Tetrahedron Letters,Vol.23,No.6,pp 659-662,1982 0040-4039/82/060659-04$03.00/0
Printed in Great Britain

ENHANCED REACTIVITY OF 1-CARBOXY-2-ETHOXY-2-IMIDAZOLINE, A BIOTIN MODEL, IN DECARBOXYLATION

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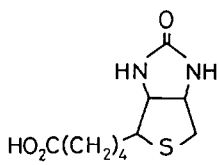
Summary: 1-Carboxy-2-ethoxy-2-imidazoline (*1*) decarboxylates five times as fast as 1-carboxy-2-imidazolidinone (*2*) in an aqueous alkaline medium.

One of the fundamental questions of biotin (*3*) chemistry is how enzymes "activate" biotin which is totally unreactive in model carboxylation reactions.[1] A facinating hypothesis is that this may be performed through enolization of the urea moiety of biotin into *4*. Thus, the putative enol form may be produced by



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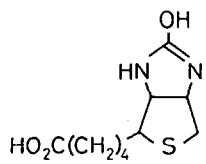

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one of the following pathways. Phosphorylation of the urea carbonyl by ATP will form a phosphoenol.[2] A proton donation from the enzyme active site to the urea carbonyl[3] or the coordination to the same moiety of a metal such as Mg^{2+} or Mn^{2+},[4,5] which are essential components in the enzymatic carboxylation, will exert a similar effect. Although it appears true that the enol form is much less stable thermodynamically,[6] it is highly nucleophilic once generated.[7] The reaction product of *4* with bicarbonate is 1-carboxylated form of *4*, which supposedly serves as the key intermediate for the subsequent transfer of carboxyl group to an acceptor substrate. The methoxycarbonyl derivative of 2-ethoxy-2-imidazoline (*5*), a model for carboxylated *4*, has been known for some time[8] and its reaction with nucleophiles was studied recently.[9] But, the chemical reactivity of *1* itself has never been investigated. In the present communication we would like to show for the first time that *1* decarboxylates rapidly in an aqueous alkaline medium.

The ^{13}C NMR spectra of *5* and *6* in D_2O are shown in Fig. 1 (A) and (C), respectively. In the ^{13}C NMR spectra taken about 9 min after addition to *5* or *6* of two molar KOH in D_2O, the peaks of *5* or *6* have disappeared and two sets of signals emerged. One of them gained intensity with time, while the other gradually disappeared. The former set remained after a prolonged reaction time and coincided with that of authentic 2-ethoxy-2-imidazoline (*7*) or 2-imidazolidinone

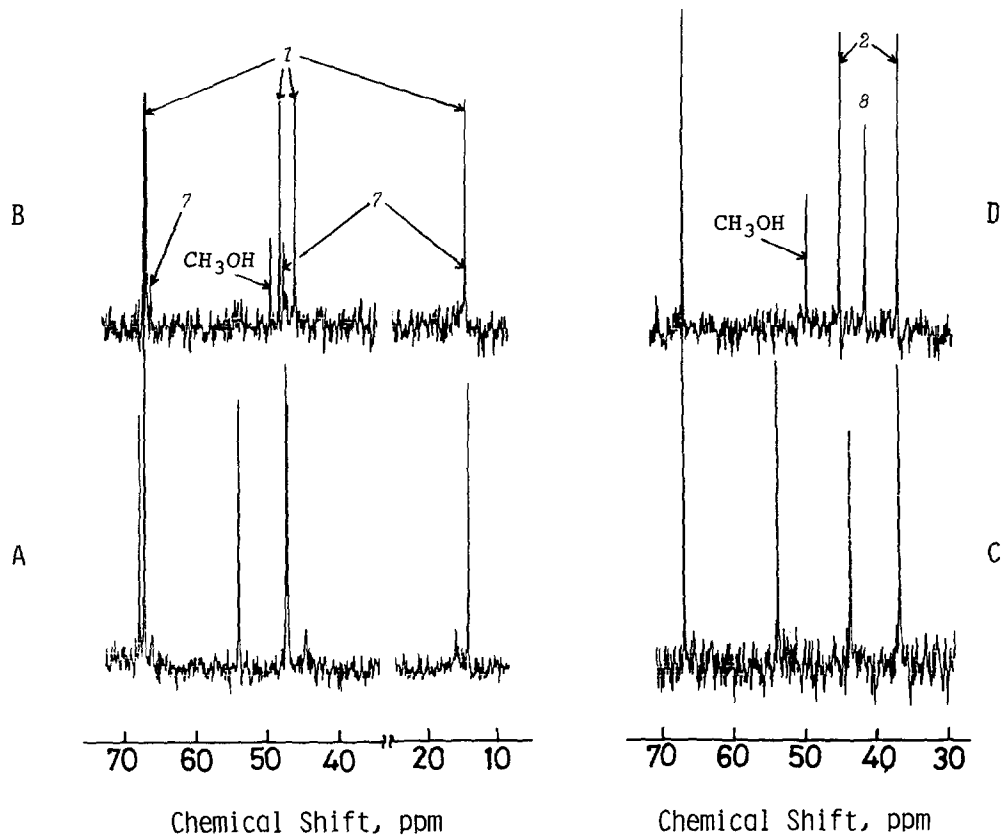
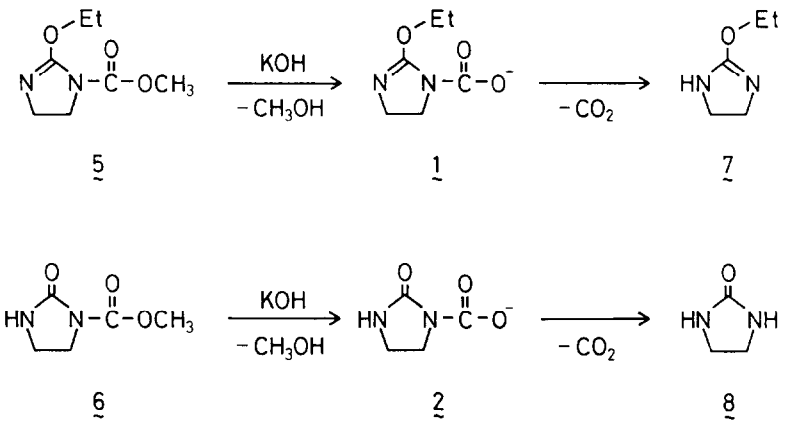


Fig. 1. ^{13}C NMR spectral changes in the reaction of *5* (A and B) and *6* (C and D) in D_2O at 25.0 °C. A and C are the spectra of *5* and *6*, respectively. B and D were determined at 9 min after addition of KOH. The peak at 67.4 ppm is that of internal standard dioxane. These spectra were obtained on a Jeol JNM-FX 90Q pulse Fourier transform NMR spectrometer operating at 22.50 MHz. Experimental parameters were the following: spectral width of 5000 Hz with acquisition of 8 K data points, 10-μs pulse, and a recovery time of 3s. Each spectrum was obtained by 150 spectral accumulations.

(*8*). Hence, the whole sequence of reactions for *5* and *6* can be depicted as in the following scheme. It is noteworthy that the reactions of *5* and *6* were not accompanied by any side reactions.[10] This is in sharp contrast to the previous findings that *5*, *6*, and related compounds underwent reactions with nucleophilies at several sites.[9,11]



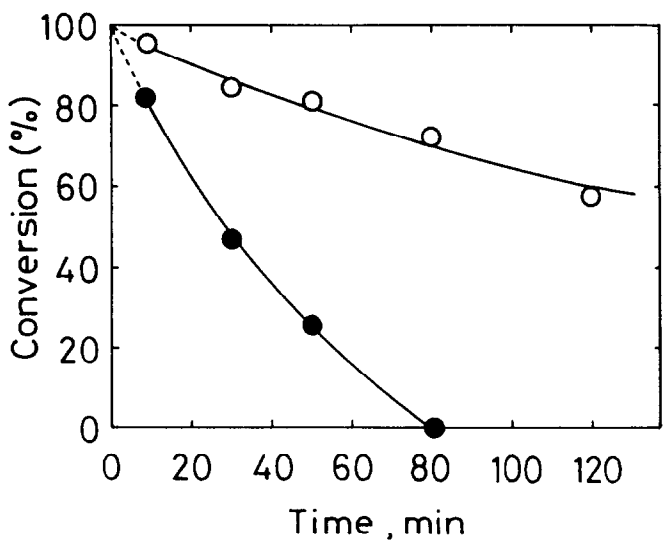


Fig. 2. Time courses for the decay of *1* (●) and *2* (○) in D_2O at 25.0 °C. The data shown here are for the carbon at 5 position of *1* and *2*.

The initial saponification of *5* and *6* takes place so rapidly that it was impossible to determine which one reacts faster than the other by the present technique. The reaction should begin with attack of hydroxide ion on methyl carbon, leading to rupture of the C(methyl)-O bond.[11] The rate of subsequent decarboxylation does differ between the two substrates (*1* and *2*) as shown in Fig. 2. The decarboxylation is complete in 80 min with *1*, while part of *2* remained even after 2 h.[1] Rough rate constants for the decarboxylation of *1* and *2*, 4×10^{-4} and 0.8×10^{-4} s^{-1}, respectively, indicates that *1* decarboxylates five times faster than *2* under the present conditions. This difference in rate arises from the fact that the tautomeric protonation at position *3* is possible in the decarboxylation of *1*, while it is not with *2*. The same reasoning applies to the reaction of *7* or *8* with carbonate derivatives such as methyl chloroformate, in which the former was found to be much more reactive than the latter (unpublished results from this laboratory). Taken together, it is concluded that the enol form is reactive both in carboxylation and decarboxylation. Although the relevance of these results to the actual mechanism of enzymic carboxylation remains to be tested, it is likely that the enolization of biotin may account for at least in part the higher reactivity of the coenzyme in enzymic reactions.

Acknowledgment This work was supported by a Grant-in-Aid for Scientific Research (No. 521325) from the Ministry of Education, Science, and Culture.

References and Note

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(Received in Japan 3 December 1981)