Effects of Metal Ions on Reactivity Patterns in the Reactions of 1-Methoxycarbonyl-2-imidazolidinone and Its Derivatives with Butylamine

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The reactions of 1-methoxycarbonyl-2-imidazolidinone, 3-acetyl-1-methoxycarbonyl-2-imidazolidinone and 1-methoxycarbonyl-*cis*-perhydrocyclopenta[*d*]imidazol-2-one with butylamine were studied in the absence and presence of various metal ions. Certain bivalent ions such as Mg^{2+}, Ca^{2+}, and Mn^{2+} enhanced an electrophilic reactivity of the methoxycarbonyl group and facilitated the transfer reaction of this group to butylamine, especially when the imidazolidinone moiety of substrates bears the methoxycarbonyl group at one N-position and a hydrogen atom at the other N-position. Whereas monovalent ions such as Na^+ and Ag^+, and bivalent ions such as Zn^{2+} and Cu^{2+}, had no appreciable effect on the reactivity, and exhibited almost the same reactivity patterns as those observed in the reactions in the absence of metal ions. A possible explanation is given in terms of the stability of coordination complexes which are formed by the interaction between the imidazolidinone moiety of substrates and added ions.

It has been postulated that a carboxylated biotin-enzyme, most probably carboxylated at the 1-N position of the biotin moiety of the enzyme, is a key intermediate in the biotin-enzyme-promoted carboxylations, and that the carbonyl group is transferred from this intermediate to a nucleophilic carbon of acyl-CoA or α-keto acids.[1,2] In order to elucidate the chemical mechanism of these enzymatic carboxylations, many model studies have been carried out by use of compounds related to biotin.[3] However, no definitive information has yet been obtained. We have recently investigated the chemistry of 1-methoxycarbonyl-2-imidazolidinone and its derivatives in a hope to gain a more insight into the chamical functions of biotin in the enzymatic carboxylations.[4]

Upon treatment with an amine, 1-methoxycarbonyl-2-imidazolidinone (**1**) is preferentially converted into 1-alkylcarbamoyl-4-methoxycarbonylethylenediamine (**2**), and the transfer of the methoxycarbonyl group to the amine is not observed.[4] Consequently, this experiment does not become in any sense a model reaction for the enzymatic carboxylations. On the other hand, it has been found that certain metal ions such as Mg^{2+} and Mn^{2+} are required for the enzymatic carbonylations.[5] These metal ions also depress the decarboxylation of 1-carboxy-2-imidazolidinone.[6] On the bases of these findings, we studied the effects of several metal ions on the reactivities of **1** and its derivatives in their reactions with butylamine. The addition of some ions including Mg^{2+} and Mn^{2+} to the reaction system exerted a dramatic change in the reactivity patterns and promoted the transfer of the methoxycarbonyl group from **1** and its derivatives to butylamine. The results are summarized in this paper.

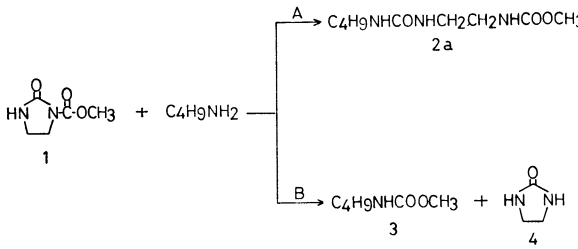
Results and Discussion

*Reaction of **1** with Butylamine.* Treatment of **1** with butylamine in the absence and presence of various metal ions gave the products listed in Table 1. The results of Table 1 demonstrate that the reaction takes place through two different paths, depending on the constituents of the reaction system (Scheme 1). In the absence of metal ions, 1-butylcarbamoyl-4-methoxycarbonylethylenediamine (**2a**) was obtained as a sole product (path A). The addition of monovalent ions such as Na^+ and Ag^+ and some bivalent ions such as Zn^{2+} and Cu^{2+} to the reaction system did not alter the above reactivity pattern. However, the addition of Mg^{2+}, Ca^{2+}, and Mn^{2+} brought about a dramatic change in the reactivity pattern and resulted in the formation of methyl butylcarbamate (**3**) and 2-imidazolidinone (**4**) (path B).

Table 1. Reaction of **1** with butylamine in the presence of metal ions[a]

Added salt	Reaction path	Products, %		
		2	**3**	**4**
None	A	95	—[b]	—
AgCl	A	96	—	—
NaCl	A	94	—	—
$CuCl_2$	A	88	—	—
$ZnCl_2$	A	86	—	—
$MgCl_2$	B	—	74	67
$MnCl_2$	B	—	63	40
$CaCl_2$	B	—	62	56

a) The reaction was carried out by refluxing an equimolar mixture of **1** and a metal chloride in butylamine for 17 h. b) The dash(—) signifies that the product was unable to be isolated.



Scheme 1.

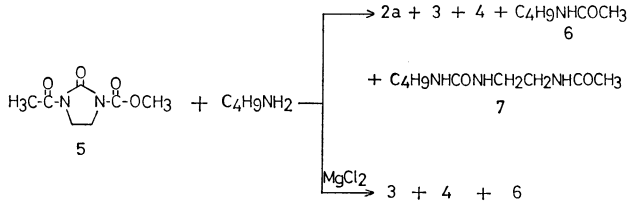
The methoxycarbonyl transfer reaction of path B occurs by an attack of butylamine on the carbonyl carbon of the methoxycarbonyl group of **1**. An analogous transfer reaction did not take place upon treatment of **2a** with butylamine in the presence of Mg^{2+} under the similar conditions.

Table 2. Reaction of **5** with butylamine in the presence of magnesium chloride[a)]

Added salt	Products, %				
	2	**3**	**4**	**6**	**7**
None	17	66	42	55	24
$MgCl_2$	—[b)]	71	67	85	—

a) The reaction was carried out by refluxing an equimolar mixture of **5** and magnesium chloride in butylamine for 17 h. b) The dash(—) signifies that the product was unable to be isolated.

Reaction of 3-Acetyl-1-methoxycarbonyl-2-imidazolidinone (5) with Butylamine. The reaction of **5** with butylamine was carried out in the absence and presence of Mg^{2+}. The products isolated are listed in Table 2. In the absence of metal ion, the reaction yielded **2a**, **3**, **4**, *N*-acetylbutylamine (**6**), and 1-acetyl-4-(butylcarbamoyl)ethylenediamine (**7**). In contrast, the reaction in the presence of Mg^{2+} afforded **3**, **4**, and **6**. These results show that the reactivity pattern is also altered by the addition of Mg^{2+}; *i.e.*, the production of ring-opening compounds, **2a**, and **7**, is completely depressed by the addition of Mg^{2+}.



Scheme 2.

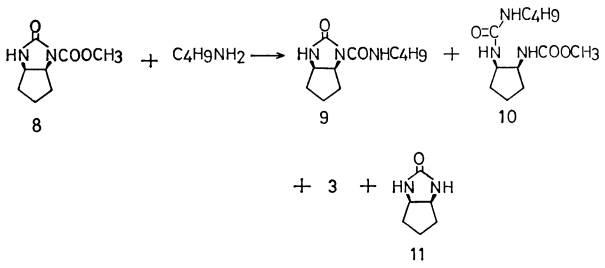
*Reaction of 1-Methoxycarbonyl-*cis*-perhydrocyclopenta*[d]*imidazol-2-one (8) with Butylamine.* The reaction of **8** with butylamine was studied somewhat in detail. The results are summarized in Table 3 and Scheme 3. In the absence of metal ions, **3**, 1-butylcarbamoyl-*cis*-perhydrocyclopenta[*d*]imidazol-2-one (**9**), *N*,*N*′-disubstituted *cis*-1,2-diaminocyclopentane (**10**), and *cis*-perhydrocyclopenta[*d*]imidazol-2-one (**11**) were obtained. For this reaction, a main reaction was an attack of butylamine on the 1-methoxycarbonyl carbon to produce **9**. Whereas the methoxycarbonyl transfer to produce **3** and **11** *via* the same mode of attack became a side-reaction. This observation implies that a leaving ability of the *cis*-perhydrocyclopenta[*d*]imidazol-2-one anion is lower than that of methoxide anion.

Table 3. The reaction of **8** with butylamine in the presence of various metal ions[a)]

Added salt	Products, %			
	3	**9**	**10**	**11**
None	7	55	15	13
AgCl	8	51	20	7
$CuCl_2$	10	52	17	15
$MgCl_2$	66	28	—[b)]	38
$MnCl_2$	68	22	—	44

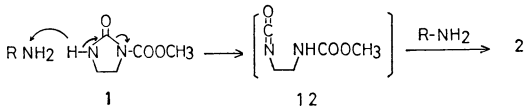
a) The reaction was carried out by refluxing an equimolar mixture of **8** and a metal chloride in butylamine for 17 h. b) The dash(—) signifies that the product was unable to be isolated.

No essential change in the reactivity pattern was observed by the addition of Ag^{+} and Cu^{2+}. However, the addition of Mg^{2+} again brought about a considerable change in the reactivity pattern. The formation of **10** was completely depressed, and the methoxycarbonyl transfer leading to **3** was highly facilitated.

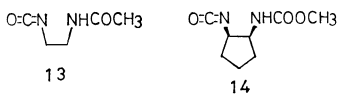


Scheme 3.

Discussion. In a previous paper,[4)] we have studied the reactions of **1**, **5**, and **8** with nucleophilic reagents in the absence of metal ions, and proposed probable pathways for these reactions. The reaction of **1** with an amine proceeds by way of the isocyanate intermediate (**12**) which has been produced by the removal of an acidic NH proton on the imidazolidinone ring of **1** by amine.



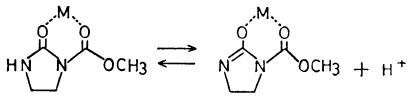
Compound **5** bears no acidic proton on the ring. For this compound, the methoxycarbonyl or acetyl group is removed at the first step by the nucleophilic attack of an amine on their carbonyl carbons. 1-Acetyl-2-imidazolidinone and **1** thus produced are converted into **7** and **2** *via* the corresponding isocyanate intermediates, **13** and **12**. These pathways explain the formation of all the products isolated. Finally, **8** is of special interest from the viewpoint that it has a more close structural resemblance to biotin than do **1** and **5**. Although **8** bears an acidic NH proton on the imidazolidinone ring, its 1-methoxycarbonyl group is attacked to produce **3**, **9**, and **11** in moderate yields. Obviously, **10** is produced *via* the isocyanate intermediate **14**.



The above reactivity patterns observed in the absence of metal ions change upon the addition of certain bivalent ions such as Mg^{2+}, Ca^{2+}, and Mn^{2+} to the reaction mixtures. These ions enhance an electrophilic reactivity of the methoxycarbonyl group and facilitate breaking of the N–$COOCH_3$ bond, especially when the imidazolidinone moiety of substrates bears the methoxycarbonyl group at one N-position and a hydrogen atom at the other N-position. In the case of **5** which bears

no hydrogen on the nitrogen atoms of the imidazolidinone moiety, the compound is, as pointed out above, at first transformed into **1** and 1-acetyl-2-imidazolidinone regardless the addition of metal ions. Since both of the products have a hydrogen on the N-position of the imidazolidinone moiety, **1** is preferentially converted into **3** and **4**, and 1-acetyl-2-imidazolidinone into **4** and **6** upon the addition of Mg^{2+}.

There is little doubt that the formation of coordination complexes as represented in formula 15 by chelating interaction between metal ions and imidazolidinone moiety is responsible for these changes. The formation of stabilized chelate ring depresses the conversion of the imidazolidinone derivatives, **1**, **5**, and **8** into the corresponding isocyanate intermediates, **12**, **13**, and **14**. It also enhances an electrophilic reactivity of the methoxycarbonyl group by its increased polarization.



$M = Mg^{2+}, Ca^{2+}, Mn^{2+}$

15

The experimental results suggest that the formation of stabilized chelate rings is favored by an association of the imidazolidinato ligand with bivalent ions, Mg^{2+}, Ca^{2+}, and Mn^{2+}, that belong to the hard metal ions in Pearson's classification.[7]

Bivalent ions, Zn^{2+} and Cu^{2+}, that belong to the borderline class in his classification and all monovalent ions do not give stabilized chelate rings.

Experimental

Materials. 1-Methoxycarbonyl-2-imidazolidinone (**1**), mp 178—179 °C, 3-acetyl-1-methoxycarbonyl-2-imidazolidinone (**5**), mp 143—144.5 °C, and 1-methoxycarbonyl-*cis*-perhydrocyclopenta[*d*]imidazol-2-one (**8**), mp 153.5—154.5 °C, were prepared by the methods described previously.[4]

*Reaction of **1**, **5**, and **8** with Butylamine.* The reaction of an imidazolidinone, **1**, **5**, or **8**, with butylamine in the absence of metal ion were conducted by refluxing a solution of 2 mmol of the respective imidazolidinone in 10 ml of butylamine for 17 h, and the products were isolated and identified by the procedures described previously.[4]

The reactions in the presence of metal ions were carried out as follows: A mixture of 2.08 mmol of an imidazolidinone, **1**, **5**, or **8**, and 2.08 mmol of a metal ion (as chloride) in 10 ml of butylamine was refluxed for 17 h. An excess of butylamine was removed by distillation, and the residue was subjected to a chlomatographic separation on silica gel column: chromatographic separations were successfully accomplished by use of the solvent systems[4] employed for the reactions in the absence of metal ions.

The products were identified by the comparisons of melting points and spectral properties such as IR, NMR, and mass spectra with those of the respective authentic specimens.

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