

# JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Registered in U.S. Patent Office. © Copyright, 1978, by the American Chemical Society

VOLUME 100, NUMBER 14

JULY 5, 1978

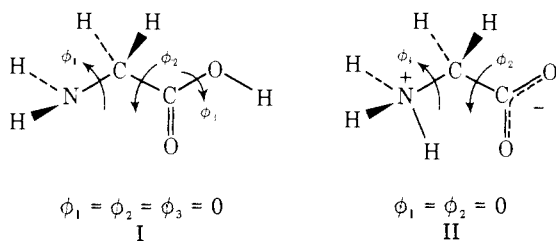
## Ab Initio Studies of the Relative Energetics of Glycine and Its Zwitterion

Y.-C. Tse,<sup>1a</sup> M. D. Newton,\*<sup>1a</sup> S. Vishveshwara,<sup>1b</sup> and J. A. Pople<sup>1b</sup>

Contribution from the Department of Chemistry, Brookhaven National Laboratory, Upton, New York 11973, and the Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213. Received November 17, 1977

**Abstract:** Ab initio molecular orbital calculations using the 4-31G atomic orbital basis set have been carried out for various conformations of the glycine zwitterion. The equilibrium conformation based on standard bond lengths and bond angles is characterized by a planar framework involving an intramolecular NH···O hydrogen bond and lies 29 kcal/mol above the equilibrium conformation for the nonzwitterionic form, implying a hydration energy of ~50 kcal/mol for the gas-phase zwitterion. Examination of the energetics of intramolecular proton transfer indicates that the zwitterionic form is associated with a very shallow local minimum characterized by an elongated NH bond (1.075 Å) and separated from the nonzwitterion by a very small barrier ( $\leq 0.5$  kcal/mol). Thus the gas-phase zwitterion is not expected to have an observable lifetime, and it is not even clear that a vibrational state would exist within the local minimum which defines it.

Glycine in the isolated state (gas phase or matrix)<sup>2</sup> is considered to exist as the nonzwitterionic structure, NH<sub>2</sub>CH<sub>2</sub>COOH, whose conformational energetics have been the subject of a recent detailed study.<sup>3</sup> The conformational angles are defined in structure I.<sup>3</sup> In many condensed phase



environments, however, e.g., the crystalline state<sup>4</sup> or aqueous solution,<sup>5</sup> the molecule adopts a preferred zwitterionic arrangement, NH<sub>3</sub><sup>+</sup>CH<sub>2</sub>COO<sup>-</sup>, whose conformational angles are defined by structure II, analogously to I.<sup>3</sup> Little is known experimentally about the molecular structure of the isolated zwitterion. The conformation of the zwitterions of glycine and other amino acids in the crystal state is generally dominated by *intermolecular* hydrogen bonds,<sup>6</sup> and accordingly ab initio theory offers a useful tool for examining the intrinsic conformational energetics of the free glycine zwitterion as well as its energy relative to that of the nonzwitterion. As noted previously,<sup>2b</sup> this relative energy in conjunction with experimental sublimation and hydration enthalpies for the solid allows one to estimate the hydration enthalpy of the gas-phase zwitterion, which can then be compared with the corresponding hydration enthalpy (~20 kcal/mol) for the nonionic species. A recent semiempirical CNDO/2 calculation<sup>7</sup> yielded a separation of ~100 kcal/mol between glycine and its zwitterion. This dif-

ference is undoubtedly exaggerated since combination of the gas-phase proton affinities of methylamine and the formate anion and the coulombic interaction between the two zwitterionic charge centers over a distance of ~3 Å<sup>8</sup> implies a separation of only ~20 kcal/mol. We may expect the true energy difference to lie somewhere between these extremes.

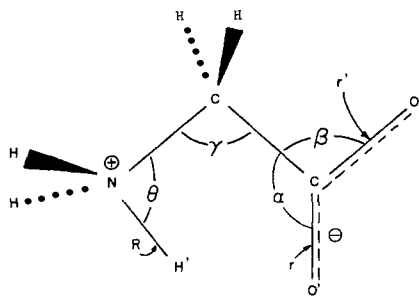
A further question of interest regards the existence of a local minimum for the gas-phase glycine zwitterion and the expected residence lifetime in such a minimum if it exists. Calculations to date<sup>7,9</sup> have constrained the NH<sub>3</sub><sup>+</sup> group to have a normal geometry (tetrahedral angles and NH bond lengths of ~1 Å), and the relative energies discussed above were based upon such an assumed structure.

### Computational Details

In the present report we employ ab initio molecular orbital theory to address the above questions, using the same split valence basis set (4-31G)<sup>10</sup> as in the previous study of glycine<sup>3</sup> and related species.<sup>11</sup> The conformational energetics of the zwitterion are first studied, using standard bond lengths and angles.<sup>12</sup> The relative energies of the equilibrium conformers for glycine and its zwitterion are then discussed and the accuracies estimated by comparison with related species of known energy. Finally, the molecular geometry of the zwitterion is allowed to relax, and a limited search is carried out for the minimum energy zwitterion structure and for the proton transfer pathway to the nonzwitterionic structure. The geometrical parameters which were varied are labeled in Figure 1.

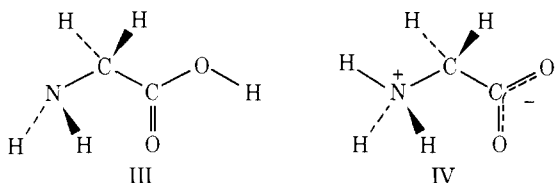
### Results

**A. Relative Energies Based on Standard Geometries.** The minimum energy conformation for the zwitterion is found to



**Figure 1.** Structural diagram of the zwitterion ( $\phi_1 = \phi_2 = 0$ ), displaying geometrical parameters varied in the energy minimization. The HCH and NCC planes are perpendicular, and the bisectors of the HCH and NCC angles are colinear. The HCH angle was kept at  $109.47^\circ$ .

be the  $\phi_1 = \phi_2 = 0^\circ$  structure II, characterized by an intramolecular hydrogen bond between a single NH bond and one of the carboxylate oxygen atoms. This is in contrast to the equilibrium for the nonzwitterion, III,<sup>3</sup> where the  $\phi_1 = 180^\circ$ ,



$\phi_2 = 0^\circ$  conformation has two NH bonds symmetrically hydrogen bonded to the carbonyl oxygen. The energy of the analogous conformation for the zwitterion, structure IV, is 2 kcal/mol above that for structure II. The equilibrium conformers of the zwitterionic and nonzwitterionic isomers are separated by 29 kcal/mol.<sup>13</sup> To assess the accuracy of this calculated energy, we note that the calculated proton affinities of the formate anion and ammonia (or methylamine) are exaggerated by very similar amounts (17 and 15 kcal/mol, respectively), as summarized in Table I. Thus the calculated relative energies of II and III are probably accurate to within a few kilocalories per mole, indicating that the gas-phase zwitterion is separated by  $\sim 1$  eV from the nonionic structure and is not an energetically important species at room temperature, a result consistent with previous expectations.<sup>2</sup> The 29-kcal/mol separation implies a hydration energy of  $\sim 50$  kcal/mol for the gas-phase zwitterion.<sup>2b</sup> This magnitude for the zwitterion hydration enthalpy is perhaps smaller than one might anticipate based on the expected occurrence of strong hydrogen bonds at the  $\text{NH}_3^+$  and  $\text{CO}_2^-$  groups.<sup>17,18</sup> In this regard, we note that in terms of population analysis, the charge separation in glycine is calculated to be appreciably less ( $q = +0.5, +0.2,$  and  $-0.7$  on the  $\text{NH}_3, \text{CH}_2,$  and  $\text{CO}_2$  groups, respectively) than the idealized unit values implied by the  $\text{NH}_3^+\text{CH}_2\text{CO}_2^-$  structure. This attenuation in charge separation combined with the relatively close proximity of the separated charges ( $\sim 3 \text{ \AA}$ ) would help to account for reduced hydrogen-bonded stabilization by the solvent, relative to that for isolated  $\text{NH}_3^+$  and  $\text{CO}_2^-$  groups. The tendency for a zwitterionic  $\text{NH}_3^+$  group to shield a carboxylate oxygen atom and reduce its tendency to act as a proton acceptor has been inferred from high-precision neutron diffraction data.<sup>6</sup>

### B. Geometry of the Zwitterion. 1. Equilibrium Geometry.

With the standard geometry<sup>12</sup> as a starting point, the geometrical parameters in Figure 1 were optimized sequentially in the order  $R, \theta, \alpha, \beta, r, r',$  and  $\gamma$ .<sup>19</sup> In the second cycle, it was not felt necessary to include  $r'$  and  $\gamma$ . The optimal parameters found were  $1.073 \text{ \AA}, 99.3^\circ, 112.0^\circ, 116.3^\circ, 1.27 \text{ \AA}, 1.23,$  and  $106.2^\circ$ , for  $R, \theta, \alpha, \beta, r, r',$  and  $\gamma$ , respectively. A third cycle of variation on the two most important parameters for the excess proton,  $R$  and  $\theta$ , led to virtually no change ( $1.075 \text{ \AA}$  and

**Table I.** Proton Affinities (PA)

Species	PA <sub>calcd</sub> <sup>a</sup>	PA <sub>exptl</sub> <sup>a</sup>	PA <sub>calcd</sub> - PA <sub>exptl</sub> <sup>a</sup>
HCOO <sup>-</sup>	359 <sup>b</sup>	342 <sup>c</sup>	17
NH <sub>3</sub>	222 <sup>d</sup>	207 <sup>c</sup>	15
CH <sub>3</sub> NH <sub>2</sub>	230 <sup>d</sup>	216 <sup>c</sup>	14

<sup>a</sup> kcal/mol. The calculated (4-31G) quantities do not include the zero-point correction, but this should have little effect on the quantities of interest (i.e., the difference between (PA<sub>calcd</sub> - PA<sub>exptl</sub>) for  $\text{CO}_2^-$  and  $\text{NH}_2$ ). <sup>b</sup> Present work, based on experimental geometries (ref 16). <sup>c</sup> Reference 14. <sup>d</sup> Reference 15.

**Table II.** Calculated Equilibrium Geometry for Glycine Zwitterion<sup>a</sup>

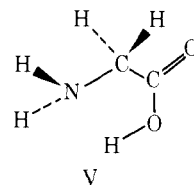
Parameter <sup>b</sup>	Magnitude <sup>c</sup>	Parameter <sup>b</sup>	Magnitude <sup>c</sup>
$R$	1.075 <sup>d</sup>	$r$	1.27
$\theta$	99.3	$r'$	1.23
$\alpha$	112.0	$\gamma$	106.2
$\beta$	116.3		

<sup>a</sup> Parameters not specified were assigned standard values.<sup>12</sup> <sup>b</sup> Defined in Figure 1. <sup>c</sup> Units of  $\text{\AA}$  and degrees for distances and angles, respectively.

$99.5^\circ$ ). The final parameters are summarized in Table II and imply that the zwitterionic structure does correspond to a local potential energy minimum. The NH bond associated with the excess proton is extended by  $0.065 \text{ \AA}$  from the reference value of  $1.01 \text{ \AA}$ ,<sup>12,20</sup> indicative of strong intramolecular hydrogen bonding. The N-H...O distance of  $1.60 \text{ \AA}$  can be compared with typical values of  $\sim 1.8 \text{ \AA}$  observed for intermolecular NH...O distances in crystalline amino acids.<sup>6</sup> Of course, the internal hydrogen bond in the zwitterion departs appreciably from linearity ( $\angle \text{NH}\cdots\text{O} = 130^\circ$ ). The calculated force constant for the NH stretching mode ( $\sim 4 \text{ mdyn/\AA}$ ) indicates the expected weakening of the NH bond; e.g., the force constant for symmetric stretching in  $\text{NH}_4^+$  is  $8.3 \text{ mdyn/\AA}$ .<sup>20</sup>

The equilibrium structure exhibits an N...O distance,  $2.42 \text{ \AA}$ , well within the van der Waals contact distance ( $2.9 \text{ \AA}$ ),<sup>21</sup> reflecting in part the effect of the electrostatic attraction between the two charged moieties.

The significance of the local minimum discussed above is clearly related to the magnitude of the barrier separating the zwitterion from the nonionic structure V. Furthermore it must



be recognized that since this barrier is found to be quite small (see below), more elaborate calculations including larger basis sets and configuration interaction<sup>20</sup> and allowing for the relaxation of all internal coordinates<sup>19</sup> might result in the washing out of this local minimum.

**2. Pathways for Proton Transfer.** To provide an initial estimate of the proton transfer barrier, the proton was moved in a least motion (linear) path from the calculated equilibrium position in the zwitterion to that corresponding to the nonzwitterionic species (structure V) with standard HOC geometry ( $r_{\text{OH}} = 0.96 \text{ \AA}$  and  $\angle \text{HOC} = 109.47^\circ$ ).<sup>23</sup> The framework geometry was frozen at the equilibrium configuration for the zwitterion. A barrier of  $2.0 \text{ kcal/mol}$  was obtained at an NH distance of  $1.25 \text{ \AA}$ . However, maintaining  $r_{\text{NH}}$  at  $1.25 \text{ \AA}$  and relaxing other geometrical parameters caused

the total energy to drop *below* that for the calculated equilibrium zwitterionic structure. Shorter NH distances (from 1.12 to 1.21 Å) were then considered, with  $\theta$ ,  $r$ , and  $\alpha$  being optimized for each point. This procedure yielded a very small barrier ( $\sim 0.5$  kcal/mol) at an NH distance of 1.18 Å ( $H\cdots O = 1.41$  Å). The calculations thus indicate that the gas-phase zwitterion most likely corresponds at best to a very shallow potential energy minimum with respect to proton transfer, and its expected lifetime would be of the order of a vibrational time scale ( $10^{-14}$ – $10^{-13}$  s) at most.<sup>24</sup> In view of the shallowness of the barrier it is not even clear that a vibrational state would be contained within the local minimum which defines the zwitterion.

**Acknowledgments.** This research was carried out in part at Brookhaven National Laboratory under contract with the U.S. Department of Energy and supported by its Division of Basic Energy Sciences. Support was also provided by NSF grant CHE 75-09808 (J.A.P.).

## References and Notes

- (1) (a) Brookhaven National Laboratory; (b) Carnegie-Mellon University.
- (2) (a) G. Junk and H. Svec, *J. Am. Chem. Soc.*, **85**, 839 (1963); (b) J. S. Gaffney, R. C. Pierce, and L. Friedman, *ibid.*, **99**, 4293 (1977); (c) Y. Grenie, J.-C. Lassegues, and C. Garrigou-Lagrange, *J. Chem. Phys.*, **53**, 2980 (1970).
- (3) S. Vishveshwara and J. A. Pople, *J. Am. Chem. Soc.*, **99**, 2422 (1977).
- (4) P.-G. Jönsson and Å Kvik, *Acta Crystallogr., Sect. B*, **28**, 1827 (1972).
- (5) W. Hüchel, "Theoretical Principles of Organic Chemistry", Vol. II, Elsevier, New York, N.Y., 1958, pp 150–157.
- (6) T. F. Koetzle and M. S. Lehmann, "The Hydrogen Bond", P. Schuster, G. Zundel, and C. Sandorfy, Ed., North-Holland Publishing Co., New York, N.Y., 1976, Chapter 9.
- (7) W. R. Oegerle and J. R. Sabin, *J. Mol. Struct.*, **15**, 131 (1973).
- (8) The nitrogen atom and the closest oxygen atom in II are separated by  $\sim 2.7$  Å. The centroid of the three ammonium protons and that of the carboxylate oxygens are separated by  $\sim 3.2$  Å.
- (9) J. A. Ryan and J. L. Whitten, *J. Am. Chem. Soc.*, **94**, 2396 (1972).
- (10) (a) R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.*, **54**, 724 (1971). (b) The reliability of the 4-31G basis has been discussed in ref 3 and 11 and in work cited therein.
- (11) M. D. Newton and G. A. Jeffrey, *J. Am. Chem. Soc.*, **99**, 2413 (1977).
- (12) J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, **89**, 4253 (1967). The partial CO double bonds in the carboxylate were assigned a distance of 1.25 Å.
- (13) The total energies (4-31G) for the equilibrium conformations are  $-282.40077$  and  $-282.35424$  au for glycine and its zwitterion, respectively.
- (14) J. L. Beauchamp, "Interactions between Ions and Molecules", P. Ausloos, Ed., Plenum Press, New York, N.Y., 1975.
- (15) H. Umeiyama and K. Morokuma, *J. Am. Chem. Soc.*, **98**, 4400 (1976).
- (16) (a) G. H. Kwei and R. F. Curl, Jr., *J. Chem. Phys.*, **32**, 1592 (1960); (b) *Chem. Soc. Spec. Publ.*, No. 11, M 107 (1958).
- (17) (a) J. D. Payzant, A. J. Cunningham, and P. Kebarle, *Can. J. Chem.*, **51**, 3242 (1973); M. Meot-Ner and F. H. Field, *J. Am. Chem. Soc.*, **96**, 3168 (1974).
- (18) (a) A. Pullman and B. Pullman, *Q. Rev. Biophys.*, **7** (4), 505 (1975); (b) A. Pullman and A.-M. Armbruster, *Chem. Phys. Lett.*, **36**, 558 (1975).
- (19) The remaining internal coordinates (CC, CN, CH, NH bond lengths, and HNC, HNH, HCC, and HCH bond angles) were not expected to depart significantly from the standard values<sup>12</sup> which they were assigned throughout the variations reported for the coordinates of primary interest.
- (20) W. A. Lathan, W. J. Hehre, L. A. Curtiss, and J. A. Pople, *J. Am. Chem. Soc.*, **93**, 6377 (1971).
- (21) L. Pauling, "The Nature of the Chemical Bond", Cornell University Press, Ithaca, N.Y., 1960, p 257.
- (22) For the effect of electron correlation on barriers to proton transfer see, for example, A. Støgård, A. Strich, J. Almlöf, and B. Roos, *Chem. Phys.*, **8**, 405.
- (23) This path does not lead to the lowest energy (structure III) isomer of glycine, but this is not significant since the exothermicity of the intramolecular proton transfer reaction far exceeds the barriers<sup>3</sup> separating the nonzwitterionic isomers.
- (24) For examples of lifetimes of species with small ( $< 5$  kcal/mol) asymmetric barriers, based on model calculations, see M. C. Flanigan and J. R. de la Vega, *J. Chem. Phys.*, **61**, 1882 (1974).

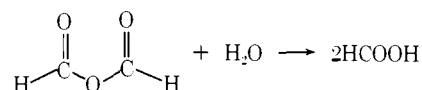
## Theoretical Calculations of the Hydrolysis Energies of Some "High-Energy" Molecules. 2. A Survey of Some Biologically Important Hydrolytic Reactions

David M. Hayes,<sup>1a</sup> George L. Kenyon,<sup>1b-d</sup> and Peter A. Kollman\*<sup>1b,e</sup>

Contribution from the Department of Pharmaceutical Chemistry, School of Pharmacy, and the Department of Biochemistry and Biophysics, School of Medicine, University of California, San Francisco, California 94143, and the Department of Chemistry, Union College, Schenectady, New York 12308. Received October 7, 1977

**Abstract:** We present ab initio calculations on most of the major classes of hydrolytic reactions of high-energy molecules of importance in biological processes. Although intramolecular (opposing resonance and electrostatic) effects play an important role in determining the energy of hydrolysis in some of these reactions, it is concluded that in those hydrolyses of most importance in energy storage and transduction ( $ATP \rightarrow ADP + \text{orthophosphate}$  and  $\text{phosphocreatine} + ADP \rightarrow \text{creatine} + ATP$ ), relative solvation energies of reactants and products are by far the most important factors in determining these energies. We applied simple reaction field equations to estimate solvation energies. By doing so, we are able to reproduce the fact that phosphoguanidinium and pyrophosphate ions have similar free energies of hydrolysis in  $H_2O$ , despite the huge calculated difference between the corresponding energies of hydrolysis in the gas phase.

Biologically important compounds with large negative free energies of hydrolysis at physiological pH have been described as "high-energy" compounds. Because of their importance in processes fundamental to the maintenance of life, these compounds have received much attention from both experimentalists and theoreticians. One of the first to consider these reactions from a theoretical viewpoint was Kalckar,<sup>2</sup> who suggested that "opposing resonance" played an important role in the large negative free energy of hydrolysis of high-energy compounds. For example, in the hydrolytic reaction



there are three important resonance structures for the anhydride reactant,

