Theoretical Studies on the Continuum Solvation of Some *N*,*N*′-Dimethyl- and *N*-Methyl,*N*′-acetyl-Guanidine and Guanidinium Conformers

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The conformational properties of neutral and protonated *N*,*N*′-dimethyl and *N*-methyl,*N*′-acetyl-guanidines have been studied in vacuo and in solution, considering either water or chloroform as solvents. Using the ab initio MP2/6-31G* optimized geometries obtained in vacuo, single-point HF/6-311++G**//MP2/6-31G* and MP2/6-311++G**//MP2/6-31G* calculations have been performed in vacuo and continuum solvent free energy calculations in solution for most of the syn (S) and anti (A) conformers (with respect to the unsubstituted nitrogen) for different tautomeric structures. The solvation free energy is considerably less favorable, as expected, for neutral than for protonated guanidines (about −11 vs −63 kcal/mol in water and about −4 vs −41 kcal/mol in chloroform for dimethyl-guanidines at the HF level; methyl-acetyl-guanidines show a slightly larger spread around those average values). The correlation contribution to the solvent effect is feeble for the protonated derivatives in solution, while it is larger (up to 4 kcal/mol in water) for the neutral conformers. The cooperative effect among the carbonyl lone pairs and the nitrogen in-plane lone pair is responsible for the fairly large solvent stabilization of the conformers with these polar groups facing each other. Several different conformers/tautomers of neutral methyl-acetyl-guanidine are within a 0.5 kcal/mol free energy range in vacuo, whereas in solution both the neutral (with a cis C═N double bond with respect to the acetyl C═O) and protonated SS methyl-acetyl conformers turn out to be slightly stabilized over the others, especially at the HF level.

Introduction

One of the attractive features of computational chemistry relies upon the possibility to consider a particular geometrical and electronic state of a flexible molecule. In this way, by analyzing the behavior of a single rotamer under specific conditions, which is usually impossible for real systems where an equilibrium mixture is present in general, one can derive useful information about the equilibrium mixture composition as well.

In biological processes, drug molecules partition between aqueous and lipid phases throughout the drug-transport process. A low dielectric constant solvent can model a slightly polar environment in a biological medium. Free energy calculations in water and chloroform permit estimation of the conformational/tautomeric equilibrium for biologically important molecules in the given solvent and consequently their partition coefficients useful in drug-design studies.[1]

Determination of the relevant molecular structure involved in the partitioning process may be complicated in cases when the biologically active component of the drug is an acid or a base. There are different possible mechanisms for partitioning. The simplest occurs when the active component takes a neutral form in both phases. At physiological pH (7.4), most bases are protonated in blood, which may be assumed for theoretical purposes as an aqueous solution. Moving to the nonpolar phase usually requires the protonated base to lose its proton. Since this latter phase, however, must be saturated with water, it is possible that the protonated base does not lose the proton but reaches stabilization with the small number of water molecules existing in the nonpolar phase.[2] A further possibility is that, if the drug contains the active component in the form of an organic salt, the protonated base and its counterion present a distribution of an ion pair.[3]

The above mechanisms for drug distribution are real possibilities for the important class of guanidine derivatives. Guanidine as a building block of several compounds of biological and therapeutic interest,[4] including arginine, has attracted much attention. Theoretical calculations have been reported in the literature either concerning the ion-pairing of its positive ions in water[5] or conformational analyses of several rotamers of di- and trisubstituted protonated derivatives.[6]

Recently, we have analyzed the conformational properties of *N*,*N*′-diaryl-guanidines in aqueous solution,[7a] resorting to free energy ab initio calculations for the diphenyl derivatives and approximate methods for the bulkier compounds. Counterion effect on the conformational equilibrium for the *N*,*N*′-diphenyl-guanidine in water was studied in the framework of a combined ab initio/Monte Carlo study.[7b] Due to the interest of this system, however, we decided to perform a more systematic study taking into account several conformers for guanidine derivatives with symmetric/asymmetric substitutions and considering both nonpolar and partly polar substituents. Accordingly, *N*,*N*′-dimethyl and *N*,*N*′-methyl-acetyl derivatives were investigated both in neutral and protonated forms, using reliable geometries deter-

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mined at the MP2/6-31G* level. An extended basis set at a correlated level, MP2/6-311++G**, was used to evaluate the free energy in the polarizable continuum model (PCM) framework,[8] in two different solvents, water and chloroform. Since guanidine and its derivatives, as generally strong bases, are protonated at physiological pH in aqueous solution, a different behavior is to be expected in chloroform and we would like to see whether a consistent result comes out from our study. The thermal corrections have been evaluated for most of the conformers in vacuo. It would be interesting to compute them also in solution, but this would require full geometry optimizations at the MP2 level in solution (employing the 6-311++G** basis set) which are far beyond our present computer resources. Moreover, this kind of calculation needs some further testing of the implementation at the MP2 level of the geometry optimization in solution. A prospective way to overcome this should be the use of the density functional theory[9,10] to include correlation effects into the geometry optimization in solution.

Brief Outline of the PCM Method

To make the paper self-contained, we briefly report a description of the procedure followed to account for the electrostatic effect felt by a quantum mechanical solute M immersed in a solvent, represented as a continuum of dielectric constant ϵ. More detailed and exhaustive descriptions can be found in the source papers of the method[8] and in a recent review.[11] However, some modifications recently introduced in the algorithms are mentioned and quoted hereafter.

The computed quantities derive from the Hamiltonian of the system, which consists of two terms, one related to the unperturbed solute, $H°(\mathrm{M})$, and the other, V_σ, to the solute−solvent interaction:

$$(H°(\mathrm{M}) + V_\sigma)\,\psi_\mathrm{M} = E_\mathrm{M}\psi_\mathrm{M} \tag{1}$$

The solute is located in a cavity,[8d,12] shaped on the solute itself, inside a dielectric medium and therefore induces an apparent charge distribution on the cavity surface. The induced distribution depends on the solute total charge distribution (electrons and nuclei) and on the apparent charge distribution as well. The apparent polarization charges corrected for their mutual polarization and for the charge escaped outside the cavity, used to polarize the solute charge distribution, consist in the present version of PCM of two sets depending on the solute electrons (e) and nuclei (N), respectively. They are computed exploiting linear equations which can be expressed in matrix form:[13]

$$\mathbf{q}^e = \mathbf{A}\mathbf{D}^{-1}\mathbf{E}_n^e; \quad \mathbf{q}^N = \mathbf{A}\mathbf{D}^{-1}\mathbf{E}_n^N \tag{2}$$

where $\mathbf{A}$ is the diagonal matrix of the surface tile areas and the elements of $\mathbf{D}$ depend on ϵ and on the geometry of the tiles only. The elements of $\mathbf{E}_n^e$ and $\mathbf{E}_n^N$ are the normal components of the electric field acting on the surface tiles due to the solute electrons and nuclei, respectively. This formulation, coupling PCM for the solute−solvent system to the boundary element method to solve the electrostatic problem, allows the computation of all the molecular properties with a single SCF calculation, instead of employing the three iterations earlier necessary.

The procedure used to normalize the polarization charge appearing on the cavity surface corresponds to the option ICOMP = 4 of PCM in Gaussian94;[14] i.e., additional charges are located on the cavity surface, according to the solute electronic density in each point belonging to it, in place of the charges that should develop in the bulk of the dielectric medium as a reaction to the escaped electronic tails.[15] The main novelty in the solvation code with respect to the PCM method already embodied in Gaussian94 is the use of the united atom topological model (UAHF) for the definition of the cavity,[12] which optimizes the van der Waals radii for atoms and atomic groups, allowing very accurate electrostatic solvation free energies, G_el, to be obtained:

$$G_\mathrm{el}^\mathrm{X} = E_\mathrm{tot}^\mathrm{X} - \frac{1}{2}\int \Gamma_\mathrm{M}(\mathbf{r})\,\mathrm{V}_o(\mathbf{r})\,\mathrm{d}\mathbf{r} \tag{3}$$

(with $E_\mathrm{tot}^\mathrm{X} = E_\mathrm{M}^\mathrm{X} + E^\mathrm{nuc}$),[8c] with X = HF or MP2. To simplify the notations, HF and MP2 are not indicated in the tables and drawings as subscripts or superscripts, but they are reported in the headings or legends only.

The solvent effect at each level is therefore defined as

$$G_\mathrm{X}^\mathrm{sol} = G_\mathrm{el}^\mathrm{X} - E_\mathrm{X}^\circ \tag{4}$$

where E_X° is the energy of the solute in vacuo at the X level. We have described thus far only the electrostatic contribution to the molecular free energy in solution, which however is made up by additional terms:

$$G_\mathrm{tot}^\mathrm{X} = G_\mathrm{el}^\mathrm{X} + G_\mathrm{cav} + G_\mathrm{dis} + G_\mathrm{rep} \tag{5}$$

The cavitation,[16] dispersion,[17] and repulsion[17] terms do not affect the solute wave function, because they do not enter into the Hamiltonian; their effect is limited to the energy. The cavitation free energy is defined as a summation over the spheres making up the cavity:

$$G_\mathrm{cav} = \sum_i^\mathrm{spheres} \frac{A_i}{4\pi R_i^2} G_i^\mathrm{HS} \tag{6}$$

with G_i^HS corresponding to the free energy of a sphere of radius R_i in a fluid of hard spheres, determined with the Pierotti's formula,[16b] weighted based on the actual solvent exposed surface, A_i, to account for the complex nonspherical shape of cavities. The dispersion and repulsion terms are computed with an atom−atom potential method,[18] using parameters developed by Caillet and Claverie.[18] The procedure implemented in PCM allows them to be computed at the same time making use of a surface integral, transformed in a sum of terms defined on each tile of the cavity surface:[19]

$$G_\mathrm{dr} = \sum_a^\mathrm{solute}\sum_s^\mathrm{solvent}\rho_s\sum_i^\mathrm{tiles} A_i C^\mathrm{dr}\,\mathbf{r}_{ai}\cdot\mathbf{n}_i \tag{7}$$

with dr equal to dis or rep, depending on the case. The sums run on the atoms a and s of the solute and solvent molecules, respectively, ρ_s is the density number of solvent molecules, A_i is the area of the tile i, $\mathbf{r}_{ai}$ is the vector joining the atom a and the tile i, while $\mathbf{n}_i$ is the unit vector normal to the tile i. For the expressions of C^dr and to gain a deeper insight in the method, the interested reader is referred to the already quoted papers.[16a,17]

All the contributions shown in eq 5 are kept apart in Tables 1−6 in order to evaluate their relative importance. Because of the definition of G^sol (eq 4), the difference in the $G_\mathrm{tot}^\mathrm{sol}$ terms is not equal to the corresponding difference in the ΔG_tot terms. Instead, the equation $\Delta\Delta G_\mathrm{tot} = \Delta\Delta E + \Delta G_\mathrm{tot}^\mathrm{sol}$ holds.

Computational Details

The systems considered are both neutral and protonated guanidines with two Hs in position N,N', respectively, substituted

TABLE 1: Relative Stability of the Neutral Dimethyl- and Methylacetyl-Guanidine Conformers Considered with Respect to dmgSA[a] and ma═gSA[b], Respectively, in Vacuo and in Water Solution at the HF and MP2/6-311++G Levels on MP2/6-31G* Optimized Geometries[c]**

	HF			MP2			free energy contributions			
rotamer	ΔE	ΔG_{tot}	G_{tot}^{sol}	ΔE	ΔG_{tot}	G_{tot}^{sol}	G_{el}^{sol}(MP2)	G_{cav}	G_{dis}	G_{rep}
dmgSA	0.	0.	−10.71	0.	0.	−9.89	−10.11	13.83	−18.41	4.80
dmgAS	2.06	2.11	−10.66	1.94	2.09	−9.74	−9.94	13.82	−18.25	4.64
dmgSS	1.71	0.88	−11.54	1.53	0.85	−10.57	−10.79	13.83	−18.35	4.75
dmgAA	6.95	6.44	−11.22	6.37	5.91	−10.34	−10.59	13.70	−18.17	4.71
ma═gSA	0.	0.	−9.40	0.	0.	−7.88	−9.18	17.04	−19.87	4.12
ma═gAS	−0.10	−0.14	−9.43	0.50	0.54	−7.84	−9.28	17.00	−20.03	4.47
ma═gSS	0.02	−1.50	−10.92	0.75	−0.79	−9.42	−10.64	16.99	−20.09	4.32
ma═gAA	8.93	6.14	−12.19	6.41	3.92	−10.37	−12.02	16.90	−19.82	4.57
m═agSA	15.24	7.14	−17.50	10.94	4.78	−14.04	−15.91	17.44	−19.94	4.38
m═agAS	7.67	4.06	−13.01	4.70	2.33	−10.26	−11.74	17.10	−19.61	3.99
m═agSS	3.95	2.91	−10.44	1.22	1.01	−8.10	−9.37	17.08	−19.85	4.05
m═agAAc	13.33	9.31	−13.42	7.54	4.76	−10.67	−12.36	16.79	−19.44	4.34
magSA	2.49	1.90	−9.99	1.26	1.68	−7.47	−8.94	17.14	−19.78	4.12
mag(up)SA	5.30	4.01	−10.69	3.59	3.30	−8.17	−9.67	17.07	−20.02	4.44

[a] The HF and MP2/6311++G** energies of dmgSA are −282.256852 and −283.243227 hartrees, respectively. [b] The HF and MP2/6311++G** energies of ma═gSA are −395.054255 and −396.358649 hartrees, respectively. [c] The total components of the solvent effect are also reported, together with their relevant contributions.

TABLE 2: Relative Stability of the Dimethyl- and Methylacetyl-Guanidinium Conformers Considered with Respect to dmgSAp[a]and magSAp[b], Respectively, in Vacuo and in Water Solution at the HF and MP2/6-311++G Levels on MP2/6-31G* Optimized Geometries[c]**

	HF			MP2			free energy contributions			
rotamer	ΔE	ΔG_{tot}	G_{tot}^{sol}	ΔE	ΔG_{tot}	G_{tot}^{sol}	G_{el}^{sol}(MP2)	G_{cav}	G_{dis}	G_{rep}
dmgSAp	0.	0.	−62.18	0.	0.	−62.19	−62.03	13.93	−19.33	5.24
dmgSSp	−0.05	−0.86	−62.99	0.27	−0.58	−63.04	−62.84	13.89	−19.47	5.39
dmgAAp	4.45	3.63	−63.00	2.61	1.73	−63.07	−63.01	13.74	−19.35	5.55
magSAp	0.	0.	−60.54	0.	0.	−58.72	−59.72	17.19	−20.63	4.44
magASp	0.89	0.33	−61.10	1.36	0.79	−59.29	−60.36	17.12	−20.68	4.63
magSSp	0.06	−1.78	−62.38	0.60	−1.37	−60.69	−61.60	17.12	−20.87	4.66
magAAp	8.53	4.92	−64.14	5.34	1.86	−62.19	−63.44	16.94	−20.75	5.06

[a] The HF and MP2/6311++G** energies of dmgSAp are −282.669337 and −283.638624 hartrees, respectively. [b] The HF and MP2/6311++G** energies of magSAp are −395.446996 and −396.740295 hartrees, respectively. [c] The total components of the solvent effect are also reported, together with their relevant contributions.

TABLE 3: Relative Stability of the Neutral Dimethyl- and Methylacetyl-Guanidine Conformers Considered with Respect to dmgSA and ma═gSA, Respectively, in Chloroform Solution at the MP2/6-311++G Level on MP2/6-31G* Optimized Geometries[a]**

	MP2		free energy contributions			
rotamer	ΔG_{tot}	G_{tot}^{sol}	G_{el}^{sol}(MP2)	G_{cav}	G_{dis}	G_{rep}
dmgSA	0.	−3.85	−3.24	10.00	−13.07	2.46
dmgAS	1.60	−4.19	−3.61	9.99	−12.96	2.39
dmgSS	1.18	−4.20	−3.60	10.01	−13.04	2.44
dmgAA	5.81	−4.40	−3.81	9.91	−12.92	2.41
ma═gSA	0.	−3.91	−4.19	12.33	−14.26	2.21
ma═gAS	0.65	−3.77	−4.09	12.30	−14.32	2.35
ma═gSS	−0.56	−4.50	−4.66	12.29	−14.41	2.29
ma═gAA	5.66	−4.66	−5.09	12.22	−14.18	2.37
m═agSA	9.29	−5.56	−6.24	12.61	−14.25	2.31
m═agAS	4.85	−3.77	−4.21	12.36	−14.07	2.15
m═agSS	1.74	−3.39	−3.65	12.35	−14.28	2.18
m═agAAc	7.42	−4.03	−4.54	12.16	−13.92	2.27
magSA	1.74	−3.44	−3.85	12.40	−14.18	2.20
mag(up)SA	3.49	−4.01	−4.37	12.36	−14.33	2.34

[a] The total components of the solvent effect are also reported, together with their relevant contributions.

TABLE 4: Relative Stability of the Dimethyl- and Methylacetyl-Guanidinium Conformers Considered with Respect to dmgSAp and magSAp, Respectively, in Chloroform Solution at the MP2/6-311++G Level on MP2/6-31G* Optimized Geometries[a]**

	MP2		free energy contributions			
rotamer	ΔG_{tot}	G_{tot}^{sol}	G_{el}^{sol}(MP2)	G_{cav}	G_{dis}	G_{rep}
dmgSAp	0.	−40.88	−39.92	10.07	−13.66	2.64
dmgSSp	−0.11	−41.26	−40.23	10.04	−13.78	2.71
dmgAAp	1.96	−41.53	−40.56	9.94	−13.67	2.76
magSAp	0.	−39.39	−39.39	12.42	−14.76	2.33
magASp	1.31	−39.44	−39.47	12.37	−14.76	2.42
magSSp	−0.12	−40.12	−39.98	12.37	−14.94	2.43
magAAp	3.65	−41.08	−41.13	12.24	−14.76	2.57

[a] The total components of the solvent effect are also reported, together with their relevant contributions.

either by two methyl groups (X = Y = CH_3), called for short "dmg", i.e., *N*,*N*′-dimethyl-guanidines, or by a methyl group and an acetyl group (X = CH_3, Y = $COCH_3$), i.e., *N*-methyl,*N*′-acetyl-guanidines, called for short "mag". For the dmg compounds, there is no ambiguity both for the neutral and protonated derivatives (see Scheme 1), while for mag the general form holds only for the protonated derivatives.

For the neutral ones we took into account three possibilities, namely mag, m═ag, and ma═g (see Scheme 2). The protonated compounds considered (a suffix p is added to their names to distinguish them from the neutral systems) are displayed in Scheme 3, while the neutral compounds are reported with their given names, whose definition is more cumbersome, in Schemes 4 and 5. The different conformers have been defined anti−anti (AA), anti−syn (AS), syn−anti (SA), or syn−syn (SS), respectively, depending on the orientation of the XY substituents in this order with respect to the unsubstituted N atom. This N forms always an amino group for protonated guanidines, while it is either an amino group or a C═NH group for the neutral

TABLE 5: Relative Stability of Four Additional Methylacetyl-Guanidine Conformers with Respect to ma═gSA in Vacuo and in Water Solution at the MP2/6-311++G Level on MP2/6-31G* Optimized Geometries[a]**

	MP2			free energy contributions			
rotamer	ΔE	ΔG_{tot}	G_{tot}^{sol}	G_{el}^{sol}(MP2)	G_{cav}	G_{dis}	G_{rep}
magAS	13.43	8.06	−13.25	−15.45	17.28	−20.06	4.98
magASc	8.21	6.25	−9.85	−11.59	16.90	−20.10	4.94
magSS	11.02	3.77	−15.13	−16.95	17.35	−20.23	4.69
magSSc	6.05	3.02	−10.91	−12.39	16.97	−20.12	4.63

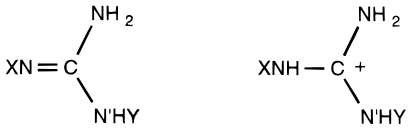
[a] The total components of the solvent effect are also reported, together with their relevant contributions.

TABLE 6: Relative Stability of Four Additional Methylacetyl-Guanidine Conformers with Respect to ma═gSA in Chloroform Solution at the MP2/6-311++G Level on MP2/6-31G* Optimized Geometries[a]**

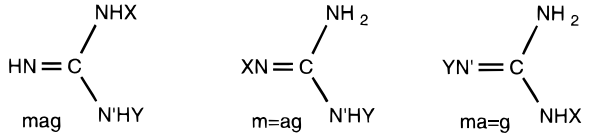
	MP2		free energy contributions			
rotamer	ΔG_{tot}	G_{tot}^{sol}	G_{el}^{sol}(MP2)	G_{cav}	G_{dis}	G_{rep}
magAS	11.27	−6.07	−6.86	12.51	−14.24	2.52
magASc	7.59	−4.54	−5.00	12.24	−14.29	2.52
magSS	8.71	−6.21	−6.78	12.56	−14.43	2.44
magSSc	5.32	−4.64	−4.95	12.29	−14.39	2.41

[a] The total components of the solvent effect are also reported, together with their relevant contributions.

SCHEME 1



SCHEME 2

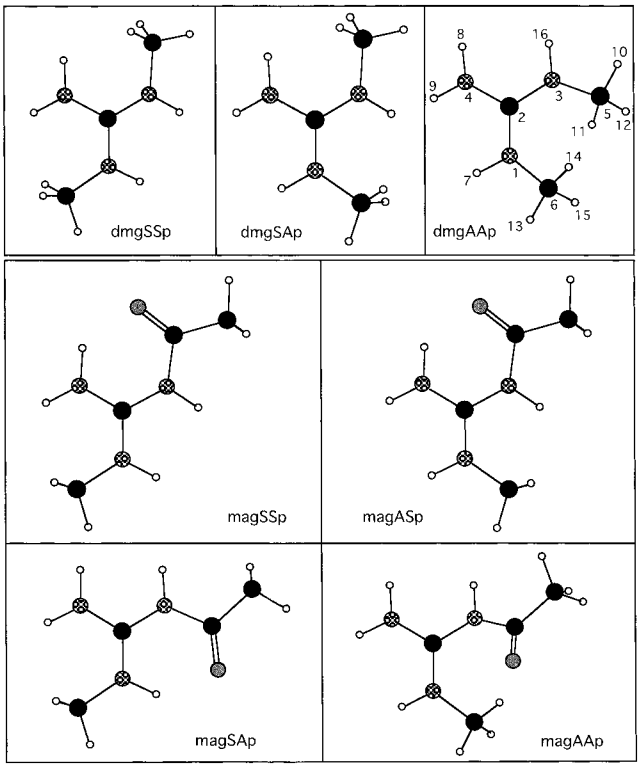


compounds. In the latter case, the H group points toward the X substituted N atom whether not otherwise stated (in the latter case "up" is added to the name, as in mag(up)SA). In the acetyl substituted compounds, the nitrogen H or lone pair is considered to be trans with respect to the adjacent C═O group when not explicitly defined to be cis (indicated by a suffix c, as in m═agAAc).

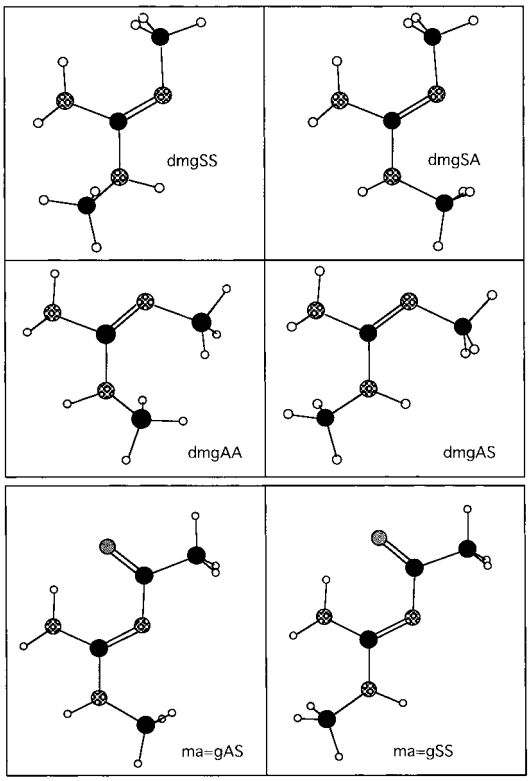
There are only three dimethyl-guanidinium rotamers due to the NH_2 group symmetry, namely dmgSSp, dmgSAp, which is equal to dmgASp, and dmgAAp. As far as the neutral *N*,*N*′-dimethyl derivatives are concerned, because of the presence of a double bond, we considered four rotamers reported in Scheme 4, all bearing a nonplanar amino group. Therefore the equality between the AS and SA conformers no longer holds. In the two *N*,*N*′-methyl-acetyl derivatives with a syn acetyl group reported in Scheme 4, the C═N and C═O double bonds turn out to be cis as in the first conformer of Scheme 5, whose acetyl group is anti; in the second one, the presence of an anti methyl group produces a steric hindrance that forces the C═O group in gauche position. Analogously a gauche conformation is found also in m═agAAc and in m═agSA. In the latter case, the repulsion is due to the in-plane nitrogen lone pair.

The in vacuo geometry optimizations and frequency analysis have been carried out at the MP2[20] level with the 6-31G* basis set,[21] utilizing Gaussian94[14] implemented in a Cray YMP 8 at the Ohio Supercomputer Center. The optimized geometries are available from the authors upon request.

SCHEME 3



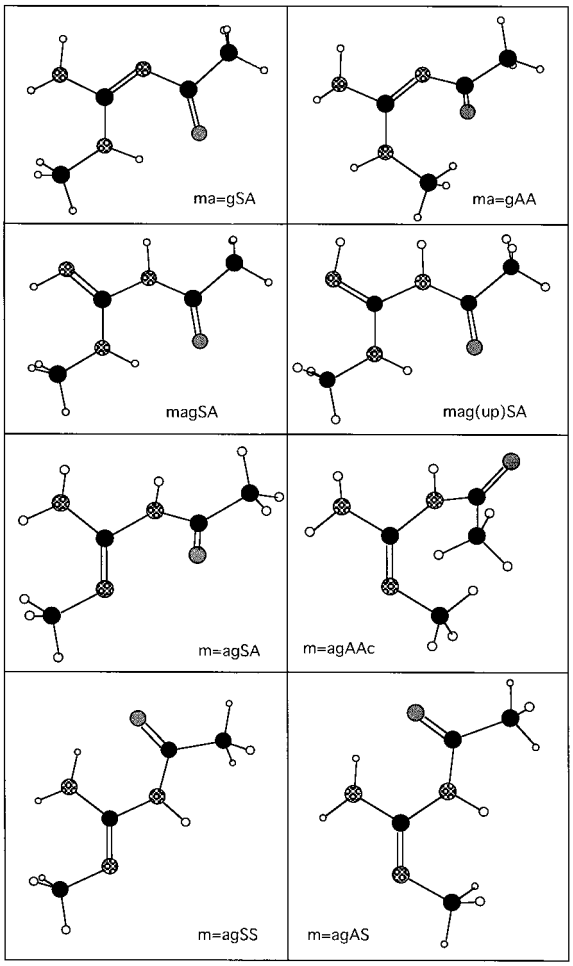
SCHEME 4



Relative free energies in the gas phase, ΔG_{gas}, in the rigid rotor/harmonic oscillator approximation were obtained based on MP2/6-311++G**//MP2/6-31G* single-point calculations.

$$\Delta G = \Delta E^0 + \Delta \mathrm{ZPE} + \Delta\Delta H^{0-T} - T\Delta\Delta S^{0-T} \qquad (8)$$

SCHEME 5



Here ΔE^0 is the quantum chemical relative energy of the conformers/tautomers, ΔZPE is the relative zero-point energy of vibrations calculated by using the MP2/6-31G* frequencies, $\Delta\Delta H^{0-T}$ and $\Delta\Delta S^{0-T}$ are the *relative changes* in enthalpy and entropy, respectively, going from 0 to T temperature, at 1 atm (Table 7).

Ab initio calculations in solution[8] at the MP2 level have been carried out employing the 6-311++G** basis set[22] and modified versions[12] of the relevant links of Gaussian94, which run on the IBM RISC 6000/580-590 workstations at ICQEM. Those modified links are presently available in the announced release of Gaussian (Gaussian98).

Results and Discussion

The in vacuo relative energies of the neutral conformers, taken into account at the HF and MP2 levels, are reported in Table 1 together with their relative solvation free energies in water. The total solvent effects are displayed at both the HF and MP2 levels, while the solvent electrostatic effect is reported only at the MP2 level, together with the cavitation, dispersion, and repulsion contributions to the free energy which allow computation of the total effect. From their values, conversely, it is possible to obtain the electrostatic effect at the HF level not reported in the table. Analogously, in Table 2 the results for the protonated conformers are reported. The first entry of each section of the tables corresponds to the most stable rotamer in vacuo at the MP2/6-311++G** level, the reference conformer, with MP2/6-31G* optimized geometry. The solvation free energy at both the HF and MP2 levels can be obtained by adding the solvent effect for the reference conformer to the relative stability, ΔG_{tot}, while ΔG_{el}(HF) can be obtained by subtracting from ΔG_{tot}(HF) the sum of the G_{cav}, G_{dis}, and G_{rep} contributions. The free energy results in chloroform can be found in Tables 3 and 4 for the neutral and protonated compounds, respectively, but only at the MP2 level. The HF results are available from the authors upon request.

TABLE 7: MP2/6-31G* Vibrational Frequencies, Intramolecular Hydrogen Bond Distances and Relative Free Energies for Optimized Structures in the Gas Phase[a]

	stretching frequencies[b]				
	NH_2	NH	CO	H···O	ΔG_{gas}
dmgSA	3692, 3578	3591			0.00
dmgSS	3698, 3583	3576			1.34
dmgAS	3663, 3550	3638			1.79
dmgAA	3654, 3542	3583			6.26
ma=gSA	3719, 3597	3452	1717	1.81	0.00
ma=gSS	3708, 3469	3655	1724	1.84	0.52
ma=gAS	3689, 3494	3636	1731	1.86	0.49
ma=gAA	3702, 3581	3647	1752		6.59
m=agSS	3703, 3543	3627	1798	1.95	0.23
m=agAS	3704, 3569	3654	1804	1.99	4.06
m=agAAc	3684, 3563	3594	1804		7.78
magSA		3566	1794	1.92	0.44
		3628 (amide)			
		3648 (HN=)			
dmgSAp	3750, 3628	3656, 3648			0.00
dmgSSp	3753, 3634	3651, 3643			0.66
dmgAAp	3740, 3615	3633, 3629			3.88
magSAp	3743, 3628	3617, 3471	1831	1.85	0.00
magSSp	3704, 3495	3650, 3617	1834	1.87	0.77
magASp	3694, 3503	3637, 3634	1839	1.88	1.61
magAAp	3725, 3597	3609, 3600	1851		6.47

[a] Vibrational frequencies, H···O distances and relative free energies in cm^{-1}, Å, and kcal/mol units, respectively. [b] Underscored frequencies correspond to vibrations involved in hydrogen bonding.

Neutral and Protonated *N*,*N*′-Dimethyl-Guanidines. The results for dimethyl-guanidines are reported in the upper part of Tables 1−4. In vacuo at the HF level, the neutral and protonated derivative stability range is within 6.9 and 4.5 kcal/mol, respectively, while the energy differences are somewhat damped at the MP2 level, becoming 6.4 and 2.6 kcal/mol. The solvent effect is considerably less favorable, as expected, for neutral than for protonated guanidines, i.e., about −11 vs −63 kcal/mol in water and about −4 vs −41 kcal/mol in chloroform (not displayed) at the HF level. The correlation effect, which is very feeble for the protonated derivatives in solution (water or chloroform), becomes ∼0.4 kcal/mol in chloroform and ∼1 kcal/mol in water for the neutral derivatives.

The relative stabilities in vacuo (empty markers) and in solution (solid markers) are graphically displayed in Figures 1−4. It is apparent that there is a very limited effect of both the level (HF or MP2) and the solvent (water or chloroform) on the mutual stability of the neutral conformers. For the protonated ones, the free energy gap is somewhat reduced at the MP2 level, while dmgSSp turns out to be slightly more stable than dmgSAp even at the MP2 level. Equilibrium mixtures are dominated by the dmgSA conformer both in the gas phase and in solution for the neutral form. A close representation of the dmgSSp and dmgSAp conformers, sensitive to the computation level, is expected in solution for the protonated species. The dmgAAp form, despite its favorable solvent effect, still does not set up a remarkable fraction in the mixture.

To evaluate the likely influence of the solvent on the solute geometry, we have optimized the structure of dmgAAp at the 6-31G* level in aqueous solution. If we pay special attention

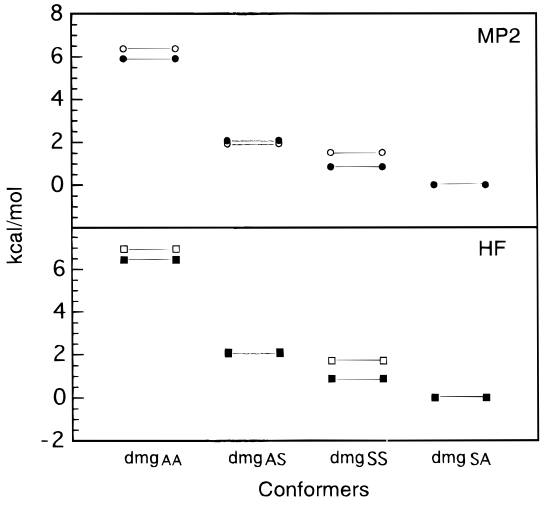


Figure 1. Total free energy differences in water for the neutral *N*,*N*′-dimethyl-guanidine conformers considered with respect to dmgSA (see Scheme 2) obtained at the HF (black squares) and MP2 (black circles) levels with the 6-311++G** basis set. The potential energy differences in vacuo at both levels (empty markers) are also displayed. Geometries were optimized at the MP2/6-31G* level. The differential total solvent effect, computed using PCM (see text), can be appreciated by the separation of the free energy with respect to the in vacuo energy.

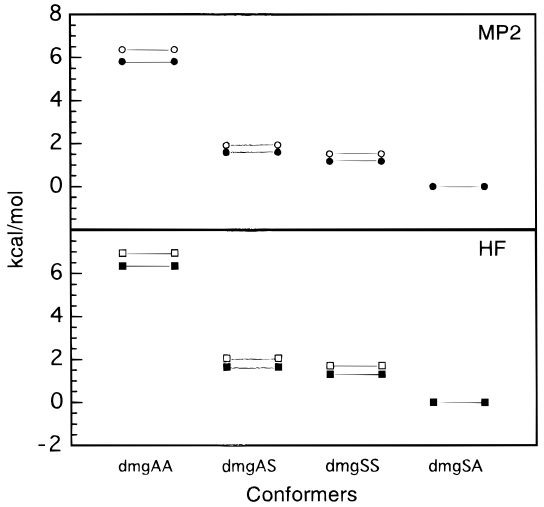


Figure 2. Total free energy differences in chloroform for the neutral *N*,*N*′-dimethyl-guanidine conformers considered with respect to dmgSA obtained at the HF (black squares) and MP2 (black circles) levels with the 6-311++G** basis set. The potential energy differences in vacuo at both levels (empty markers) are also displayed. Same remarks as in Figure 1.

to the values of τ, the 6−1−2−4/5−3−2−4 dihedral angles (see Scheme 3), which are different from 180° because of the methyl group steric hindrance, we find that their equilibrium values turn out to be 205.62° in vacuo and 206.10° in aqueous solution at the HF level, while the differential solvation free energy is slightly more favorable than the internal energy for τ below 202° and less favorable for τ greater than 210°.

The basis set effect is very feeble; the curves related to the free energy gap with respect to the structure exhibiting the most stable dihedral angle obtained for several values of τ computed at the MP2/6-311++G** level are almost exactly superimposed to those computed at the MP2/6-31G* level. Therefore, since the optimization at the MP2 level is much more expensive, we carried out single-point MP2/6-31G* calculations in vacuo and in aqueous solution for several values of these dihedral angles. The MP2 equilibrium values for τ turn out to be larger than the

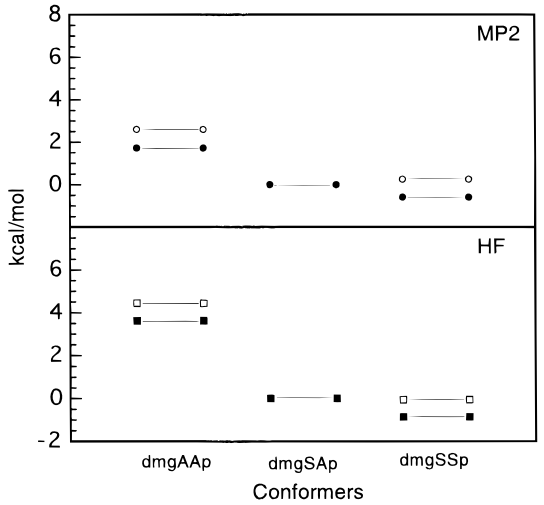


Figure 3. Total free energy differences in water for the protonated *N*,*N*′-dimethyl-guanidine conformers considered with respect to dmgSAp═dmgASp (see text and Scheme 1) obtained at the HF (black squares) and MP2 (black circles) levels with the 6-311++G** basis set. The potential energy differences in vacuo at both levels (empty markers) are also displayed. Same remarks as in Figure 1.

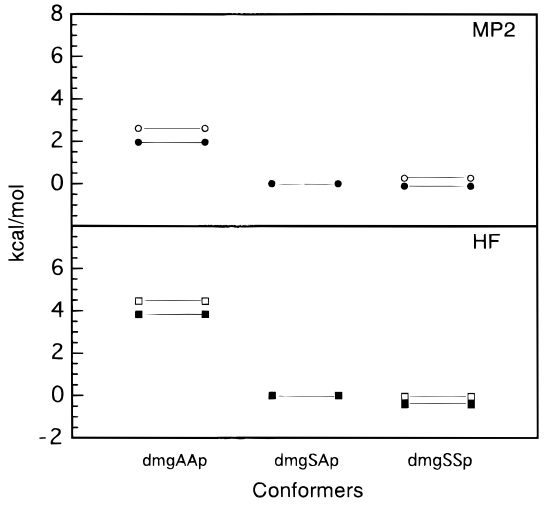


Figure 4. Total free energy differences in chloroform for the protonated *N*,*N*′-dimethyl-guanidine conformers considered with respect to dmgSAp═dmgASp obtained at the HF (black squares) and MP2 (black circles) levels with the 6-311++G** basis set. The potential energy differences in vacuo at both levels (empty markers) are also displayed. Same remarks as in Figure 1.

HF ones but almost identical in vacuo (209.80°) and in solution (209.82°). Again, the MP2 curve in solution is smoother than the MP2 curve in vacuo below 206° and steeper above 212°.

In summary, the solvent effect cannot remarkably distort the geometry, which seems to be strongly determined by internal forces, not challengeable by the solvent interaction.

Neutral and Protonated *N*-Methyl,*N*′-acetyl-Guanidines. Results for methyl-acetyl-guanidines are reported in the lower part of Tables 1−4. The relative stability of the neutral conformers is within 15 and 11 kcal/mol at the HF and MP2 levels, respectively, of the most stable conformer in vacuo (Table 1). Using relative free energies (Table 7) the gas-phase equilibrium mixture contains fractions of about 33%, 22%, 16%, 15%, and 14% for the ma═gSA, m═agSS, magSA, ma═gAS, and ma═gSS conformers/tautomers, respectively. (For comparison with in-solution mixtures, the equilibrium was calculated at $T = 310$ K, which is the relevant temperature for the human organism.)

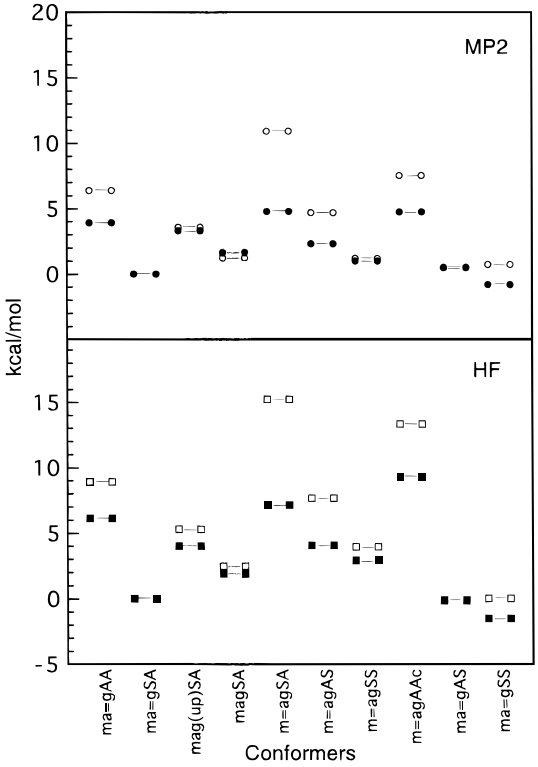


Figure 5. Total free energy differences in water for the neutral *N*,*N*′-methylacetyl-guanidine conformers considered with respect to ma═gSA (see text and Scheme 3) obtained at the HF (black squares) and MP2 (black circles) levels with the 6-311++G** basis set. The potential energy differences in vacuo at both levels (empty markers) are also displayed. Same remarks as in Figure 1.

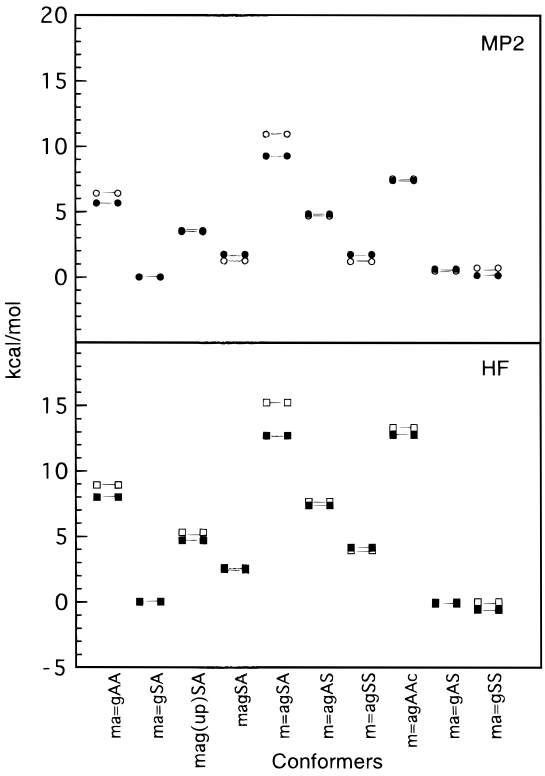


Figure 6. Total free energy differences in chloroform for the neutral *N*,*N*′-methylacetyl-guanidine conformers considered with respect to ma═gSA obtained at the HF (black squares) and MP2 (black circles) levels with the 6-311++G** basis set. The potential energy differences in vacuo at both levels (empty markers) are also displayed. Same remarks as in Figure 1.

The solvent effect, much more favorable for the conformers higher in energy, reduces the relative stability range to about 5 kcal/mol in water at the MP2 level, while in chloroform it remains slightly larger than 9 kcal/mol (Figures 5 and 6). Nonetheless, these stabilized structures are still too high in free energy to appear in the equilibrium mixture. In contrast, smaller solvent effects for the low-energy structures lead to an equilibrium composition entirely different from that in the gas phase. Considering the same corrections as in the gas phase (the determination of vibrational frequencies requests in-solution optimized structures that are not available at this level at present, as stated in the Introduction), the equilibrium mixture in water contains 69% ma═gSS, 13% SA, and 5% AS. Out of other tautomers, only the m═agSS takes about 13%. The composition in chloroform is 66% ma═gSS, 18% SA, 7% AS, 5% m═agSS, and 4% magSA. Thus, ma═gSS is the dominant conformer in both solvents in comparison to SA in the gas phase and the fractions of all other isomers are reduced in solution.

The gas-phase, protonated *N*,*N*′-methyl-acetyl-guanidinium ion is comprised of 74% SA, 21% SS, and 5% AS. Increasing polarity of the solvent leads to a switch in the magnitude of the SA and SS fractions; compositions are 50% SA, 46% SS, and 4% AS, in chloroform, and 86% SS, 12% SA, and 2% AS, in water. The fraction of the magAAp conformer is negligible in any equilibria.

The solvent effect, because of the presence of the more flexible and polar acetyl group, is less independent of the conformation. For neutral guanidines, it varies from −9 to −17 and from −4 to −7 kcal/mol in water and in chloroform, respectively, at the HF level, with a sharp enhancement for the protonated ones (−61/−64 kcal/mol in water and −40/−42 kcal/mol in chloroform). The inclusion of correlation effects reduces

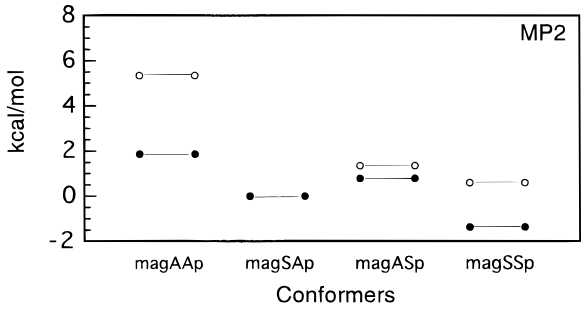


Figure 7. Total free energy differences in water for the protonated *N*,*N*′-methylacetyl-guanidine conformers considered with respect to magSAp (see Scheme 1) obtained at the MP2 (black circles) level with the 6-311++G** basis set. The potential energy differences in vacuo (empty circles) are also displayed. Same remarks as in Figure 1.

the solvent effect more than in the case of dimethyl-guanidines, i.e., by 2−3 kcal/mol in water (−7/−14 and −59/−62 kcal/mol) and by ∼1 kcal/mol in chloroform (−3/−6 and −39/−41 kcal/mol, respectively, for the neutral and protonated conformers). The solvation free energies of the methyl-acetyl-guanidinium conformers are within about 3 kcal/mol in water at the MP2 level (Figure 7), with a sensitive stabilization of the magSSp form over magSAp in water and with nearly equal fractions in chloroform (Figure 8). Importance of careful calculations is revealed for this system. The largest electrostatic solvent effect for the magAAp conformer was predictable based on its four N−H bonds supporting each other in the solvent polarization. There is an intramolecular hydrogen bond for all three other conformers weakening the solvent polarization in this region. There are three N−H bonds with possible cooperation in polarization for each of the SA and AS conformers. The

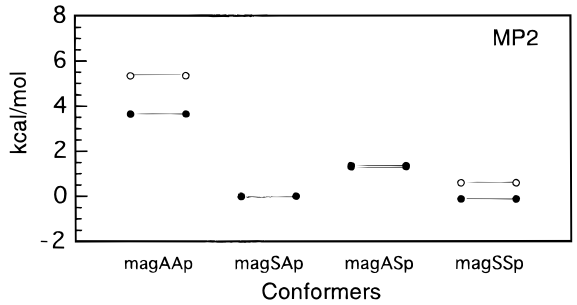
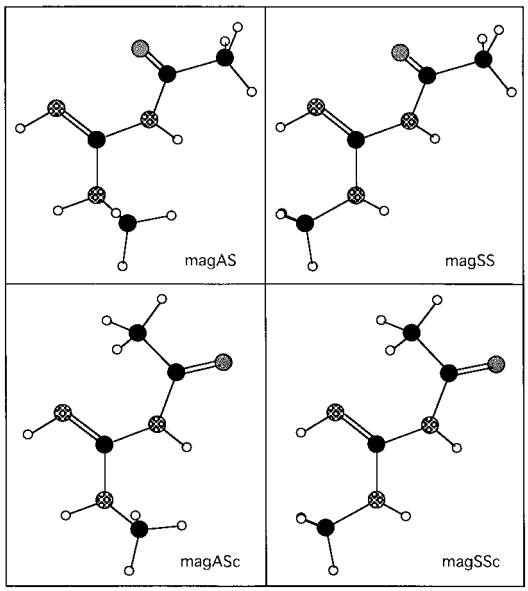


Figure 8. Total free energy differences in chloroform for the protonated *N,N′*-methylacetyl-guanidine conformers considered with respect to magSAp (see Scheme 1) obtained at the MP2 (black circles) level with the 6-311++G** basis set. The potential energy differences in vacuo (empty circles) are also displayed. Same remarks as in Figure 1.

SCHEME 6



magSSp form has only two cooperating N−H bonds (exposed to the solvent), yet this conformer results in the second most favorable solvent effect within the series in both solvents.

Additional mag Conformers. Since the N in-plane lone pair can have a sensitive effect in stabilizing conformers without intramolecular H-bonds in a polar solvent, the interest is here focused on two methyl-acetyl-guanidines (magAS and magSS, see Scheme 6) both with the C═NH group. Because of the absence of intramolecular H-bonds, however, they are noticeably unfavored in vacuo and differ sensitively from the magSA conformer already considered.

To shed some light on the interactions taking place in these rotamers, the conformers magASc and magSSc, also reported in Scheme 6, were examined as well. The results obtained for these four additional conformers are reported in Tables 5 and 6, for water and chloroform, respectively. The solvent effect is much more favorable for magAS and magSS than for magASc and magSSc, as expected, because the cis peptide bond makes the two polar groups (the N hydrogen and the carbonyl O) point toward the same portion of the cavity surface, thus producing two opposite effects that compensate each other to a large extent. Furthermore, in parallel with the formation of the cis peptide bond, the cooperativity of the N(═C) and O(═C) lone pairs in the polarization process is canceled. In magSSc, however, the two almost parallel N−H bonds display a solvent interaction more favorable than the analogous arrangement of a C═NH group and the N−H bond found in magASc. This occurs also in magSS with respect to magAS; in both conformers, however, the most favorable interaction with the polar solvent is produced by the cooperative effect of the N and O lone pairs. A comparable effect is found also in m═agSA, which displays a similar arrangement though involving the lone pair of the methyl-substituted N. In fact, this conformer has the largest solvent effect at any levels and in both solvents (Tables 1 and 3). In all the cases we examined however, the solvent effect, though very favorable, is not sufficient to reverse the stability order.

Electrostatic vs Total Results. It can be easily seen that the two repulsive terms (G_{cav} and G_{rep}), in general, counterbalance or turn out to be slightly larger than the attractive one (G_{dis}), making the electrostatic contribution almost coincide with the total free energy. This is especially the case for the protonated mag derivatives in chloroform and for the protonated dmg conformers in water. On the contrary, for the protonated mag conformers in water, the cavitation and repulsion terms prevail over the dispersion attraction, while for the protonated dmg conformers in chloroform, the dispersion attraction prevails over the repulsive terms.

For the neutral mag compounds, the total free energy is always less favorable than its electrostatic component by 0.2−0.8 kcal/mol in chloroform and by 1.2−2.2 kcal/mol in water; the contributions with a noticeable excursion are the repulsive ones, while the dispersion attraction is fairly constant. For the neutral dmg conformers, the total free energy is slightly less favorable than its electrostatic component by about 0.2 kcal/mol in water, whereas it is more favorable by about 0.6 kcal/mol in chloroform. The nonelectrostatic terms however for these compounds represent only a small percentage of the solvent effect.

Reliability of the present results, in the absence of available experimental data for the equilibrium composition of the dimethyl and methyl-acetyl substituted guanidines, can be assessed on the basis of the work of Barone et al.[12] Using the PCM method with the UAHF model and the charge normalization method ICOMP = 4, as was done also in the present study, the rms error for the free energy of hydration for 43 neutral molecules is 0.21 kcal/mol using the HF/6-31G* level. The rms error for 28 ions was 1.25 kcal/mol. In comparable cases when using the HF/6-311+G** level, the hydration free energies lowered by about 1 kcal/mol for neutral molecules and by some tenths of a kcal/mol for a positive ion.[12]

Relative Partitioning Constants. The 6-311++G** basis used in the present study is close to the 6-311+G** basis used in ref 12. Even assuming that our calculated G_{tot}^{sol} values are too negative by 1−2 kcal in the *separate* solvents, their *difference* could be quite reasonable. In fact, calculating the partitioning constant, P, the equation $-\Delta G°/2.3RT = \log P = \log(c_{chl}/c_w)$ holds. Assuming that the zero-point and frequency dependent thermal corrections for the internal free energy of a specific structure are similar in water and chloroform, $\Delta G°$ may be approximated by the differences of the G_{tot}^{sol} terms in Tables 1−6. This approximation may be supported by results of Wong et al.,[23] who optimized the geometry of small, polar molecules in solution at the HF/6-31G** level, using a spherical cavity and solvent dielectric constants of 2 and 35.9. Geometric changes as compared to the gas-phase structure did not exceed 0.008 Å for bond lengths and 0.5° for bond angles. Changes in the frequency-dependent free energy corrections at $T = 298$ K amounted to some hundredths of a kcal/mol. Additional evidence that this approximation is satisfactory can also be obtained from earlier PCM results.[24]

Comparisons of the terms both at the HF and MP2 levels show about 6 kcal/mol more negative values for the dmg compounds in water than in chloroform. This value corresponds to log $P = -4.2$ at $T = 310$ K, thus the *N*,*N*′-dimethyl-guanidine stays practically in the aqueous phase. Even if we assume that the free energy difference in solution is overestimated by as much as 2 kcal/mol, the log *P* value is −2.8, allowing partitioning ratio of 1:660. Partitioning of the protonated form is even less possible because of the large G_{tot}^{sol} difference of about 22 kcal/mol. A similar free energy difference (19−21 kcal/mol) has been found for the protonated methyl-acetyl derivative (Tables 2 and 4).

For the methyl-acetyl derivative, free energy differences for the lowest energy, neutral conformer/isomer (ma═gSS, ma═gSA, ma═gAS) are 4−5 kcal/mol, corresponding to log *P* values of −2.8 to −3.5 kcal/mol. These values are still too negative for a remarkable partitioning into chloroform, but allow an important conclusion to be drawn: an acetyl instead of methyl substitution to guanidine leads to an increase of about one unit in the chloroform/water log *P* value. This conclusion seems to be much unexpected if considering the polar carbonyl group in the acetyl substituent. Interestingly, just the appearance of this polar site decreases the polar surface of the molecule in low-energy conformations. The N−H bonds are fully exposed to solvation in the (neutral and protonated) dimethyl-guanidine conformers. By replacing a methyl group with an acetyl group, N−H···O═C intramolecular hydrogen bonds are formed in SA, AS, and SS conformations. By this interaction not only does the entering polar C═O becomes less exposed to solvation but also an N−H bond (which was fully solvated in dimethyl-guanidine) becomes partially buried in solution. This effect is more important in water than in chloroform because of the larger solvent effect of the more polar solvent onto a polar bond. As a result, the stabilization of the methyl-acetyl derivatives is reduced in water as compared to the dimethyl derivative, thus leading to an increase of log *P*. These results indicate the possible estimate of the substituent effect on log *P*, using ab initio calculations. Guanidine-based drugs with optimized partitioning character may be developed accordingly, although the theoretical prediction has not been verified because of the absence of experimental data. Based on reliably optimized geometries, the significance of intramolecular hydrogen bonds can be assessed, and this structural peculiarity can be used in interpreting results unusual when considering only the chemical characters of substituents.

Overall, solvation free energies and relative log *P* values are remarkably affected by the formation of an intramolecular hydrogen bond. Its effect on the vibrational spectra and on the gas-phase free energy is discussed below.

Vibrational Frequencies and Hydrogen Bond Structure. Calculated N−H and C═O stretching frequencies are collected in Table 7. The NH_2 group has an asymmetrical and a symmetrical N−H stretching vibration generally about 3520 and 3400 cm^{-1}, respectively, in primary amides.[25] Our previous results indicate[26] that harmonic frequencies based on MP2/6-31G* optimized geometries are overestimated by about 3% on the average. Table 7 contains uncorrected frequencies, while in calculating the ΔZPE values for obtaining ΔG_{gas}, a factor of 0.97 was applied. Underscored frequencies refer to vibrations involved in an intramolecular hydrogen bond.

All three N−H vibrational frequencies for the dmg derivative show a conformational dependence. NH frequencies are generally between those for the NH_2 group. The $\Delta\nu$ range is 44 cm^{-1} for the NH_2 vibrations (but the asymmetrical vibration is higher than the symmetrical one by about 100 cm^{-1}) and 62 cm^{-1} for the NH vibrations. Frequency-dependent thermal corrections amount to 0.1−0.2 kcal/mol when comparing the ΔE^{MP2} and ΔG_{gas} values in Tables 1 and 7, respectively. (The positions of the dmgAS and dmgSS conformers are reversed in the two tables.)

Decidedly different results have been obtained for the methyl-acetyl derivative with a possible intramolecular hydrogen bond. The asymmetrical NH frequency is about 3700 cm^{-1} ($\Delta\nu = 35$ cm^{-1}) and is fairly insensitive to the hydrogen bond formation. The $\Delta\nu$ range shows a value similar to that of the dmg compounds, thus indicating a moderate conformational dependence. The symmetrical NH (lower by 121 cm^{-1} in the ma═gAA and m═agAAc tautomers without an intramolecular hydrogen bond) shows $\Delta\nu$ ranges of 128 and 120 cm^{-1} in the ma═g and m═ag series, respectively. The $\Delta\nu$ value for the separate NH vibration amounts to 203 cm^{-1} in the ma═g series, while it is only 60 cm^{-1} in the m═ag series, where this bond is not involved in intramolecular hydrogen bonds. The $\Delta\nu$ value is 82 for magSA with three different types of N−H bonds.

The C═O stretching frequencies show a lower sensitivity to the involvement in hydrogen bonds. The $\Delta\nu$ values have a range of 35 cm^{-1} in the ma═g series and only of 6 cm^{-1} in the m═ag series. A slight red-shift was calculated between the mag and m═ag tautomers.

The H···O distances of the hydrogen bond are shorter by about 0.1 Å in the ma═g series (1.81−1.86 Å) as compared to m═ag values of 1.95−1.99 Å. The red-shift for the corresponding N−H and C═O frequencies reflects the hydrogen bond effect; the shorter the H···O distance, the lower the frequency. This is far not true for the relative gas-phase free energies; m═agSS has a relative ΔG value of only 0.23 kcal/mol, while it has a relatively long intramolecular hydrogen bond of 1.95 Å. The ma═gSS and ma═gAS isomers have ΔG values of 0.52 and 0.49 kcal/mol, respectively, while their H···O distances amounting to 1.84 and 1.86 Å show a reverse order as compared to the ΔG values. Even more irregular results are obtained if the $\Delta G - \Delta E$ values are considered. The thermal corrections are, e. g., −0.99, −0.82, and −0.01 kcal/mol for m═agSS, magSA, and ma═gAS, respectively.

By examining the terms contributing to the thermal corrections, the vibrational entropy revealed to be mostly responsible for the above corrections. More precisely, the entropy contribution due to the lowest vibrational frequency covers the largest part of the calculated relative free energy corrections: −0.81 and −0.54 kcal/mol for m═agSS and magSA, respectively. The corresponding value calculated for ma═gAS is about 0. Thus, the "anomalous" behavior of the thermal correction is not due to the shift in the N−H and C═O frequencies.

In the ma═g series, the lowest vibrational frequency is about 70 cm^{-1} and the vibration is extended over the whole molecule. In contrast, the lowest frequency is 17 cm^{-1} for m═agSS and 27 cm^{-1} for magSA. In both cases, the vibration involves almost exclusively the motion of the hydrogens belonging to the acetyl-methyl group. In fact, it is true only if there is an intramolecular hydrogen bond in the mag and the m═ag tautomer. No such decrease was found for the m═agAAc structure without hydrogen bonds, while a moderate decrease to 47 cm^{-1} was found for the m═agAS conformer with an internal hydrogen bond.

Thus, we found that the large free energy correction is related to the decrease of the lowest vibrational frequency value. This decrease emerges only for structures with an intramolecular hydrogen bond, *and with the CH₃−CO−NH−C substructure*.

For the ma═g tautomers with a $CH_3-CO-N═C$ substructure, no lowest frequency below about 70 cm^{-1} was found.

The tautomers with the $CH_3-CO-N═C$ moiety are lower in energy (Table 1) presumably due to a larger π-electron delocalization and because of a geometry allowing formation of short hydrogen bonds. The m═ag and mag structures cannot form such short intramolecular hydrogen bonds, but the created structure allows larger flexibility for the acetyl-methyl (but not for the simple methyl group of the molecule) which structural feature produces a relative stabilization in free energy. These results emphasize the importance of considering the internal free energy and not only the internal energy in theoretical calculations. For systems where the relative energies of the isomers are within about 1 kcal/mol, such unforeseen effects may largely influence the calculated equilibrium composition.

Frequencies for the protonated species are calculated to be somewhat larger than those for the neutral ones. The $\Delta\nu$ values are 13−27 cm^{-1} for dmgp structures, indicating smaller conformation dependence than for the neutral species. N−H frequencies decrease by 94−102 cm^{-1} in the magp series upon hydrogen-bond involvement, as compared to the magAAp structure, without intramolecular hydrogen bond. The decrease in the C═O frequencies is up to 20 cm^{-1}. The free energy corrections are 0.39 kcal/mol for dmgSSp and 0.17−0.25 kcal/mol for magSSp and magASp. Large values, 1.13−1.27 kcal/mol, were obtained for the AAp conformers, indicating the inherently larger rigidity of this conformation as compared to the SS, SA, and AS conformations.

Conclusions

This study performs a geometry optimization in aqueous solution at the HF level with a fairly large basis set (6-31G*) for a particular cation, magAAp, obtaining a structure very similar to the in-vacuo optimized geometry. The effect of the solvent on the internal geometry is very limited, and this occurs even on the dihedral angles, where a larger effect could be expected. This fact indirectly supports the use of the in-vacuo optimized geometries. A systematic analysis of the solvent effect at the HF and MP2/6-311++G** levels has been carried out on several isomers and rotamers of *N*,*N*′-dimethyl and *N*-methyl,*N*′-acetyl-guanidine and guanidinium with geometries optimized in vacuo at the MP2/6-31G* level and two different solvents (water and chloroform) in the PCM framework. In-vacuo geometry optimizations for the methyl-acetyl derivative favor neutral tautomers having the $CH_3-CO-N═C$ moiety, which allows formation of intramolecular hydrogen bonds shorter than in tautomers with the $CH_3-CO-NH-C$ substructure. The latter tautomeric structure produces, however, remarkably larger vibrational entropy which leads to relative stabilization in the internal free energy.

As a general rule, the solvent effect is much larger for the protonated compounds than for the neutral ones. The different permittivity of the two solvents (water and chloroform) is resented more by the neutral compounds. Especially at the MP2 level, there is a damping effect of the solvent that tends to equalize the free energies of the various conformers in solution. Interestingly enough, even the HF picture is generally adequate to evaluate and compare the conformational preferences of these species in vacuo and in solution. This was hardly predictable because compounds with a possibly delocalized π-system are expected to show a much larger sensitivity to correlation effects upon conformational change. The nonelectrostatic components of the solvation free energy, due to their compensating character, play a minor role both in water and in chloroform for these systems.

Calculated partitioning constants between the two solvents indicate that the protonated species stays in the aqueous phase assuming that immiscible solvents are modeled by the present method. The neutral forms of both guanidine derivatives stay practically in the aqueous phase too. An acetyl substitution of guanidine as compared to a methyl one increases, however, the log *P* value by about a unit. Theoretical determination of the substituent effect on the partitioning constant as shown here may be useful in designing substituted guanidine drugs with optimized partitioning character.

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References and Notes

(1) *3D-QSAR in Drug Design*; Kubinyi, H., Ed.; ESCOM: Leiden, 1993.

(2) Fan, W.; Tsai, R.-S.; El Tayar, N.; Carrupt, P.-A.; Testa, B. *J. Phys. Chem.* **1994**, *98*, 329.

(3) Pagliara, A.; Carrupt, P.-A.; Caron, G.; Gaillard, P.; Testa, B. *Chem. Rev.* **1997**, *97*, 3385.

(4) (a) Durant, G. J.; Roe, A. M.; Green, A. L. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Butterworth: London, 1970; Vol. 7, Part 1. (b) Ganelin, C. R.; Durant, G. J. *Burger's Medicinal Chemistry*; Wiley: New York, 1981; Part III, p 487.

(5) Boudon, S.; Wipff, G.; Maigret, B. *J. Phys. Chem.* **1990**, *94*, 6056.

(6) Muller, G. W.; Walters, D. E.; DuBois, G. E. *J. Med. Chem.* **1992**, *35*, 740.

(7) (a) Alagona, G.; Ghio, C.; Nagy, P. I.; Durant, G. J. *J. Phys. Chem.* **1994**, *98*, 5422. (b) Nagy, P. I.; Durant, G. J. *J. Chem. Phys.* **1996**, *104*, 1452.

(8) (a) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117. (b) Bonaccorsi, R.; Cimiraglia, R.; Tomasi, J. *J. Comput. Chem.* **1983**, *4*, 567. (c) Bonaccorsi, R.; Cimiraglia, R.; Tomasi, J. *Chem. Phys. Lett.* **1983**, *99*, 77. (d) Pascual-Ahuir, J. L.; Silla, E.; Tomasi, J.; Bonaccorsi, R. *J. Comput. Chem.* **1987**, *8*, 778.

(9) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, 1989.

(10) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(11) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

(12) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210.

(13) Cammi, R.; Tomasi, J. *J. Chem. Phys.* **1994**, *100*, 7495.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, rev. D4; Gaussian, Inc.: Pittsburgh, PA, 1995.

(15) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151.

(16) (a) Cossi, M.; Tomasi, J.; Cammi, R. *Int. J. Quantum Chem. Symp.* **1995**, *29*, 695. (b) Pierotti, R. A. *Chem. Rev.* **1976**, *76*, 717.

(17) Cossi, M.; Mennucci, B.; Cammi, R. *J. Comput. Chem.* **1996**, *17*, 57.

(18) (a) Pertsin, A. J.; Kitaigorodsky, A. I. *The Atom-Atom Potential Method*; Springer-Verlag: Berlin, 1986; p 141. (b) Caillet, J.; Claverie, P.; Pullman, B. *Acta Crystallogr.* **1978**, *B34*, 3266.

(19) (a) Floris, F.; Tomasi, J. *J. Comput. Chem.* **1989**, *10*, 616. (b) Floris, F.; Tomasi, J. *J. Comput. Chem.* **1991**, *12*, 784.

(20) (a) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. (b) Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem.* **1976**, *10s*, 1. (c) Krishnan, R.; Frisch, M. J.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 4244.

(21) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (b) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

(22) Hehre, W. J.; Radom, L.; Schleyer, P.v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(23) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1645.

(24) (a) Bonaccorsi, R.; Ojalvo, E.; Tomasi, J. *Collect. Czech. Chem. Commun.* **1988**, *53*, 2320. (b) Alagona, G.; Bonaccorsi, R.; Ghio, C.; Tomasi, J. *Graphical Description on the Solute Surface of the Solvation Energy and Solvent Transfer Energy*; 8th Annual Conference Molecular Graphics Society, St. Andrews (Scotland), 1989. (c) Bonaccorsi, R.; Floris, F.; Tomasi, J. *J. Mol. Liquids* **1990**, *47*, 25. (d) Bonaccorsi, R.; Floris, F.; Palla, P.; Tomasi, J. *Thermochim. Acta* **1990**, *162*, 213.

(25) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; Wiley: New York, 1981.

(26) (a) Nagy, P. I.; Durant, G. J.; Smith, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 2912. (b) Nagy, P. I.; Ulmer, C. W., II; Smith, D. A. *J. Chem. Phys.* **1995**, *102*, 6812.