RESEARCH ARTICLE

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A COMPARATIVE STUDY OF THE HYDRATION OF ALIPHATIC ANIMO ACIDS BY CNDO/2 AND AB INITIO MOLECULAR ORBITAL CALCULATIONS

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Abstract

The interaction of aliphatic amino acids with water has been studied using glycine as an example. The relative stability of the possible coordination sites has been evaluated using the semiempirical CNDO/2 method and ab initio calculations with minimal Gaussian basis sets. The abilities and limitations of both computational frameworks are critically discussed and a model for the full hydration shell of glycine and the coresponding stabilization energy are given.

Introduction

Biological processes occur almost exclusively in aqueous solution. Theoretical studies on biologically relevant molecules should not be restricted, therefore, to the isolated molecule in the gas phase, but include all relevant interactions with the solvent as well. In this work we therefore intended to evaluate the significance of the interaction of an amino acid with water, and as an example, the glycine molecule was chosen in its zwitterionic form, as this form is known to be the dominant one at physiological pH values[1].

The size of the system under investigation necessarily involves some restrictions in the accuracy of the computational approach. We have chosen, therefore, the most standardized semi-empirical molecular orbital procedure (CNDO/2) for the calculation of the energy optimized geometries of the glycine/water adducts. For the optimized

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+ Permanent address: Department of Chemistry, Faculty of Science, University of Innsbruck, Innrain 52a A-6020 Innsbruck, Austria geometries, ab initio calculations have been performed with well-tested minimal Gaussian basis sets[2], in order to compare the stabilization energies predicted by both procedures and to evaluate possible artefacts due to the approximations of the semi-empirical framework.

Methods

The geometry of glycine was taken from experimental data[3] and kept constant throughout the calculations, as well as the intramolecular parameters of water. The intermolecular parameters have been optimized with respect to total energy. The possible coordination sites for water on the glycine zwitterion investigated in this work are illustrated in Figure 1.

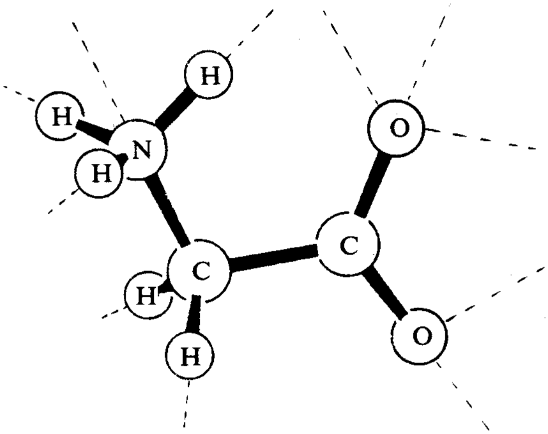

Fig. 1 Investigated locations of water in the surrounding of the glycine zwitterion

The CNDO/2 method was used in its original parametrization[4], the ab initio Hartree-Fock MO calculations were done with a self-written program adapted to the IBM computer of Chulalongkorn University, where all calculations have been performed.

Evaluation of all data has been perfromed using the supermolecule approach[5].

Results and Discussion

Geometry Optimization

Figure 2 illustrates the optimized geometrical arrangements for the glycine zwitterion with one water molecule. Nine hydration sites are possible but not all of them can be realized simultaneously, so that the decision on the final hydration structure will depend on the relative energies of these sites.

Comparison with ab initio data on hydration structures of other systems containing the NH_3^+ and COO^- group[6] allows us to conclude, that the determination

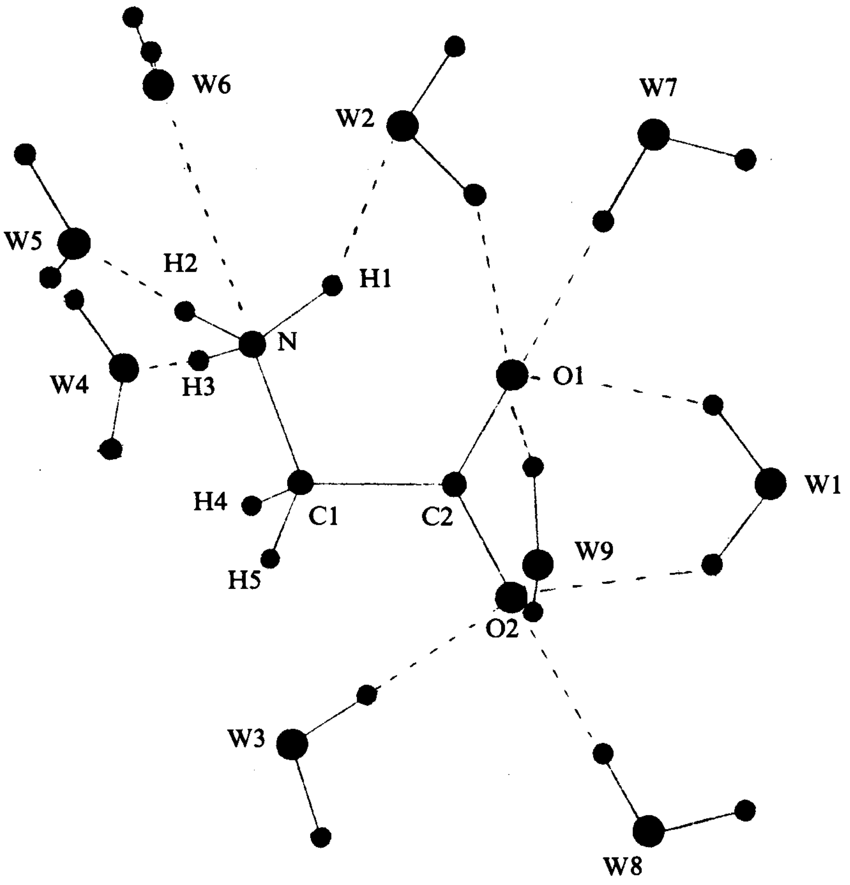

Fig. 2 Optimized glycine/water adduct geometries

of geometries by the CNDO/2 method should be reliable, as far as the location and orientation of the water molecules is concerned. This is not true, however, for the hydrogen bond distances, as has been shown already in many studies in the past[7], as CNDO and INDO methods always lead to too short H-bonds. It has been suggested, therefore, to perform semiempirical studies on hydrogen bonded systems with H-bonds fixed at the standard value of 2.75 Å, and all of these studies have led to satisfactory results[8].

For this reason, we have performed another set of calculations, where the orientation of the water molecules was maintained as resulting from the optimization, but with the hydrogen bond distances elongated to 2.75 Å, compared to 2.2 - 2.5 Å resulting from the optimization procedure.

These geometries have been used also in the ab initio calculations.

Interaction Energies

The CNDO/2 interaction energies obtained within the optimization (E_O) and those with fixed hydrogen bonds of 2.75 Å (E_F) are collected together with the corresponding data from our ab initio calculations (E_A) in Table 1.

The strong overestimation of stabilization energies using the optimized CNDO H-bond lengths can be easily recognized from this comparison. The values obtained with fixed H-bond distances are much more realistic and of the same magnitude as the ab initio data. A peculiarity is found, however, in the relative series of stability of CNDO and ab initio data.

Position 2 (Figure 2) seems to be more favoured by the CNDO method than it is in the ab initio calculations. This is not surprising, however, as the CNDO method always overemphasizes any geometrical arrangement leading to a cyclic structure, as it is the case for the water orientation in position 2. This has to be regarded, therefore, rather as an artefact of the semi-empirical method.

Due to the use of minimal basis sets in our ab initio calculations, we still have to expect some artificial contribution to the stabilization energies due to basis set superposition errors. For this reason, some tentative calculations have been performed using the counterpoise correction procedure[9], which is in principle able to predict the upper limit of such basis set superposition errors. This procedure did not lead to reasonable correction factors, however, probably due to the fact that the upper limit is never reached within our system and that it is difficult to estimate the real contributions for the very different geometrical arrangements in the various glycine/water complexes. For this reason, another procedure to estimate the "real" complexation energies was employed, which is based on a comparison of ab initio calculations on a smaller model system with minimal basis set as well as a near Hartree-Fock limit basis set.

For this comparison we have chosen the water dimer, whose interaction energy at the fixed H-bond distance of 2.75 Å results to be -11.5 kcal/mole. Near Hartree-Fock limit, this energy is calculated to be 3.67 kcal/mole[10], the corresponding hydrogen bond distance being approximately 3 Å. Multiplication of the glycine/water stabilization energies by the factor 0.32 seems to be reasonable therefore, in order to obtain realistic stabilization energies on an absolute scale. Comparison with several previous investigations on basis set effects[11] allows the conclusion, however, that the relative energies series for various conformations is not influenced significantly by the use of minimal basis sets, and that these data can be regarded as reliable, therefore.

Realizing the maximal possible degree of hydration of the glycine zwitterion, use of the most stabilizing water positions leads to the structure illustrated in figure 3, which is in good agreement also with the prediction for the most Prominent water locations of a Monte-Carlo simulation concerning the hydration of this compound[12].

Final CNDO/2 and ab initio calculations have been performed, therefore, for

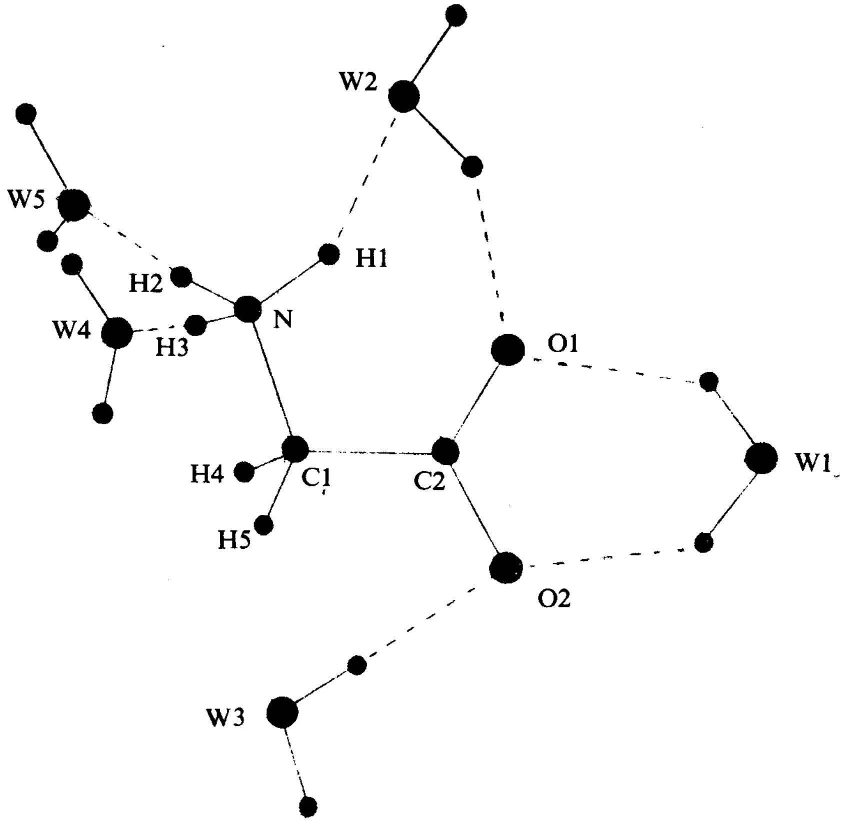

Fig. 3 Resulting model for full first hydration shell of zwitterionic glycine

this structure, including all of the water molecules simultaneously in the computation. This procedure led to total hydration energies of 61.7 kcal/mole within the CNDO/2 framwork and to 89.7 kcal/mole for the ab initio method with the minimal basis set. Applying the aforementioned correction procedure, the over-all first shell hydration energy can be estimated to be 28.7 kcal/mole for the glycine molecule in its zwitterionic form. This is still a very significant amount of stabilization and it has to be assumed, therefore, that the structure as suggested in Figure 3 will be the dominant one in aqueous solution and hence be determining all reactions of glycine in biological systems. In a forthcoming study we will investigate the influence of this hydration shell on conformational changes of the glycine molecule[13].

Finally, some tentative CNDO/2 calculations have been performed in order to investigate the possibility of formation of a second hydration shell. In these calculations, one of the water molecules of the first shell has been linked to further water molecules,

TABLE 1. CALCULATED INTERACTION ENERGIES (KCAL/MOLE) FOR THE WATER/GLYCINE SYSTEM IN VARIOUS GEOMETRICAL ARRANGEMENTS ACCORDING TO FIGURE 2 (E_O = fully optimized CNDO/2 geometry, E_F = with fixed hydrogen bond distances and CNDO/2, E_A = geometries of E_F with ab initio method and minimal basis set)

Position (cf. Fig. 2)	E_O	E_F	E_A
1	-27.1	-10.5	-14.8
2	-30.1	-15.7	-20.3
3	-22.7	-14.7	-17.6
4	-14.9	-11.2	-20.8
5	-14.9	-11.2	-20.8
6	-10.0	-4.5	-5.0
7	-14.3	-9.3	-15.2
8	-13.4	-8.8	-14.2
9	-16.3	-10.1	-9.3

TABLE 2. CALCULATED DIFFERENCES IN ELECTRON DENSITY DISTRIBUTION ON GLYCINE ATOMS DUE TO FIRST SHELL HYDRATION.

		CNDO/2	ab initio
H 1		-0.014	-0.015
H 2	N	-0.025	-0.037
H 3		-0.025	-0.037
H 4	C	-0.001	-0.005
H 5		-0.001	-0.005
N		+0.072	+0.152
C 1		-0.001	-0.038
C 2		-0.013	-0.059
O cis		+0.007	+0.025
O trans		+0.013	+0.024

bonded to the first one by another hydrogen bond. The resulting energies range in the same order as the solvent-solvent interaction itself, indicating that the formation of a well-ordered second hydration shell is unlikely.

In order to describe the influence of hydration on the molecular properties, especially the reactivity of glycine, the hydration induced changes in the electronic density on all atoms have been evaluated by the MULLIKEN population analysis[14]. The qualitative picture (cf. Table 2) is in full agreement for both calculation methods, but the all-electron ab initio method shows more pronounced charge transfers than the CNDO calculations, restricted to valence electrons only.

The most characteristic feature is the polarization of almost all bonds in the molecule, especially in the polar NH_3^+ group. For the intramolecular structure, this should mean a certain contraction of bonds, connected with slightly increased acidity of the NH hydrogens and an increased reactivity, especially in the COO^- region.

Acknowledgement

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บทคัดย่อ

ได้ศึกษาปฏิกิริยาระหว่างกรดอะมิโนไกลซีนกับน้ำ โดยใช้ CNDO/2 method และ ab initio calculation และบรรยายถึงข้อดีและข้อจำกัดของวิธีการทั้งสอง รวมทั้งเสนอ model สำหรับ hydration shell ของไกลซีนด้วย