Folding of Methylene Groups in Linear Glutaramide Analogues

Eloísa Navarro, Carlos Alemán,* and Jordi Puiggalí*

Contribution from the Departament d'Enginyeria Química, Escola Tècnica Superior d'Enginyers Industrials, Universitat Politècnica de Catalunya, Avinguda Diagonal 647, Barcelona E-08028, Spain

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Abstract: We have synthetized and solved by X-ray diffraction the crystalline structure of the compound *N,N'*-dipropylglutaramide. The conformational preferences "*in vacuo*" of the model molecule *N,N'*-dimethylglutaramide have also been studied using quantum mechanical calculations at the HF/6-31G*, HF/6-311G**, and MP2/6-31G levels. Furthermore, the effect of water on the stability of the different conformations was modeled. The results indicate that the TTGGTT conformation is favored for the glutaramide analogue. Finally, quantum mechanical calculations on *N,N'*-dimethylsuccinamide at the HF/6-31G* level provide an explanation of the folded conformation observed in crystal succinamide and adipamide units. These results contrast with the all-*trans* conformation expected in polymethylenic segments.

Introduction

It is well known that methylene units usually adopt an all-*trans* conformation. For instance, in butane the experimental *trans−gauche* (T−G) difference ranges from 0.5 to 0.9 kcal/mol[1] and the T conformation is also favored from quantum mechanical calculations by 0.75 kcal/mol.[2] The same is true of *n*-pentane where the TT-to-TG energy experimentally ranges from 0.46[3] to 0.56[4] kcal/mol, and again quantum mechanics gives a value of about 0.76 kcal/mol.[5] Furthermore, X-ray analysis showed an all-*trans* conformation for the crystalline part of polyethylene chains.[6] The same behavior has been observed when several methylene units are attached to an amide group. Thus, the investigation of a series of X-ray crystallographic studies of oligomeric models of polyamides indicated that the central methylene groups usually adopt a *trans* conformation.[7] Consequently, X-ray diffraction data for standard aliphatic polyamides (nylons) have usually been refined considering that the aliphatic segment keeps an all-*trans* conformation.[8] This was demonstrated in an early study for the crystalline phase of nylon 66, in a detailed comparison between molecular dynamics computer simulations and experimental NMR spectroscopy.[9] However, this situation may be different in some cases for linear and small organic compounds with amide units. Thus, if a small number of methylene groups are present, the repulsive interactions between the amide groups can induce folding of the methylene units in order to give a more favorable orientation. This is the goal of the present study. Due to the structural importance of this feature for organic and macromolecular chemistry, we have undertaken a study of the conformational preferences of two glutaramide analogues (R_1-$NHCO(CH_2)_3CONHR_1$, $R_1 = C_3H_7$ and CH_3) in the solid state using X-ray crystallography and "*in vacuo*" using quantum mechanical calculations. Furthermore, the effect of water on the stability of the different conformations was modeled using Tomasi's SCRF algorithm[10] implemented in the AM1 (AM1/MST) semiempirical framework.[11,12]

Methods

Synthesis. *N,N'*-Dipropylglutaramide was prepared by reaction of glutaryl chloride with 1-propylamine in CH_2Cl_2 using triethylamine as a proton acceptor. The compound was recrystallized from ethyl acetate, giving a white powder in a 65% yield. Mp: 148−151 °C (uncorrected). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.92 ppm (t, 6H, $-CH_2CH_2CH_3$), 1.52 ppm (m, 4H, $-CH_2CH_2CH_3$), 1.93 ppm (m, 2H, $-CH_2-$, β-glutaryl), 2.27 ppm (t, 4H, $-CH_2-$, α-glutaryl), 3.21 ppm (m, 4H, $-CH_2CH_2CH_3$), 6.03 ppm (s, 2H, $-NH-$). ^{13}C NMR (300 MHz, $CDCl_3$): δ 11.35 ppm ($-CH_2CH_2CH_3$), 22.10 ppm ($-CH_2-$, β-glutaryl), 22.27 ppm ($-CH_2CH_2CH_3$), 33.58 ppm ($-CH_2-$, α-glutaryl), 41.96 ppm ($-CH_2CH_2CH_3$), 174.47 ppm ($-CO-$, amide). The purity was determined by HPLC: column RP-18 Spherisorb ODS-2, 25 × 0.4 cm; particle size 5 μm; UV λ = 210 nm; flow rate 1 mL/min; eluent 50% MeOH + 50% H_2O; sample concentration 1 mg/mL; injection 20 μL. The compound was detected at t_R = 5.13 min (purity 95%).

X-ray Diffraction. Colorless bars (0.2 × 0.1 × 0.04 mm^3) were obtained by slow cooling from an ethyl acetate solution (1 mg/mL, 60 °C). X-ray data were collected at room temperature using an Enraf-Nonius CAD-4 diffractometer with Cu Kα radiation (λ = 1.541 78 Å) and a graphite monocromator (2θ < 136, ω scanning mode). Cell parameters (a = 28.57(2) Å, b = 5.155(2) Å, c = 8.796(3) Å; α = 90.00(3)°, β = 99.28(4)°, γ = 90.00(4)°) were refined by least squares on the basis of 20 independent reflections. Three reflections were monitored every hour during data collection and showed that the fluctuation of intensity was less than 2%. A total of 1171 independent reflections was collected (h = −34 to +33, k = 0−6, l = 0−10).

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Intensity data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods using the SHELXS-86[14] computer program package. From the relationships between equivalent atoms in the crystal, it was unambiguously established that the space group was monoclinic $C2/c$ ($Z = 8$). The structure was then refined by a full matrix least-squares procedure.[15] An E-map revealed all the non-hydrogen atoms, whereas the hydrogen atoms bonded to the C2, C3, N4, and C7 atoms were placed in the positions found in the difference Fourier density maps. The remaining hydrogen atoms were included at calculated positions. All the hydrogen atoms were refined with geometrical constraints ("ride model"). The final R and weighting R factors ($1/w = \sigma^2(F_o^2) + (0.3157P)^2 + 11.75P$ where $P = [\max(F_o^2,0) + 2F_c^2]/3$) were 0.0947 and 0.246, respectively, for 699 reflections with $I > 2.5\sigma(I)$. The maximum and minimum heights found in the difference Fourier map were −0.43 and +0.26 e/Å^3. A micro-Vax 2000 computer was used for all the calculations.

Quantum Mechanical Calculations. A conformational search was performed in order to characterize the symmetric minima of *N,N'*-dimethylglutaramide. The search strategy adopted combined two procedures. First, a contour map of the conformational energy versus the dihedral angles ψ ($\psi_1 = \psi_2$) and ν ($\nu_1 = \nu_2$) was calculated using a grid of 20° at the semiempirical AM1 level.[15] Then the minima on the energy surface were located and characterized first at the *ab initio* HF/3-21G[16] level and then at the HF/6-31G* [17] level. In order to investigate the effect of the basis set and electronic correlation, single point energy calculations were performed on the HF/6-31G* geometries at the HF/6-311G** and MP2/6-31G[18] levels. Thus, comparison between MP2/6-31G*//HF/6-31G* and MP2/6-31G//HF/6−31G* relative energies in related compounds suggests that the latter represent the effect of the electron correlation contribution[19] reasonably well.

The effect of water was examined following the SCRF procedure developed by Miertus, Scrocco, and Tomasi,[10] which gives acceptable estimations of the free energies of hydration.[20] This strategy computes the total free energy as the addition of three contributions, cavitation, van der Waals, and electrostatic:

$$\Delta G_{solv} = \Delta G_{cav} + \Delta G_{vw} + \Delta G_{el} \quad (1)$$

The cavitation was computed using Pierotti's theory,[21] and the van der Waals contribution was evaluated from a molecular surface area using a linear relation found by Tomasi and co-workers.[22] The electrostatic contribution was computed using the SCRF method at the AM1 level, with the algorithm developed by Luque and Orozco.[11,12] The solute/solvent interface was built using a molecule-shaped algorithm.[23] According to previous studies[24] the cavity was located at 1.20 times the van der Waals radii of the different atoms [C, N, 1.5 Å; O, 1.4 Å; H, 1.2 Å; H (bound to heteroatoms), 1.0 Å]. All the macroscopic parameters defining the water in the continuum calculations were taken at 298 K.

Ab initio calculations were performed with Gaussian-92.[25] Semiempirical calculations were carried out with a modified version[26] of the MOPAC[27] computer package. All the calculations were performed on the CRAY-YMP and IBM/3090 at the CEntre de Supercomputació de CAtalunya (CESCA).

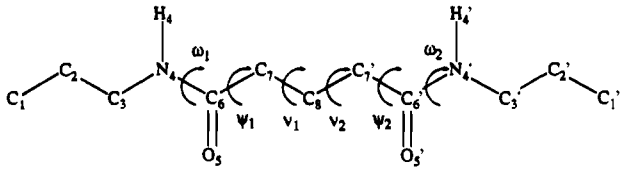

Figure 1. Atom numbering scheme and torsional angle definition for *N,N'*-dipropylglutaramide.

Table 1. Fractional Coordinates with Estimated Standard Deviations in Parentheses and Equivalent Isotropic Thermal Parameters (Å^2) for pGp

atom	X/A	Y/B	Z/C	B_{eq}
C1	0.2046(3)	−0.459(2)	0.3347(9)	7.24
C2	0.1676(2)	−0.300(2)	0.396(7)	6.11
C3	0.1321(2)	−0.184(1)	0.274(5)	4.16
N4	0.0966(2)	−0.0352(8)	0.3373(4)	3.76
H4	0.0917(2)	−0.0710(8)	0.4290(4)	3.33
C5	0.0713(2)	0.1518(9)	0.2614(4)	2.88
O6	0.0760(1)	0.2142(7)	0.1310(3)	4.26
C7	0.0372(2)	0.291(1)	0.3503(5)	3.51
C8	0.0000(0)	0.450(2)	0.2500(0)	3.60

Table 2. Selected Torsion Angles for pGp and Geometrical Parameters for N−H···O=C Hydrogen Bonds

(a) Selected Torsion Angles

group	atoms	angle (deg)
propyl	C1−C2−C3−N4	179.1(6)
propyl	C2−C3−N4−C6	$\varphi_1 = 156.8(5)$
glutaric	C3−N4−C6−C7	$\omega_1 = -177.7(5)$
glutaric	N4−C6−C7−C8	$\psi_1 = -164.3(4)$
glutaric	C6−C7−C8−C7′	$\nu_1 = 70.9(4)$

(b) Hydrogen Bond Geometry

d(H4···O5) (Å)	2.04
d(N4···O5) (Å)	2.89
∠(N4H4···O5) (deg)	170.3

Results and Discussion

A schematic representation of the model molecule *N,N'*-dipropylglutaramide (pGp) is shown in Figure 1 together with the definition of internal rotation angles. Table 1 shows a list of the final atomic coordinates and their estimated standard deviations. Final molecular parameters such as selected internal rotation angles and hydrogen bond geometry are reported in Table 2. Experimental values for bond distances and bond angles are consistent with known literature data for amide groups and paraffin chains. The amide group is planar, and the root-mean-square distance of the atoms from the average plane is less than 0.013 Å. A stereoview of the molecule is shown in Figure 2. Molecular symmetry is characterized by a binary axis through the middle of the polymethylenic segment. Thus, the torsional angles of the two halves are equal. The main feature of pGp is that an all-*trans* conformation is not observed and the −NHCO(CH$_2$)$_3$CONH− segment adopts a TTGGTT conformation (Table 2). This pleated conformation produces a rotation of 149° between the C−O directions.

pGp crystallizes in a $C2/c$ space group, and the unit cell contains four molecules, two of which are identical and have

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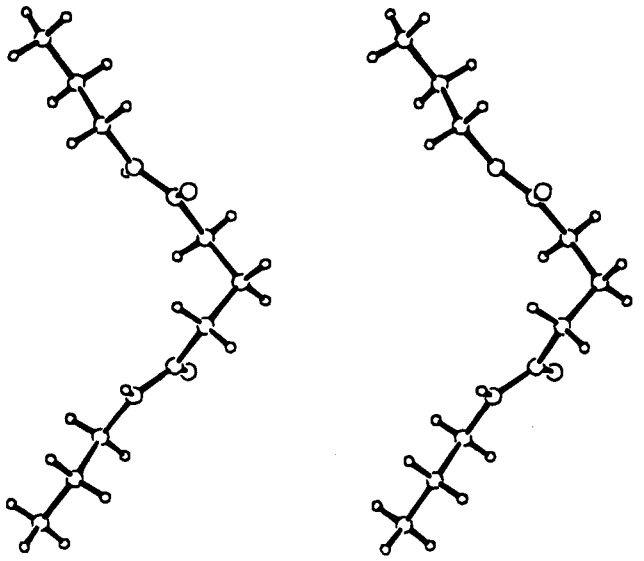

Figure 2. Stereopair showing the conformation in the crystalline state of pGp. Note the folded conformation of the glutaryl residue.

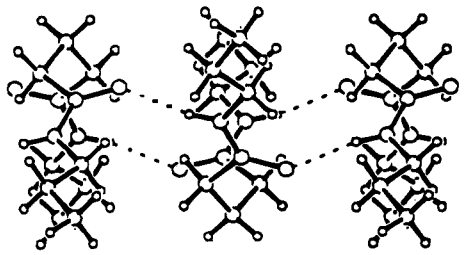

Figure 3. View of three hydrogen-bonded molecules down the *a* axis. Hydrogen bonds are indicated by dashed lines and are established along the *c* axis direction. Note that adjacent molecules are mirror images.

the parameters given in Table 2. The other two molecules are related by a glide plane and are their mirror images. Hydrogen bonds with lengths and angles within the standard range are formed between molecules related by a glide plane (Figure 3) and are established according to nearly opposite directions. Projections of the structure are shown in Figure 4. Note that there are two layers of molecules along the *a* crystal axis and that each layer is composed of both mirror images. The crystal is organized with fully extended propyl chains, which are loosely packed at the surface of interaction among the terminal methyl groups. Indeed a rather large degree of thermal disorder has been found for the propyl chains, as in other compounds studied by us.[28-30]

Quantum mechanical calculations were performed on the model molecule *N,N'*-dimethylglutaramide (mGm). Thus, in order to reduce the size of the molecule, the propyl terminal groups were replaced by methyl groups. Only two minimum energy conformations were found at the *ab initio* HF/6-31G* level. These are displayed in Table 3 and correspond to TSTTST (**I**) and TTGGTT (**II**) conformations; the latter is 1.9 kcal/mol more favored than the former. Conformational angles for **II** are very similar to those found experimentally for pGp. Although the TTTTTT (**III**) conformation was not found as a minimum, its conformational energy was computed by keeping all the ψ_i and ν_i fixed, while all the other geometrical parameters were relaxed. The conformer **III** was less stable than **II** by 2.7 kcal/mol. This result has a parallel in *N,N'*-dimethylmalonamide, where the all-*trans* conformation is unfavored due to the repulsive interactions between the close oxygen atoms.[31] In both pGp and mGm we also have an odd number of methylenes between the two amide groups, and although the repulsive interactions are smaller than in *N,N'*-dimethylmalonamide due to the increase in the number of central methylenes, they are present in the all-*trans* conformation.

In order to investigate the effect of the basis set and the electronic correlation, single point calculations were performed for the minimum energy conformations at the HF/6-311G** and MP2/6-31G levels. In all cases **II** is the most stable conformation, in good agreement with the crystallographic data. The $\Delta\Delta G$ values of solvation computed for the two minima at the AM1/MST level are displayed in Table 3, where the hydrophi-

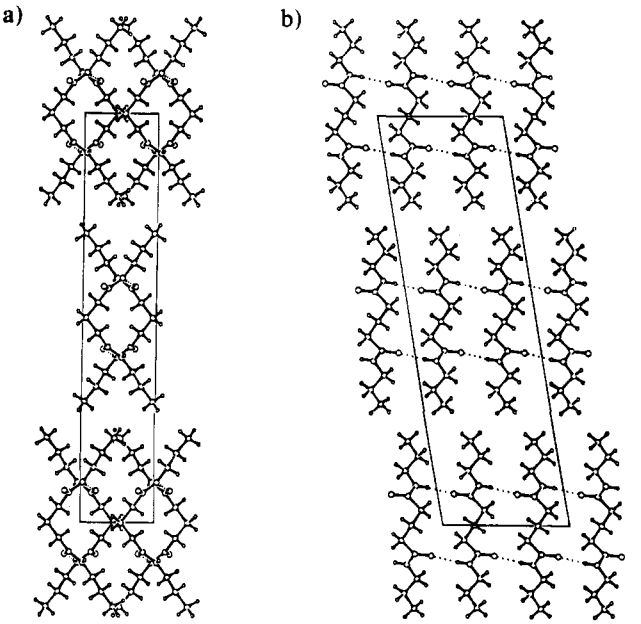

Figure 4. Projections of the crystalline structure of pGp onto the *ab* plane (a) and the *ac* plane (b). The unit cell is shown by thinner lines while hydrogen bonds are indicated by dashed lines. In (a) the mirror image molecules are at different levels in the *c* direction. In (b) neighboring molecules in consecutive layers are at different levels in the *b* direction.

Table 3. Selected Torsional Angles[a] (deg), Relative Energies[b] (kcal/mol), Relative Solvation Free Energies (kcal/mol), and Crystallographic Hydrogen Bond Geometry for the Glutaramide Analogues under Study[c]

		computed	
	crystal	**I**	**II**
ω_i (deg)	−177.8	−177.9	174.0
ψ_i (deg)	−164.0	128.2	−165.7
ν_i (deg)	70.1	173.3	66.3
ΔE(HF/6-31G*//HF/6-31G*)		1.9	0.0
ΔE(HF/6-311G**//HF/6-31G*)		2.0	0.0
ΔE(HF/6-31G//HF/6-31G*)		2.5	0.0
ΔE(MP2/6-31G//HF/6-31G*)		2.3	0.0
$\Delta\Delta G_{sol}$(AM1/MST)		0.0	1.4

[a] The conformational angles are defined as follows: ω_i, C3−N4−C6−C7 and C7′−C6′−N4′−C3′; ψ_i, N4−C6−C7−C8 and C8−C7′−C6′−N4′; ν_i, C6−C7−C8−C7′ and C7−C8−C7′−C6′. [b] Level of energy calculation//level of geometry optimization. [c] Crystal data correspond to *N,N'*-dipropylglutaramide, whereas computational results refer to *N,N'*-dimethylglutaramide.

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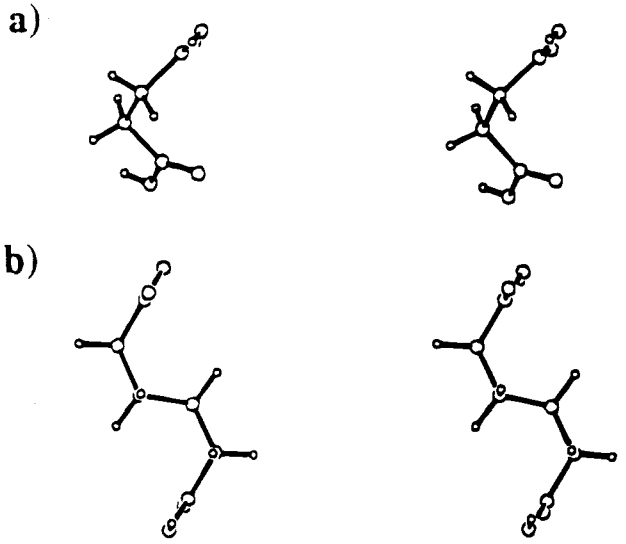

Figure 5. Stereopairs showing the folded conformation of the succinyl (a) and adipoyl (b) residues in the crystalline state of the molecules *N,N'*-succinylbis(*N*-propylglycinamide) and *N,N'*-adipoylbis(*N*-propylglycinamide).

licity order **I** > **II** is stated. However, the preference of **I** over the **II** conformer by 1.4 kcal/mol is lower than the energy difference *in vacuo* by around 1 kcal/mol. These results indicate that solvation does not alter the conformational preferences. To our knowledge, there is no study of the total ΔG of solvation on glutaramide analogues with which to compare our SCRF estimates. However, in a recent study Luque and Orozco[32] demonstrated the suitability of the AM1/MST method in amide compounds, even taking into account that the AM1 method is unable to represent the electronic properties accurately.

In a recent study on the tendency of glycine residues to adopt the Polyglycine II[33] conformation in their copolyamides with aliphatic compounds, we crystallized, among others, *N,N'*-succinylbis(*N*-propylglycinamide) and *N,N'*-adipoylbis(*N*-propylglycinamide).[30] These compounds have succinamide ($NHCO(CH_2)_2CONH$) and adipamide ($NHCO(CH_2)_4CONH$) moieties, respectively, in which, contrary to expectations, the torsional angles are not all-*trans*. Thus, the succinamide unit presents a TTGTT conformation, and a $T\bar{S}GT\bar{G}ST$ conformation has been found in the adipamide unit. Both conformations are shown in Figure 5. Although at a first term we may expect a different behavior for compounds with an even or an odd number of methylene units, the results reported for succinamide and adipamide in glycine derivatives agree with those obtained in the present study for both pGp and mGm glutaramide analogues.

In order to confirm the agreement found between succinamide and glutaramide units, we performed quantum mechanical calculations on the *N,N'*-dimethylsuccinamide (mSm). Thus, we attempted to characterize as energy minima at the HF/6-31G* level both the expected all-*trans* conformation and the experimentally-found conformation. In this case, we found and characterized the all-*trans* conformation ($\psi_i = 179.9°$, $\nu_1 = -179.9°$) as an energy minimum, since the carbonyl oxygens atoms have opposite orientations and then no repulsive electrostatic interactions are possible between them. On the other hand, in agreement with experimental data, the minimum energy structure with the central methylene units in a *gauche* conformation is 1.5 kcal/mol more favored with respect to the all-*trans* conformation. However, it must be stressed that the X-ray conformation ($\psi_i = -172.2°$, $\nu_1 = 75.3°$) is not well reproduced by quantum mechanical calculations where an asymmetric conformation is found ($\psi_1 = -169.7°$, $\nu_1 = 73.9°$, $\psi_2 = -101.5°$). This is not a surprising feature since previous studies demonstrated that crystal environment effects are required for the determination of the structure of molecules with close amide groups.[31,34,35] For example, the conformation of *N,N'*-dipropylmalonamide is symmetric ($\psi_i = 114.8°$) in the solid state,[29] whereas quantum mechanical calculations provide an asymmetric conformation ($\psi_1 \approx 111°$, $\psi_2 \approx 56°$) for *N,N'*-dimethylmalonamide.[31]

Conclusions

These results indicate that, in some cases, the methylene units tend to fold in a *gauche* conformation. This folding has been described in the present study for glutaramide analogues taking into account three different environments, as noted by solid-state experiments and calculations *in vacuo* and in solution. Thus, in the present case intermolecular hydrogen bonds and water have only a moderate influence. The equilibrium T−G of the methylene units is basically attributed to the interactions between the amide and retro-amide links. However, it should be considered that when glutaramide has hydrogen-bonding donor groups at the end, like $R_1 = H$, the situation is different. Thus, in these cases the two terminal $-NH_2$ groups participate in two hydrogen bonds each.[36,37] On the other hand, when glutaramide has substituents in any of the methylene carbon atoms[37,38] or halocarbon terminal groups,[39] hydrogen bonds could also change the conformational preferences of the molecule. For instance, an intramolecular hydrogen bond between the backbone and side chain in *N*-pivalyl-*N'*-methyl-L-glutamine-*N*-methylamide was found by Marraud and coworkers.[37]

Folding of methylene groups has recently been observed in glycine derivatives with succinamide and adipamide units. Quantum mechanical calculations on mSm corroborate a preference for a *gauche* conformation in linear succinamide analogues, in which due to their even number of methylene groups, another type of interaction is involved. These results should be taken into account when both the crystallographic data and the defects in crystals of polyamides with related groups are modeled.

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