Quantum Mechanical Conformational Analysis of β-Alanine Zwitterion in Aqueous Solution

Peter Aadal Nielsen,[†] Per-Ola Norrby,[†] Tommy Liljefors,[†] Nadia Rega,[‡] and Vincenzo Barone*[,‡]

Contribution from the Department of Medicinal Chemistry, Royal School of Pharmacy, Copenhagen, Denmark, and Dipartimento di Chimica, Università Federico II via Mezzocannone 4, I-80134 Napoli, Italy

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Abstract: The conformational behavior of β-alanine zwitterion in aqueous solution has been investigated by post-Hartree−Fock and density functional methods using the polarizable continuum model (PCM) for the description of the solvent. Our results show that the PCM is able to reproduce the delicate balance between intramolecular hydrogen bridges and preferential solvation of isolated charged groups in determining the overall conformational preferences without any need of explicit solvent molecules. From a methodological point of view, the Hartree−Fock method is not sufficiently reliable for quantitative predictions of conformer equilibria, whereas approaches including electron correlation (DFT, MP2, MP4) perform remarkably well when using medium size basis sets including diffuse functions. Vibrational averaging arising from the torsional motion around the central CC bond leads to vicinal NMR coupling constants (J) in remarkable agreement with experiments when using an extended Karplus-type equation for the torsional dependence of J.

Introduction

The conformational characteristics of biomolecules are of paramount importance for understanding both their reactivity and their affinity for specific receptors. This has stimulated the development of very powerful computational strategies both at the quantum mechanical (QM) and molecular mechanical (MM) level. However, the natural ambient of these systems is an aqueous solution and solute−solvent interactions can often strongly modify the behavior of isolated molecules. This is particularly important for flexible molecules whose bioactive conformation often does not correspond to the most stable unbound structure. Thus the energy needed to reach the active conformation is an important factor in structure−activity studies and its accurate evaluation is mandatory for the usefulness of any model.[1,2] As a matter of fact an overestimation of a conformational barrier by just 1.4 kcal/mol leads to a reduction of the activity by an order of magnitude.

While explicit inclusion of solvent molecules in numerical simulations (either molecular dynamics (MD) or Monte Carlo (MC)) is providing interesting results, computational times remain very long, thus limiting the range of investigable phenomena essentially to short-time local fluctuations. This is stimulating increased attention toward continuum or mixed discrete/continuum representations of the solvent which are much more computationally effective.[3] However, coupling of continuum solvent approaches and MM methods requires a careful investigation of parameters and neglects polarization effects, which can be, sometimes, very important.[4] For instance, in connection with previous work on the zwitterionic ligands at 4-amino butyric acid (GABA) and glutamic acid receptors we have experienced some problems in the locations of the conformational energy minima (the ligands are shown in Figure 1, a and b, respectively). In these unpublished calculations we have used two different force fields, AMBER* and MM3*, in connection with continuum solvent models, as implemented in MacroModel v.6.5.[5] The calculations employing the AMBER* force field show that the internal energy of the folded conformers is approximately 20 kcal/mol lower than that of the corresponding extended conformers. On the other hand, the MM3* force field shows an internal energy difference favoring the extended conformers by approximately 1 kcal/mol. The same trends have been found in a recent work on the ornitine amino acid, and it has been suggested that these problems might be due to a combination of low accuracy of the force fields and of the GB/SA solvent model.[6]

Ab initio calculations in a vacuum of zwitterionic compounds, which have the possibility of forming internal hydrogen bonds generally induce a proton transfer leading to the formation of the neutral compound.[7,8] While explicit addition of just one

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* Address correspondence to this author. E-mail: enzo@chemna.dichi.unina.it.

[†] Royal School of Pharmacy.

[‡] Università Federico II.

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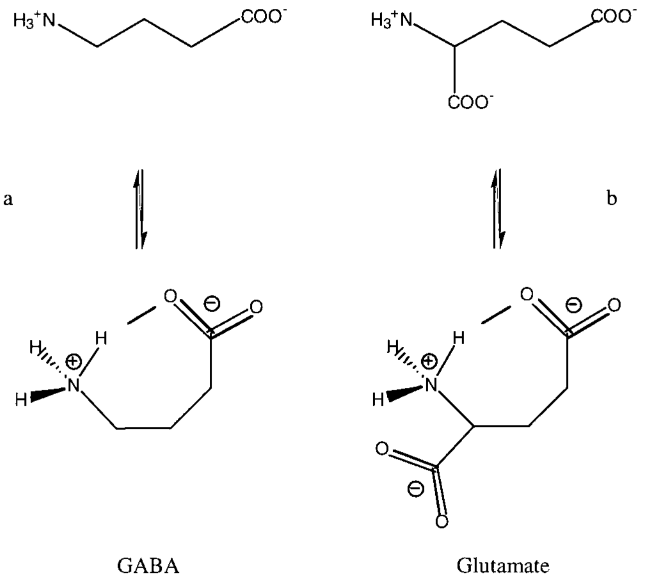

Figure 1. Conformational equilibrium between the extended and folded conformers of GABA (a) and glutamate (b). In the folded conformations an intramolecular hydrogen bond is formed.

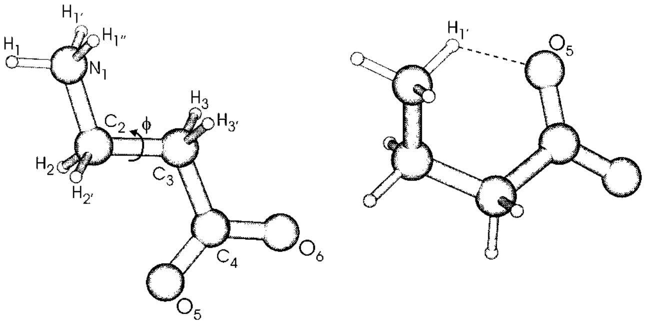

Figure 2. Atom numbering and structures of gauche and anti conformers of BAZ optimized using the C-PCM at the HF/6-31+G* level.

water molecule is often sufficient to obtain the zwitterionic local minimum characteristic of aqueous solutions,[9−11] we think that a continuum solvent model could offer a more balanced description of short- and long-range effects.[12−14]

We have chosen as a test case the β-alanine zwitterion (BAZ) shown in Figure 2 since from one side this molecule is sufficiently small to allow high quality quantum mechanical (QM) computations and, from another side, its conformational behavior in aqueous solution has been recently established by NMR spectroscopy.[15,16] Moreover the dependence of NMR vicinal coupling constants on rotation around the $C_{sp3}-C_{sp3}$ bond is well described by the Karplus equation.[17,18]

Previous ab initio calculations for BAZ in a vacuum favor the gauche conformer by approximately 20 kcal/mol.[15,19,20] Note that, as mentioned above, a full geometry optimization of the zwitterionic species in its gauche conformation leads to the transfer of one ammonium proton to the carboxylate group. The energy differences quoted above have been calculated either for the optimum geometries in solution[15] or for structures with constrained N−H distances.[19] NMR data obtained in aqueous solution show that gauche and anti conformers have nearly the same stability with, at most, a slight preference for the anti conformer.[15,16] Previous results obtained with high-level ab initio calculations employing the Poisson−Boltzmann continuum description implemented in the Jaguar package[21] show that the anti conformer is favored by 2−3 kcal/mol in aqueous solution.[15] Gregorie et al. have suggested that the most probable shortcoming of this approach is the lack of explicit water molecules which might change the relative stability of the two conformers.[15] Here we reinvestigate this problem using post-Hartree−Fock (HF) and density functional (DF) methods coupled to the polarizable continuum model (PCM).[3c] Since the direct experimental result is the vicinal NMR coupling constant between methylenic hydrogen atoms, we thought it interesting to compute this quantity as well. To this end we have used an extended Karplus equation for describing the torsional dependence of J, together with the torsional potential obtained by our QM computations. Averaged values of J have been obtained by a numerical solution of the Schrödinger equation governing the torsional motion. This allows an unbiased comparison between experimental and computed quantities depending only on the parametrization and applicability of the extended Karplus equation.

Computational Methods

All the calculations were carried out using a modified version of the Gaussian package.[22] The equilibrium structures were fully optimized in solution at the HF level using the 6-31+G* and 6-311+G** basis sets.[23] These geometries were employed for single-point B3LYP/6-31+G*, MP2/6-31+G*, and MP4(sdq)/6-31+G* calculations[23] used for MPn computations in solution polarization charges obtained at the HF level (HFPC model).[24] Harmonic frequencies of the HF/6-31+G* structures were computed by fully analytical procedures to obtain zero-point energies (ZPE) and thermal corrections to standard free energies in the usual rigid-rotor harmonic-oscillator approximation using our recent implementation of analytical second derivatives in solution.[24−27] We have used in all cases the conductor version of PCM (C-PCM)[28,29]

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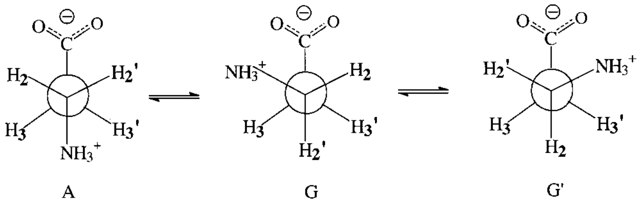

Figure 3. Newmann projections of stable conformers of BAZ.

employing the HF parametrization of our united atom topological model (UAHF)[27] for generating solute cavities.

In PCM the variation of the free energy when going from vacuum to solution is composed of the work required to build a cavity in the solvent (cavitation energy, G_{cav}) together with the electrostatic (G_{el}) and nonelectrostatic ($G_{\mathrm{disp}} + G_{\mathrm{rep}}$) work connected with charging the solvent and switching on solute−solvent interactions.[24] Besides these terms (whose sum is referred to as W^0), we have taken into account the contributions to free energies issuing from the solute partition functions (W^{T}) assuming that the solute has a very large volume available in solvent and that it can freely rotate. In summary the standard free energy difference ΔG^0_{ij} between conformers i and j is given by

$$\Delta G^0_{ij} = \Delta E^0_{ij}(\mathrm{vac}) + \Delta W^0_{ij} + \Delta W^{\mathrm{T}}_{ij} \tag{1}$$

The populations of gauche and anti conformers were obtained to a first approximation by a simple Boltzmann weighting taking into account that there are two equivalent gauche conformers (G^+ and G^-). A more refined procedure is based on the large amplitude path (LAP) obtained optimizing all the remaining geometric parameters at selected values of a distinguished coordinate (in the present case the N1−C2−C3−C4 dihedral angle φ shown in Figure 2). The arc length s along this path in mass weighted Cartesian coordinates provides a suitable progress variable (large amplitude coordinate, LAC) for computing the vibrational states supported by the torsional motion using an improved version of the numerical procedure described in refs 30 and 31. Then the expectation value $\langle O \rangle_T$ of a given observable at absolute temperature T is given by

$$\langle O \rangle_T = \frac{\sum_j \langle j|O(s)|j\rangle \exp[(\epsilon_0 - \epsilon_j)/KT]}{\sum_j \exp[(\epsilon_0 - \epsilon_j)/KT]} \tag{2}$$

where $O(s)$ is the expression giving the variation of the observable as a function of the LAC, and $|j\rangle$ is a vibrational eigenstate with eigenvalue ϵ_j. Since we know the dihedral angles between vicinal protons at each value of the LAC s, we can use any reliable functional relationship between vicinal proton−proton coupling constants and the associated torsional angle. The most refined empirical equations of this kind take into account also the electronegativity of further substituents of the C atoms in question and their positions with respect to coupling protons. Among these so-called extended Karplus equations we have selected the equation proposed in ref 32, which has an overall rms error of only 0.36 Hz for a set of 299 couplings. All these computations were performed by our DiNa package.[30,31]

Results and Discussion

Proton NMR spectra (300 MHz) recorded at room temperature show that BAZ behaves as a A_2B_2 system, with a vicinal $^3J(H_AH_B)$ coupling constant of 6.70 Hz.[15] This can be considered the averaged value of the two coupling constants $^3J(H_2H_3)$ and $^3J(H_2H_{3'})$ (see Figure 3): since the experimental signal shows a line width of 0.7 Hz**,** the primitive coupling constants cannot differ by more than 0.8−0.9 Hz.[15,16]

Table 1. Structural Parameters (Å and deg) of Gauche and Anti Conformers of BAZ Optimized in Aqueous Solution Employing C-PCM with Different Basis Sets

structural parameters[a]	HF/6-31+G*		HF/6-311+G**	
	gauche	anti	gauche	anti
	distances			
H1′−N1	1.016	1.017	1.016	1.016
N1−O5	2.766		2.765	
H1′−O5	2.029		2.024	
C4−O5	1.247	1.243	1.243	1.237
	angles			
H1N1C2	108.97	111.42	108.71	111.18
C3C4O5	117.69	118.30	117.56	118.28
N1H1′O5	127.34		127.77	
H1′O5C4	106.84		107.12	
	dihedrals			
N1H1′O5C4	−20.0		−19.8	
N1C2C3C4	−61.8	180.0	−61.5	180.0

[a] Numbering is according to Figure **2**.

When only gauche and anti conformers are significantly populated it is straightforward to show that

$$J_{23} = J^A_g + \frac{1}{2} f_G (J^G_{g'} + J^G_a - 2J^A_g)$$

$$J_{23'} = J^A_a - f_G (J^A_a - J^G_g) \tag{4}$$

where upper case letters represent the mutual orientation of NH_3^+ and COO^- groups, lower case letters refer to the mutual orientation of methylene hydrogen atoms, and

$$f_G = \frac{2\exp\left(\frac{-\Delta G^{GA}}{RT}\right)}{1 + 2\exp\left(\frac{-\Delta G^{GA}}{RT}\right)} \tag{5}$$

is the fraction of the gauche conformer calculated according to a Boltzmann distribution. Of course the factor 2 takes into account the presence of degenerate G^+ and G^- conformers.

Values corresponding to different mutual orientations of ionized groups and hydrogen atoms can be calculated by the equation proposed by Altona and co-workers.[32] Assuming that gauche and anti minima correspond exactly to $\varphi = 60°$ and $\varphi = 180°$, respectively, the experimental averaged value of $^3J(H_AH_B)$ leads to nearly equal amounts of A, G^+, and G^- conformers (35, 32.5, and 32.5%, respectively), i.e., to a free energy difference of about 0.1 kcal/mol between gauche and anti conformers.

Fully relaxed structures of gauche and anti conformers of BAZ were obtained in aqueous solution using the C-PCM method at the HF/6-31+G* and HF/6-311+G** levels. The different optimized structures are shown in Table 1.

Computation of harmonic frequencies shows that both anti and gauche conformers are true energy minima in aqueous solution. From Table 1 it is obvious that extending the basis set from 6-31+G* to 6-311+G** does not lead to any significant difference. Thus HF computations are quite basis set independent at least starting from the 6-31+G* level. Although the use of diffuse functions in continuum solvent models is quite delicate, they are mandatory for a correct description of the anionic head of BAZ and previous studies have shown that the compensation procedures implemented in

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Table 2. Conformational Energy Differences (kcal/mol) of Conformers Optimized in Aqueous Solution Using the C-PCM at Different Optimization Levels and Basis Sets and Corresponding Population of Gauche Form

geometry level/ basis set	level/basis set	ΔE(vac) (gauche − anti)	ΔW^0 (gauche − anti)	ΔG (gauche − anti)[a]	gauche config. (in %)[a,b]
HF/6-31+G*	HF/6-31+G*	−20.69	19.00	−0.99	91.4
HF/6-31+G*	MP2/6-31+G*	−21.14	21.40	0.96	28.3
HF/6-31+G*	MP4/6-31+G*	−21.04	21.46	1.12	23.2
HF/6-31+G*	B3LYP/6-31+G*	−20.75	21.40	1.35	17.0
HF/6-31+G*	MP2/6-311+G**	−20.96	21.40	1.13	22.8
HF/6-31+G*	MP4(SDQ)/6-311+G**	−20.92	21.40	1.17	21.6
HF/6-311+G**	HF/6-311+G**	−20.46	18.77	−0.99	91.4
HF/6-311+G**	MP2/6-311+G**	−20.99	21.47	1.18	21.5

[a] Calculated at 298 K with eq 1, where the terms $\Delta W_{ij}^{\mathrm{T}}$ are calculated at the HF/6-31+G* level. [b] Calculated at 298 K with eq 5.

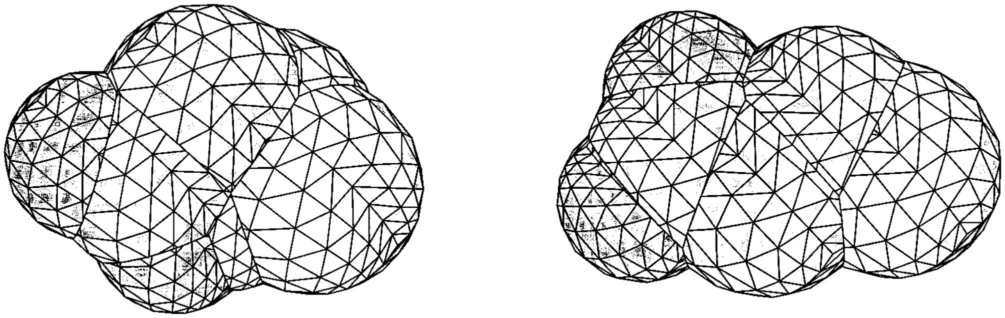

Figure 4. C-PCM cavities including gauche (on the left) and anti (on the right) conformers of BAZ.

PCM are sufficiently robust to handle diffuse functions properly.[26−28]

The N1C2C3C4 dihedral angle of the gauche conformer is 61.5°, whereas previous studies found values of 50°,[15] 44°,[19] and 55°,[20] either using structures optimized in solution or freezing the N−H distances to avoid proton transfer. The corresponding angle in the structures optimized in water is 62.5°, 58.0°, and 62.5° at the HF/6-31G**, LMP2/cc-pVTZ, and B3LYP/cc-pVTZ levels, respectively.[15]

Energy calculations performed in a vacuum at the HF/6-31+G* level using geometries optimized in solution show that the gauche conformer is favored by 20.7 kcal/mol due to its ability to form intramolecular H-bonds between carboxylate and ammonium groups. It is remarkable that this value is very similar by all the quantum mechanical models and basis sets employed in the present study (see Table 2) and that it resembles previously reported energy differences for the breaking of an internal hydrogen bond in zwitterionic systems.[2,15,19] According to this analysis only the gauche conformer would be present in the gas-phase contrary to the interpretation of NMR data in aqueous solution.[15,16]

However, solute−solvent interactions stabilize the anti conformer by about 20 kcal/mol (see Table 2) leading to comparable stability for both conformers in aqueous solution. Also in this case different methods and basis sets provide similar results, although HF computations slightly underestimate the stabilization of the anti conformer with respect to approaches including electron correlation. A more detailed analysis of this trend can be done considering solute cavities shown in Figure 4.

To proceed further we recall that, besides the nearly constant cavitation, dispersion, and repulsion terms (collectively referred to as W_{nel}), W^0 contains electrostatic (W_{el}) and polarization (W_{pol}) terms. The former contribution represents solute−solvent interactions with the solute wave function already polarized by the solvent and the latter takes into account the work needed to polarize the solute wave function from its optimum value in a vacuum. Of course only W_{el} can be dissected into contributions originating from different spheres of the cavity, but Table 3 shows that W_{pol} is quite similar for gauche and trans conformers. Then, it is quite apparent that the largest contributions to W_{el} are due to the ionized moieties of BAZ, which are more exposed to the solvent in the anti conformer than in its gauche counterpart.

Table 3. Partition of the Solute−Solvent Electrostatic Interaction W_{el} (kcal/mol) and of the Cavity Surface (Å^2) into Spheres Centered on Different Solute Atoms

	gauche		anti	
	surface	W_{el}	surface	W_{el}
N_1	32.14	−20.64	36.23	−32.52
C_2	21.83	−4.98	20.75	−4.26
C_3	22.29	−2.00	21.50	−2.70
C_4	12.89	−4.12	13.33	−5.19
O_5	12.01	−11.29	15.34	−18.23
O_6	16.59	−20.98	16.58	−22.56
W_{pol}	10.26		12.71	
W_{nel}	−0.44		−0.38	
W^0	−54.19		−73.13	

[a] Note that hydrogen atoms are contained in the same sphere of the atom to which they are bonded.

The free energy differences between gauche and anti conformers calculated in solution are given in Table 2 for different computational levels. Using HF/6-31+G* frequencies without any scaling gives a thermal contribution favoring the anti conformer by 0.70 kcal/mol, which leads to the fractions of gauche conformers reported in the same table.

Including correlation effects at the MP2 level changes the HF free energy difference by 1.95 kcal/mol (from −1.69 to 0.26 kcal/mol), leading from a gauche to an anti global energy minimum. Nearly identical results are obtained at the MP4-(sdq) level and also B3LYP results are not very different, so that all the PCM computations using correlated quantum mechanical models are in basic agreement with the experimental estimate of the energy difference. This represents a significant improvement compared to previous published results, which favor the gauche conformer by 2−3 kcal/mol using HF/6-31G**, LMP2/cc-pVTZ, and B3LYP/cc-pVTZ computations in aqueous solution.[15] Thus proper inclusion of solvent and

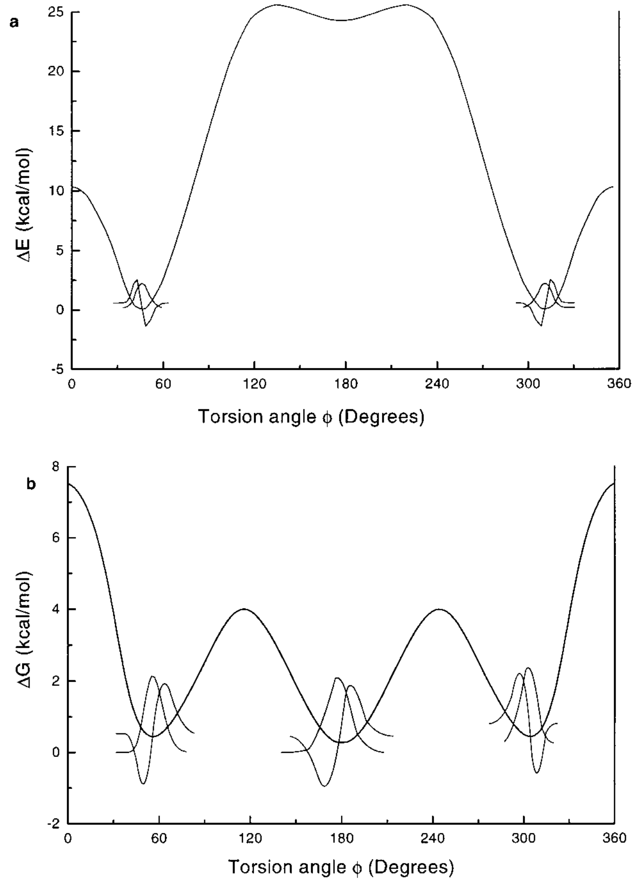

Figure 5. Torsional potentials and vibrational eigenfunctions obtained in a vacuum (a) and in aqueous solution (b) by the DiNa program.

correlation effects seems to have a crucial effect on the calculations.

A more sophisticate analysis was performed considering the torsional motion around the N1C2C3C4 dihedral angle (ϕ) as the single large amplitude mode of the molecule, i.e., optimizing all the remaining geometrical parameters at selected values of ϕ. Figures 5a and 5b show the potential energy curves obtained in a vacuum and in solution by single point MP2 computations at HF geometries together with low energy vibrational wave functions.

Note that the anti conformer is a local minimum in a vacuum, separated by a low barrier from the gauche absolute minima; as a consequence, the lower energy vibrational levels involve the gauche conformer only. In solution the anti conformer becomes the global minimum, separated by a torsional barrier of 3.3 kcal/mol from the gauche forms, with low energy vibrational states localized on each minimum.

Comparing both curves we can notice that the gauche energy minimum corresponds to values of the torsional angle of about 50° and 61° respectively in a vacuum and in solution: a smaller dihedral angle leads to a shorter distance between the ammonium and the caboxylate groups, indicating that the intramolecular hydrogen bond is stronger in a vacuum than in water.

The values of $^3J(H_AH_B)$ along the path were calculated by using the extended Karplus equation proposed by Altona and co-workers[32] and then averaged at 298 K according to eq 2.

The coupling constants of gauche and anti conformers are quite different (5.92 and 8.8 Hz, respectively) and none of them is in agreement with the experimental value. On the other hand, vibrational averaging at room temperature leads to the computed value in full agreement with its experimental counterpart (6.67 vs 6.70 Hz). This finding points out at the same time the reliability of the extended Karplus equation of ref 32 and the usefulness of our integrated approach including both solvent and vibrational averaging effects.

Concluding Remarks

Zwitterionic compounds are of great interest in medicinal chemistry due to their ability to bind proteins (receptors or enzymes), but computations on this class of compounds by standard methods are often unreliable due to the overestimation of internal hydrogen bonds. In this study we present high level ab initio calculations including solvent effects, which provide promising improvements in the balance between intramolecular hydrogen bonds and solute−solvent electrostatic interactions.

In a vacuum the calculated free energy difference between the gauche and the anti conformer is above 20 kcal/mol. When solvent effects are included the energy difference is strongly reduced, leading, in agreement with experimental data, to a very similar stability of gauche and anti conformers. Then, thermal and degeneracy contributions further reduce the energy difference and inclusion of correlation contributions finally leads to a slight preference for the anti conformer. At this level, a quantitative agreement is reached between quantum mechanical computations and experimental data, which is a significant improvement over previous high level ab initio studies. Thus, the present results show that PCM is a very powerful tool for describing the behavior in solution of compounds able to form intramolecular hydrogen bonds. Direct computation of vicinal NMR coupling constants including vibrational averaging effects confirms this conclusion further and paves the route for more reliable quantum mechanical studies of biomolecules in solution.

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