Pergamon

Tetrahedron Letters 39 (1998) 6271–6272

TETRAHEDRON
LETTERS

Mechanism of Decarboxylation of 1,3-Dimethylorotic Acid Revisited: Trapping of the Reaction Intermediate

Michael P. Nakanishi and Weiming Wu*

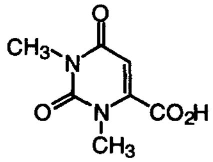
Department of Chemistry and Biochemistry, San Francisco State University, San Francisco, CA 94132

Received 12 May 1998; revised 18 June 1998; accepted 21 June 1998

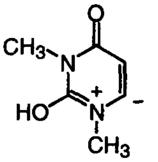
Abstract. The decarboxylation of 1,3-dimethylorotic acid was investigated to study the nature of the reaction intermediate. 6-Benzyl-1,3-dimethyluracil was isolated when the decarboxylation was carried out in benzyl bromide, indicating the involvement of a carbon-6 centered nucleophilic intermediate in the reaction pathway. © 1998 Elsevier Science Ltd. All rights reserved.

Orotidine-5'-monophosphate decarboxylase catalyzes the conversion of orotidine 5'-monophosphate to uridine 5'-monophosphate,[1] the final step of de novo pyrimidine nucleotide biosynthesis. This reaction is mechanistically intriguing because it does not appear that the intermediate can be stabilized by charge delocalization into an electron sink.[2] Nevertheless, it is an extremely proficient catalyst.[3]

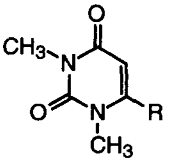
Beak and Siegel examined the nonenzymatic decarboxylation of 1,3-dimethylorotic acid (**1**) and related compounds as models for the enzymatic reaction.[4] They have suggested that the reaction intermediate prior to the formation of **3** is ylide **2**, which is stabilized through dipole induction by the positively-charged nitrogen-1.



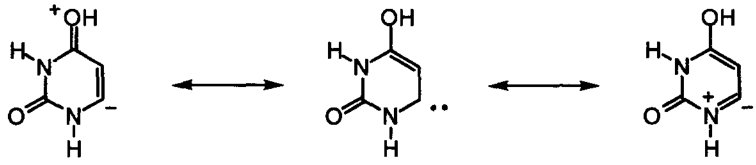
1



2



3 R = H
7 R = CH_2Ph



4 **5** **6**

Lee and Houk carried out quantum mechanical calculations of the energies of the ground state and potential intermediates in the decarboxylation of anionic orotate and found that protonation at O-4 gave a stable intermediate that has both a zwitterionic (**4**) and a neutral carbene (**5**) resonance structure as shown above.[5] Our recent study on the decarboxylation of citrazinic acid provided some experimental evidence for this proposal since the loss of the proposed positive charge at position-1 does not greatly reduce the reaction rate.[6]

PII: S0040-4039(98)01331-8

In this communication, we report the isolation of 6-benzyl-1,3-dimethyluracil (**7**) as a result of the trapping of the reaction intermediate in the decarboxylation of 1,3-dimethylorotic acid with benzyl bromide. We have sought to trap the intermediate to gain insight into the nature of the model reaction since the existence of an intermediate has never been demonstrated. The decarboxylation of acid **1** was thus carried out in refluxing benzyl bromide (198 °C). After three hours, compound **7** was isolated by column chromatography, in about 10% yield along with other products including about 40% 1,3-dimethyluracil (**3**). The possibility that **7** is the product from the reaction of uracil **3** and benzyl bromide is ruled out since refluxing **3** in benzyl bromide does not yield **7**. Uracil **7** was characterized with NMR experiments and mass spectroscopy. The electrospray mass spectrum of the compound in 5% acetic acid/acetonitrile shows a M+1 peak of 231, corresponding to the protonated form of the proposed structure. The ratio of intensities of the M+1 and M+2 peaks also correlates well with the one calculated from the molecular formula using natural abundance of ^{13}C. Proton NMR shows singlets at δ of 6.73 ppm and 3.67 ppm, corresponding to H-5 and the benzylic methylene group, respectively. Experiments based on the nuclear Overhauser effect (NOE) show close proximity between the methylene and N1-methyl groups (a ca. 25% enhancement at the methylene peak upon irradiation of the N1-methyl absorption), suggesting that the benzyl group is at carbon-6, not carbon-5. Unlike 1,3-dimethyluracil (which yields dimethylurea and formylacetate),[7] compound **7** does not hydrolyze under basic conditions. This observation is consistent with its assigned structure since the base-catalyzed hydrolysis is proposed to be initiated by Michael addition of hydroxide anion to carbon-6[7] and it is conceivable that the rate of the reaction is retarded by the presence of the benzyl group.

The isolation of uracil **7** has demonstrated for the first time that a discrete intermediate is formed in the decarboxylation of 1,3-dimethylorotic acid (**1**) and that the intermediate is a carbon-6 centered nucleophile. Although the results appear to support the carbanionic nature of the intermediate, they do not distinguish between the ylide and carbene structures since this type of carbene is considered to be nucleophilic and is stabilized by ylide resonance (see structure **6**).[8,9]

Acknowledgment. This work was supported by a grant from National Center for Research Resources (Research Infrastructure in Minority Institutions (P20 RR11805) with funding from the Office of Research on Minority Health), National Institutes of Health. We are indebted to Dr. Ursula Simonis and Mr. Wee Tam (SFSU) for the NOE experiment and Dr. Ten-Yang Yen (Biomedical Research Mass Spectrometry Facility, SFSU) for obtaining the mass spectrum of uracil 7. We also thank Drs. Clifford Berkman, Scott Gronert, and James Keeffe (SFSU) for helpful discussions.

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