prepared through the methylation of orotic acid (from Sigma) as reported by Curran and Angier [10]. The same method was used to prepare **3** from 2-pyridone-6-carboxylic acid (from Aldrich). Acid **4** was prepared from 4-pyrone-2-carboxylic acid (from TCI America) as reported by Beak and Siegel [1]. The identity and purity of the synthesized compounds was verified by their $^{1}$H NMR spectrum, mass spectrum, and melting point.

## 3. Results and discussion

It has been reported that the observed rate constant for the decarboxylation of 1,3-dimethylorotic acid does not change much in different solvent due to cancellation of the solvent effects on the equilibrium constant, $K$, and the rate constant for the loss of $CO_2$, $k$ [1]. As solvent polarity increases, the equilibrium constant for zwitterion formation increases, but the rate constant for the loss of $CO_2$ of the zwitterion decreases [1,11]. Since the observed rate constant for the reaction is equal to the product of $K$ and $k$, the lack of a solvent effect is considered to reflect the compensatory changes in the two steps [1].

Ionic liquids, on the other hand, may prove useful in changing the equilibrium constant for the formation of the zwitterion. Most of the measurements of the polarity of ionic liquid solvents have placed them to be comparable to or slightly more polar than those of polar aprotic solvents such as dimethyl sulfoxide (DMSO) or tetramethylenesulfone (sulfolane) [12–14]. For example, the dielectric constants of DMSO and sulfolane (46.7 and 44, respectively) are in the range (40–55) reported for imidazolium-based ionic liquids [12]. However, the positively charged heterocyclic ring structures (imidazolium and pyridinium) may stabilize the zwitterion structure via electrostatic interactions.

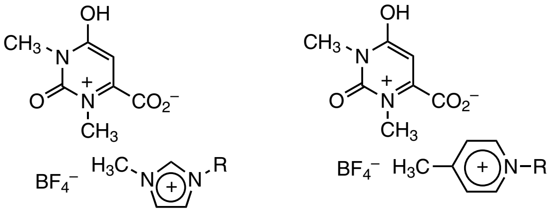
The rate constants for decarboxylation of acids **1** and **3** were shown in Table 1. Unfortunately, the data for acid **4** were not available. As discussed above, acid **4** decarboxylates about 3000 times faster than **1** or **3**, consequently the reaction temperatures for convenient measurement are much lower (~120 °C), at which a homogeneous solution of acid **4** in ionic liquid cannot be obtained. The two ionic liquid solvents employed are 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim]^+[BF_4]^-$) and 1-butyl-4-methylpyridinium tetrafluoroborate ($[bmp]^+[BF_4]^-$). The rate constants in sulfolane were available from our previous study [7].

The utilization of ionic liquids as solvents for the decarboxylation of orotic acid analogues provided a rate enhancement of about 3-fold. Rate acceleration of this size may not look large, however, the absence of solvent effect when other solvents were employed makes this result rather interesting and significant [1]. Furthermore, the rate acceleration corresponds to about 1 kcal/mol reduction in activation energy, $\Delta\Delta G^{\ddagger}$, at the reaction temperature. It should be pointed out that this change in activation energy compares favorably to the contribution provided by hydrogen bonds to the pyrimidine carbonyl oxygens, as demonstrated by quantum mechanical calculation in quite non-polar medium and by a mutagenesis study on orotidine 5′-monophosphate decarboxylase [9,15]. Therefore, the modest effect of ionic liquid solvents on the reaction rate is meaningful and important. Ionic liquids have been shown to catalyze reactions that involve charge development in the transition state [16].

The effect of solvents on the decarboxylation of orotic acids can be complicated due to the compensatory consequences on the equilibrium constant, $K$, and the rate constant for the loss of $CO_2$, $k$ [1]. The rate constant $k$ in ionic liquid is likely to be similar to or smaller than that in sulfolane due to the relatively similar polarity of the ionic liquids and sulfolane. The polarity effect on the equilibrium constant $K$ is likely to be similar as well. Furthermore, even if the polarity of ionic liquids and sulfolane are different, the

Table 1
Rate constants of orotic acid analogues in selected solvents at 206 °C

| Substrate | Rate constant ($s^{-1}$) | | |
|---|---|---|---|
| | Sulfolane | $[bmim]^+[BF_4]^-$ | $[bmp]^+[BF_4]^-$ |
| Acid **1** | $7.5 \pm 1.3 \times 10^{-4}$ | $2.1 \pm 0.2 \times 10^{-3}$ | $2.1 \pm 0.3 \times 10^{-3}$ |
| Acid **3** | $1.2 \pm 0.2 \times 10^{-3}$ | $2.9 \pm 0.8 \times 10^{-3}$ | $3.1 \pm 0.8 \times 10^{-3}$ |



Scheme 3.

polarity effect on *K* and *k* should cancel each other out [1]. The near identical results in two ionic liquids (Table 1) might have underscored this point. However, the ion-pair nature of ionic liquid solvents may be ideal in stabilizing the zwitterion structure **5**, which has a large degree of charge separation. For example, the ion pairs in ionic liquids can form electrostatic interactions with the dipole of zwitterion **5** as speculated in Scheme 3. It has been previously shown that ionic liquids accelerate the rates of reactions where the starting materials are charge-neutral and the formation of the activated complex involves development of charges [16]. This interaction will stabilize the zwitterion and thus increase the equilibrium constant *K* and consequently the observed rate constant. The overall rate acceleration is quite modest since the interaction described is random and not pre-organized.

Our results have demonstrated that the rate for the decarboxylation of orotic acid and analogues is enhanced when ionic liquids are utilized as reaction solvent. The rate enhancement could be a result of the stabilization of the zwitterionic intermediate by the ion pairs in ionic liquids. Therefore, the results reported here can be viewed as further support for the mechanistic proposal for the decarboxylation of orotic acid analogues that involves the formation of a zwitterion as an intermediate [1,7].

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