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Bivalent cation binding effect on formation of the peptide bond

Milan Remko^{a,*}, Bernd Michael Rode^b

^a Department of Pharmaceutical Chemistry, Comenius University, Odbojarov 10, SK-832 32 Bratislava, Slovak Republic

^b Institute of General, Inorganic and Theoretical Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

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Abstract

The reactions between formic acid (or glycine) and ammonia, without and with Mg^{2+} , Ni^{2+} and Cu^{2+} cations as catalysts, have been studied as model reactions for peptide bond formation using the Becke3LYP functional and 6-311 + G(d,p) basis set of DFT theory. Enthalpies and free energies for the stationary points of each reaction have been calculated to determine the thermodynamics of reactions investigated. A substantial decrease in reaction enthalpies and free energies was found for formic acid-ammonia and glycine-ammonia reactions catalysed by Mg^{2+} , Ni^{2+} and Cu^{2+} ions compared with those of the uncatalysed amide bond formation. The catalytic effect of the transition metal ions Ni^{2+} and Cu^{2+} is of similar strength and more pronounced than that of the Mg^{2+} cation. © 2000 Elsevier Science B.V. All rights reserved.

1. Introduction

The molecular events that preceded the formation of life have been and still are subject of intensive studies. One of the major objectives in origin of life studies is to identify the significant events in the prebiotic formation of first proteins from amino acids and their precursors. There have been numerous attempts [1–3] to prepare peptides from simpler compounds under conditions that resemble those of the primitive earth, and the presence of divalent cations (e.g., Mg^{2+} , Cu^{2+} , Ni^{2+} , etc.) can enhance such a formation of peptides [4,5]. A detailed analysis of the effect of bivalent metal ions is complicated due to the lability of the metal complexes [6,7],

which, on the other hand is needed for the release of newly formed peptides to the solution. Among all the reactions proposed so far for the formation of peptides under primordial earth conditions, the salt-induced peptide formation reaction (SIPF) would appear to be the simplest and most universal mechanism known to date [3]. The *bis*-glycinato-copper(II) complexes [8,9] were used as models for investigation of the effect of bivalent cations and NaCl on the formation of peptides.

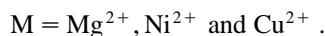
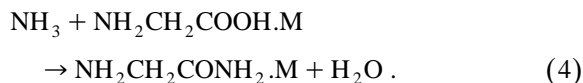
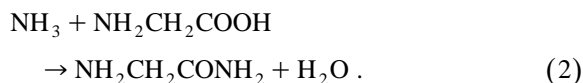
The absence of experimental structural data of the mechanism of peptide bond formation presents a challenge to the application of quantum chemical methods to obtain an insight into the mechanism of peptide bond formation. Although several theoretical studies on uncatalysed and catalysed peptide bond formation have been reported [10–15], only very limited investigation of these aspects in the presence

* Corresponding author. Fax: +421-7-55572065; e-mail: remko@fpharm.uniba.sk

of divalent cations have been carried out. Loew et al. [12] carried out quantum chemical investigations (at MP4(SDQ)/6-31G ** //STO-3G level of theory) on the reaction between glycine and ammonia molecules with magnesium cation Mg^{2+} as a catalyst. The present work reports the results of a systematic theoretical examination of peptide bond formation model reactions studying the formation of formamide and water from ammonia and formic acid and the formation of amide and water from ammonia and glycine. Special attention was paid to geometries, reaction enthalpies, entropies and free energies and to how these quantities are changed by catalytic effects induced by some bivalent cations.

2. Computational details

All compounds were optimized with the GAUSSIAN 98 program [16] employing the electron correlated Becke3LYP functional [17–19] with the polarized triple zeta split valence 6-311 + G(d,p) basis set as implemented in the GAUSSIAN 98 package of computer codes [16]. For Ni and Cu we used the Wachters–Hay [20,21] all electron basis set. The relative Becke3LYP energies are often in excellent agreement with high level ab initio results [22,23]. Vibrational frequency calculations of the reactants and reaction products give the zero point vibrational energies and the number of imaginary frequencies [24]. Enthalpies, entropies and free energies were computed for both the uncatalysed (reactions 1 and 2) and catalysed (reactions 3 and 4) peptide bond formation reactions.



The structure of chelated glycine (I) and its amide (II) is shown on Fig. 1. The structure of the complexes of formic acid and formamide with the metal

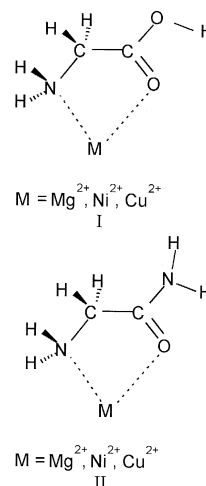


Fig. 1. Structure of $\text{NH}_2\text{CH}_2\text{COOH} \cdot \text{M}$ (I) and $\text{NH}_2\text{CH}_2\text{-CONH}_2 \cdot \text{M}$ (II) complexes.

ions studied was the same as in our previous publications [25–27].

3. Results and discussion

3.1. Molecular structures

Selected parameters of the B3LYP/6-311 + G(d,p) optimized geometries of the metal-coordinated reactants and products are given in Table 1. The B3LYP/6-311 + G(d,p) geometry and energy of water and ammonia were taken from our previous work [27]. An analysis of the harmonic vibrational frequencies at the B3LYP/6-311 + G(d,p) level of theory of the reactants and reaction products revealed that these species are minima (zero number of imaginary frequencies).

Metal co-ordination of the carbonyl group oxygen of formic acid and formamide results in changes in the optimum geometry of the parent bases. The C = O bond is elongated and the C–O and C–N bonds are considerably shortened (by about 0.05–0.1 Å). The H–C = O angle decreases and the H–C–O and C–O–H angles increase upon complexation (Table 1). The equilibrium distances $\text{O} \cdots \text{M}$ ($\text{M} = \text{Mg}^{2+}, \text{Ni}^{2+}$ and Cu^{2+}) increase in the order: $d_{(\text{O} \cdots \text{Ni}^{2+})} < d_{(\text{O} \cdots \text{Mg}^{2+})} \leq d_{(\text{O} \cdots \text{Cu}^{2+})}$. The computed C = O \cdots M ($\text{M} = \text{Mg}^{2+}, \text{Ni}^{2+}$ and Cu^{2+}) angles

Table 1

B3LYP/6-311 + G(d,p) optimized relevant bond lengths (Å), bond angles (deg) and dihedral angles (deg) for the metal-coordinated reactants and products

Par.	HCOOH.M				NH ₂ (H)C = O.M			
		Mg ²⁺	Ni ²⁺	Cu ²⁺		Mg ²⁺	Ni ²⁺	Cu ²⁺
$d_{\text{NH(OH)}}$	0.971	0.980	0.988	0.987	1.009	1.018	1.023	1.023
$d_{\text{C-H}}$	1.098	1.092	1.098	1.100	1.106	1.091	1.097	1.100
$d_{\text{C=O}}$	1.199	1.269	1.288	1.282	1.213	1.287	1.307	1.299
$d_{\text{C-O}}$	1.346	1.265	1.255	1.256				
$d_{\text{C-N}}$					1.361	1.294	1.285	1.286
$d_{\text{X...M}}$		1.854	1.768	1.865		1.822	1.749	1.853
< HCN					112.4	117.8	120.0	120.3
< H _c NC ^a					119.5	122.5	122.6	123.0
< H _t NC ^a					121.4	120.3	120.2	119.9
< C = O...M		161.3	136.6	148.1		163.8	135.3	151.2
< HC = O	125.3	121.6	122.3	120.3				
< HC-O	109.6	114.2	116.7	116.8				
< COH	107.9	117.0	118.8	119.0				
Par.	NH ₂ CH ₂ COOH.M				NH ₂ CH ₂ CONH ₂ .M			
		Mg ²⁺	Ni ²⁺	Cu ²⁺		Mg ²⁺	Ni ²⁺	Cu ²⁺
$d_{\text{C-C}}$	1.512	1.519	1.498	1.506	1.539	1.533	1.507	1.517
$d_{\text{C=O}}$	1.205	1.253	1.273	1.267	1.218	1.272	1.297	1.291
$d_{\text{C-O}}$	1.353	1.280	1.267	1.271				
$d_{\text{C(O)-N}}$					1.366	1.307	1.297	1.299
$d_{\text{C-N}}$	1.454	1.510	1.521	1.515	1.450	1.510	1.520	1.513
$d_{\text{N...M}}$		2.127	1.901	1.988		2.126	1.900	1.987
$d_{\text{O...M}}$		1.939	1.791	1.880		1.907	1.771	1.857
< C-C = O	125.2	121.8	118.2	120.3	122.4	119.3	115.7	117.4
< C-C-O	111.7	114.3	118.9	117.0				
< N-C-C	110.5	107.0	106.7	109.1	115.4	111.0	106.5	108.8
< C-C(O)-N					115.0	119.5	124.3	122.5
< C = O...M		116.0	117.2	115.3		117.4	118.1	116.5
< C-N...M		106.5	110.1	108.5		105.9	108.9	107.5
< N...M...O		84.7	87.7	86.9		84.9	87.5	86.6
< N-C-C = O	19.9	0.8	1.0	1.1	-11.7	-12.1	-14.8	-15.8
< N-C-C-N					169.3	169.2	167.0	166.3
< C-C = O...M		179.8	0.0	-0.2		4.3	3.1	4.2

^aH_c labels the hydrogen *cis* to the oxygen, while H_t labels the hydrogen *trans* to it.

are about 135–165° and considerably tilted away from the C = O axis. Larger deviation of the C = O...M bond from linearity was found in the case of co-ordination of the transition metals Ni²⁺ and Cu²⁺. The Ni²⁺ and Cu²⁺ ions are approximately oriented towards one lone pair of carbonyl oxygen. The differences in tilting of Mg²⁺ and transition metal ions Ni²⁺ and Cu²⁺ could be explained by the different nature of electron distribution of Mg²⁺ (main group element), and Ni²⁺ and Cu²⁺ (transition metals) cations.

Experimental evidence [28,29] and ab initio calculations [30–32] have indicated the formation of an intramolecular hydrogen bond between the NH₂-group and the COOH-backbone of neutral glycine. The initial Becke3LYP optimizations were also performed for two H-bonded structures Gly I and Gly II (in this contribution we follow the convention of Stepanian et al. [29] for numbering the isomers). On the other hand, the extended structure of glycine (Gly III, Fig. 1) represents the most realistic conformation for this compound present in metal chelated

systems [33]. Suitable starting geometries for glycine complexes with divalent cations were generated from di-coordinated complexes [33] (involving both carbonyl and amino group as shown in Fig. 1). From experimental investigations [4,7,34] it is known, that the α -amino acids and their derivatives prefer to form five-membered chelate rings with metal cations. Structures I and II, Fig. 1 illustrate the chelated complexes of glycine and its amide. The chelate rings of $\text{NH}_2\text{CH}_2\text{COOH}\cdot\text{M}$ and $\text{NH}_2\text{CH}_2\text{CONH}_2\cdot\text{M}$ ($\text{M} = \text{Mg}^{2+}$, Ni^{2+} and Cu^{2+}) complexes are practically planar (Table 1). Upon co-ordination the geometry of glycine and its amide changes considerably. The C=O and C–N bonds are by 0.05–0.08 Å longer and C–O bond is smaller compared to the uncatalysed reaction. The valence angles C–C=O and N–C–C are appreciably smaller (by 3–8°) in chelated systems. The metal cations approach carbonyl oxygen atom approximately in the direction of its lone pair (the C=O...M angles are about 115–118°). Glycine and amide molecules are slightly pyramidal at nitrogen of the CH_2NH_2 group. In chelated complexes I and II, Fig. 1 the pyramidalization of this nitrogen is substantially larger, which is a result of coordination of metal cations Mg^{2+} , Ni^{2+} and Cu^{2+} to the nitrogen of that group. The N...M bond ($\text{M} = \text{Mg}^{2+}$, Ni^{2+} and Cu^{2+}) is about 0.1–0.2 Å longer than the O...M distance (Table 1) and oriented towards the lone pair of nitrogen (the C–N...M angles are of 106–110°). The N...M...O angle of the ‘bifurcated’ metal bond is practically the same in both glycine and amide complexes.

3.2. Reactivity

Table 2 summarizes the reaction enthalpies, entropies and free energies. The reaction enthalpies for all eight reactions investigated are negative (exothermic reactions). The computed entropies for catalysed and uncatalysed reactions are small (1–5 cal mol^{−1} K^{−1}). Hence the effect of entropy for these gas-phase reactions is very small. Computed enthalpies and free energies are very close and follow the same trend in the reactivity of compounds studied.

The uncatalysed reaction of formic acid with ammonia [$\text{NH}_3 + \text{HCOOH} \rightarrow \text{NH}_2\text{HCO} + \text{H}_2\text{O}$ (1)] is slightly exothermic (by about −2 kcal mol^{−1}). A lower experimental value of $\Delta G^{298} = -0.3$ kcal mol^{−1} was computed for this reaction from the experimental heats of formation in the gas phase [11]. A comparison of the Mg^{2+} –catalysed reaction with the uncatalysed reaction (1) shows a considerable decrease (by about 24 kcal mol^{−1}) of the free energy (Table 2). The transition metal cations Ni^{2+} and Cu^{2+} behave similarly. However, in comparison with the Mg^{2+} –catalysed reaction the computed free energy is lower by another 7.7 kcal mol^{−1}. Thus, the transition metal cations are more efficient catalysts in the formation of amide from formic acid. The catalytic effect of Ni^{2+} and Cu^{2+} on the reaction (1) is practically identical (Table 2).

The reaction of glycine conformers investigated with ammonia [$\text{NH}_3 + \text{NH}_2\text{CH}_2\text{COOH} \rightarrow \text{NH}_2\text{CH}_2\text{CONH}_2 + \text{H}_2\text{O}$ (2)] is energetically equally

Table 2

Reaction enthalpies, entropies and free energies for the Mg^{2+} , Ni^{2+} and Cu^{2+} –catalysed NH_3 –formic acid and NH_3 –glycine reactions

No.	Reaction	ΔH^{298} kcal mol ^{−1}	ΔS^{298} cal mol ^{−1} K ^{−1}	ΔG^{298} kcal mol ^{−1}
1	$\text{NH}_3 + \text{HCOOH} \rightarrow \text{NH}_2\text{CHO} + \text{H}_2\text{O}$	−2.4	−1.0	−2.1
3a	$\text{NH}_3 + \text{HCOOH}\cdot\text{Mg}^{2+} \rightarrow \text{NH}_2\text{CHO}\cdot\text{Mg}^{2+} + \text{H}_2\text{O}$	−27.2	−2.5	−26.5
3b	$\text{NH}_3 + \text{HCOOH}\cdot\text{Ni}^{2+} \rightarrow \text{NH}_2\text{CHO}\cdot\text{Ni}^{2+} + \text{H}_2\text{O}$	−34.0	−1.2	−33.6
3c	$\text{NH}_3 + \text{HCOOH}\cdot\text{Cu}^{2+} \rightarrow \text{NH}_2\text{CHO}\cdot\text{Cu}^{2+} + \text{H}_2\text{O}$	−34.6	−1.4	−34.2
2a	$\text{NH}_3 + \text{NH}_2\text{CH}_2\text{COOH (Gly I)} \rightarrow \text{NH}_2\text{CH}_2\text{CONH}_2 + \text{H}_2\text{O}$	−0.5	0.3	−0.6
2b	$\text{NH}_3 + \text{NH}_2\text{CH}_2\text{COOH (Gly II)} \rightarrow \text{NH}_2\text{CH}_2\text{CONH}_2 + \text{H}_2\text{O}$	−1.1	1.7	−1.6
2c	$\text{NH}_3 + \text{NH}_2\text{CH}_2\text{COOH (Gly III)} \rightarrow \text{NH}_2\text{CH}_2\text{CONH}_2 + \text{H}_2\text{O}$	−1.9	1.0	−2.2
4a	$\text{NH}_3 + \text{NH}_2\text{CH}_2\text{COOH}\cdot\text{Mg}^{2+} \rightarrow \text{NH}_2\text{CH}_2\text{CONH}_2\cdot\text{Mg}^{2+} + \text{H}_2\text{O}$	−18.9	−2.8	−18.0
4b	$\text{NH}_3 + \text{NH}_2\text{CH}_2\text{COOH}\cdot\text{Ni}^{2+} \rightarrow \text{NH}_2\text{CH}_2\text{CONH}_2\cdot\text{Ni}^{2+} + \text{H}_2\text{O}$	−23.1	−4.8	−21.6
4c	$\text{NH}_3 + \text{NH}_2\text{CH}_2\text{COOH}\cdot\text{Cu}^{2+} \rightarrow \text{NH}_2\text{CH}_2\text{CONH}_2\cdot\text{Cu}^{2+} + \text{H}_2\text{O}$	−22.3	−4.2	−21.0

favorable as that of formic acid with ammonia [reaction (1)]. The free energy of this reaction is negative and small (about -0.6 to (-2.2) kcal mol $^{-1}$). The transition metal cations Ni $^{2+}$ and Cu $^{2+}$ exhibit again the largest catalytic effect. However, the decrease of free energy is by some 8.5–13.2 kcal mol $^{-1}$ lower than that determined for the catalysed reaction of formic acid with ammonia (Table 2). The different magnitude of the catalytic effect of Mg $^{2+}$, Ni $^{2+}$ and Cu $^{2+}$ cations on the two reactions of amide formation could be explained by the different stabilization of reactants and reaction products. In the case of reaction (1) the reactant formic acid binds metal cations substantially less strongly than the reaction product (formamide) [25,27]. The increase of interaction energies in formamide in comparison with formic acid correlates with the mesomeric effect of OH and NH $_2$ groups. The more electronegative oxygen leads to significantly lower electron donation from OH relative to NH $_2$ [25]. The co-ordination of glycine and its reaction product results in structurally very similar five-membered rings (Table 1). The structural similarity of metal complexes of reactant and product also brings some energetic similarity and the differentiating effect of OH and NH $_2$ substituents is much weaker. Compared with the uncatalysed reactions (1, 2) the much lower free energies of reaction in the metal ion catalysed reactions indicate that metal ions are indeed highly efficient catalysts in the formation of peptide bond.

4. Summary and conclusions

Our model calculations indicate that divalent metal ions, in particular of first row transition metals, can play an important role in the formation of peptide bonds. This fits well into recent findings of metal-ion catalysed peptide formation reactions under conditions prevailing on the primitive earth. Investigations involving the inclusion of solvent molecules in the catalytic process might reveal further interesting details of the underlying mechanism.

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