Preferences of the Oxalamide and Hydrazide Moieties in Vacuum and Aqueous Solution. A Comparison with the Amide Functionality

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A theoretical study of the conformational preferences, changes in energy, and charge distribution for the oxalamide and hydrazide moieties of *N*,*N′*-dimethyloxalamide and *N*,*N′*-diacetylhydrazine is presented. Both gas-phase and aqueous environments have been simulated at the ab initio level using different basis sets and including electron correlation effects at the MP4 level. Three and four minimum energy conformations have been found for the oxalamide and hydrazide moieties, respectively. Results are in agreement with available experimental data obtained by X-ray crystallography. The inclusion of water largely affects not only the relative energy between the minima but also the charge distribution of the different structures. The main trends predicted for the oxalamide and hydrazide groups have been compared with those displayed by the amide bond of *N*-methyacetamide, which were computed at the same levels of theory.

Introduction

The incorporation of nonstandard amino acids with well-defined stereochemical and functional properties is a useful tool for the design of peptides and protein engineering.[1] Two different strategies are usually employed to obtain noncoded α-amino acid residues. The first one is based on side chain modifications, in which case the amide bond is not changed. Within this strategy, the α,α-dialkylated glycines constitute the most widely studied class of amino acids,[2−4] being used as scaffolding blocks in the design of protein and enzyme mimetics due to their backbone rigidity.

The second strategy used to generate noncoded α-amino acids is to modify the nature of the peptide bond. More specifically, an important effort has been devoted to retromodification, i.e., reversal of the direction of the amide group, during the last 15 years. Thus, retropeptides have been used in protein engineering to design secondary structure motifs[5] as well as to prepare biactive peptides with enhanced stability toward enzymatic degradation.[6] Within this strategy, the preparation of new retro-bispeptides having the oxalamide (−NH−CO−CO−NH−) moiety located at the center has become of great interest. Thus, a range of retro-bispeptides have been prepared[7] and could be used soon for designing enzyme mimics and potential inhibitors. Furthermore, it has been conjectured that the closely related moiety α-keto amide (−NH−CO−CO−), which is present in powerful immunosuppressants such as rapamycin and FK-506,[8] plays a a key role in the binding to protein immunophilins and in inhibiting their *cis* ↔ trans isomerase.

On the other hand, retroamide and oxalamide linkages are also of great importance in the material science field, since they are included in aliphatic polyamides,[9,10]i.e., nylons. Furthermore, the hydrazide (−CO−NH−NH−CO−) moiety, which is the reversal of the oxalamide moiety, has been also included in some polyamides.[11] Complex structures, different to the extended conven-

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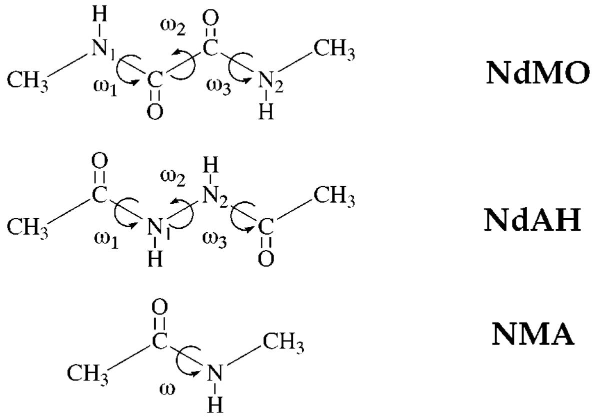

Figure 1. Chemical structures of the model molecules investigated in the present work: *N,N′*-dimethyloxalamide (NdMO), *N,N′*-diacetylhydrazide (NdAH), and *N*-methylacetamide (NMA). The dihedral angles are indicated.

tional ones, have been found in some cases.[9,10d] Thus, nylons with retroamide and oxalamide linkages tend to adopt conformations with several hydrogen bonding directions when the polymer contains an aliphatic segment with a suitable number of methylene units.

Understanding of the molecular and electronic structure of the functional groups is essential to explain the conformational properties and dynamics of the molecules. Within this context, the amide group has been extensively investigated for the last 15 years using both experimental[12] and theoretical[13] methods. The results have provided important information about both the *cis* ↔ trans equilibrium and the peptide bond isomerization in proteins and other polymers. On the other hand, the effects of the retroamide group on the chemical and electronic structure of peptides have been also investigated.[5,14] Recently, the conformational properties of the α-keto amide moiety have also been studied in *N,N′*-dimethyl-α-ketopropanamide.[15] However, to the best of our knowledge the structure of the oxalamide and hydrazide moieties have not been investigated at the present time.

In this paper different aspects of the oxalamide and hydrazide moieties are presented. For this purpose both the conformational preferences and the changes in charge distribution of *N,N′*-dimethyloxalamide and *N,N′*-diacetylhydrazine (see Figure 1), abbreviated NdMO and NdAH respectively, are studied in different environments using theoretical methods. Ab initio methods with inclusion of Møller−Plesset (MP) electron correlation effects[16] are used. All the conformations are studied in a vacuum and aqueous solution, the latter being modeled by using Tomasi's self-consistent reaction-field (SCRF) algorithm.[17] A comparison between the oxalamide and hydrazide moieties with the amide group has also been performed. For this purpose, calculations have been extended to *N*-methylacetamide, abbreviated NMA.

Methods

Molecular Structure and Gas-Phase Energy Calculations. The model molecules NdMO and NdAH are displayed in Figure 1. The dihedral angles ω_1, ω_2, and ω_3 are defined for the two compounds considering the carbon and nitrogen atoms of the backbone. Eight minima may be anticipated for the potential energy hypersurface $E = E(\omega_1,\omega_2,\omega_3)$ by combining the minimum energy positions cis (c) and trans (t) around each dihedral angle. However, due to both the chemical and molecular symmetry, the number of expected minima can be reduced to six. These six conformations were used as starting points in geometry optimizations.

Geometry optimizations of NdMO and NdAH were performed at the Hartree−Fock (HF) level with the 6-31G(d)[18] and 6-311G(d,p)[19] basis sets and at the MP2 level with the 6-31G(d) basis set. Force constants analysis was carried out to verify the minimum nature of the conformations. Energy evaluations were performed by single point calculations at the MP4/6-31G(d) level on the MP2/6-31G(d) optimized geometries.

To establish a comparison between the new insights gained for the oxalamide and hydrazide moieties and those of the amide group, additional calculations were required. The minimum energy conformations of NMA (Figure 1) were characterized at the MP2 level by using the 6-31G(d) basis set. Single point energy calculations at the MP4/6-31G(d) level were performed on the MP2/6-31G(d) geometries. Accordingly, the changes in energy and charge distribution of NdMO, NdAH, and NMA were compared at the same level of theory.

Solvation Calculations. The effects of water on the energy and charge distribution of the conformers was examined following the polarizable continuun model developed by Miertus, Scrocco, and Tomasi (MST).[17] Calculations with this SCRF method were performed in the framework of the ab initio HF level using the 6-31G-(d) basis set (MST/6-31G(d)). Luque and Orozco[13h] used the MST/6-31G(d) method to study the solvation of the NMA system. The good results achieved by these authors indicate that MST/6-31G(d) is a suitable method to investigate the solvation of NdMO and NdAH.

The MST method considers the solvent as a continuum dielectric with a cavity accurately modeled on the solute. The solvent reacts against the solute charge distribution, generating a reaction field (V_R). The electrostatic interaction between the solute and the solvent is introduced as a perturbation operator in the solute Hamiltonian (eq 1).

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$$(H^\circ + V_R)\psi = E\psi \quad (1)$$

The reaction field operator is described in terms of an apparent set of point charges spread over the solute/solvent interface, i.e., the solute cavity (eq 2). The apparent charge density is determined by solving the Laplace equation (eq 3) at the cavity surface by imposing the suitable boundary conditions. In eq 3 both the solute and the solvent contributions to the electrostatic potential, i.e., V_ρ and V_σ, respectively, are taken into account. It should also be noted that the solute electrostatic potential was rigorously computed from HF/6-31G(d) wave functions.

$$V_R = \sum_i \sigma(s_i)S_i/|r - r_o| = \sum_i q_i/|r - r_o| \quad (2)$$

$$\sigma(s_i) = -\{\epsilon - 1/4\pi\epsilon\,[\partial(V_\rho(r) + V_\sigma(r))/\partial n]\} \quad (3)$$

Results and Discussion

Gas-Phase Energy Calculations for the Oxalamide and Hydrazide Moieties. The ω_1, ω_2, and ω_3 dihedral angles for the minimum energy structures of NdMO and NdAH are displayed in Tables 1 and 2, respectively. The details about the geometry of the nitrogen atoms, i.e., planar or pyramidal, in each of the minimum energy structures are given in Tables 3 and 4 for NdMO and NdAH, respectively. Finally, the relative energies between the different minima for NdMO and NdAH are shown in Tables 5 and 6, respectively.

Three miniminum energy conformations (Figure 2) were characterized for NdMO at the different levels of theory. For the three minima, the dependence of both the molecular geometries and relative energies on the level of theory is small. The lowest energy minimum corresponds to the ttt, in which the three dihedral angles adopt a trans conformation. The ctt structure, in which the dihedral angle ω_1 adopts a cis conformation, exists as a local minimum, being 6.2 kcal/mol higher in energy than the ttt conformer at the highest level of theory (see Table 5). The less stable minimum corresponds to the csc, in which the central dihedral angle ω_2 adopts a *skew* (s) conformation with a value of 144.8°. It is worth noting that the values predicted by HF/6-31G(d) and HF/6-311G-(d,p) geometry optimizations for such angle are 7.9° and 11.3° smaller than that provided by MP2/6-31G(d) geometry optimizations. The csc minimum is 12.7 kcal/mol less stable than the all-trans global minimum at the highest level of theory. Inspection of Figure 2 reveals that the low stability of the csc conformation is due to the unfavorable steric interactions between the oxygen atoms and the end methyl groups. Thus, the distance between the oxygen and the carbon atoms (2.816 Å) is slightly lower than the sum of their van der Waals radii.

The planar or pyramidal geometry of the nitrogen atoms has been investigated for the minimum energy conformations of NdMO. This is usually represented by the sum of the three bond angles around the nitrogen. Thus, a value closer to 360° indicates a greater degree of planarity. Table 3 shows the sum of these angles at each nitrogen atom for the three minimum energy conformations characterized at the MP2/6-31G(d) level. It is worth noting that the two nitrogen atoms of NdMO retain almost perfect planar geometry in all cases.

Inspection of the relative energies obtained at the different levels of theory for NdMO reveals the small effect of both the basis set and electron correlation. For the ctt conformation such effects are almost negligible, whereas for the csc minimum the basis set and electron correlation change the total energy difference by 1.4 and 1.8 kcal/mol, respectively. Such variations lie in the range 9−12% of the relative energies.

Recent studies on FK506 and related antibiotics have pointed out the key role of the −NH−CO−CO− moiety as a structural element involved in binding to protein immunophilins and in inhibiting their rotational activity.[8d,e] Furthermore, it has been proposed that this inhibition may be a consequence of a twisted preference of the CO−CO bond. The rotational surface of FK506 was recently modeled by using simple molecules such as α-ketoethanamide ($NH_2-CO-CHO$) and α-ketopropanamide ($(CH_3)_2N-CO-CO-CH_3$).[15] It is worth noting that the energy difference found for the ttt and csc minima of NdMO are in good agreement with the values predicted at the HF/6-31G(d) level for those molecules.

Full agreement with the gas-phase calculations has been found in the solid state, since a ttt conformation has been reported for NdMO.[20] Moreover, an inspection to Cambridge Structural Data Base[21] (CSDB) revealed that, in addition, 12 acyclic or large cyclic compounds with oxalamide moieties have been solved. In all cases the ttt conformation was found with the maximum deviations of 8.6° [22] and 6.2° [23] for the CO−NH and CO−CO bonds, respectively. It is worth noting that this preferred conformation appears to be independent of the type and size of the groups attached at the ends of the oxalamide moiety. Thus, the intermolecular interactions in the solid state seem to favor the trans conformation or at least are not strong enough to destabilize it. In the same way, all the structures postulated for even and odd polyoxalamides are based on a rigid trans conformation for the oxalamide group,[10] whereas a variable conformation is derived for the polymethylenic segment.[10d] A different conformation has only been found in small cyclic compounds due to the requirements imposed by geometrical constraints. Thus, as expected, the ccc is the characteristic conformation of 1,4-dihydro-2,3-quinoxalinedione derivatives[24] (15 compounds reported in the CSDB), where the oxalamide moiety belongs to a six-membered ring.

Four minimum energy conformations were found for NdAH (see Table 2), which are displayed in Figure 3. The lowest energy minimum corresponds to the tgt, in which the central angle ω_2 adopts a folded gauche conformation, whereas ω_1 and ω_3 remain trans. Thus, the folding around the N−N bond allows the formation of electrostatic interactions between the N−H and O═C groups, the distance between the hydrogen and oxygen atoms being 2.78 Å. The ttt minimum conformation is 1.3 kcal/mol less stable than tgt at the best level of theory (see Table 6). Accordingly, an energy contribution of about 0.6−0.7 kcal/mol can be estimated for each of the electrostatic interactions formed in the tgt conformation. It is worth noting that for the ttt structure the electronic

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Table 1. Minimum Energy Conformations[a] of *N,N′*-Dimethyloxalamide (NdMO) Obtained at Different Levels of Theory

level	ttt			ctt			csc		
	ω_1	ω_2	ω_3	ω_1	ω_2	ω_3	ω_1	ω_2	ω_3
HF/6-31G(d)	180.0	180.0	180.0	0.0	180.0	180.0	3.1	136.9	3.6
HF/6-311G(d,p)	180.0	180.0	180.0	0.5	−173.4	−177.1	3.5	133.5	3.5
MP2/6-31G(d)	180.0	180.0	180.0	0.1	180.0	180.0	1.8	144.8	1.9

[a] t, c, and s refer to trans, cis, and skew, respectively. Dihedral angles in degrees.

Table 2. Minimum Energy Conformations[a] of *N,N′*-Dimethylhydrazide (NdAH) Obtained at Different Levels of Theory

level	tgt			cgt			ttt			csc		
	ω_1	ω_2	ω_3	ω_1	ω_2	ω_3	ω_1	ω_2	ω_3	ω_1	ω_2	ω_3
HF/6-31G(d)	−163.9	67.6	−163.9	−19.4	−81.2	−169.3	180.0	−179.7	180.0	−14.3	118.8	−14.3
HF/6-311G(d,p)	−164.0	68.4	−164.0	−18.5	−81.8	−169.9	179.3	−178.6	−179.9	−14.3	118.7	−14.3
MP2/6-31G(d)	−162.1	60.5	−162.0	−24.0	−73.7	−170.3	173.7	−140.2	173.7	−14.2	117.5	−14.3

[a] t, c, g, and s refer to trans, cis, gauche, and skew respectively. Dihedral angles in degrees.

Table 3. Values of the Three Bond Angles (in Degrees) around Each Nitrogen Atom and Their Respective Sum for the Three Minimum Energy Conformations[a] of *N,N′*-Dimethyloxalamide (NdMO)

angle[b]	ttt	ctt	csc
$\angle C(H_3)-N_1-C(=O)$	122.9	130.4	129.4
$\angle C(H_3)-N_1-H$	121.9	117.8	117.9
$\angle H-N_1$-C(=O)	115.2	111.8	112.2
Σ	360.0	360.0	359.5
$\angle C(H_3)-N_2-C(=O)$	122.9	122.6	129.4
$\angle C(H_3)-N_2-H$	121.9	122.0	117.9
$\angle H-N_2-C(=O)$	115.2	115.3	112.2
Σ	360.0	359.9	359.5

[a] Minimum energy conformations characterized at the MP2/6-31G(d) level were considered. [b] See Figure 1 for the labels on the nitrogen atoms.

Table 4. Values of the Three Bond Angles (in Degrees) around Each Nitrogen Atom and Their Respective Sum for the Four Minimum Energy Conformations[a] of *N,N′*-Dimethylhydrazine (NdAH)

angle[b]	tgt	ttt	cgt	csc
$\angle C(H_3)-N_1-C(=O)$	116.3	116.4	118.8	122.3
$\angle C(H_3)-N_1-H$	116.8	123.5	110.9	114.9
$\angle H-N_1-C(=O)$	112.1	111.2	114.3	118.4
Σ	345.2	351.1	344.0	355.6
$\angle C(H_3)-N_2-C(=O)$	116.3	116.4	120.5	122.3
$\angle C(H_3)-N_2-H$	116.8	123.5	115.5	114.9
$\angle H-N_2-C(=O)$	112.1	111.2	120.8	118.4
Σ	345.2	351.1	356.8	355.6

[a] Minimum energy conformations characterized at the MP2/6-31G(d) level were considered. [b] See Figure 1 for the labels on the nitrogen atoms.

Table 5. Relative Energies (in kcal/mol) in the Gas-Phase between the Three Minimum Energy Conformations of *N,N′*-Dimethyloxalamide (NdMO) Computed at Different Levels of Theory

level[a]	ttt	ctt	csc
HF/6-31G(d)//HF/6-31G(d)	0.0	6.8	14.4
HF/6-31G(d)//HF/6-31G(d)[b]	0.0	6.8	14.5
HF/6-311G(d,p)//HF/6-311G(d,p)	0.0	6.7	13.1
HF/6-311G(d,p)//HF/6-311G(d,p)[b]	0.0	6.8	13.1
MP2/6-31G(d)//MP2/6-31G(d)	0.0	6.6	13.3
MP2/6-31G(d)//MP2/6-31G(d)[b]	0.0	6.5	13.2
MP4/6-31G(d)//MP2/6-31G(d)	0.0	6.3	12.8
MP4/6-31G(d)//MP2/6-31G(d)[c]	0.0	6.2	12.7

[a] Level of energy calculation//level of geometry optimization. [b] Zero point energies and thermal corrections are included. [c] Zero point energies and thermal corrections were computed at the MP2/6-31G(d) level and added to the MP4/6-31G(d) energies.

Table 6. Relative Energies (in kcal/mol) in the Gas-Phase between the Four Minimum Energy Conformations of *N,N′*-Dimethylhydrazide (NdAH) Computed at Different Levels of Theory

level[a]	tgt	ttt	cgt	csc
HF/6-31G(d)//HF/6-31G(d)	0.0	3.2	1.7	2.6
HF/6-31G(d)//HF/6-31G(d)[b]	0.0	3.1	1.7	2.4
HF/6-311G(d,p)//HF/6-311G(d,p)	0.0	2.8	1.8	2.8
HF/6-311G(d,p)//HF/6-311G(d,p)[b]	0.0	2.7	1.8	2.7
MP2/6-31G(d)//MP2/6-31G(d)	0.0	1.1	1.2	2.4
MP2/6-31G(d)//MP2/6-31G(d)[b]	0.0	0.9	1.2	2.2
MP4/6-31G(d)//MP2/6-31G(d)	0.0	1.5	1.4	2.6
MP4/6-31G(d)//MP2/6-31G(d)[c]	0.0	1.3	1.4	2.4

[a] Level of energy calculation//level of geometry optimization. [b] Zero point energies and thermal corrections are included. [c] Zero point energies and thermal corrections were computed at the MP2/6-31G(d) level and added to the MP4/6-31G(d) energies.

correlation induces a considerable distortion in the central dihedral angle ω_2. Thus, although this angle changes from trans to *skew*, this conformation will be also called ttt in order to avoid confusions with the structures optimized at the HF level. The next minimum corresponds to the cgt, which is almost isoenergetic to the ttt one. This structure is stabilized only by one electrostatic interaction between the N−H and O═C groups, the distance between the hydrogen and oxygen atoms being 2.83 Å. Finally, csc is the less favored minimum energy conformation for NdAH, being 2.4 kcal/mol less stable than tgt at the highest level of theory.

Table 4 reports the values of the three bond angles around each nitrogen atom of NdAH and their respective sum for the four minimum energy conformations characterized at the MP2/6-31G(d) level. It is worth noting that in all cases the sum of three angles deviate from 360°. The deviations from this ideal value range from 3.7° to 16.0°, indicating the piramidality of the nitrogen depends on the conformation. The largest degree of pyramidality appears for the cgt and tgt conformations suggesting that it corresponds to the structures with the dihedral angles ω_2 in *gauche*. It should be mentioned that even the nitrogen atoms of ttt presents a certain degree of puckering, indicating that the pyramidality of the nitrogen atoms is an intrinsic characteristic of NdAH.

Inspection to the relative energies derived at the different computational levels (Table 6) shows that the extension of the basis set from 6-31G(d) to the 6-311G(d,p) does not modify the results. The largest effect is the stabilization of the ttt minimum by 0.4 kcal/mol, which correspond to a 13% of the relative energy. However, the electronic correlation effects introduced via Møller−Plesset perturbation theory are considerably large and cannot be neglected. Thus, the change from the HF/6-

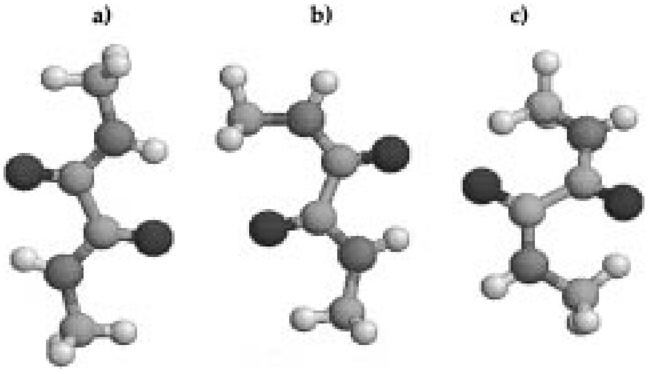

Figure 2. Minimum energy conformations characterized for *N*,*N′*-dimethyloxalamide (NdMO) at the MP2/6-31G(d) level: ttt (a), ctt (b), and csc (c).

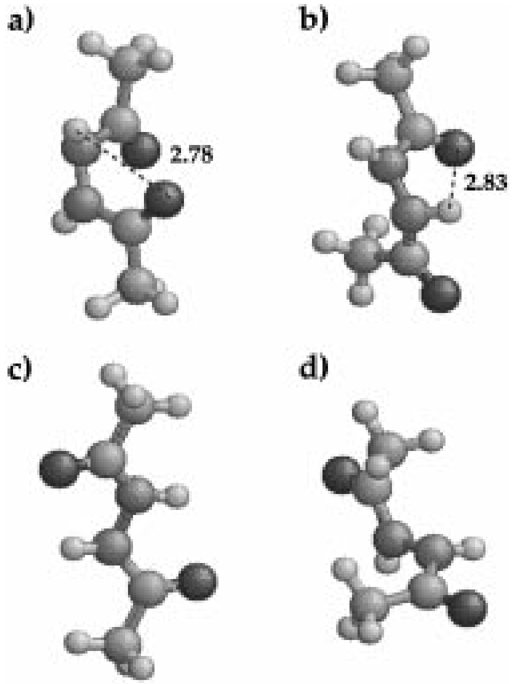

Figure 3. Minimum energy conformations characterized for *N*,*N′*-diacetylhydrazide (NdAH) at the MP2/6-31G(d) level: tgt (a), cgt (b), ttt (c), and csc (d).

31G(d)//HF/6-31G(d) level to the MP4/6-31G(d)//MP2/6-31G(d) one involves a reduction in the relative energy of 1.8 and 0.3 kcal/mol for the ttt and ctg minima, respectively. Thus, the large stabilization (about 60%) of the ttt conformation with respect to the global minimum can be understood by considering that electronic changes in the amide bonds that constitute the hydrazide moiety occur when the N−N bond rotates from the trans to gauche. Such changes are also reflected at the structural level for the ttt conformation, inducing a deviation of 40° from the planarity of the dihedral angle ω_2.

Table 7. Free Energies of Solvation (ΔG_{sol}), Relative Free Energies of Solvation ($\Delta\Delta G_{sol}$), and Conformational Free Energy Differences ($\Delta\Delta G_{conf}$) in Water between the Three Minimum Energy Conformations of *N*,*N′*-Dimethyloxalamide (NdMO)[a]

	ttt	ctt	csc
ΔG_{sol}[b]	−5.6	−6.0	−8.4
$\Delta\Delta G_{sol}$	2.8	2.4	0.0
$\Delta\Delta G_{conf}$[c]	0.0	5.8	9.9

[a] All the values in kcal/mol. [b] Computed at the MST/6-31G(d) level. [c] Estimated by adding $\Delta\Delta G_{sol}$ to the relative energy computed at the MP4/6-31G(d)//MP2/6-31G(d) level.

Table 8. Free Energies of Solvation (ΔG_{sol}), Relative Free Energies of Solvation ($\Delta\Delta G_{sol}$), and Conformational Free Energy Differences ($\Delta\Delta G_{conf}$) in Water between the Three Minimum Energy Conformations of *N*,*N′*-Dimethylhydrazide (NdAH)[a]

	tgt	ttt	cgt	csc
ΔG_{sol}[b]	−9.5	−9.4	−11.4	−11.4
$\Delta\Delta G_{sol}$	1.9	2.0	0.0	0.0
$\Delta\Delta G_{conf}$[c]	0.5	1.9	0.0	1.0

[a] All the values in kcal/mol. [b] Computed at the MST/6-31G(d) level. [c] Estimated by adding $\Delta\Delta G_{sol}$ to the relative energy computed at the MP4/6-31G(d)//MP2/6-31G(d) level.

The crystal structure of NdAH[25] presents a ttt conformation, which is different from the lowest energy minimum obtained in the gas-phase. Thus, in this case, the intramolecular interactions destabilize the tgt conformation. However, an inspection to the CSDB[21] shows that the dihedral angles are rather variable, in good agreement with quantum mechanical calculations. For instance, a tst conformation is found for the 1-(4-*n*-heptylbenzoyl)-2-(cyanoacetyl)hydrazine compound.[26] Different structures based on −XCONHNHCOX− (X = H, NH, O, or S) moieties have been solved and also display this variability. Thus, the N−N bond adopts a trans conformation in N,N′-diformohydrazide[27] (X=H), but it changes to *skew* (ω_2=105°) when the compound is crystallized together with 18-crown-6.[28]Biurea[29] (X = NH) adopts the csc conformation, which was characterized as a minimum in the gas-phase for NdAH. Much more interesting are the compounds with X = S (dipotassium 1,2-hydrazine-bis(monothiocarboxylate) dihydrate,[30] *S*,*S′*-dimethyl 1,2-hydrazine-bis(monothiocarboxylate)[30]) or X = O (1,2-hydrazinedicarboxylic acid diethyl ester,[31] *N*,*N′*-bis((*p*-chlorophenoxy)carbonyl)hydrazine dihydrate[32]) since they present the predicted lowest energy conformation tgt. More specifically, the torsion angle associated to the NH−NH bond ranges in absolute values from 73° to 91°. The hydrazide moiety can also be found in different cyclic compounds constituted by five- or six-membered rings.[21] In these cases a characteristic ccc conformation results, as happens with the cyclic oxalamide derivatives.

Aqueous Solution Energy Calculations for the Oxalamide and Hydrazide Moieties. The free energies of solvation computed at the ab initio MST/6-31G-(d) level for NdMO and NdAH are shown in Tables 7 and 8, respectively. Conformational free energies (ΔG_{conf}), which were derived by adding $\Delta\Delta G_{sol}$ to the gas-phase energy computed at the highest theoretical level, are also included.

The ΔG_{sol} values for NdMO state the following order of hidrophilicity: csc ≫ ctt > ttt. Thus, the nonplanar

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Table 9. Mulliken Charges (in Units of Electron) for the ttt Conformation of *N,N′*-Dimethyloxalamide (NdMO) and *N,N′*-Dimethylhydrazide (NdAH) in Gas-Phase and Aqueous Solution

	NdMO		NdAH	
	vacuum	water	vacuum	water
N	−0.7957	−0.7758	−0.5863	−0.5895
H(N)	0.3982	0.4409	0.4364	0.4464
C(O)	0.7092	0.7404	0.7498	0.7805
O	−0.6235	−0.7179	−0.6399	−0.7081
C(N)	−0.2553	−0.2869		
C(C)			−0.5749	−0.5769
H(C)	0.1891	0.1998	0.2049	0.2161

minimum csc has a larger dipole moment than the planar minima ctt and ttt (0.00, 0.31, and 2.38 D for the ttt, ctt, and csc minimum energy conformations, respectively, considering the molecular geometries optimized at the MP2/6-31G(d) level), providing the best electrostatic interaction with the solvent. Inspection of $\Delta\Delta G_{\mathrm{conf}}$ values reveals that the change from gas-phase (Table 5) to aqueous solution destabilizes the global minimum by 0.4 and 2.8 kcal/mol with respect to the ctt and csc minima, respectively. These results point out the role of bulk water in the conformational preferences of the oxalamide moiety, since the nonplanar conformation csc is stabilized by a 20% with respect to the planar ones.

The results for NdAH indicate that the solvation for this compound is better than for NdMO. Thus, the ΔG_{sol} values are considerably lower for the former than for the latter, indicating a better solute−solvent interaction. This feature should be explained on the basis of the molecular charge distribution. Table 9 shows the atomic charge distribution for the ttt conformation of both NdMO and NdAH. The results indicate that in the hydrazide moiety charges are more separated than in the oxalamide one.

Comparison of ΔG_{sol} values indicates that the cgt and csc minima are better solvated than the ttt and tgt ones by about 2 kcal/mol. This finding is easily explained for the cgt conformer since its dipole moment is larger than those of the other minimum energy conformations. Thus, the dipole moments for the ttt, cgt, tgt, and csc minimum energy conformations are 0.14, 6.51, 2.78, and 0.18 D, respectively, considering the molecular geometries optimized at the MP2/6-31G(d) level. On the other hand, the large stabilization of the csc conformer probably stems from the greater solvent-accessibility of the polar atoms, which increases the magnitude of attractive solute−solvent electrostatic interactions.

An analysis of the $\Delta\Delta G_{\mathrm{conf}}$ values (Table 8) shows that water changes the conformational preferences found in the gas-phase for NdAH. Thus, the large stabilization provided by the solvent to the cgt conformation with respect to the tgt one reverts the energy order in solution, the latter being 0.5 kcal/mol less stable than the former. On the other hand, the ttt conformation is 1.9 kcal/mol less stable than the cgt global minimum, although it remains unaltered with respect to tgt. Finally, the csc conformation is strongly stabilized, being 1.0 and 0.5 kcal/mol less favored than cgt and tgt, respectively.

The combined analysis of the Mulliken charges and dipole moments provides a picture of the changes induced by water in the molecular charge distribution of NdMO and NdAH. Atomic charges for the ttt conformation of the two compounds in both gas-phase and aqueous solution are displayed in Table 9. This conformation has been selected because it was characaterized as an energy minimum for both NdMO and NdAH. Thus, it corresponds to the global minimum for NdMO and is destabilized by only 1.3 kcal/mol for NdAH. Furthermore, analysis of the atomic charges predicted for NdMO in the gas-phase reveals that they are not at all sensitive to the conformation (data not shown), the largest variation being 0.03 electrons at the hydrogen atom of the amide groups. A small conformation-dependent charge distribution is also found for NdAH when the charges computed in the gas-phase for the tgt, ttt, and cgt conformations are compared (the largest change is 0.07 electrons at the carbon atom of the amide groups). It should be mentioned that a completely different charge distribution was obtained for the csc conformation. Thus, atomic charges predicted for this conformation are about 0.2−0.3 electrons smaller than those displayed in Table 9 for the ttt conformation. However, the csc conformation is unfavored with respect to the global minimum by 2.4 kcal/mol.

Table 10. Dipole Moments (in Debyes) for the Different Conformations of NdMO and NdAH in the Gas-Phase and Aqueous Solution Computed from HF/6-31G(d) Wave functions[a]

	conformation	μ_{gp}	μ_{aq}	$\mu_{\mathrm{aq}}/\mu_{\mathrm{gp}}$
NdMO	ttt	0.00	0.00	
	ctt	0.31	0.42	1.35
	csc	2.38	3.07	1.29
NdAH	tgt	2.78	3.71	1.33
	ttt	0.14	0.18	1.29
	cgt	6.51	8.34	1.28
	csc	0.18	0.24	1.35

[a] Molecular geometries optimized at the MP2/6-31G(d) level were considered.

It is worth noting that charges for the two compounds are slightly different (Table 9). The largest difference is detected at the nitrogen, which is more negative (around 0.2 electrons) for NdMO than for NdAH. However, charges for the carbonyl carbon, oxygen, and amide hydrogen atoms are larger (around 0.02−0.04 electrons) for NdAH than for NdMO. Charges of the end methyl groups partially compensate for differences in charges of nitrogen atoms. Thus, the methyl groups of NdAH increases its negative charge by 0.2 electrons with respect to those of NdMO.

Results displayed in Table 9 indicate that water increases the charge separation, since in general charges are enhanced. The oxygen is the most sentitive atom to charge variations by the solvent because its charge increases by about 0.10 and 0.07 electrons for NdMO and NdMA, respectively. In general, it can be stated that the increase of the charges produce an enhancement of C−O and N−H bond dipoles. This is also indicated in Table 10, where dipole moments for all the minimum energy conformations of both NdMO and NdAH in the gas-phase and aqueous solution are displayed. Note that the variations in the dipole moment range from 28 to 35%.

Comparison with the Amide Group. NMA is the most simple and suitable molecule to establish a comparison between the amide group and both the oxalamide and hydrazide moieties of NdMO and NdAH, respectively. Geometry optimizations of the t and c minimum energy conformations were performed at the MP2/6-31G(d) level, and their energies were evaluated by single point calculations at the MP4/6-31G(d) level. Results are displayed in Table 11.

As was expected, t is the most stable minimum energy conformation, c being 2.1 kcal/mol less favored. This value

Table 11. Minimum Energy Conformations, Relative Energies in the Gas-Phase (ΔE), Free Energies of Solvation ($\Delta G_{\rm sol}$), Relative Free Energies of Solvation ($\Delta\Delta G_{\rm sol}$) and Conformational Free Energy Differences ($\Delta\Delta G_{\rm conf}$) for the Two Minimum Energy Conformations of *N*-methylacetamide (NMA)[a]

	t	c
ω_1[b]	177.1	14.1
ΔE (MP2/6-31G(d)//MP2/6-31G(d))	0.0	2.2
ΔE (MP2/6-31G(d)//MP2/6-31G(d))[c]	0.0	2.2
ΔE (MP4/6-31G(d)//MP2/6-31G(d))	0.0	2.1
ΔE (MP4/6-31G(d)//MP2/6-31G(d))[d]	0.0	2.1
$\Delta G_{\rm sol}$[e]	−9.2	−9.9
$\Delta\Delta G_{\rm sol}$	0.7	0.0
$\Delta\Delta G_{\rm conf}$[f]	0.0	1.4

[a] t and c refer to trans and cis, respectively. Dihedral angles (see Figure 1) and energies in degrees and kcal/mol, respectively. [b] Obtained from geometry optimizations at the MP2/6-31G(d) level. [c] Zero point energies and thermal corrections are included. [d] Zero point energies and thermal corrections were computed at the MP2/6-31G(d) level and added to the MP4/6-31G(d) energies. [e] Computed at the MST/6-31G(d) level. [f] Estimated by adding $\Delta\Delta G_{\rm sol}$ to the relative energy computed at the MP4/6-31G(d)//MP2/6-31G(d) level.

agrees with that obtained by Orozco and Luque[13h] using molecular geometries optimized at the HF/6-31G(d) level. The $\Delta G_{\rm sol}$ values at the HF/6-31G(d) level are also displayed in Table 11, where the hidrophilicity order c > t is stated. The c conformer is stabilized relative to the t by 0.7 kcal/mol. This small $\Delta\Delta G_{\rm sol}$ value should be attributed to the low difference between the dipole moments, i.e., 4.07 and 4.34 D for the t and c conformations, respectively. Furthermore, both recent experimental[33,34] and computational[13d,13e,13h] studies also provided small $\Delta\Delta G_{\rm sol}$ values for the c−t equilibrium. The $\Delta\Delta G_{\rm conf}$ values indicate the preference of the t over the c conformer by 1.4 kcal/mol.

Comparison between the relative energies obtained for NMA and those displayed in Tables 5 and 6 for NdMO and NdAH, respectively, suggests a larger similarity with the later than with the former. Thus, the energy difference between the global and the local minima is lower for NdAH than for NdMO. This should be attributed to the steric interactions between the oxygen atoms and the methyl groups which produce an energy rise. However, inspection to the dihedral angles displayed in Tables 1−4 reveals that NMA is more similar to NdMO than to NdAH from an electronic point of view. Thus, the nitrogen atoms of NMA and NdMO present a planar geometry whereas those of NdAH show a degree of pyramidality which, in addition, depends on the conformation. These results indicate that for NdAH the bonds associated to the rotations ω_1 and ω_3 do not present an amide resonance similar to that of NMA. Furthermore, no remainder of π-conjugated bonds is displayed by ω_2, which behaves as a typical single bond.

Table 12. Values of the C(═O)−N Bond Lengths (in Å) for the Minimum Energy Conformations[a] of *N*,*N′*-Dimethyloxalamide (NdMO), *N*,*N′*-Dimethylhydrazine (NdAH), and *N*-Methylacetamide (NMA)

compound	conf[b]	C(═O)−N$_1$	C−(═O)−N$_2$
NdMO	ttt	1.346	1.346
	ctt	1.353	1.350
	csc	1.357	1.357
NdAH	tgt	1.397	1.397
	ttt	1.369	1.369
	cgt	1.403	1.381
	csc	1.389	1.389
NMA	t	1.367	
	c	1.372	

[a] Minimum energy conformations characterized at the MP2/6-31G(d) level were considered. [b] See Figure 1 for the labels on the nitrogen atoms.

Table 13. Mulliken Charges (in Units of Electron) and Dipole Moments (in Debyes) for the t and c Minimum Energy Conformations of *N*-Methylacetamide (NMA) in the Gas-Phase and Aqueous Solution

	gas-phase		aqueous solution	
	trans	cis	trans	cis
N	−0.7891	−0.7728	−0.7833	−0.7738
H(N)	0.3816	0.3903	0.4124	0.3982
C(O)	0.7533	0.7442	0.7690	0.7650
O	−0.6307	−0.6205	−0.7219	−0.7199
C(N)	−0.2875	−0.2806	−0.2849	−0.2864
H(CN)	0.1892	0.1792	0.1903	0.1929
C(C)	−0.5777	−0.5959	−0.5757	−0.5923
H(CC)	0.1941	0.1992	0.2045	0.2105
μ	4.07	4.34	5.30	5.63

Table 12 compares the C(═O)N bond lengths for NMA, NdMO, and NdAH. In all cases the shortest values are obtained for the trans conformations, i.e., t conformation for NMA and ttt conformations for both NdMO and NdAH. It is worth noting that NdMO presents shorter bond lengths than NMA, indicating an increase of the partial double bond character in the former. On the other hand, the C(═O)N bond lengths for the lowest energy conformation of NdAH are 0.03 Å larger than that of NMA, revealing a reduction of the partial double bond character. Conversely, the ttt conformation is able to retain the same C(═O)N bond length as the t conformation of NMA.

Comparison of $\Delta G_{\rm sol}$ values for NdMO and NdAH (Tables 7 and 8, respectively) with those obtained for NMA (Table 11) reveals the following order of hydrophilicity: NdAH > NMA > NdMO. This trend is consistent with the charge separation displayed by the different compounds (see Tables 9 and 13). Atomic charges and dipole moments in both gas-phase and aqueous environments are shown in Table 13. Charges for the t and c conformations are very similar, the largest difference being around 0.02 electrons. On the other hand, water increases the charge separation, since in general charges are enhanced. Thus, increases of about 1.2 D in the dipole moments are found (variations of up to the 30% in the dipole). Oxygen is the most sensitive atom to charge variations by the solvent, its charge increasing by around 0.1 electrons. The carbonyl carbon enlarges its positive charge by around 0.02 electrons, which increases the C−O bond dipole. Similar behavior is shown by the amide hydrogen. Finally, the nitrogen atom remains unaffected by water.

Comparison of the charge distributions obtained for NMA with those provided for NdMO and NdAH reveals a larger similarity with the former than with the latter. The largest difference between NMA and NdAH corresponds to the N−H group, which is about 0.2 and 0.05 electrons for the nitrogen and hydrogen atoms, respectively. On the other hand, charges obtained for the oxalamide moiety compare quite well with those pre-

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dicted for the amide group, suggesting a strong similarity in the charge distribution.

Conclusions

The conformational preferences of the oxalamide and hydrazide moieties are quite different irrespective of the environment, as noted by the energies computed for the different minima at the ab initio level in a vacuum and in aqueous solution. ttt is the most stable conformation for NdMO, the next minimum being less stable by 6.2 kcal/mol in the gas-phase and 5.8 kcal/mol in water. This should be attributed to the unfavorable interactions between the oxygen atoms and the methyl groups that appear in the ctt and csc minima. On the other hand, NdAH presents four minima whose relative energies are lower than 2.4 kcal/mol in both gas-phase and aqueous solution. The lowest energy conformation corresponds to tgt in the gas-phase and cgt in aqueous solution.

Water has an important effect in determined the electronic charge distribution of the oxalamide and hydraize moieties in solution. The variations in the molecular dipoles of NdMO and NdAH are about 30%. Oxygen is the most sensitive atom to the presence of water, which produces an increase of about 0.07−0.1 electrons in its negative charge. On the other hand, the charge of the nitrogen atom remains unaltered when the molecule changes from gas-phase to aqueous solution.

Comparison with the results obtained at the same level of theory for the amide group indicates that NdAH is quite different from NMA. Thus, the former compund presents pyramidality in the nitrogen atoms, indicating a reduction in the resonance of the two amide groups. Furthermore, the N−N bond behaves as single bond, suggesting that no connection exits between the two amide units. Conversely, NdMO presents some similarities with NMA. Thus, there is a resemblance between the amide resonance and charge distribution of NdMO and those of NMA. Overall these results suggest that different properties should be expected for peptidomimetics with oxalamide and hydrazide moieties.

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