Stabilization of the glycine zwitterionic form by complexation with Na^+ and Cl^-: an *ab initio* study

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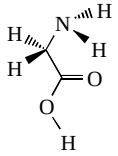
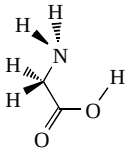
Ab initio [MP2(full)/6-31G**] calculations predict that the glycine zwitterionic form bridged with NaCl is more stable than the isomeric complexes of the neutral forms.

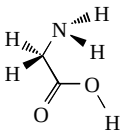
The zwitterionic form of amino acids dominates in the aqueous media of biological systems.[1] Gas phase experimental data[2-4] and numerous *ab initio* calculations[4–9] show that the simplest amino acid glycine exists only in the neutral forms **1**, **2** and **3**, whereas the zwitterionic form **4** is not observed; that is, it does not correspond to a minimum on the potential energy surface (PES).



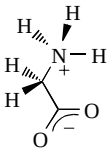
1, C_s



2, C_1



3, C_1



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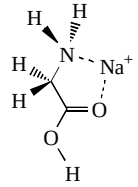
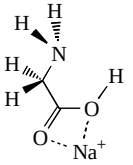
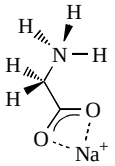
Both theoretical and experimental studies[2–8] point to the crucial role of medium effects on the existence and stability of the zwitterionic form of glycine. Recent *ab initio* calculations predict that the glycine zwitterionic form can be stabilised, *i.e.*, corresponds to the minimum on the PES, when it forms an H-bonded cluster with at least two water molecules.[5,6] At the same time, it is well known[1] that in biological systems amino acids form salts and various complexes with alkali metals (Na^+, K^+),[9,10] copper (Cu^+)[11,12] or other ions,[1,13] which stabilise the zwitterionic form. Here, we report on *ab initio* [MP2(full)/6-31G**][14] calculations of glycine complexes **5**–**7** with the cation Na^+,



5, C_1

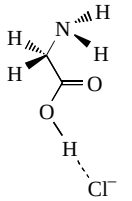


6, C_s

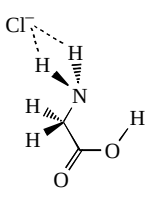


7, C_s

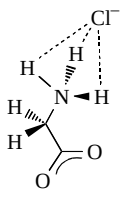
complexes **8**–**10** with the anion Cl^-



8, C_s



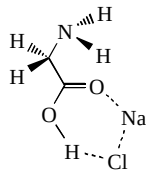
9, C_1



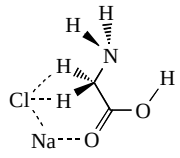
10, C_1

and complexes **11**–**13** with undissociated sodium chloride. Our results indicate that only complexation of a glycine molecule simultanuously with the two counterions Na^+ and Cl^- results in the stabilization of zwitterionic form **13** relative to isomeric complexes **11**, **12** formed by neutral glycine.

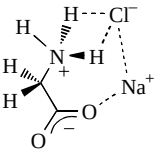
According to the MP2(full)/6-31G** calculations, all structures **5**–**13** correspond to minima ($\lambda = 0$, hereafter λ designates the number of hessian negative eigenvalues at a given stationary point) on the PES. Various other possible structures of the complexes have also been studied but have been found to correspond



11, C_s



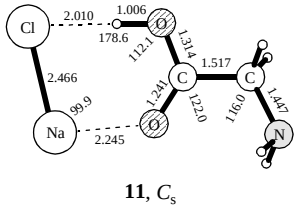
12, C_1



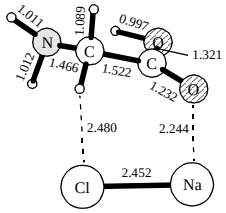
13, C_1

to the stationary points with $\lambda \geq 1$. Therefore, they are not considered here. The calculated molecular structures, geometries and energy parameters of complexes **5**–**13** are given in Figure 1 and Table 1.

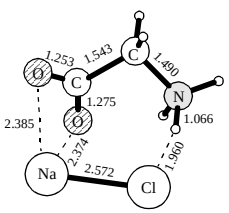
The counterions Na^+ and Cl^- stabilise glycine zwitterionic forms **7** and **10**, respectively, *i.e.*, calculations predict the correspondence to local minima on the PESs. However, complex **7** is less stable than the neutral form of glycine **5** and **6**, and anionic complex **10** is less stable than **8**, **9**. Only the cooperative influence of the two counterions makes the zwitterionic form **13** preferred in energy (0.5 kcal mol^{-1}) as compared to the most stable complex of the neutral form of glycine **11**. Accounting for ZPE makes the zwitterionic form less stable than the neutral form **11** by 0.5 kcal mol^{-1}. The same tendency is observed for relative enthalpy, whereas the behaviour of the relative free energy (G) coincides with that of the relative free energy (E). The complexation energy of **13** calculated without accounting for a basis set superposition error (BSSE)[15] is 32.9 kcal mol^{-1}. We will compare it with the value 32.4 kcal mol^{-1} for the complexation energy of the neutral form **11** (in both cases, complexation energies are estimated as the difference $\{E_{tot}$(**13** or **11**) – $-[E_{tot}$(**1**) + E_{tot}(NaCl)]}, where E_{tot} is the total energy of **13**, **11**, **1** or NaCl, respectively). Note that the C_1-structure of **13** is skewed toward a helical form (see Figure 1). The geometric parameters of glycine forms **1** and **2** are markedly changed under complexation with NaCl: all valent bonds participating in interactions with Na and Cl are elongated by ~0.03 Å, as is the NaCl



11, C_s



12, C_1



13, C_1

Figure 1 Geometry parameters of glycine complexes with NaCl **11**, **12** and **13**, as calculated by the MP2(full)/6-31G** method. Bond lengths and angles are given in angström units and degrees, respectively.

Table 1 *Ab initio* MP2(full)/6-31G** data for the structures of **5**–**13**.[a]

Structure	E_{tot}/a.u.	E/kcal mol^{-1}	E_{ZPE}/kcal mol^{-1}	H^b/kcal mol^{-1}	G^b/kcal mol^{-1}	ω_1/cm^{-1}
5, C_1	–4 45.40111	0	0	0	0	85
6, C_s	–4 45.39513	3.75	2.94	3.04	4.84	80
7, C_s (ZW)	–4 45.39686	2.67	2.80	2.80	2.51	102
8, C_1	–7 43.36694	0	0	0	0.48	43
9, C_1	–7 43.36631	0.39	1.34	1.16	0	34
10, C_1 (ZW)	–7 43.36347	2.18	2.71	2.44	1.62	80
11, C_s	–9 05.26099	0.50	0	0	2.84	41
12, C_1	–9 05.25422	4.75	4.73	4.70	6.82	40
13, C_1 (ZW)	–9 05.26178	0	0.47	0.01	0	92

[a]E_{tot} and E are the total and relative energies (1 a.u. = 627.5095 kcal mol^{-1}); E_{ZPE} is the relative energy including a harmonic zero-point correction; H is the relative enthalpy; G is the relative free energy; ω_1 is the smallest vibration frequency. [b]Thermochemistry data are given at T = 298.15 K and P = 1 atm.

distance increased on 0.1 Å. It should be noted that the electric dipole moment of the zwitterionic form of complex **13** (3.84 D) is smaller than that of **11** (6.83 D) and **12** (5.10 D) by a factor of about two. This fact testifies to a partial screening of the charges on the NH_3^+ and CO_2^- groups in the complex.

In conclusion, the calculations show that the counterions not only stabilise the zwitterionic form of glycine but also convert it to the dominating form in the complex with NaCl. Obviously, the zwitterionic form of glycine in biological systems is stabilised by interactions with both water molecules and counterions. The cooperative medium effect can increase the zwitterionic stability.

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