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**Interaction of alanine with lithium. I- the alanine–Li -n (H<sub>2</sub>O)  
n (0–2) complexes**

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**ABSTRACT**

The energy minima of systems made of an alanine molecule, a lithium cation and a various number of water molecules have been determined with the help of quantum mechanical computations at the B3LYP Density Functional Theory level of computation and the standard 6-311++G (d,p) basis set. Several structures, close in energy are found and the presence of one or two water molecules around the cation modifies the order of stability. The results are discussed in view of better understanding the structure of aqueous solutions of these species and the possible interactions of lithium cations with peptides.

**Keywords:**DFT quantum mechanical computations; Lithium–alanine interactions; Hydration; Aqueous solution

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## INTRODUCTION

Alkali metals chemistry has received an increasing interest during the past decades [1–6]. Their cations play an important role, especially in biochemical processes. They interact with proteins and peptides to control structural and regulating properties [7–11]. They are essential to maintain the osmotic equilibrium in living cells and play an important role in transport processes through cell membranes [1–4]. The role of alkali cations in peptide conformation deserves special attention and the study of their interaction with aminoacids is expected to give a support to structural assumptions made necessary to interpret some molecular Biology phenomena.

For the time being, most of the experimental or theoretical studies deal with lithium, sodium and potassium cations interacting with a ligand in the gas phase [12–17].

Alanine is chosen as representative of a backbone unit in a protein. In order to simulate what may occur in biology, where water is an important component, we intend to perform a study of the various conformations of the complexes made of a  $\text{Li}^+$  ion with an alanine molecule and a variable number of water molecules. In order to compare our data with the previously obtained ones, we start this study by examining the bare complexes. Then we analyze the case of the clusters formed with water molecules.

## COMPUTATIONS

The computations have been performed with the GAUSSIAN 98 package [18] in the Density Functional Theory formalism. The data have been obtained with the hybrid B3LYP functional [19, 20] and the 6-311++G(d,p) basis set. The geometry of the complexes has been fully optimized.

## RESULTS AND DISCUSSION

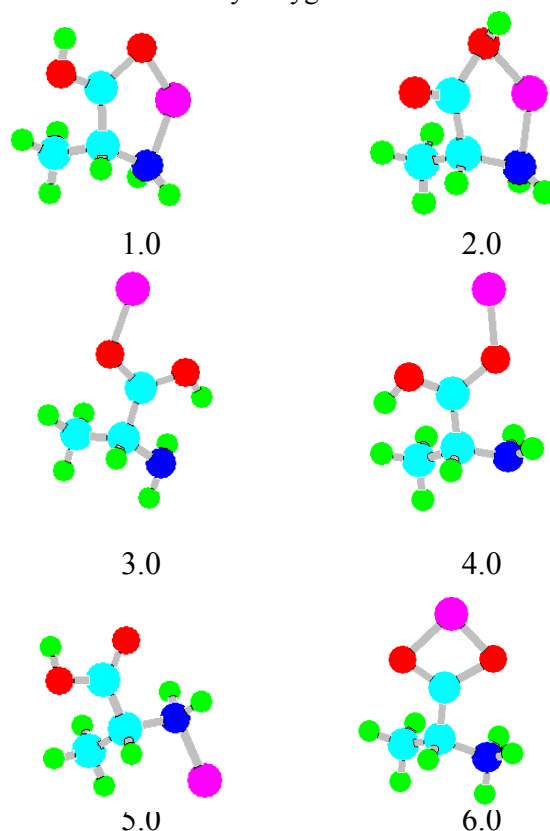
The alanine– $\text{Li}^+$  complexes considered in this study are similar of the 7 low-energy structures (alanine– $\text{Li}^+$ ) analyzed by Hoyau et al. [15]. The various structures are designated with a number corresponding to the numbers introduced in this reference and a decimal

number indicating the number of water molecules in the cluster.

### Complexes of without water molecule

The structures corresponding to energy minima are displayed in Fig. 1 and the energetic data are collected in Table 1. The present results agree qualitatively with those of Ref. [15]. The only difference, it is that we use from alanine ligand instead of alanine. The purpose of this study being the analysis of the changes in the relative stability induced by the complexation of these structures by water molecules.

According to the notations defined above, the bare complexes are denoted by n.0 and the most stable form is 1.0, followed by 6.0 in which the aminoacid is in the zwitterionic form. The next one, 3.0 corresponds to the latter in which a proton of the ammonium group has shifted towards the oxygen atom to give rise to the molecular form of alanine. This process is accompanied by a shift of the cation towards the carbonyl oxygen.



**Fig.1.** Structure of energy minima of bare alanine– $\text{Li}^+$  complexes.

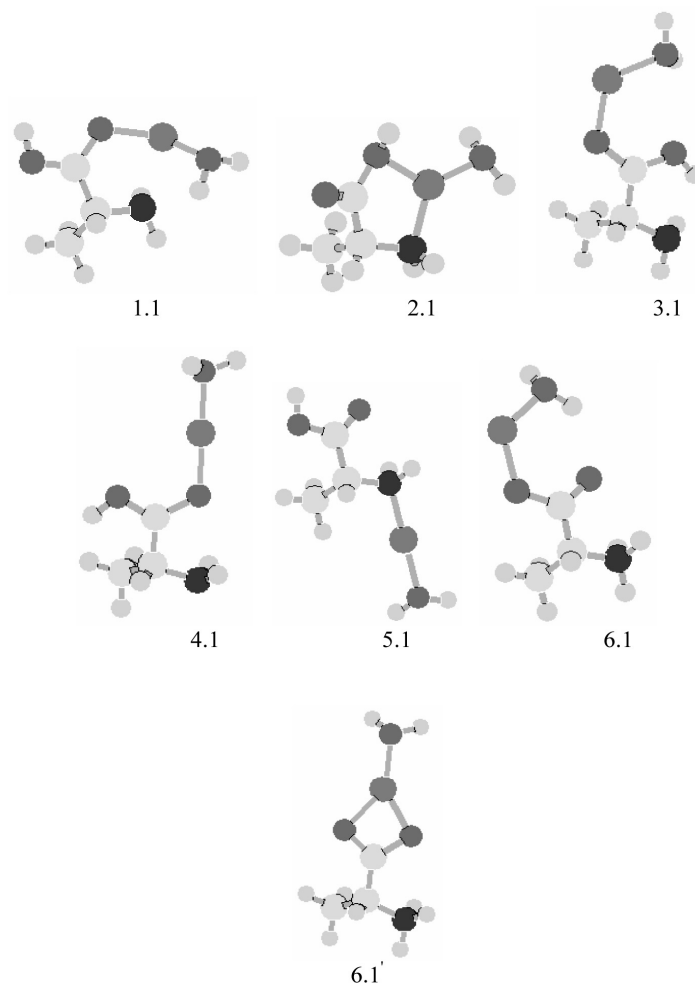
**Table 1.** Energetic data for the bare complexes represented in Fig. 1

Structure	Energy (Hartree)	Relative energy (kcal/mol)
1.0	-331.145869	0.00
6.0	-331.1323975	8.45
3.0	-331.1253562	12.87
2.0	-331.1249251	13.14
4.0	-331.1085635	23.41
5.0	-331.1055571	25.30

**Clusters with one water molecule**

The stable structures represented in Fig 2 derive from the previous ones. The most stable one, 6.1 corresponds to the zwitterionic form 6.0 in which the water molecule is inserted between the cation and the carbonyl oxygen. The corresponding molecular form 6.1' is very close in energy as seen in Table 2, and energy amount for the two forms is also very close.

Another structure very close in energy to the previous ones is denoted 6.10. It corresponds to structure 6.0 in which the water molecule interacts with the cation only. Table 2 gives the energies of hydration of the bare complexes to form the monohydrated ones. These energies are of the expected order of magnitude.

**Fig.2.** Structure of energy minima of alanine- $\text{Li}^+$  complexes with 1 water molecule, and of the transition state (TS) between structures 6.1 and 3.1.

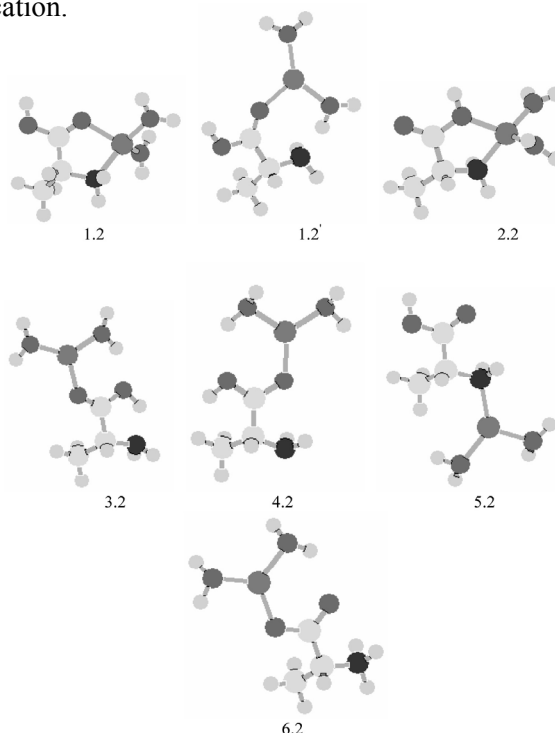
**Table 2.** Energetic data for the complexes with 1 water molecule represented in Fig. 2

Structure	Energy (Hartree)	Relative energy (kcal/mol)	Hydration energy (kcal/mol)
6.1	-407.6049593	0.00	-28.91
6.1'	-407.6047259	0.15	-28.75
3.1	-407.6000994	3.05	-30.27
2.1	-407.5955074	5.93	-27.66
1.1	-407.5738081	19.55	-0.90
4.1	-407.5723841	20.44	-23.41
5.1	-407.566336	24.22	-21.51

### Clusters with two water molecules

The 6 stable forms are represented in Fig. 3 and their energies are given in Table 3. Again, the most stable structure (3.2) contains a water molecule in a bridge position between the cation and the hydroxy group, the other ligands of the cation being the carbonyl group and the second water molecule. This structure obtained by adding a complexing water molecule to the previous most stable form 3.1. The corresponding zwitterionic structure (6.2) has higher energy, but the difference is (7.36 kcal/mol). the very low-energy structure, having almost the same energy of 3.2, called 1.2' corresponds to structure 1.1 with 1 water molecule solvating the cation.

By comparison with structure 1.1, the water molecule which bridges the cation–nitrogen distance is expelled and enters the solvation shell of the cation in order to achieve the tetra-coordination of the cation. Nevertheless, another structure derived from 1.1 by adding a solvating water molecule on the cation, denoted as 1.20, is also found as an energy minimum, very close to the previous one. The energy changes accompanying the addition of the second water molecule to the previous complexes is less than when the first water molecule is added to the bare complexes, but the processes are still exothermic.

**Fig-3.** Structure of energy minima of alanine- $\text{Li}^+$  complexes with 2 water molecules.

**Table 3.** Energetic data for the complexes with 2 water molecules represented in Fig 3

Structure	Energy (Hartree)	Relative energy (kcal/mol)	Hydration energy (kcal/mol)
3.2	-484.0719754	0.00	-28.470568
1.2'	-484.0677839	2.63	-42.3384135
1.2	-484.0657954	3.88	-21.6893811
6.2	-484.0602389	7.36	-18.056161
2.2	-484.0576246	9.00	-22.3468234
4.2	-484.0326025	24.71	-21.1553074
5.2	-484.025957	28.88	-20.7804329

## DISCUSSION

From this study it appears clearly that a cation like lithium interacts strongly with alanine, even when the aminoacid is not ionized or is in its zwitterionic form. Solvation by water molecules is also an efficient process, at least when one or two molecules interact with the cation. In the present case, considering two water molecules does not change qualitatively the conclusions, in particular for the most stable structure. One may therefore predict that considering more water molecules around the cation may not introduce great changes to the present conclusions. The various structures examined here are rather close in energy, and one can anticipate that aqueous solutions of alanine and a lithium salt may constitute a rather complicated system, with much chemical equilibrium and fast inter conversion of the species. These findings may be used as a basis for a study of different systems made of other aminoacids and other cations although additional phenomena may occur, in particular because of the presence of side chains which may also interact with the cations.

In addition the interaction of complexes with bigger cations with water may require more than two water molecules to reach what looks like here a steady state of hydration. Finally, most of the structures found in this study may be found as well in peptides. Except the zwitterionic forms, all the other structures look possible when alanine is condensed with other aminoacids, in particular those in which the cation is complexed by the oxygen atom of the carbonyl group and the nitrogen atom of the amino one.

## CONCLUSIONS

This preliminary study brings additional information on the interaction of the reference aminoacid, alanine, with the simplest alkaline cation, lithium, in the presence of water molecules as it may occur in a peptide. It shows that aqueous solutions of these species are expected to be rather complex, with many fast chemical equilibria. This should be confirmed by studying a system closer to the actual situation of a solution, including long-range electrostatic interactions and a study of these species embedded in a continuum is in progress.

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