complicated by the presence of groups other than hydrocarbons in the guest molecules. Small changes in the geometry or polarity of hydrocarbon derivatives can greatly change the energy and free energy of cyclodextrin inclusion complexes;[1–5] therefore, additional studies like the present one will be needed to determine the role of the hydrocarbon moiety in stabilizing these adducts. The vapor pressure method is practically the only technique capable of yielding reliable thermodynamic results for complexes of the slightly soluble hydrocarbons.

Acknowledgment. The research described here was supported by the National Science Foundation (Grant CHE-8103084). The authors would like to thank Professor Richard Taylor for many helpful discussions and for providing samples of the cyclodextrins.

Registry No. α-Cyclodextrin benzene complex (1:1), 30915-12-9; α-cyclodextrin benzene complex (2:1), 88945-47-5; α-cyclodextrin benzene complex (1:2), 88932-63-2; β-cyclodextrin benzene complex (1:1), 88932-64-3; β-cyclodextrin benzene complex (2:1), 88932-65-4; γ-cyclodextrin benzene complex (1:1), 88932-66-5.

Conformational Energy of Glycine in Aqueous Solutions and Relative Stability of the Zwitterionic and Neutral Forms. An ab Initio Study

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Received July 6, 1983

Abstract: A recently developed method permits one to evaluate with ab initio LCAO–MO–SCF procedures the free energy and the enthalpy of solution of molecular species as well as the change in energy arising from changes in molecular structure and conformation. The method is here applied to study the conformational surface of the two forms of glycine, NT and ZW, with the STO-3G and 4-31G basis sets. The influence of the basis set and other computational parameters on the conformational surface is systematically examined in order to assess the reliability of the results. The differences in energy (internal energy, free energy, enthalpy) between NT and ZW in vacuo as well as in solution are also determined. The ΔH value for the passage $NT_{gas} \rightarrow ZW_{sol}$ is equal to −19.5 kcal/mol at 298 K, while the experimental value is −19.2 kcal/mol. An analysis of the whole energy cycle involving both forms of glycine indicates that the aforementioned good agreement between experimental and computed values takes advantage of some compensation of errors but that the magnitude of these errors could be greatly reduced within the context of the present computational method.

1. Introduction

A procedure recently elaborated in our group[1,2] makes possible, with a reasonable computational effort, the ab initio evaluation of physicochemical properties of solutes in dilute solutions. The basic procedure may be adapted to several specific problems, a part of which has been considered in previous papers (solvent shift of electronic spectra,[2,3] changes in the free energy of solutions produced by light absorption or emission,[4] solvent effect on chemical reaction energy profile and mechanism[5]). We shall consider here the application of this method to the evaluation of conformational energies of solutes. As a test case, we have chosen the aqueous solution of glycine. This molecule can be found in a zwitterionic form (ZW), stable in solution and in crystals, and in a neutral form (NT) which is stable in the gas phase. Consequently, the investigation will be extended to the evaluation of the relative stability of these two forms. Some attention will be paid to the assessment of the computational procedure, and an appropriate analysis of the degree of confidence of the results having a direct physicochemical interest will be done.

Glycine, being one of the simplest molecules of biochemical interest, has been the object of numerous theoretical investigations. We dispense with a rather long list of papers which should include in vacuo calculations performed at different levels of accuracy as well as calculations involving also the solvent, the references more pertinent to the discussion being quoted at the appropriate places. A few years ago we published a comparison of conformational maps of ZW and NT glycine obtained with empirical, semiempirical, and ab initio procedures[6] (hereafter called paper 1). In most calculations reported in this paper, we have employed the same set of computational parameters as in the ab initio SCF STO-3G computations of paper 1 (internal geometry, basis set, selections of points in the conformational space, fitting procedure, ecc.) to make an immediate comparison of the two sets of results. Actually, the only difference is due to the introduction in the molecular hamiltonian of a one-electron operator taking into account the interaction of the solvent. Extension of the basis set and changes in internal geometry will be also considered in order to shed more light on the dependence of the results on these parameters.

2. Outline of the Computational Method

The basic documentation of the method has been done in a preceding paper[1] to which reference is made for a more detailed description. The solvent is represented by a continuous dielectric with a cavity accurately modeled on the solute; in conformational calculations the shape of the cavity will depend on the considered conformation. The electrostatic solute–solvent interaction is represented by an operator $\hat{V}_\sigma(r)$ added to the Hamiltonian $\hat{H}_M{}^0$ of the solute M in vacuo

$$\hat{H}_M = \hat{H}_M{}^0 + \hat{V}_\sigma \tag{1}$$

[†] Istituto di Chimica Quantistica ed Energetica Molecolare.

[‡] Istituto di Chimica Fisica.

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Table I. Minimum Energy Conformation and Rotational Barriers[a] for the ZW Form of Glycine

		min energy conf	φ rotation		ψ rotation	
			conf	barrier	conf	barrier
in vacuo	STO-3G	(0,0)	(60,0)	6.7	(60,90)	12.1
in water	STO-3G	(0,0)	(60,0)	1.97	(60,90)	4.4
in water[b]	STO-3G	(0,0)	(60,0)	3.6	(60,90)	7.4
in vacuo[c]	STO-3G	(0,0)	(60,0)	5.8	(60,90)	11.1
in water[c]	STO-3G	(0,0)	(60,0)	1.6	(60,90)	4.0
in vacuo	4-31G	(0,0)	(60,0)	2.5	(60,90)	12.0
in water	4-31G	(60,0)	(0,0)	0.7	(60,90)	5.4

[a] In kcal/mol. [b] Values obtained with cavity radii = $1.2R_{\mathrm{vdW}}$. [c] Values obtained with standard geometry.

The potential V_σ corresponds to mutual solute–solvent polarization effects, a part of which is given by the well-known solvent reaction field. The actual definition of $\hat{V}_\sigma$ derives from the evaluation of an apparent charge distribution $\sigma(\boldsymbol{s})$ on the cavity surface. $\sigma(\boldsymbol{s})$ is related to the normal component, at point $\boldsymbol{s}$ of the surface, of the total potential gradient

$$\sigma(\boldsymbol{s}) = \frac{\epsilon - 1}{4\pi\epsilon}\left(\frac{\partial V_{\mathrm{tot}}}{\partial \boldsymbol{n}}\right)_{s-} \tag{2}$$

and depends on the electrostatic potential arising both from the polarized total charge distribution ρ_{M}' of the solute and from the σ distribution itself ($V_{\mathrm{tot}} = V_{\rho'} + V_\sigma$). An iterative calculation of σ, using the Hamiltonian defined in (1), is thus necessary.

Numerical computations are performed by approximating $\sigma(\boldsymbol{s})$ with a suitable number of point charges q_{Ki} placed at the center $\boldsymbol{s}_{Ki}$ of tesseral portions ΔS_{Ki} of a cavity defined in terms of a set of interlocking spheres K. The operator $\hat{V}_\sigma$ assumes thus the following approximate form

$$V_\sigma(\boldsymbol{r}) = \int_\Sigma \frac{\sigma(\boldsymbol{s})}{|\boldsymbol{r} - \boldsymbol{s}|}\,\mathrm{d}s \simeq \sum_K\sum_i \frac{q_{Ki}}{|\boldsymbol{r} - \boldsymbol{s}|}(\Delta S_{Ki})^{-1} \tag{3}$$

At the end of this iterative calculation, separately performed for every conformation of M, the program gives as main output the solvent perturbed wave function of M and the corresponding expectation value of $\hat{H}_{\mathrm{M}}$

$$E' = \langle\psi'|H_{\mathrm{M}}|\psi'\rangle \tag{4}$$

calculated here in the SCF approximation.

The energetic quantity of primary interest is

$$F = E' - \frac{1}{2}\int V_\sigma \rho_{\mathrm{M}}'\,\mathrm{d}\boldsymbol{r} \tag{5}$$

which has the status of a free energy.[4]

It is convenient to make reference to free energy changes, and the conformational maps displayed in the following section regard changes in free energy with respect to one suitably selected conformation.

Also, it is convenient in some cases to use as reference a standard composed by a mole of gaseous M plus the dielectric without the solute. In such a case we may define an electrostatic contribution to the solution ΔF as

$$\Delta F_{\mathrm{sol}} = -P\Delta V + F - E^0 \simeq -RT + F - E^0 \tag{6}$$

where $E^0 = \langle\psi^0|H_{\mathrm{M}}{}^0|\psi^0\rangle$ is the expectation value of the energy for gaseous M. The conformational maps reported in the following section also include a contribution corresponding to the work spent for the formation of the appropriate cavity in the solvent. The formulas given by Pierotti[7] have been employed.

An evaluation of ΔH_{sol} at the same level of approximation may be obtained by adapting to the present computational scheme the numerical algorithm suggested by Miertuš and Tomasi[8] and tested in that paper for the classical electrostatic case. From the thermodynamic relation

$$\Delta H = \Delta F - T\left(\frac{\partial}{\partial T}\Delta F\right)_P \tag{7}$$

and assuming that the temperature dependence of ΔF is given only by changes with temperature of the dielectric constant ϵ and of the volume v of the cavity we may derive

$$\Delta H_{\mathrm{sol}} = \Delta F_{\mathrm{sol}} - T\left(\frac{\partial}{\partial v}\Delta F_{\mathrm{sol}}\right)_p \frac{\mathrm{d}v}{\mathrm{d}T} - T\left(\frac{\partial}{\partial \epsilon}\Delta F_{\mathrm{sol}}\right)_p \frac{\mathrm{d}\epsilon}{\mathrm{d}T} \tag{8}$$

The derivatives of ΔF_{sol} are obtained numerically, by repeating the calculations of F for $\epsilon \pm \Delta\epsilon$ and for $R_K \pm \Delta R$ (R_K: cavity radii). The other derivatives of eq 8 are taken from experimental data concerning water at 298 K. With respect to the version of the computational scheme given in ref 8 we have here added improved computer routines to save computational time and a more precise estimate of the cavity volume, by exploiting the relation[9]

$$v = \int_\Sigma \frac{1}{3}\boldsymbol{r}\cdot\boldsymbol{n}\,\mathrm{d}s \simeq \frac{1}{3}\sum_K\sum_i \boldsymbol{s}_{Ki}\cdot\boldsymbol{n}_{Ki}\Delta S_{Ki} \tag{9}$$

with numerical values already used in the main calculation. It must be stressed that ΔF_{sol} and ΔH_{sol} only refer to the electrostatic components. A more detailed analysis, which introduces these electrostatic contributions in a model statistical partition function of the solution (including also translational, rotational, vibrational, and dispersion contributions to ΔF) has been published elsewhere.[10] For comparison with thermodynamical data attention should be also paid to the definition of standards and to the entropic contributions due to our choice of a solute fixed at a given position in the laboratory frame.[11]

3. Conformational Results

3.1. Internal Rotations of the Zwitterion Form (ZW). As in paper 1, we neglect here changes in the internal geometrical parameters on the whole conformational space. Each conformation is identified by the value of the rotation angles $\varphi = \mathrm{C'C_\alpha NH'}$ and $\psi = \mathrm{OC'C_\alpha N}$, and it will be denoted as (φ,ψ). For the reader's convenience we report in Figure 1 the nuclear skeleton in the starting (0,0) conformation, as well as the internal geometrical parameters.

In Figure 2 the conformational map obtained with the STO-3G basis is shown (compare with Figure 1 of part 1). The effect of the solvent in lowering the barriers is evident (see also Table I of the present paper). Planar structures ($\psi = 0$) are preferred both in vacuo and in solution, because electrostatic interactions between the $\mathrm{NH_3}^{+\delta}$ and $\mathrm{CO_2}^{-\delta}$ groups favor this spatial arrangement. The position of the minimum on the φ coordinate is the result of a balance between the opposite influence of two factors, namely the electrostatic interaction between NH and a O lone pair (favoring $\varphi = 0°$) and the repulsion between N and

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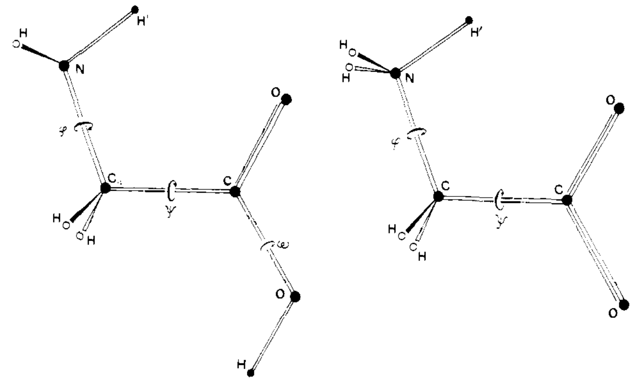

Figure 1. Molecular skeleton and reference conformation for the zwitterionic (ZW) and neutral (NT) form of glycine. For the rotational angles φ = $C'C_\alpha NH$, ψ = $OC'C_\alpha N$, and ω = $HOC'C_\alpha$, the usual convention for the sign has been adopted, namely for an angle τ = ABCD the rotation is positive if the bond CD, viewed from B toward C, rotates clockwise. The internal parameters are: C–C': 1.52 Å, C'–O: 1.27 (1.24); C'–O'':1.27 (1.43); C–N 1.47, C–H 1.09; N–H: 1.03; O–H:(0.97) $C_\alpha C'O$: 119° (120°); OC'O: 122° (120°); C'OH (120°); the other angles are tetrahedral. Values in parentheses refer to the NT form.

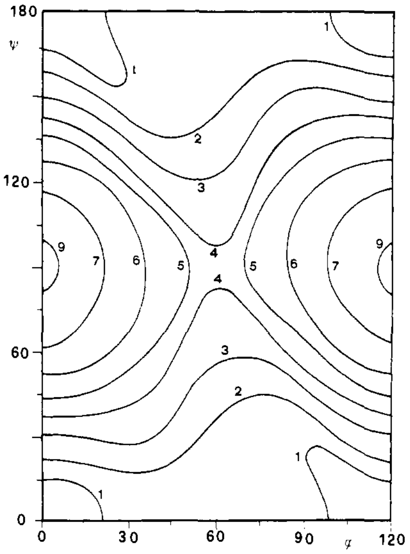

Figure 2. Internal rotation potential map for the ZW form of glycine in water obtained with the STO-3G basis. The curves are given in kcal/mol. Note that the surface near the (60,0) conformation is very flat.

C_α hydrogen atoms (favoring φ = 60°). We recall that calculations available in the literature may be divided into two sets, the first giving (0,0) and the second (60,0) as the most stable conformation (see paper 1 for a discussion on this point).

The numerical results obviously depend to some extent on the parameters employed in the calculations. We shall give concise information about the influence of different choices of: (a) the number of steps in the iterative calculations of $\hat{V}_\sigma$ and E', (b) the shape of the cavity, (c) the internal geometry of the solute, and (d) the basis set.

The influence of other parameters specific of this method, namely the number and the disposition of tesserae in which the cavity surface has been partitioned, have been examined with sufficient details in preceding papers (see, e.g., ref 1). Tesserae with angular increments $\Delta\theta = \Delta\varphi$ = 22.5° are sufficient to give results independent of the disposition of the tesserae and sufficiently close to the asymptotic value corresponding to a very large number of tesserae. Cavitation energy terms, for which other formulas are available, contribute unimportantly to the conformational surface: the largest difference in the conformational space is in fact 0.06 kcal/mol.

(a) Convergence in the Iterative Determination of V_σ. To estimate the convergence rate of the process which determine σ and V_σ we report in Table II the value of E^0 and the values of F obtained at three successive steps of this process for some selected ZW conformations. In the same table we report also the results referring to the 4-31G basis. The convergence in the evaluation of the solute polarization may be appreciated by inspecting the values of the dipole moment given in the same table. In all cases stable values are reached in a few steps. The results reported in the main tables and figures refer to the third step of this computational cycle. It is worth noticing, for future applications to larger solutes, that calculations at the first step reproduce with fair accuracy the main features of the conformational surfaces (errors of the order of 0.1–0.2 kcal/mol).

Table II. Tests on the Convergence Rate in the Iterative Calculation of Solvent Effects[a,b]

	STO-3G		4-31G	
	ΔF_{sol}	μ	ΔF_{sol}	μ
ZW(0,0)				
in vacuo		11.97		13.13
I step	−50.5	13.49	−46.0	15.08
II step	−56.5	13.69	−53.2	15.42
III step	−57.3	13.72	−54.4	15.48
ZW(60,0)				
in vacuo		12.34		13.34
I step	−55.4	13.77	−49.2	15.25
II step	−61.3	13.95	−56.5	15.62
III step	−62.0	13.98	−57.7	15.62
ZW(60,90)				
in vacuo		12.41		13.48
I step	−58.2	13.80	−52.9	15.36
II step	−64.4	13.95	−60.6	15.64
III step	−65.0	13.97	−61.8	15.68

[a] ΔF in kcal/mol, μ in debyes. [b] The E^0 values are: STO-3G (0,0) = −278.96062, (60,0) = −278.94996, (60,90) = −278.94128; 4-31G (0,0) = −282.34758, (60,0) = −282.34356, (60,90) = −282.32844.

(b) Shape of the Cavity. The definition of a suitable cavity in the dielectric simulating the actual solvent presents several problems. For a thorough analysis of the general problems related to the definition of a cavity in a medium actually composed by molecules with finite size, reference is made to a recent paper by Blaive and Metzger.[12] This is not the appropriate place to discuss again this aspect of the problem, which could, however, have some influence on actual utilizations, and we shall limit ourselves to more practical aspects of the question.

It has been shown in ref 1 that the size of the cavity has a noticeable effect on the absolute value of E'. Several tests, performed on the occasion of preceding investigations, indicated that a fairly satisfactory choice of the cavity is given by spheres centered on the solute nuclei (or on the central nucleus of small groups such as CH_3, CH_2, etc.) with radii equal to 1.2 times the van der Waals values ($R_K = 1.2R_{vdW}$). In the case of ZW the presence of localized electric charges on the anionic and cationic heads makes this choice questionable. We have so performed a set of intermolecular distance optimizations for $M{\cdot}H_2O$ complexes with the STO-3G and 4-31G bases for different configurations and conformations of the complex (for a definition of these two terms in the present context, see Alagona et al.[13]). As solutes M we have selected the couples NH_3–NH_4^+, CH_3NH_2–$CH_3NH_3^+$, HCOOH–$HCOO^-$, CH_3COOH–CH_3COO^-, and NH_2CH_2COOH–$NH_3^+CH_2COO^-$. By comparing the optimum H_2O–M distance in all the parallel calculations performed for these couples we have derived as an empirical rule that in ZW the cavity radii should be reduced by 0.4 Å for the NH_3 and O spheres ($R_K = 1.2R_{vdW} - 0.4$) while the original value ($R_K = 1.2R_{vdW}$) should kept unaltered for the $C_\alpha H_2$ and C' spheres. It may be worth stressing that this empirical rule is in fair agreement with the results of Monte Carlo calculations performed by Romano and Clementi on aqueous solutions of glycine[14] on the basis of pre-

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viously determined ZW–H_2O interaction potential.[15]

A change of this type has a sizeable effect on the surface: we have reported in Table I the barriers obtained with the original radii; the whole surface has deviations of the same order but maintains a similar shape. The difference in the ΔF_{sol} values is quite remarkable; for example, $\Delta F_{sol}(0,0)$ passes from −57.3 kcal/mol to −36.2 kcal/mol if the $1{,}2R_{vdW}$ values are adopted. This influence of the cavity size on ΔF_{sol} values will be considered again in a following section regarding the relative stability of NT and ZW forms in solution.

Other choices of the cavity shape seem to us not satisfactory. There are in fact internal tests concerning the σ charge distribution which indicate that the present choice is preferable. We have tried cavities composed by a single sphere and cavities in which the whole anionic head is represented by one sphere. We do not consider it necessary to detail here the results obtained with such unsatisfactory cavities.

(c) Internal Geometry of the Solute. A very limited number of investigations on the effect of solvent on the internal geometry of the solute have been thus far performed with the present method. However, some information may be deduced from ref 5: the influence of a solvent with high dielectric constant (ϵ = 80) on organic solutes is small even if the solute has a relatively high permanent dipole (e.g., H_2CO and H_3COLi). On the contrary, the effect is large for solutes in which the heterolytic bond disruption is easy.

In ZW the solvent could presumably induce a different separation of the two charged heads. A limited surface scan performed with the present method (minimization of F) indicates a tendency toward larger values of the $NC_\alpha C'$ angle and of the NC_α and $C_\alpha C'$ distances. We have, however, limited ourselves to a very rough exploration without any serious attempt to optimize geometry in solution.

The most accurate geometry optimization of ZW in vacuo has been performed, to the best of our knowledge, by Tse et al.[16] for the (0,0) conformation at the SCF level with the 4-31G basis. STO-3G calculations with this geometry give an improvement of the in vacuo energy ΔE^0 = −29.1 kcal/mol, and a lowering of F of 11.9 kcal/mol.

Calculations of conformational maps using this geometry have little sense, because the largest deviations of internal parameters with respect to the standard ones are due to the intramolecular H bonding between N–H and O at the (0,0) conformation. It is well-known that rotational surfaces are better reproduced if one introduces the rigid rotor approximation with respect to the use of internal geometrical parameters determined at one particular geometry where specific intramolecular interactions are present. The other possible choice is of course an optimization of geometry performed at each rotational angle.

To give an idea of the effect of the change of some structural parameters we report in Table I the barriers obtained with the standard geometry (and a distance R–O = 1.25 Å in the partial carboxylate double bond, as suggested by Pople's group[16,17]).

(d) Influence of the Basis Set. In the large variety of atomic bases available today, we have decided to select for this comparison only one, namely the 4-31G one. The "defects" of this basis are well-known, and particularly disturbing will be in the present case the tendency of this basis to give too large dipole moments, and presumably a too large value of the solvent reaction field. More reliable bases are, however, out of the question because they involved a computational effort not necessary at the present stage of the research and excessive for our budget. The 4-31G basis being one of the more exploited bases, its limits are better known than for alternative bases of analogous dimensions, and so we have to consider it expedient to use it. Some results obtained with other bases will be reported in a following section.

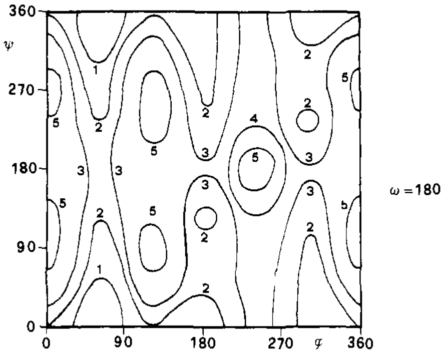

Figure 3. Internal rotation potential map for the NT form of glycine in water (STO-3G basis). The map refers to conformations having ω = 180°.

The change of conformational energy of ZW in vacuo due to changes in the basis set has been already discussed in paper 1. The 4-31G surface is flatter than the STO-3G (while for neutral analogous compounds the opposite trend is more frequent); the enlargment of the basis set produces a change in the φ barrier from 6.7 to 2.5 kcal/mol and in the ψ barrier from 12.1 to 4.4. (Little is known about the effect of changes in the internal geometry on the in vacuo conformational surface of ZW).

In solution, the results may also depend on the ability of a given basis to describe on the one hand the solute charge distribution (and of consequence the electric field produced by M on the cavity) and on the other hand the polarization of M induced by the solvent.

In the ZW the overestimation of μ given by the 4-31G basis is lesser than in analogous neutral compounds, probably because this molecule has two charged heads. In fact, the dipole moment in vacuo passes from 11.97 D (STO-3G) to 13.13 D (4-31G) and to 13.85 D (6-31G).[18] Mulliken population analysis and molecular electrostatic maps (not reported here for the sake of brevity) reinforce this impression.

The greater flexibility of the 4-31G basis in reproducing polarization effects may be estimated by looking at change in μ induced by the solvent: for the (0,0) configuration STO-3G and 4-31G calculations give $\Delta\mu$ = 1.75 and 2.35 D, respectively. Changes in μ, however, are not sufficient to appreciate the variations in solution energy produced by this enlargement of the basis set. The barriers and the minimum of the 4-31G surface are reported in Tables I and II. There is a modest increase in the ψ barrier (from 4.4 to 5.4 kcal/mol). The height of the φ barrier is reduced to 0.7 kcal/mol, and its position is shifted. The question of the position of this barrier has been mentioned before. It becomes evident that an accurate assessment of the position of this barrier requires a batter appraisal of internal forces obtained with better wave functions at optimized geometries and probably with a more detailed model of the solution.

The inclusion of the solvent has a lower influence on the repulsion between N and C_α hydrogen atoms than on the interaction between NH and O lone pairs. Some trial calculations on ZW–$(H_2O)_n$ clusters (n = 1–5) in the supermolecule approximation suggest a stabilization of the (0,0) conformation via a bridge between NH and O provided by a water molecule (unpublished results). In our opinion, this result could be to some extent an artifact of the supermolecule approximation, which emphasizes locally bounded structures because it neglects a part of the solute–solvent interactions and the thermal average on spatial distribution of solvent molecules. The question of the position of the φ barrier remains thus unanswered.

3.2 Internal Rotation in the Neutral Form (NT). The stable form of glycine in water is the zwitterion. A detailed analysis of the conformational characteristics of NT in aqueous solutions is therefore of little practical interest. We shall also report,

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(14) (a) Romano, S.; Clementi, E. *Gazzetta* **1978**, *108*, 319–328. (b) Romano, S.; Clementi, E. *Int. J. Quantum Chem.* **1978**, *14*, 839–850.

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Table III. Relative Energy of Some Conformations of NT Glycine (kcal/mol)

present notation	ref 19 notation	ref 18 notation	STO-3G in water	STO-3G in vacuo	4-21G[a] in vacuo	4-31G[b] in vacuo	6-31G[c] in vacuo
(60,0,180)	I	(0,0,0)	0	0	0	0	0
(240,180,0)	II	(0,180,0)	1.4	2.8	2.2	2.6	2.7
(60,180,180)	III	(180,180,180)	2.7	2.7	1.9	2.2	2.5

[a] Reference 19. [b] Reference 18. [c] Reference 17.

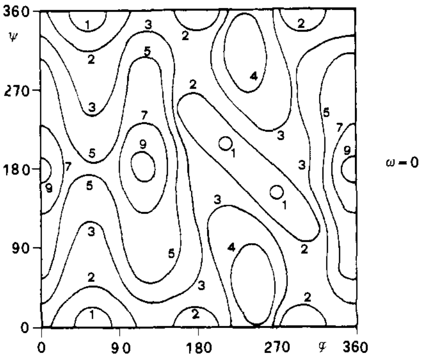

Figure 4. As Figure 3, but for conformations having $\omega = 0°$.

however, some results for the NT conformational surface because it may be of some interest for the general problem of evaluating conformational surfaces in solution.

The conformations of NT are defined in terms of three rotational angles (φ,ψ,ω). Figure 1 reports the starting (0,0,0) conformation and the sense of rotation for ω = HOC'C$_\alpha$. As in paper 1, we report only two bidimensional conformational surfaces, related to $\omega = 0°$ and $\omega = 180°$; in solution, as well as in vacuo, the planar conformations of the COOH group (ω = 0 or 180°) correspond to lower energies.

Figure 3 and 4 of the present paper relate to Figures 6a and b of paper 1. The general shape of the conformational surface is not heavily affected by the solvent, the most remarkable change being a general lowering of conformational energy differences.

A particular feature of this conformational surface deserves a comment because it could offer a hint on the proton transfer mechanism in glycine. Before doing so, it is convenient to better assess the reliability of STO-3G surfaces. Recently, Schäfer et al.[19] have determined the best internal geometry in vacuo with the 4-21G basis for three conformations of NT: (60,0,180) called I in ref 19, (240,180,0) called II, and (60,180,180) called III. The resulting energies are reported in Table III and compared with our results. The combined effect of a change of basis and a geometry optimization has a little effect on the relative energies. Calculations for the same conformers performed with larger bases lead to the same conclusion (see Table III again) which may be further confirmed by the 4-31G map for (φ,ψ) conformations at $\omega = 180°$ presented by Vishveshwara and Pople.[17] Having more confidence now on the STO-3G conformational surfaces at fixed internal geometry, we may remark that structure II of Schäfer et al. is (at least in the STO-3G approximaion) a saddle point in a low-energy valley corresponding to a disrotatory motion of the NH_2 and COOH groups. This valley is still present when solvent effects are taken into account (see Figure 4). Test calculations on the NT-H_2O system indicated that a proton transfer mechanism via a bridging water molecule could be possible. It is not necessary to repeat again our doubts on the possible artifacts of the supermolecule approach, and for reasons which will be made evident in a following section, the investigation of the proton-transfer mechanism with a mixed continuum-discrete model (e.g., a solvation cluster immersed in the dielectric and treated with appropriate statistical techniques) requires a better basis.

3.3. The Classical Description of the Solvation Free Energy. Before closing this section, we wish to make one point which could be of some interest for future research on more complex solutes.

Table IV. Comparison of Quantum Mechanical and Classical Evaluation of ΔF_{sol} (kcal/mol)

	STO-3G			4-31G		
	qu mech	class.	Δ	qu mech	class.	Δ
ZW(0,0)	−57.3	−50.4	6.9	−54.4	−45.8	8.6
ZW(60,0)	−62.1	−55.4	6.7	−57.7	−49.1	8.6
ZW(60,90)	−65.0	−58.2	6.8	−61.8	−53.0	8.8

A lower level approximation for the evaluation of ΔF_{sol} consists in neglecting the changes in the solvent kinetic energy and in solvent polarization. This approximation does not require the solution of a quantum mechanical Schroedinger equation for the solution. It is in fact sufficient to known the electric field produced by the charge distribution of the unperturbed solute on the cavity surface, a quantity which is obtainable from previous quantum mechanical calculations in vacuo. In this approximation ΔF_{sol} is given by the simple formula[8]

$$\Delta F_{\text{sol}} = \frac{1}{2}\int \rho_{\text{M}}{}^0 V_\sigma{}^0 \mathrm{d}\tau = \frac{1}{2}\sum_K \sum_i V\rho_{\text{M}}{}^0(\mathbf{s}_{Ki}) q_{Ki}{}^0 \qquad (10)$$

We compare in Table IV a few values of ΔF_{sol} obtained with formulas 6 and 10. It may be seen that this approximation, called in ref 8 the classical approximation, may be of some value to get an approximate estimate of ΔF_{sol} (in a perturbative scheme the differences between formulas 6 and 10 correspond to second order effects). In addition, when ΔF_{sol} calculations are interrupted at the first iterative step (see section 3.1a), classical and quantum mechanical results agree within 0.01 kcal/mol.

4. Relative Stability of the NT and ZW Forms

The enthalpy change for the reaction $\text{NT}_{\text{gas}} \rightarrow \text{ZW}_{\text{sol}}$ has been determined by Gaffney et al.[20] on the basis of experimental data by exploiting the relation

$$\Delta H(\text{NT}_{\text{gas}} \rightarrow \text{ZW}_{\text{sol}}) = \Delta H_{\text{diss}} - \Delta H_{\text{sub}} \qquad (11)$$

where ΔH_{diss} and ΔH_{sub} are the solution and sublimitation heats of solid glycine. The value given in ref 20 is −19.2 ± 1 kcal/mol at 298 K, where the uncertainty range regards the sublimation heat only, a relatively higher, but not quantified error, being associated with the dissolution heat.[20]

To reproduce this datum it is reasonable to select the best available geometries for NT_{gas} and ZW_{sol}. We have so selected conformation I of Schäfer et al.[18] for NT_{gas} and conformation (60,0) of our earlier calculations for ZW_{sol}. Calculations with the 4-31G basis give $\Delta F(\text{NT}_{\text{gas}} \rightarrow \text{ZW}_{\text{sol}}) = -16.5$ kcal/mol. The evaluation of the entropic correction in solution according to formula 8 gives $T(\partial \Delta F_{\text{sol}})/(\partial T)_P = 3.0$ kcal/mol, and consequently $\Delta H(\text{NT}_{\text{gas}} \rightarrow \text{ZW}_{\text{sol}}) = -19.5$ kcal/mol. This almost perfect numerical coincidence is surely due to a fortuitous compensation of errors. It has already been stated that the present calculations neglect several free energies contributions in vacuo as well as in solution for which a complete compensation is not expected.

A substantial error in the prediction of relative energies may derive from poor appreciations in E^0 and F differences. The energy difference $\Delta E^0{}_{\text{pt}} = E^0(\text{ZW}_{\text{gas}}) - E^0(\text{NT}_{\text{gas}})$ is generally called proton transfer energy. We have collected in Table V a set of $\Delta E^0{}_{\text{pt}}$ values, taken in part from preceding calculations to show

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(19) (a) Schäfer, L.; Sellers, H. L.; Lovas, F. J.; Suenram, L. D. *J. Am. Chem. Soc.* **1980**, *102*, 6568–6569. (b) Sellers, H. L.; Schäfer L., *J. Am. Chem. Soc.* **1978**, *100*, 7728–7729.

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Table V. Effect of Basis Set and Internal Geometry on the Evaluation of the in Vacuo Proton Transfer Energy ΔE^0_{pt} (kcal/mol)

basis set or method	geometry ref ZW	geometry ref NT	ΔE^0_{pt}	calc ref
PCILO	6	6	−73.7	6
CNDO	6	6	−85.1	6
CNDO	22	22	−93.1	22
STO-3G	6	6	−82.3	this work
STO-3G	17[a]	17[a]	−89.6	this work
STO-3G	16[b]	19[c]	−64.5	this work
MIN(6.3/3) → [2.1/2]	22	22	−93.1	22
4-31G	6	6	−20.1	this work
4-31G	17[a]	17[a]	−29.2	16
4-31G	17[a]	19[c]	−33.8	this work
4-31G	6	19[c]	−38.0	this work
4-31G	16	19[c]	−26.1	this work
SV(6.3/3) → [3.2/2]	22	22	−40.0	22
6-31G	17[a]	17[a]	−43.0	18
DZ(9.5/4) → [4.2/2]	22	22	−32.8	22
DZP(9.5.1/4.1) → [4,2.1/2,1]	22	22	−37.3	22

[a] Standard geometry. [b] Optimized geometry in vacuo (4-31G basis). [c] Optimized geometry in vacuo (4-21G basis).

how dependent this value is on basis set and geometry. The minimal bases, STO-3G and contracted (63/3),[21] gives an unrealistic overestimination of the proton transfer energy, and for this reason are not suited to study the proton transfer equilibrium. The homogeneous set of results given by Voogd et al.[21] suggests that calculations with DZP bases should be free from serious basis size errors. It should be desirable to have a geometry optimization at this level of accuracy, to settle definitively also the question of geometry dependence.

Less abundant are the results concerning the proton transfer energy in solution, $\Delta F_{pt} = F(\mathrm{ZW}_{\mathrm{sol}}) - F(\mathrm{NT}_{\mathrm{sol}})$, but the available data indicate that there is a basis set and geometry dependence similar to that found in the ΔE^0_{pt} case. At the 4-31G level the ΔF_{pt} values range in the interval −12, −5 kcal/mol according to the geometry selected for the calculation. By combining the values employed in our preceding estimate of $\Delta F(\mathrm{NT}_{\mathrm{sol}} \rightarrow \mathrm{ZW}_{\mathrm{sol}})$ with the best values obtained for $\mathrm{NT}_{\mathrm{sol}}$ and $\mathrm{ZW}_{\mathrm{gas}}$ we obtain $\Delta F_{\mathrm{pt}} = -5.6$ kcal/mol at 298 K. There is, however, no experimental value to compare. Lamborelle and Tapia[22] presented estimates of the proton energy transfer in solution based on two versions of an effective Hamiltonian, the self-consistent reaction field (SCRF) theory and the virtual charge model (VCM). Both Hamiltonians contain parameters to be fitted by comparison with experimental data. Unfortunately, the numerical results presented in that paper refer to CNDO calculations which grossly overestimate the stability of the NT form;[23] there is however, as in our STO-3G calculations, a clear tendency to reduce the energy gap between the two species in solution.[24] Monte Carlo calculations[14] give an estimate of glycine–water potential energy for both forms, and of water–water potential energies in bulk water and in dilute solutions of NT and ZW. From these data we may try to derive some data of interest to us. The change in potential energy for the proton transfer ZW(sol) → NT(sol) is −18.9 kcal/mol at $T = 300$ K: this value is outside the previously mentioned interval −12, −5 kcal/mol for ΔF_{pt} and related to 4-31G calculations. It must be remarked that these MC calculations are based on single ζ wave functions for glycine.[15,25] The basis set employed in these calculations shares the defects of other minimal basis: for example, the proton transfer energy in gas is $\Delta E^0_{\mathrm{pt}} = 67.6$ kcal/mol (compare with results given in Table V). The limitations of the basis do not permit us to use these MC results to estimate the relative stability of neutral and zwitterionic forms, though they may be of some interest to compare changes in the solute–solvent potential energy of different amino acids in the same form (ZW or NT).

5. Conclusion

A computational method able to treat solvent effects in an ab initio SCF scheme has been here applied for the first time to determine conformational energies. The determination of preferred conformations in solution being a problem of particular interest for organic solutes of medium and large size, particular attention has been devoted to the results obtainable at the lowest level of accuracy. It has been evident that though the computational scheme requires approximately three SCF steps to reach a good appreciation of the solute–solvent polarization effects, the first step gives conformational energy differences with errors of the order of 0.1–0.2 kcal/mol. A simpler approximation, which neglects solute polarization, and then avoids SCF computations on the solute–solvent system, gives conformational energy differences with errors of the same magnitude, in the present case at least. The STO-3G basis is able to reproduce the main features of the conformational surface, when compared with results obtained with larger basis sets.

A second point considered in this paper regards the relative energy of neutral and zwitterionic glycine. This investigation has not taken into account vibrational and rotational/librational contributions to the free energy, which however could also be computed with the available set of ab initio programs at the cost of an extra computational effort, or evaluated from other sources with a relatively small error, as has been indicated in our preceding paper.[10] The evaluation of the relative energy in the frozen nuclei approximation requires, however, a better basis set than conformation calculations. Proton transfer energies computed with a minimal basis are completely unrealistic, and analysis of the available data suggests the use of optimized geometries at DZP basis level. This kind of calculation requires today a sizable computational effort for larger molecules of bioorganic interest, but they are not beyond the present possibilities. The computational method considered here, without introducing empirical parameters (the only existing parameter concerning the size of the solvent cavity has been determined by means of ab initio computations on solute–solvent dimers) seems to be able, when applied to wave functions of adequate accuracy, to give reasonable estimates of the proton transfer energy in solution. In this case some contributions to ΔF related to solute–solvent interactions cancel out at a fair extent: cavitation contributions are less than 2 kcal/mol, and according to an approximate estimate of the dispersion contributions[26] the combined influence of cavitation and dispersion–repulsion free energy differences should be of the order of 1–2 kcal/mol.

The most interesting result for which there is also available the experimental value is the heat of transfer of glycine from the gaseous state to the solution: $\mathrm{NT}_{\mathrm{gas}} \rightarrow \mathrm{ZW}_{\mathrm{sol}}$. The experimental value is $\Delta H = -19.2 \pm 1$ and we found, with the best available geometries, $\Delta H = -19.5$ kcal/mol. Though this agreement benefits from some compensation of errors, the analyses reported in the preceding section indicate that the results here displayed give an essentially correct estimate on the energetics of these processes and that future more refined calculations will produce but small corrections to them.

Registry No. Glycine, 56-40-6.

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(23) For CNDO results see: (a) ref 6; (b) Imamura, A.; Fujita, H.; Nagata, C. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3118–3123.

(24) In the STO-3G basis we obtain $\Delta F_{\mathrm{pt}} = +34.5$ kcal/mol (compare with $\Delta E^0_{\mathrm{pt}} = +82.3$ kcal/mol). Lamborelle and Tapia (ref 22) suggest +25 kcal/mol for the SCFR method and +10.1 for the VC model.

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