

## The Influence of Hydration on the Rotational Barriers of Glycine

Prayong B. Doungdee<sup>a</sup>, Sirirat U. Kopkol<sup>a</sup>, and Bernd M. Rode<sup>b, \*</sup>

<sup>a</sup> Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok, Thailand

<sup>b</sup> Institut für Anorganische und Analytische Chemie, Universität Innsbruck, A-6020 Innsbruck, Austria

(Received 23 May 1986. Accepted 11 June 1986)

The influence of a full first hydration shell on the energy barriers related to conformational changes of glycine has been studied by means of molecular orbital calculations. The energy optimized pathway is discussed and compared with that of the isolated molecule, evaluating the possibility of corotation of the hydration shell during conformational changes.

(Keywords: Amino acid; Conformation; Hydration)

### *Der Einfluß der Hydratation auf die Rotationsbarrieren von Glycin*

Es wurde mit Hilfe einer Molekülorbitalrechnung der Einfluß der vollen ersten Hydrathülle auf Rotationsbarrieren bei Konformationsänderungen im Glycinmolekül untersucht. Es wird ein energieoptimierter Rotationsverlauf diskutiert und mit dem des freien Moleküls verglichen, wobei insbesondere die Möglichkeit einer Korotation der Hydrathülle beachtet wird.

### Introduction

Conformational changes of amino acids in aqueous solution are essential for their flexibility in biochemical reactions under physiological conditions. Knowledge of the barriers to internal rotation for the molecules in the gas phase is not sufficient, however, for the discussion of the behaviour in solution, as such molecules interact strongly with the solvent [1], due to the polar zwitterionic form present at physiological *pH* values.

For this reason, inclusion of the first full hydration shell seems to be essential for the discussion of such barriers. The use of computational

chemistry within the supermolecule approach [2] of the general MO concept provides still some information beyond the experimental possibility, as the question, whether the hydration shell is rotated together with the respective part of the amino acid molecule, can be dealt with at molecular level.

For this investigation, the glycine molecule has been taken as an example, which is still economic with respect to required computing times and yet a molecule containing all essential features of an aliphatic amino acid.

### Computational Procedure

As a first step, the orientation of water molecules around the glycine zwitter ion has been optimized, using the semi-empirical CNDO/2 procedure. As this procedure is known to be satisfactory in the treatment of hydrogen bonded systems only if the H-bond distance is kept constant during the calculations [3], an average experimental value of 2.75 Å for this distance was maintained throughout the optimization procedure. The geometrical parameters of glycine and water were taken from the experimental data [4, 5].

Figure 1 illustrates the optimized geometrical arrangements for the glycine zwitterion with one water molecule. Ten local minima for the first shell hydration sites are found but not all of them can be occupied simultaneously. For a prediction of the complete hydration structure, the interaction energies at these sites have been evaluated also by *ab initio* calculations [9] and the most stable hydration structure determined in this way contains five water molecules as indicated in Fig. 2. This optimized structure of the first hydration shell is also in good agreement with previous *Monte-Carlo* studies on the hydration of glycine [6]. For the optimized hydrated glycine, CNDO/2 calculations on the energy barriers to internal rotation concerning both angles relevant for the conformation have been carried out, evaluating the energy surface pointwise ( $\Delta\Phi$ ,  $\Delta\Psi = 5^\circ$  per point). During the conformational changes related to these internal rotations, the possibility of a corotating hydration shell has been studied as well as the case of rotation within statically remaining shell, in order to evaluate the relative energy differences for both options.

All calculations have been performed at the computer center of Chulalongkorn University, using a modified CNDO/2 program in its original parametrization [8].

### Results and Discussion

In agreement with previous investigations on the molecular structure, the CNDO/2 procedure also predicted the conformation  $(\Phi, \Psi) = (0, 0)$ , in

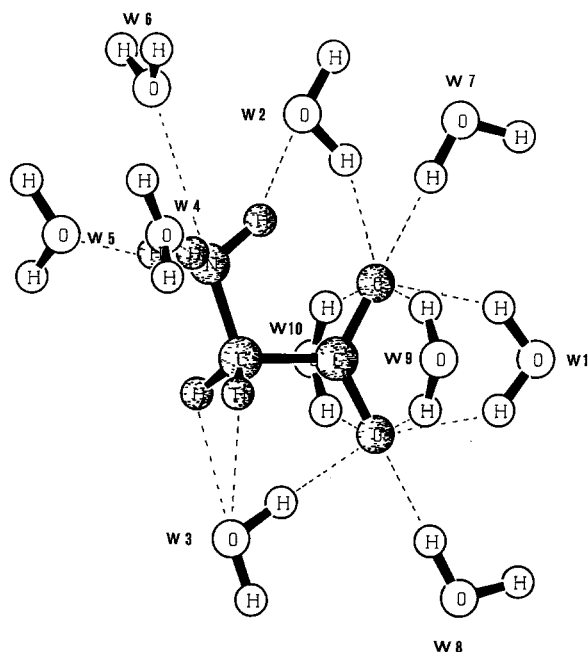
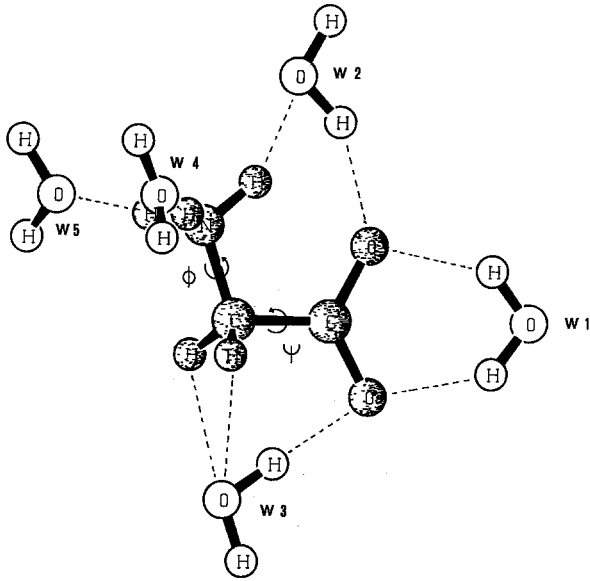


Fig. 1. The ten possible positions of water molecules around glycine zwitterion

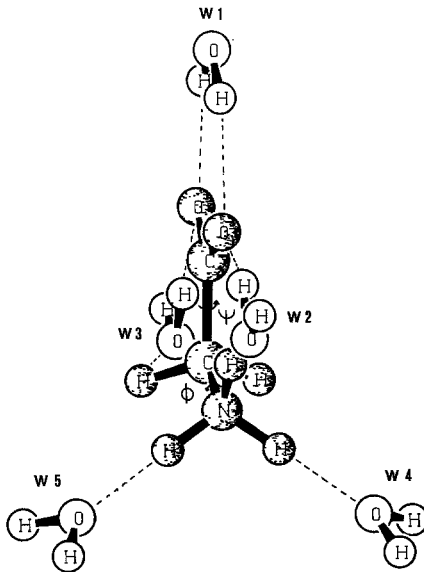
which all heavier atoms and one NH hydrogen are situated in a plane, to be the most stable arrangement. The formation of a first shell hydration sphere does not change the equilibrium structure of glycine. Rotation has been investigated for both angles, starting from the conformation (0,0) up to the conformation (60,90), where the molecule experiences the strongest possible conformational change due to internal rotation.

For the isolated molecule, rotation of angle  $\Phi$  to the conformation (60,0), represents the peak of the barrier, which is still quite low, being 3.3 kcal/mol. Rotation of angle  $\Psi$  from conformation (0,0) to (0,90) leads to a barrier of 10.4 kcal/mol, whereas a rotation of  $\Psi$  starting from (60,00) to (60,90) needs only 5.8 kcal/mol. It is obvious, therefore, that the minimum pathway should consist of two parts, the first one being dominated by a rotation of angle  $\Phi$ , and the second one a subsequent rotation of angle  $\Psi$  leading to the final conformation (60,90), with an overall barrier height of 9.1 kcal. Due to thermal energy within  $kT$  at room temperature, a maximal distortion of the angle  $\Phi$  of  $\pm 15$  degrees can be expected.

It is obvious, that a semiempirical molecular orbital method without full geometry relaxation procedure cannot be expected to be very reliable



A



B

Fig. 2. The glycine zwitterion with 5 water molecules in the first hydration shell, in two different projections (A and B)

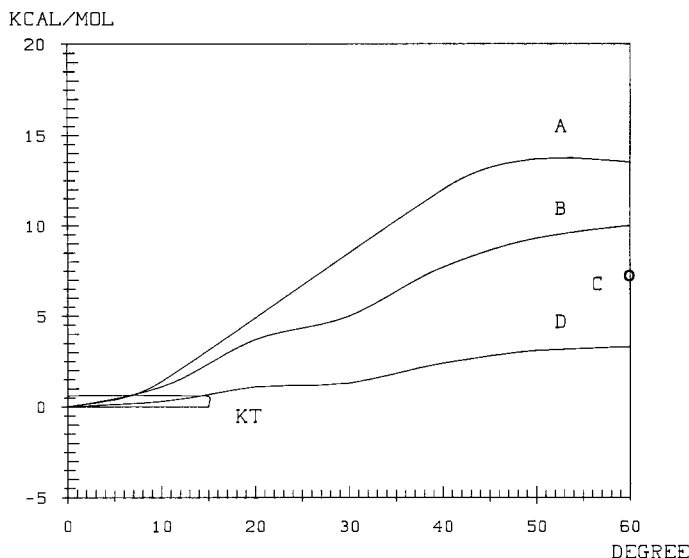


Fig. 3. The rotation pathway of glycine zwitterion including 5 water molecules in the first hydration shell, fixing  $\Psi = 0$ , rotating  $\Phi$  from 0 to 60. *A* Fixing the hydration shell, rotating the  $-\text{NH}_3^+$  group alone. *B* Fixing waters, 1,3, rotating the  $-\text{NH}_3^+$  group and water 2,4,5 around the C—N bond. *C* Energy obtained after rotation of the  $-\text{NH}_3^+$  group and waters 2,4,5 to 60°, and optimizing the hydration shell again. *D* The rotation of glycine zwitterion without hydration shell, fixing  $\Psi = 0$ , rotating  $\Phi$  from 0 to 60

in terms of absolute energies. However, within the same system it can be assumed, that the errors related to the semiempirical framework and to the neglect of further contributions (e.g. correlation energy) remain rather constant, so that the relative scale of energies, which is relevant for our comparison, will be reflected satisfactorily.

After inclusion of the hydration sphere to the glycine zwitter ion, the barrier shapes illustrated in Fig. 3 have been obtained for the rotation of angle  $\Phi$  from conformation (0,0) to (60,0). The different graphs represent the possibilities to rotate the  $\text{NH}_3^+$  group either breaking the bonds of the hydration water or corotating its solvation sphere (graph A and B in Fig. 3 respectively). The respective barrier energies are 13.5 and 10.5 kcal/mol.

As previous semiempirical and *ab initio* investigations [9] have shown, that the binding of the first shell hydration water to the surrounding water molecules does not produce a well-ordered rigid second solvation shell, it has to be assumed, that corotation of the remaining first shell waters, especially of water 2 in Fig. 2 leads to a considerable lowering of the barrier to 6.5 kcal/mol (point C in Fig. 3) so that this relaxation process of the first hydration shell has to be considered essential. Compared to the

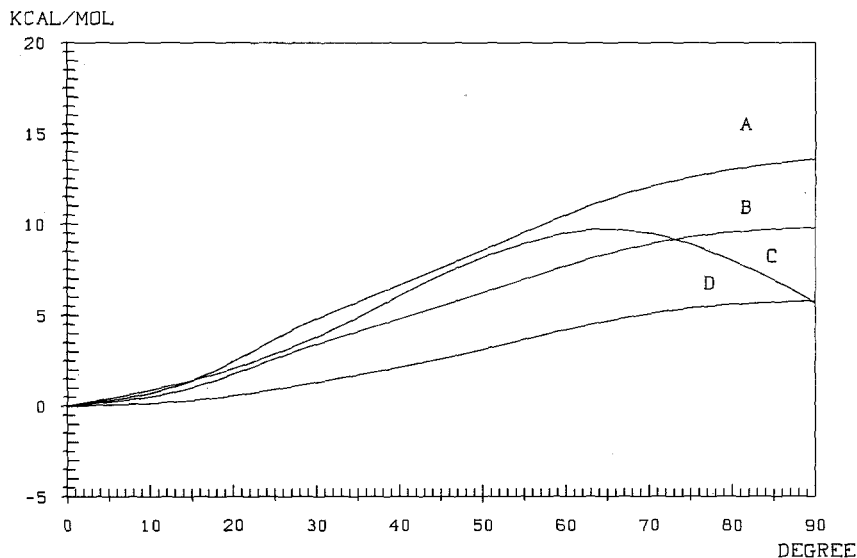


Fig. 4. The rotation pathway of glycine zwitterion including the 5 water molecules in the first hydration shell, fixing  $\Phi = 60$ , rotating  $\Psi$  from 0 to 90. *A* Fixing waters 1,3, rotating  $\text{—COO}^-$  group alone. *B* Fixing water 3, rotating  $\text{—COO}^-$  group and water 1 around the C—C-bond. *C* Rotating  $\text{—COO}^-$  group and waters 1,3. *D* The rotation of glycine zwitterion without hydration shell, fixing  $\Phi = 60$ , rotating  $\Psi$  from 0 to 90

isolated molecule (graph D in Fig. 3), rotation needs more energy for the hydrated molecule, and the vibrational range within  $kT$  becomes smaller ( $\pm 7$  degrees).

The subsequent step of rotation from conformation (60,0) to (60,90) leads to a barrier of 13.6 kcal/mol for rotation of the  $\text{COO}^-$  group within a fixed hydration sphere (graph A in Fig. 4). Corotation of water 1 (graph B in Fig. 4) which is bound to this group symmetrically, lowers the barrier to 9.8 kcal/mol. If again a corotation and relaxation of water 3 is taken into account, no significant lowering of the barrier is obtained, but the shape of the rotational barrier changes remarkably, showing the peak at conformation (60,65) and reaching a value even slightly lower than for the isolated molecule at conformation (60,90) (graph C in Fig. 4). The overall barrier for the complete conformational change of hydrated glycine zwitterion amounts therefore to 16.3 kcal/mol and is reached at conformation (60,65), the full rotation to conformation (60,90), however, differs from the initial state only by 12.2 kcal/mol.

Hydration therefore heightens the barrier by about 80%, but the difference between conformations (0,0) and (60,90) only by about 35%.

This result is of particular interest, as it shows, that hydration does not only influence the individual molecule, but it can also change the relative stabilities of molecular conformation.

This behaviour will be of considerable importance, when conformation dependent reactions are studied in biochemical processes, where the adaptation of the conformation to a receptor molecule is essential in many cases. Theoretical studies on such conformational questions should, therefore, always include consideration of the influence of hydration.

### Acknowledgements

Generous supply of computing time by the computer center of Chulalongkorn University is gratefully acknowledged.

### References

- [1] *Rowe JJM, Hinton J, Rowe KL* (1970) *Chem Rev* 70: 1
- [2] *Hobza P, Zahradnik R* (1980) *Weak intermolecular interactions in chemistry and biology*. Elsevier, p 200
- [3] *Schuster P, Jakubetz W, Beier G, Meyer W, Rode BM* (1974) *Chemical and biochemical reactivity*. In: *Bergmann G, Pullmann B* (eds) *The Jerusalem symposia on quantum chemistry and biochemistry*, vol VI. Jerusalem, pp 257–282
- [4] *Imamura A, Fumita H, Nagata C* (1969) *Bull Chem Soc Jap* 42: 3118
- [5] *Benedict WS, Gailar N, Plykr Eark K* (1956) *J Chem Phys* 24: 1139
- [6] *Clementi E* (1980) *Computational aspects for large chemical systems: lecture notes in chemistry*, vol 19. Springer, Berlin Heidelberg New York, pp 94 ff
- [7] *Pople JA, Segal GA* (1965) *J Chem Phys* 43: 136
- [8] *Pople JA, Santry DP, Segal GA* (1965) *J Chem Phys* 43: 129
- [9] *Doungdee PB, Kopkol SU, Rode BM* (1985) *J Sci Soc Thailand* 11: 113