Acid Catalysis of the Transformation of 1-Methoxycarbonyl-2-imidazoline to 1-Methoxycarbonyl-2-imidazolidinone, a Carboxybiotin Model

Hiroki KONDO,* Katsuhito MIURA, and Junzo SUNAMOTO
Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Nagasaki 852
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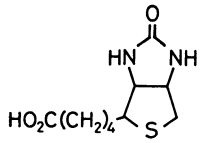
Synopsis. The transformation of 1-methoxycarbonyl-2-ethoxy-2-imidazoline into 1-methoxycarbonyl-2-imidazolidinone a 1-carboxybiotin model, is facilitated by acid.

Activation of biotin (**3**) through enolization of its urea moiety to form an isourea structure is an attractive hypothesis to account for the much higher reactivity of the coenzyme in enzymatic carboxylation reactions.[1] The putative enolbiotin may be generated by a variety of means, *e.g.*, phosphorylation by ATP of the urea moiety.[2] 2-Methoxy-2-imidazoline (**4**), a model for



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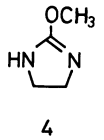

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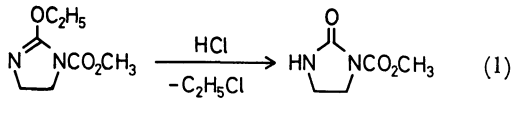
enolbiotin, shows a much higher nucleophilicity than the corresponding keto compound toward carboxylic esters.[3] The problem is that the enol form is regarded much less stable thermodynamically, and hence is unlikely to be present in a significant amount.[4] In addition, the isolated intermediate of biotin carboxylation is always 1-carboxybiotin (in its methyl ester form) and it serves as a carboxyl donor in the subsequent transcarboxylase reaction.[5] Therefore, if the enolbiotin hypothesis is correct, the question how the carboxylated enolbiotin is converted to the keto form should be answered unequivocally. We found that 1-methoxycarbonyl-2-imidazoline (**1**) is readily converted to 1-methoxycarbonyl-2-imidazolidinone (**2**) in the presence of acid such as hydrochloric acid and trifluoroacetic acid.

Results and Discussion

1 is a stable, isolable 2-alkylisourea derivative, just like 1,3-diisopropyl-2-ethylisourea.[6] It was established that 2-alkylisoureas undergo an S_N2 reaction with a nucleophile such as phenol to give alkyl phenyl ether and urea.[7] Reaction of **1** under acidic conditions apparently follows a similar pathway. Thus, treatment of **1** with hydrochloric acid in chloroform at 30 °C converts **1** into **2** quantitatively (Eq. 1). Since the pK_a value of **4** in water is 9.1,[3] **1** should be present in the protonated form at 3-N position under the present conditions. The



1 2 (1)

Table 1. Effect of acid strength on the rate of transformation of **1** into **2**

Acid	Solvent	pK_a[a]	Temp/°C	k_{obsd}/s^{-1}
HCl[b]	$CDCl_3$	−6.1	30	5×10^{-4}
Picric Acid[b]	DMSO-d_6	−0.2	25	2×10^{-4}
CF_3CO_2H	—	0.25	70	6.2×10^{-5}
CF_3CO_2H[c]	—		70	1.1×10^{-3}
$(CH_3O)_2PO(OH)$[b]	$CDCl_3$	1.29	60	0

a) Value in water. b) Equimolar to **1**. c) Thiophenol was added in 15-fold excess over **1**.

reaction can be carried out also in trifluoroacetic acid at 70 °C to produce **2** and ethyl trifluoroacetate (Table 1). Addition of 15-fold molar excess of thiophenol enhances the conversion rate by 18-fold, the reaction product being solely ethyl phenyl sulfide besides **2**. On the other hand, dimethyl hydrogenphosphate was found to be without effect under comparable conditions. These data indicate that the transformation reaction is highly dependent upon the acidity of the catalyst employed and the presence of a nucleophile as the ethyl acceptor (Table 1).[8] Picric acid is an exception. It has a pK_a value comparable to that of trifluoroacetic acid, but is by far the more effective than the latter. Thus, the rate constant for the transformation in DMSO-d_6 is 2×10^{-4} s^{-1} in the presence of equimolar picric acid at 25 °C. It should be noted that neither the reaction rate nor the reaction product (1-ethoxy-2,4,6-trinitrobenzene) is altered by the addition of excess thiophenol. This anomalous behavior of picric acid may be explicable in terms of formation of a picrate or the like with substrate prior to the transformation. This is reminiscent of a fact that in model as well as in enzymatic systems prior formation of a complex between substrate and catalyst is one of the driving forces for the efficient catalysis to occur.[9]

A similar acid catalysis of acyl transfer was observed for *O*-benzoyl-*N*,*N*-dimethyl-*N*′-(*N*-methyl-2,4-dinitroanilino)isourea, an isolable *O*-acylisourea derivative.[10] This reaction was accompanied by an intramolecular acyl migration to the imine nitrogen, though at low pH values such as 1 the proportion of the side reaction was suppressed to such an extent that the intermolecular reaction predominates by a large margin. It is noted that an analogous intramolecular alkyl migration has not been observed for **1** under the present conditions. The thermodynamic instability of 2-alkyl- or 2-acylisourea relative to the urea must be primarily responsible for the ready transformation of **1** into **2**,[4,11] and acid facilitates the reaction.[12] It would not be unrealistic to assume that the putative 1-carboxy-*O*-phosphoenolbiotin might be converted analogously to 1-carboxybiotin at the enzyme active site, possibly by general acid catalysis.

Experimental

2-Imidazolidinone (**5**) was obtained from Wako Pure Chemical Ind. 2-Ethoxy-2-imidazoline (**6**) was prepared according to a literature.[13] 1-Methoxycarbonyl-2-imidazolidinone (**2**) was synthesized by reaction of **5** with methyl chloroformate:[14] mp 179—181 °C (lit,[14] mp 180 °C). 1-Methoxycarbonyl-2-ethoxy-2-imidazoline (**1**) was prepared either by reaction of **6** with methyl chloroformate or by reaction of **2** with triethyloxonium tetrafluoroborate:[15] mp 67—69 °C (lit,[15] mp 67—70 °C). Reaction rates for the transformation of **1** into **2** were determined by ^{1}H NMR spectroscopy on a JEOL JNM-MH-100 spectrometer under conditions given in Table 1.

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References

1) H. G. Wood and R. E. Barden, *Annu. Rev. Biochem.*, **46**, 385 (1977).
2) R. Kluger and P. D. Adawadkar, *J. Am. Chem. Soc.*, **98**, 3741 (1976).
3) A. F. Hegarty, T. C. Bruice, and S. J. Benkovic, *J. Chem. Soc., Chem. Commun.*, **1969**, 1173.
4) G. M. Maggiora, *J. Theor. Biol.*, **43**, 51 (1974).
5) R. B. Guchhait, S. E. Polakis, D. Hollis, C. Fenselau, and M. D. Lane, *J. Biol. Chem.*, **249**, 6646 (1974).
6) E. Schmidt and W. Carl, *Justus Liebigs Ann. Chem.*, **639**, 24 (1961).
7) F. L. Bach, *J. Org. Chem.*, **30**, 1300 (1965).
8) It does not appear feasible to correlate rates with acid strength in a quantitative manner, because pK_a values in water were used for the reaction in organic media and reactions were carried out in various solvents. Nevertheless, the rate difference among acids is large enough to offset this solvent effect.
9) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York (1969), Chap. 1.
10) A. F. Hegarty, M. T. McCormack, G. Fergason, and P. J. Roberts, *J. Am. Chem. Soc.*, **99**, 2015 (1977).
11) M. J. Cravey and H. Kohn, *J. Am. Chem. Soc.*, **102**, 3928 (1980).
12) Similar treatment of 2-ethoxy-2-imidazoline (**6**) with acid did not provide 2-imidazolidinone (**5**) without serious side reactions, which were not identified yet.
13) R. N. Boyd and M. Meadow, *Anal. Chem.*, **32**, 551 (1960).
14) H. J. Schaeffer and P. S. Bhargava, *J. Pharm. Sci.*, **53**, 137 (1964).
15) H. Kohn, M. J. Cravey, J. H. Arceneaux, R. L. Cravey, and M. R. Willcott; *J. Org. Chem.*, **42**, 941 (1977).