

# Polarization Effects on Amino-Acid Conformation

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A modified CNDO/2 method was used to calculate the conformational energy surface of zwitterionic glycine in a simulated polarizable environment. While the calculated global minimum for the *in vacuo* glycine zwitterion corresponds to an eclipsed conformation, the allowance of even a small degree of environmental polarisability inverts the relative stabilities of the staggered and eclipsed forms. The results indicate that *in vacuo* models may be unreliable, even for supposedly 'inert' media, and that the significance of environmental polarizability should be considered in the calculation of short-range potentials.

**Key words:** Glycine, Solvation effects, Polarization, Virtual charge model, Short-Range Potentials

## 1. INTRODUCTION

Over the past two decades numerous methods have been developed to account for solvent effects [1-4] which have long been known to play a central role in the structure and function of biological molecules [5]. Nevertheless, *in vacuo* calculations are still commonly pursued in modelling the behaviour of biopolymers [6]. It seems reasonable to wonder whether the interaction between a solute molecule and a postulated inert solvent environment could be sufficiently small that the properties of the solute could be reliably calculated by quantum chemical calculations performed on the isolated *in vacuo* molecule. Clearly, if this approximation is not tenable, doubt is cast on the validity of *in vacuo* calculations, not only by quantum chemical methods, but also by procedures that are based on the representation of intermolecular interactions by simple atom-pair potentials.

In this study we examine a molecule of biological interest, the irreducible element of peptides and proteins - zwitterionic glycine ( ${}^{-}\text{O}_2\text{C}-\text{CH}_2-\text{NH}_3^{+}$ ), for which there is disagreement between the results of experimental measurements made in supposedly 'inert' environments and of quantum chemical calculations on the isolated molecule. Molecular conformations are specified using the torsional angles  $\phi$  and  $\psi$  in accordance with the IUPAC-IUB convention [7]. In the case of glycine  $\psi$  governs the  ${}^{-}\text{O}_2\text{C}-\text{CH}_2$  bond and  $\phi$  the  $\text{CH}_2-\text{NH}_3^{+}$  bond.

## 2. CALCULATION METHOD

Calculations were performed using the CNDO/2 (Complete Neglect of Differential Overlap) method described by Pople and Beveridge [8], and later modified by Constanciel and Tapia [9] to incorporate the VCM (virtual charge model) as a means of modelling solvent effects. CNDO/2 is by definition an approximate method and is not, therefore, quantitatively perfectly accurate. However, for electron-donor-acceptor interactions, particularly for moderately strong intermolecular and intramolecular H-bonds, CNDO/2 is quite reliable [10].

In the VCM [9] a polarizable environment is accounted for by associating with each solute atom A, bearing a partial atomic charge  $Q_A$ , a virtual charge  $Q'_A$  given by

$$Q'_A = -\left(1 - \frac{1}{D}\right)Q_A \quad (1)$$

where the effective dielectric constant  $D$  is related to the bulk dielectric constant by

$$D = \sqrt{\epsilon} \quad (2)$$

The virtual charges polarize the solute and as required interatomic electrostatic interactions are attenuated by a factor of  $1/\epsilon$ . However, the virtual charges polarize the solute, thereby altering the partial atomic charges and consequently the electrostatic interaction energies.

The VCM also includes the Born solvation energy of the partial atomic charges, given by

$$E_{\text{Born}} = -\frac{1}{2}(1 - D^{-2})Q_A^2\gamma_{AA} \quad (3)$$

where  $\gamma_{AA}$  is the one-centre coulombic integral

$$\gamma_{AA} = \int \mu_A(1)\mu_A(1)\frac{1}{r_{12}}v_A(1)v_A(1)d\tau \quad (4)$$

The partial atomic charges are themselves conformationally dependent, resulting in a complex conformational dependence for the total solvation energy. Thus, the action of a solvent on a solute cannot be regarded as simply the attenuation of interatomic electrostatic interactions (including H-bonds) by a dielectric environment.

The VCM considers only bulk or continuum environmental effects and cannot account for specific solvent-solute interactions. However, the method may be usefully applied where either bulk effects dominate the interaction of a molecule with its environment or where one is interested in the bulk component of environmental effects. Our task here is to compare the effect of the bulk dielectric of an 'inert' medium with the results of *in vacuo* calculations, in order to assess the role of the polarizability of the environment, and explain the disagreement between the observed and predicted conformations of zwitterionic glycine.

### 3. ZWITTERIONIC GLYCINE

Microwave studies indicate that glycine does not exist as the zwitterion in the gas phase [11,12]. However, where the angle  $\phi$  has been experimentally determined in the solid phase (in the zwitterion of glycine and related compounds) it is nearly always near  $60^\circ$ , corresponding to the staggered conformation [13]. More specifically, in the case of glycine itself  $\phi$  has been determined by neutron diffraction to be roughly  $60^\circ$  for the  $\alpha$ -crystalline form [14].

Most reliable calculation methods (e.g. *ab initio*, CNDO/2, PCILO) yield similar conformational energy surfaces for zwitterionic glycine *in vacuo*, and predict the protonated amino group ( $-\text{NH}_3^+$ ) to exist in the eclipsed conformation ( $\phi = 0$ ) reflecting a strong intramolecular H-bond. By contrast, methods using empirical functions predict it to adopt the staggered conformation ( $\phi = 60$ ) [13,15].

If the steric energy is similar to that in ethane [16] one would expect the staggered conformation to be favoured by about 12-13 kJ/mole in the absence of a H-bond. An intramolecular H-bond, typically about 21 kJ/mole [10], should favour the eclipsed conformation. Since the quantum chemical methods referred to 'recognise' hydrogen-bonding they predict the eclipsed conformation to be the more stable, with a low energy barrier to internal rotation (usually about 12-13 kJ/mole or less), reflecting a fine balance between electrostatic and non-electrostatic interactions [13]. (All computational procedures, empirical [15] or otherwise, predict  $\psi = 0$  in agreement with experiment [13].)

Clearly some critical factor is being neglected in the calculations;; we now consider the polarizability of an 'inert' environment.

#### 4. RESULTS AND DISCUSSION

In the calculations the crystal lattice is treated as a polarizable continuum and zwitterionic glycine as a 'solute' in a solid 'solvent'. In the absence of experimental data we consider a value of  $D = 2$  ( $\epsilon = 4$ ) as a reasonable one for glycine crystals on the basis of the dielectric constants (at  $17^\circ - 22^\circ$ ) of similar systems; solid urea ( $\epsilon = 3.5$ ), acetic acid ( $\epsilon = 4.1$ ) and acetamide ( $\epsilon = 4.0$ ) [17]. Greenberg et al. [18] used a dielectric step function with  $D = 2$  for distances greater than  $3.5 \text{ \AA}$  which agrees well with the value used here. However, recognising the inexactitude in the concept of dielectric constant at a molecular level, calculations were also performed using a series of  $D$  values.

The CNDO/2 *in vacuo* conformational energy surface for the zwitterion, identified as the total energy of the solute-system, was calculated at  $15^\circ$  resolution using the bond lengths and angles given in [19].

The *in vacuo* global minimum is at ( $\phi = 0, \psi = 0$ ) - the eclipsed conformation in agreement with earlier calculations but in disagreement with experiment. For the condensed phase environment modelled with  $D = 2$  ( $\epsilon = 4.0$ ) the global minimum occurs at ( $\phi = 60, \psi = 0$ ) - the staggered conformation. Clearly even a low dielectric environment, in fact any condensed phase environment whatsoever, is sufficient to reverse the relative stabilities of the eclipsed and staggered forms. In fig. 1 the  $\phi$  dependence of the energy is plotted (at  $\psi = 0$ ) for various values of  $D$  and clearly shows the greater stability of the staggered conformation ( $\phi = 60$ ) at very small  $D$  values. While one expects a H-bond to be destabilized by a polarizable environment it is striking how sensitive the system is.

One can conclude that even the weak dielectric constant ( $\epsilon = 4$ ) of crystalline zwitterionic glycine sufficiently weakens the intramolecular H-bond so that the staggered conformation is adopted in agreement with experiment. Intermolecular interactions in crystals may indeed further stabilize this conformation but our calculations suggest that the polarizable environment is alone sufficient to account for the observed structure.

We note that solvation calculations where the partial atomic charges were held fixed at their *in vacuo* values did not reflect the same environmental sensitivity. Partitioning of the calculated energy showed that electron redistribution within the solute glycine on solvation to be a critical component of the total solvent effect.

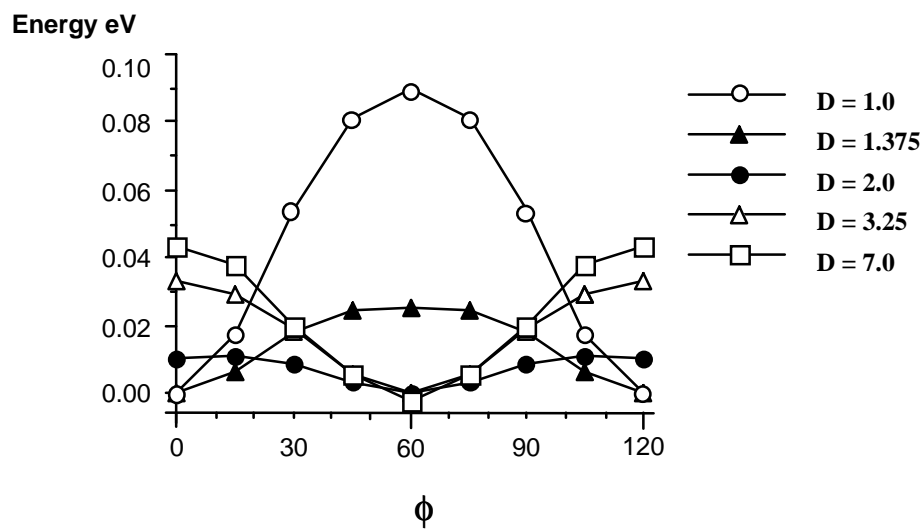
#### 5. CONCLUSION

Atomistic simulations, originally designed for ionic systems, are increasingly being applied to covalent systems. Our calculations suggest that two-, three- and four-body potentials should be based on quantum chemical calculations which explicitly model environmental polarizability. Modelling of the solvent environment in an atomistic simulation by application of a Born-type model on top of *in vacuo* based potentials may not adequately model solvation.

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**Figure 1.** Conformational energy of zwitterionic glycine as a function of  $\phi$  for various dielectric constants,  $D$  ( $\psi = 0$ ).