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Conformational Analysis of Succinamide Analogues

Carlos Alemán,* Eloísa Navarro, and Jordi Puiggalí*

Departament d'Enginyeria Química, E.T.S. d'Enginyers Industrials, Universitat Politècnica de Catalunya, Diagonal 647, Barcelona E-08028, Spain

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An ab initio quantum mechanical study of the conformational preferences on *N,N'*-dimethylsuccinamide has been performed at the HF/6-31G*, HF/6-31++G**, MP2/6-31G*, MP3/6-31G*, and MP4(SDTQ)/6-31G* computational levels. Furthermore, the effect of an aqueous environment has been simulated with a SCRF method using a 6-31G* basis set. Results show the intrinsic tendency of the central methylene units to adopt a *gauche* conformation. This result contrasts with the *all-trans* conformation expected in polymethylenic segments, although it is in good agreement with recent experimental data. Finally, the variation of the charge distribution with the conformation has been investigated and compared with that of other retroamide compounds.

Introduction

Recently, we have studied the conformational preferences of glutaramide analogues ($R_1NHCO(CH_2)_3CONHR_1$, R_1 = C_3H_7 and CH_3) in the solid state using X-ray crystallography and in vacuo using quantum mechanical calculations.[1] The results clearly indicate that the central methylene units do no keep a *trans* (T) arrangement and tend to fold in a *gauche* (G) conformation. More specifically, all the compounds investigated adopt a TTGGTT structure which was characterized as the lowest minimum energy conformation at the ab initio HF/6-31G* level. Furthermore, the TTTTTT was not found as a minimum energy conformation and was estimated to be 2.7 kcal/mol less stable than the TTGGTT. This is a very interesting result since it is well-known that methylene units usually adopt an *all-trans* conformation; for instance, the experimental T−G difference in *n*-butane is ~0.5−0.9 kcal/mol.[2,3] Furthermore, X-ray experiments showed an *all-trans* conformation for the crystalline part of polyethylene chains.[4]

The folding of methylene groups in linear glutaramide analogues should be explained in terms of repulsive interactions between the close oxygen atoms. Thus, glutaramide has an odd number of methylenes between the two amide groups, and therefore, strong repulsive interactions between the close oxygen atoms are present in the *all-trans* conformation. A similar situation is observed in the *N,N'*-dimethylmalonamide ($CH_3NHCOCH_2CONHCH_3$) where the *all-trans* conformation is also unfavored due to the repulsive interactions between the oxygen atoms, although in this case they are much stronger than in glutaramide by the decrease in the number of methylenes.[5] In this case, due to the absence of central methylene torsional angles, the malonamide folds around the (C=O)−CH_2 bonds in order to put in opposite directions the close oxygen atoms.

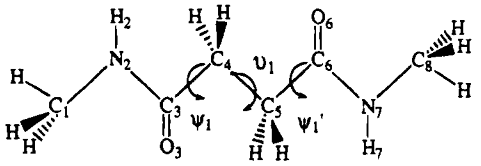

Figure 1. Atom numbering scheme and definition of torsional angles for *N,N'*-dimethylsuccinamide.

On the other hand, a very different behavior should be expected for succinamide ($-NHCO(CH_2)_2CONH-$) and adipamide ($-NHCO(CH_2)_4CONH-$) derivatives, in which due to the even number of methylene units an *all-trans* conformation without C=O· · ·O=C repulsive interactions is expected. In a recent work devoted to the study of the tendency of glycine residue to adopt the polyglycine II conformation[6] in its copolyamide with aliphatic compounds, we crystallized among others *N,N'*-succinylbis(N-propylglycinamide) and the *N,N'*-adipoylbis(*N*-propylglycinamide).[7] These compounds have succinamide and adipamide moieties, respectively, in which, contrary to expectations, the conformations are not *all-trans*. Thus, the succinamide unit presents a TTGTT conformation, and a TS$\bar{G}$TG$\bar{S}$T conformation has been found in the adipamide unit. These results are of great importance in organic chemistry since there is no apparent reason for the folding of methylene groups in such compounds.

The aim of the present work is to investigate and understand the structure of linear diamide analogues with an even number of methylene units. Thus, we performed a study of the conformational preferences of the linear *N,N'*-dimethylsuccinamide (Figure 1) using ab initio quantum mechanical calculations. Furthermore, charge distribution and the effect of water on the different conformers have been studied in order to gain insight into different aspects of the folding of methylene units in such compounds.

Methods

Molecular Structure and Gas Phase Energy Calculations. An exploration of the conformational space was performed in order to characterize the minimum energy structures of the *N,N'*-dimethylsuccinamide. Geometry optimizations

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* To whom correspondence should be addressed.

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were performed at the ab initio HF/6-31G*[8] level. The analytical second derivatives were then obtained to verify the minimum nature of the conformations. Five minima were characterized, four of them being equivalent and isoenergetic due to the chemical symmetry of the molecule. In order to investigate the effect of the basis set single point energy calculations were performed at the HF/6-31++G** level.[9] Møller–Plesset (MP) perturbation treatment[10] was used to compute the electron correlation corrections to the energy. MP2 and MP3 corrections were computed at the 6-31G* level. Additionally, in order to verify the results for the more important conformations, electron correlation contributions were calculated at the full MP4 level of theory (MP4(SDTQ) level) on a small model compound.

The thermodynamics in vacuum was computed by correcting the differences in electronic energy to enthalpies at 298 K using eq 1

$$\Delta H^{298} = \Delta E^{\circ}_{\rm ele} + \Delta E^{\circ}_{\rm vib} + \Delta E^{\circ}_{\rm rot} + \Delta\Delta E^{\circ}_{\rm vib} + \Delta\Delta E^{\circ}_{\rm rot} \qquad (1)$$

where $\Delta E^{\circ}_{\rm ele}$ is the electronic energy difference, $\Delta E^{\circ}_{\rm vib}$ and $\Delta E^{\circ}_{\rm rot}$ are the vibrational and rotational corrections at 0 K, and $\Delta\Delta E^{\circ}_{\rm vib}$ and $\Delta\Delta E^{\circ}_{\rm rot}$ are the thermal corrections. The entropic correction to the enthalpy was computed from the HF/6-31G* frequency analysis following the standard formulas. Then, the free energy difference between two different conformations **I** and **II** was computed according to eq 2

$$\Delta G^{298,\mathrm{I\text{-}II}} = \Delta H^{298} - T\Delta S^{298} - RT \ln 4 \qquad (2)$$

where the last term is due to the presence of three additional minima which are equivalent and isoenergetic to **I**.

Solvation Calculations. The effect of water on the energy of the conformers was examined following the SCRF developed by Miertus, Scrocco, and Tomasi (MST),[11] which gives good estimations of the free energies of hydration.[12] This strategy computes the free energy as the addition of three contributions: cavitation, van der Waals, and electrostatic (eq 3).

$$\Delta G_{\rm solv} = \Delta G_{\rm cav} + \Delta G_{\rm vdW} + \Delta G_{\rm ele} \qquad (3)$$

The cavitation was computed using Pierotti's theory,[13] and the van der Waals contribution was evaluated from a molecular surface area using a linear relation found by Tomasi and coworkers.[14] The electrostatic term was determined in a SCRF procedure where the effect of water is represented by a set of virtual charges $\{Q_{\rm i}\}$ on the molecular cavity surface (eq 4)

$$H = H^{\circ} + \sum\nolimits_{\rm i} Q_{\rm i}/R_{\rm i} \qquad (4)$$

where H° is the solute nonperturbed Hamiltonian. These charges are determined from the gradient of the molecular electrostatic potential (MEP) at the cavity surface by solving the Laplace equation. The electrostatic term was calculated from the HF/6-31G* wavefunction. The solute/solvent interface was built using a molecule-shaped algorithm.[15] According to Orozco and Luque,[16,17] the cavity was located at 1.2 times the van der Waals radii of the different atoms [O, 1.4 Å; H, 1.12 Å; H(on heteroatoms), 1 Å; C, 1.5 Å; N, 1.5 Å]. All the macroscopic parameters defining the water in the continium calculations were taken at 298 K. The free energy of reaction in water was evaluated by the classical thermodinamical scheme:

$$\Delta G^{\rm reacc,aq} = \Delta G^{\rm reacc,vac} + \Delta\Delta G_{\rm sol} \qquad (5)$$

Charge Calculations. Electrostatic properties of the different conformers were analyzed from MEP-derived (electrostatic) charges. Electrostatic charges were determined following Momany's procedure,[18] where the quantum mechanical MEP is fitted to a set of monopoles centered at the nuclei. A set of points were generated in four Connolly's layers[19] placed at 1.4, 1.6, 1.8, and 2.0 times the van der Waals radii of the atoms. A density of 5 points/Å^2 was used to guarantee the quality of the fitting.[20,21] No dipole was imposed to the fitting, which allows the SCF and electrostatic dipoles to be compared so as to analyze the quality of the electrostatic charges.

Ab initio calculations were performed with Gaussian-92[22] and Monstergauss[23] computer programs. MEP and charges were determined with the MOPETE/MOTODO set of programs.[24] All the calculations were performed with an IBM 3090/600 and a CRAY-YMP of the Centre de Supercomputació de Catalunya (CESCA).

Results and Discussion

Gas Phase Energy Calculations. The results from the ab initio SCF geometry optimizations on the potential energy surface of *N,N'*-dimethylsuccinamide using a 6-31G* basis set are shown in Table 1. The lowest energy conformation found is the C_7 (intramolecular seven-membered hydrogen-bonded system inducing), referred to as **I**, which has an asymmetric behavior on the ψ_1 and ψ_1' dihedral angles. Thus, due to the chemical and molecular symmetry of the *N,N'*-dimethylsuccinamide one half of the molecule should be symmetrically related to the other half of the molecule. However, the tendency to form an intramolecular hydrogen bond results in different values of ψ_1 and ψ_1' (−169.7° and −101.5°, respectively). Equivalent and isoenergetic minima with torsional angles $\psi_1,\psi_1' \approx 169.7°, 101.5°; 101.5°, 169.7°; -101.5°, -169.7°$ have also been found (data not shown). A similar behavior has been recently observed in *N,N'*-dimethylmalonamide, where the theoretical minima predicted at the same computational level present a clear intramolecular six-membered hydrogen bond system.[5] The C_7 intramolecular hydrogen bond geometry is characterized by $R_{\rm H\cdots O}$ = 2.67 Å and <N−H···O = 115.9°. Furthermore, minimum **I** presents another unusual structural feature, since the torsional angle around the central carbon atoms adopts a *gauche* conformation (υ_1 = 73.9°). Figure 2a shows a stereopair drawing of the

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Table 1. Ab Initio HF/6-31G* Geometrical Parameters[a] of *N,N'*-Dimethylsuccinamide

parameter	I[b]	II[b]	III[b]	expl[c]
C1–N2	1.448	1.447	1.448	1.430
N2–C3	1.347	1.350	1.355	1.347
C3–C4	1.522	1.519	1.521	1.515
C4–C5	1.530	1.521	1.520	1.532
C5–C6	1.521	1.519	1.521	1.515
C6–N7	1.349	1.350	1.355	1.347
N7–C8	1.446	1.447	1.447	1.430
H2–N2	0.994	0.993	0.994	
O3=C3	1.205	1.203	1.200	1.189
O6=C6	1.204	1.203	1.200	1.189
H7–N7	0.996	0.993	0.994	
∠C1–N2–C3	121.9	121.7	120.9	120.8
∠N2–C3–C4	115.2	114.9	114.9	113.3
∠C3–C4–C5	113.0	112.0	111.9	113.1
∠C4–C5–C6	111.7	112.0	111.6	113.1
∠C5–C6–N7	115.9	114.9	114.9	113.3
∠C6–N7–C8	120.7	121.7	121.2	120.8
∠H2–N2–C3	118.3	119.2	118.6	
∠O3=C3–N2	122.2	122.1	122.5	122.6
∠O6=C6–C5	120.8	123.0	122.5	124.1
∠H7–N7–C6	116.3	119.2	117.8	
C1–N2–C3–C4 (ω_1)	178.7	180.0	175.8	−176.1
N2–C3–C4–C5 (ψ_1)	−169.7	179.9	−172.2	−172.2
C3–C4–C5–C6 (υ_1)	73.9	180.0	75.3	75.3
C4–C5–C6–N7 (ψ_1')	−101.5	−179.8	172.2	172.2
C5–C6–N7–C8 (ω_2)	173.4	180.0	173.8	176.1

[a] Distances in Å; bond and torsional angles in deg. [b] **I** and **II** refer to the minimum energy conformers on the HF/6-31G* potential energy surface. **III** refers to the conformation generated by holding the ψ_1, υ_1, and ψ_1' dihedral angles fixed at the experimental values, while all the other geometrical parameters were relaxed (see text). [c] Parameters determined for the succinyl moiety of the *N,N'*-succinylbis(*N*-propylglycinamide) by X-ray crystallography.

minimum **I** where both the intramolecular hydrogen bond and the folded methylene unit can be clearly observed.

Another minimum energy conformation has been characterized for the *N,N'*-dimethylsuccinamide. This is the *all-trans* conformation (**II**), which is 1.5 kcal/mol less stable than **I**. A plot of the minimized structure is given in Figure 2b. Inspection of the Cambridge Structural Database showed that this is the conformation usually adopted by aliphatic succinamides,[25,26] as expected for polymethylenic units. The structure determined for *N,N'*-succinylbis(*N*-propylglycinamide)[7] is not a local minimum on the HF/6-31G* ab initio potential energy surface of *N,N'*-dimethylsuccinamide. However, its conformational energy was computed by holding the ψ_1, υ_1, and ψ_1' torsional angles fixed, while all the other geometrical parameters were relaxed. The final structure (**III**) was less stable than **I** by 1.8 kcal/mol. As can be seen from Figure 2c this conformation has a binary axis through the middle of the $-CH_2-$ methylene segment, which maintains the adirectional configuration of the molecular chain.

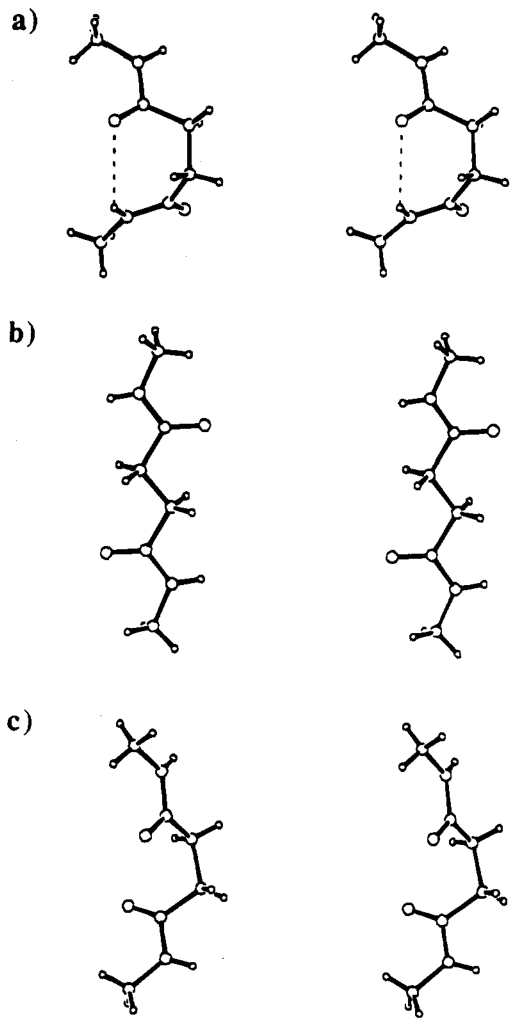

Figure 2. Stereopairs of *N,N'*-dimethylsuccinamide. (a) Lowest energy conformation for an isolated molecule. Note the C_7 intramolecular hydrogen bond (indicated by dashed lines) which stabilizes the conformation. (b) *All-trans* conformer detected also as a minimum energy for an isolated molecule. (c) TTGTT conformation for the succinamide unit as detected in solid state. In this case molecular symmetry is characterized by a binary axis through the middle of the $-CH_2-$ methylenic segment.

The dependence of bond lengths and bond angles on the conformation is very small (see Table 1). For instance, the distance N–H varies from 0.993 to 0.996 depending on whether its is involved in a hydrogen bond or not. The largest change of bond length occurs for C4–C5 which varies from 1.530 Å (**I**) to 1.521 Å (**II**). The largest change of bond angles occurs for H7–N7–C6 which varies from 116.3° (**I**) to 119.2° (**II**). X-ray geometrical parameters determined for the succinyl moiety of *N,N'*-succinylbis(*N*-propylglycinamide)[7] are also included in Table 1. As can be seen a good agreement was found between theoretical and experimental bond lengths and bond angles. The large difference of a bond length and a bond angle occurs for C=O and C5–C6–N7, respectively, which are overestimated at the HF level.

To study the effect of the basis set and electronic correlation, single point calculations were performed for the three conformers at the HF/6-31++G**, MP2/6-31G*, and MP3/6-31G* computational levels. Results are shown in Table 2. Conformer **I** is the lowest energy structure at all the computational levels considered. This must be attributed to the additional stability provided by the intramolecular hydrogen bond. Regarding conformers **II** and **III**, the former seems to be stabilized with respect to the latter when the size of the basis set is increased. Thus, at the HF/6-31++G** level **II** has been stabilized by around 0.5 kcal/mol with respect to the results at the HF/6-31G* level, whereas **III** has been unstablized by around 0.2 kcal/mol. On the contrary, electron correlation effects seems to provide a larger unstabilization to conformer **II** than to **III**. Thus, MP2/6-31G* and MP3/6-31G* calculations indicate that **III** is favored over **II**

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Table 2. Relative Energies[a] (in kcal/mol) of the *N,N'*-Dimethylsuccinamide Conformers

	I	II	III	
HF/6-31G*//HF/6-31G*	ΔE	0.0	1.46	1.84
HF/6-1G*//HF/6-31G*	ΔG^{298}	0.0	0.80	
HF/6-31++G**//HF/6-31G*	ΔE	0.0	0.99	2.07
HF/6-31++G**//HF/6-31G*	$\Delta G^{298,b}$	0.0	0.33	
MP2/6-31G*//HF/6-31G*	ΔE	0.0	3.66	2.72
MP2/6-31G*//HF/6-31G*	$\Delta G^{298,b}$	0.0	3.00	
MP3/6-31G*//HF/6-31G*	ΔE	0.0	2.90	2.40
MP3/6-31G*//HF/6-31G*	$\Delta G^{298,b}$	0.0	2.24	
MP4(SDTQ)/6-31G*//HF/6-1G*	ΔE^{c}		0.43	0.0

[a] Level of energy calculation // level of geometry optimization. [b] Includes enthalpic and entropic corrections computed at the HF/6-31G* level. [c] Computed on a small model compound (see text).

by 0.94 and 0.50 kcal/mol, respectively. These results, which are in agreement with experimental data for *N,N'*-succinylbis(*N*-propylglycinamide),[7] suggest the need to account for the correlation effects to obtain reliable representation of conformational preferences. In order to verify this point, we carried out further, more rigorous calculations of the electron correlation energy contributions for the conformations **II** and **III** up to the full fourth-order Møller–Plesset theory (MP4(SDTQ)) level. Due to the size of the molecule under consideration, we selected a small model compound which contains half of the molecule ($CH_3NHCOCH_2CH_3$). First, geometries were optimized at the HF/6-31G* level by held fixed the ψ_1 and v_1 torsional angles at the corresponding values. Results are displayed in Table 2. Conformer **III** was favored by 0.43 kcal/mol, indicating a good agreement with the MP2 and MP3 results for the full molecule.

Enthalpic corrections and the $-T\Delta S$ entropic contribution needed to correct ΔE to ΔG^{298} were calculated at the HF/6-31G*//HF/6-31G* level. These corrections are significant, since a value of 0.66 kcal/mol is found. The ΔG^{298} for conformers **I** and **II** are included in Table 2. Inclusion of enthalpic and entropic corrections introduces numerical changes in the results, but the behavior of the different methods is the same. Results show that enthalpic and entropic effects decrease the energy difference between **I** and **II**, but **I** is the most favored conformer yet. The best estimates of the free energy variation in gas phase between **I** and **II** is 2.2 kcal/mol. No correction was applied to conformer **III** since it is not a local minimum.

The preceding discussion states that quantum mechanical calculations correctly represent the conformational preferences of the methylene segment on the succinyl moiety, in good agreement with X-ray crystallography experiments. Thus, results clearly indicate that the central methylene unit tends to fold in a *gauche* conformation. The lowest minimum energy structure is a seven-membered hydrogen-bonded ring. It appears, therefore, that the calculations which we have showed do predict a correct structure probably present in the gas phase, since packing interactions have not been introduced in our theoretical calculations. In the crystallized compounds the optimal conformation should appears at ψ_1 and ψ_1' similar to those of **III** in order to form infinite networks of hydrogen bonds like those found experimentally (Figure 3). A similar behavior has also been observed in malonamide derivatives.[5,28] One reason for this behavior may be that infinite chains of hydrogen bonds apparently have a lower energy than isolated bonds.[27] Furthermore, as can be noted from Table 2, conformer **III** is stabilized with respect to the *all-trans* conformer when electronic correlation effects are included in energy calculations. Thus, **I** and **III** differ only in the value of ψ_1', showing that both structures have a *gauche* conformation in the central methylene unit.

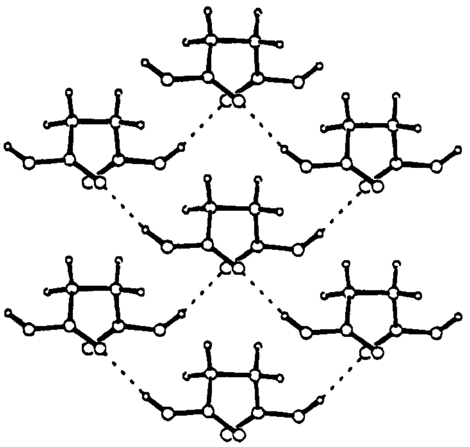

Figure 3. Down the chain axis view of *N,N'*-succinylbis(*N*-propylglycinamide) showing the molecular packing between a central chain and its six nearest neighbors. Only the central succinamide units have been represented. Note the intermolecular hydrogen bonding system (dashed lines) which is established according to two directions. As indicated in the text the succinamide units adopt a symmetric conformation characterized by a binary axis. Furthermore, the central methylenic bond has a *gauche* conformation.

In summary, the present results indicate that the folded conformation observed in the succinamide moiety[7] must be explained in terms of both (i) the interactions between the amide and retroamide links which make the *gauche* conformation favored over the *trans* conformation in the central methylene unit, even when an even number of methylene units are present, and (ii) the packing interactions which change the torsional angle ψ_1' from −101.5° to 172.2° in order to form infinite networks of hydrogen bonds. In contrast, the folding of methylene units in glutaramide analogues was attributed only to the strong repulsive interactions between the amide and retroamide links. Furthermore, its is irrespective of the environment as noted by solid-state experiments and in vacuo and solution calculations (1). The TTGTT conformation found experimentally[7] in succinamide (conformer **III**) presents a common feature with the TSST conformation characteristic of symmetric malonamides.[5,28] This is a 120° rotation between both carbonyl directions, being in succinamide due to the *gauche* conformation of the central bond. In contrast, the $TS\bar{G}TG\bar{S}T$ conformation observed for the adipic moiety[7] has the carbonyl groups oriented in opposite directions.

Energy Calculations in Water. Orozco and Luque recently demonstrated[20,29] that the change of the molecular geometry upon solvation has a negligible effect on the thermodynamic parameters. Therefore, considering

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(30) Geometry optimizations in the solvent phase for the three conformers of *N,N'*-dimethylsuccinamide with the dihedral angles of the backbone fixed at the values of the gas-phase minima indicate that the change in $\Delta\Delta G$ of solvation due to the effect of the solvent on the molecular geometry is very small (0.1 kcal/mol).

Table 3. Contributions (in kcal/mol) to the ΔG of Solvation[a] of N,N′-Dimethylsuccinamide Computed at the 6-31G* Level

	ΔG_{ele}	ΔG_{cav}	ΔG_{vdW}	ΔG_{sol}	$\Delta\Delta G_{sol}$
I	−17.15	20.84	−17.56	−13.87	0.40
II	−17.56	21.02	−17.73	−14.27	0.00
III	−16.62	20.56	−17.22	−13.28	0.99

[a] A cavity size equal to 1.2 times the van der Waals atomic radii was used. The temperature was taken equal to 298 K.

Table 4. Free Energy Differences (in kcal/mol) at 298 K in Water between the Two Minimum Energy Conformations of N,N′-Dimethylsuccinamide

	I	II
HF/6-31G*	0.0	0.39
HF/6-31++G**	0.07	0.00
MP2/6-31G*	0.00	2.59
MP3/6-31G*	0.00	1.83

Table 5. Computed Electrostatic Charges for the Three Conformers of N,N′-Dimethylsuccinamide

atom	I	II	III
C1	−0.1012	−0.1902	−0.0590
N2	−0.6142	−0.5945	−0.6472
C3	0.7386	0.7866	0.7417
C4	−0.0406	−0.1472	−0.2210
C5	−0.1966	−0.1368	0.0351
C6	0.7006	0.7817	0.6580
N7	−0.5884	−0.5912	−0.6115
C8	−0.0996	−0.1904	−0.0626
H−C1	0.0930	0.1127	0.0819
H2−N2	0.3401	0.3392	0.3517
O3═C3	−0.5946	−0.6075	−0.5790
H−C4	0.0228	0.0366	0.0587
H−C5	0.0577	0.0351	0.0063
O6═C6	−0.6059	−0.6064	−0.5647
H7−N7	0.3501	0.3371	0.3354
H−C8	0.0886	0.1127	0.0824
μ_{SCF}[a]	3.906	0.004	3.110
μ_{ele}[b]	3.930	0.004	3.190

[a] Dipole moments (in D) computed from the SCF wavefunctions.
[b] Dipole moments (in D) computed from electrostatic charges.

the expensiveness of the solvent phase geometry optimizations the use of gas-phase optimized geometries seems fully justified. The ΔG of solvation for the three conformers of *N,N′*-dimethylsuccinamide at the 6-31G* level are displayed in Table 3, where the hydrophylicity order **II** > **I** > **III** is stated. Results indicate that the experimental structure is less solvated than the *all-trans* by 1 kcal/mol. This effect can be roughly explained by the orientation of the polar amide groups in **I** and **III** (see Figures 2a and 2c) which are less accessible to the solvent than in **II** (Figure 2b). Thus, the present results state that the ΔG of solvation of the extended form **II** is favored over the hydrogen-bonded conformer **I** by 0.4 kcal/mol.

The ΔG of reaction (eq 5) for **I** and **II** are displayed in Table 4. The values at the Møller−Plesset and HF/6-31++G** levels were derived by adding the ΔG of solvation computed at the 6-31G* level to the ΔG in gas phase. The stability of the folded conformer **I** with respect the *all-trans* **II** is decreased to 0.39 (HF/6-31G*), −0.07 (HF/6-31++G**), 2.59 (MP2/6-31G*), and 1.83 (MP3/6-31G*) kcal/mol. The results point out the important role of the electron correlation on this conformational equilibrium. MP calculations show that the conformational preferences of *N,N′*-dimethylsuccinamide are governed by the existence of an intramolecular hydrogen bond in both solution and vacuum. On the contrary, HF calculations provide an almost isoenergetic conformation in solution due to the fact that a monodeterminantal wave function gives a poor representation of the hydrogen-bonding interactions. Thus, the stability of the folded conformation is clearly underestimated at the HF level.

Charge Calculations. The molecular wavefunction and the electrostatic properties vary with the conformation, and therefore, the analysis of the atomic point charges provides a picture of the change in the charge distribution with the conformations. This analysis has been recently performed on the *N,N′*-dimethylmalonamide,[31] and the results indicated that the atoms buried in the malonyl residue are very sensitive to the environment. Furthermore, in retromodified peptide bonds the electron donation by the C═O groups makes the α-carbon very negative for all the conformations considered, whereas in usual amino acids it has a charge of approximately zero.[32−34] The present calculations can help us to compare the charge distributions of the malonyl and succinyl residues and to investigate the dependence of the atomic point charges on the conformation. For this purpose, electrostatic charges for the three conformers of *N,N′*-dimethylsuccinamide were computed at the HF/6-31G* level.

Table 5 shows the electrostatic charges of the three conformers examined. The MEP was calculated at about 5200 points for each conformer. The root mean square (rms) values range between 1.1 and 1.3 kcal/mol, indicating a good fitting. Table 5 also includes dipole moments determined from electrostatic charges and from SCF wave functions. As can be seen, they exhibit a high degree of similarity supporting the reliability of the charges. A detailed inspection of the data reveals that the change in the conformation leads to variation in the partial charge of those atoms buried within the succinamide moiety. However, this variation, although far from negligible, is considerably smaller than the observed in α-amino acids,[31−34] especially in the malonamide unit which is very sensitive to the environment. A detailed inspection to the negative values of electrostatic (Table 5) charges on C4 and C5 atoms point out the electron donation by the neighbouring carbonyl groups. This is especially remarkable for the *all-trans* conformation (**II**), where other effects like intramolecular interactions and the unusual *gauche* conformation of the methylenic segment are not present.

Conclusions

The folding of methylene groups was recently described for glutaramide analogues, where an odd number of methylene units are present. The results shown in this work clearly indicate that the central methylene groups of the succinamide moiety also tend to fold in a *gauche* conformation. This is a highly favored conformation irrespective of the environment as noted by the relative free energies of 2.24 and 1.83 kcal/mol computed at the MP3/6-31G* level between the folded and *all-trans* minima in vacuum and in solution.

The theoretical lowest energy minima appears with an intramolecular seven-membered hydrogen-bonded sys-

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tem. However, when the compound is packed in a crystal the ψ_1' angle changes from −101.5° to 172.2° involving both peptide bonds in the formation of an infinite hydrogen bond system (Figure 3). We conclude, therefore, that the ψ_i angles found experimentally[7] are due to an optimization of the packing and hydrogen bonding interactions found in the crystal, whereas the *gauche* conformation of the central methylene group is an intrinsic property of the succinamide molecule. Furthermore, comparison between different computational methods indicates that correlation correction stabilizes the experimental conformation with respect to the *all-trans* by 0.5 kcal/mol.

Finally, charge distribution calculations point out the electron donation by the carbonyl group to the carbon atoms of the methylene units. However, in this case the charge distribution is less sensitive to the conformational changes than other retroamide compounds like the *N,N'*-dimethylmalonamide. Thus, the largest variations were approximately 0.2 electrons.

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