Can We Predict the Conformational Preference of Amides?

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Received March 5, 2001

To what extent, if any, is the conformation of secondary amides revealed by theory? This question has now been addressed by computational methods using calculations at the B3LYP/6-31G* level of theory and ^{1}H NMR spectroscopy. Both gas-phase and solvent studies predict a *Z*-anti conformation to be the lowest in energy for an evaluated series of acetamides. Moreover, *Z*-anti conformations may also be inferred from the chemical shifts of the N−CHα protons determined by NMR spectroscopy. Thus, a proton situated anti to the N−H proton consistently appears ∼0.8 ppm further downfield than a proton situated gauche to the N−H proton. This finding, which could only be derived by using the DFT calculations of conformational preference as a guide to interpret the NMR data, might prove to be useful as a simple and convenient methodology for establishing amide conformation experimentally.

Introduction

If there is a functional group relevant to life processes, it must surely be the amide linkage. Dazzling proteins and ubiquitous enzymes aside, amide bonds are the building blocks of a series of important naturally occurring substances that includes glycoproteins or sphingolipids, as well as synthetic polyamides and pharmaceuticals. The key structural features of amides, especially short C−N bond lengths and hindered rotation about the C−N bond, have long been known.[1] In fact, the determination of the barrier to rotation in amides and thioamides has been a favorite domain of dynamic NMR and other spectroscopic techniques,[2] not only in solution but also in the gas phase.[3]

It is now well established that *E*/*Z* isomerism arises from delocalization of the lone pair on nitrogen into the π^* orbital of the carbonyl group, which gives the single bond some double-bond character and slows rotation. While this simple scheme has long held interest for chemists, an alternative and otherwise complementary vision supported by theoretical calculations has been provided by Wiberg and his associates. This description suggests a greater charge and energy distribution along the C−N bond.[4]

The importance of this isomerization in amides lies beyond the pure scope of structure and reactivity. A series of enzymes called immunophilins, which elicit immunosuppressive effects, catalyzes the interconversion of cis and trans rotamers of peptidyl bonds.[5] These enzymes, collectively known as "rotamases", accelerate the otherwise slow folding of proline-containing polypeptides.[6,7] Moreover, individual rotamers of certain drugs involving amide or thioamide bonds are required for high-affinity receptor binding.[8]

The rotational pathway is largely governed by steric and electronic effects provided by substituents around the C−N bond. Thus, the effects of carbonyl substituents[9] and substituents at nitrogen[10] on the barriers to rotation for simple amides have been documented, yet no definitive conclusions have been provided. Furthermore, varied results are encountered in solution with respect to studies in the gas phase.[11]

The conformational preference of *Z* and *E* amides, however, is still unclear, and opposite results can be

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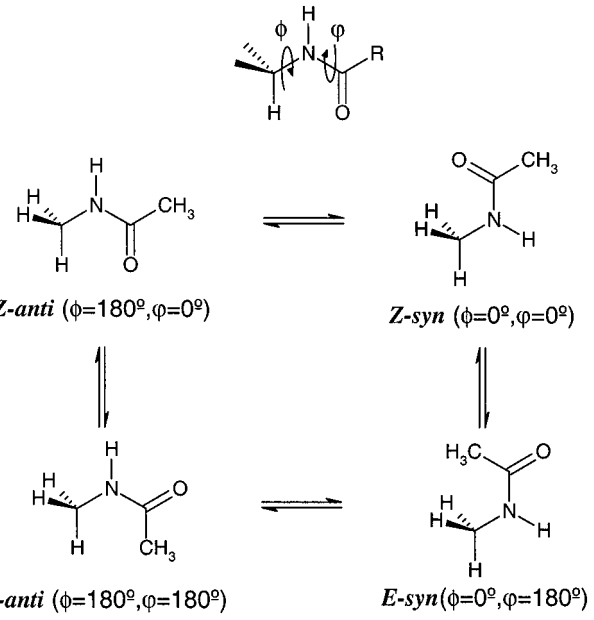
10.1021/jo0102361 CCC: $20.00
Published on Web 10/05/2001

Chart 1. Syn and Anti Conformations for *Z* and *E* Isomers of *N*-Methylacetamide



extracted from previous works. The rotational pathway for *N*-methylacetamide as a function of the amide torsion angles ϕ and φ is depicted in Chart 1.

Jorgensen and Gao encountered little orientational preference in the gas phase for the methyl group on nitrogen, and at the HF/6-31G* level of theory, the syn conformer is lower in energy by 0.5 and 0.1 kcal/mol for the *Z* and *E* isomers of *N*-methylacetamide, respectively. In contrast, the rotated anti conformer is preferred at the HF/3-21G* level for the *Z* isomer by 0.3 kcal/mol.[12] Moreover, studies on dimers of *N*-methylacetamide and *N*-methylacetamide−water in order to elucidate hydrogen bond strengths also reveal that syn conformers for both *Z* and *E* isomers are the preferred orientations.[11d] In a further study, in which geometrical parameters were taken from reported crystal structures, Itai and co-workers found again that the syn conformation was more stable for *Z* and *E* isomers of *N*-methylacetamide by means of ab initio Hartree−Fock calculations using the standard 4-31G, 4-31G*, and 6-31G* basis sets.[13] Likewise, Guo and Karplus have performed Hartree−Fock (with 6-31G, 6-31G*, and 6-31G** basis sets) and MP2 (with the 6-31G* basis set) studies of hydrogen bonding of *N*-methylacetamide complexes, in which this amide is bonded to water and/or formamide. In contrast with isolated *N*-methylacetamide, where the conformations with the different methyl orientations have similar energies ($\Delta E \sim 0.1$ kcal/mol), all the hydrogen bonded systems are predicted to have a syn conformation stabilized by 0.2−0.9 kcal/mol.[14]

These findings clearly contrast the situation encountered in glycoamides,[15,16] a key structural motif of some naturally occurring antibiotics, for which spectroscopic and crystal data as well as semiempirical calculations do support a prevalent anti conformation. In fact, a set of empirical correlations can be obtained from NMR data in solution,[15] which have proved to be adequate for use in structural assignment of *E* and *Z* isomers of amidosugars.[17] It is obvious, however, that the conformational preference of glycosyl amides and, in general, geminally substituted amides at nitrogen cannot directly be inferred from simple amides. Such complex derivatives can support anomeric effects in the same way as their carbon analogues such as acetals or aminals.[18,19] In addition, steric effects become crucial as the larger substituent will adopt the orientation syn to the carbonyl oxygen atom. Variable conformations may also be found in twisted amides, possibly for simple steric considerations.[20]

Within this conformational context, it is also worth mentioning a series of key contributions by Krimm and co-workers who did calculations on the vibrational spectra of *N*-methylacetamide and small peptides. These studies were devoted to the assignment of bands proposed to be characteristic of a structure.[21] In general, such calculations provide evidence for the existence of *N*-methylacetamide conformations that differ in the orientation of their methyl hydrogens, although two conformers (syn and anti) dominate the spectra. The most stable geometry of isolated cis *N*-methylacetamide was found to have a *C*-methyl hydrogen eclipsing the oxygen and an *N*-methyl hydrogen eclipsing the NH. The most stable trans conformer had the same local eclipsed conformations. In a recent study as well, Tasumi and co-workers have studied the effect of intermolecular hydrogen bonding on the amide I mode of *N*-methylacetamide.[22] These authors found that hydrogen bonding to the carbonyl group induces a 20−25 cm^{-1} shift toward lower wavenumbers, while those induced by bonding to the NH group are 15−20 cm^{-1}. Nevertheless, in the case of *N*-methylformamide, ab initio calculations and the microwave spectrum in the frequency range of 18−40 GHz

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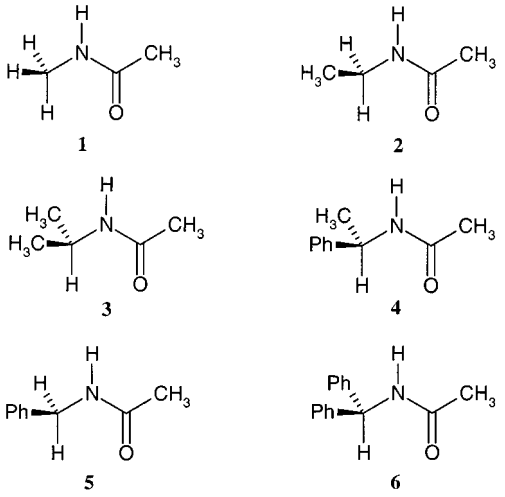
Chart 2



did not allow the equilibrium conformation of the methyl group to be found.[23] While the assignment of a conformation-sensitive band in the vibrational spectra of peptides and proteins can make it a useful probe of their secondary structure, it is dubious that ro-vibrational spectra can compete with the modern and increasingly sophisticated NMR methods for the direct determination of conformations for proteins (vide infra).

With the above-mentioned premises, we decided to carry out a computational reinvestigation of the conformational behavior of secondary amides **1**−**6** (Chart 2). In addition to gas-phase studies, we have also examined the role of the solvent in determining the stability of the rotational isomers. As we shall see later, these models have been shown to be quite adequate at reproducing experimental magnitudes obtained from NMR spectra in solution.

Results and Discussion

To minimize the computational cost, our preliminary screening was performed by means of semiempirical MO calculations at the PM3 level,[24] a robust method that often gives good agreement with experiment, and using the Gaussian 94 package.[25] Unfortunately, PM3 calculations yielded disparate results, and thus they predicted an *E*-anti conformation for **2**, **3**, **5**, and **6**, whereas the *E*-syn structure was more stable for **1**. For **4**, the *Z*-anti disposition was found to be the lowest in energy, while the *E*-syn orientation was also more stable than the *E*-anti conformation. It has been suggested that because amide is a highly polarized functional group, semiempirical methods currently available cannot satisfactorily reproduce its most stable structure.[13]

Gratifyingly, consistent results could be obtained via density functional calculations based on Becke's three-parameter hybrid[26] involving the gradient-corrected correlation functional of Lee, Yang, and Parr[27] and using the standard 6-31G* basis set.[28] This consistency reinforces the importance, which has become a tenet of modern computational chemistry, of using theoretical methods involving some type of electronic correlation (either ab initio or DFT).[29]

For each compound **1**−**6**, and starting from only either the *Z* or *E* amide, we performed a complete conformational analysis around the amide function, at the PM3 level of theory, by rotating the torsion angle about the N−Cα bond with a 30° step and taking as the starting reference the syn conformation ($\phi = 0°$). The most stable conformers for *Z* and *E* amides obtained by this systematic procedure were optimized at that level, and finally, such minima were fully optimized without any constraints at the B3LYP/6-31G* level of theory.

For amides **3**, **4**, and **6**, bearing only one hydrogen atom on Cα, the conformational pathway is similar to that found previously for carbohydrate-derived amides,[16] with two minima positioned close to syn and anti conformations ($\phi = 0$ and 180°, respectively). The results obtained for these substances at the B3LYP/6-31G* level are listed in Table 1, which predict that the most stable rotamers correspond to an anti arrangement ($\Delta E_{\text{syn-anti}}$ ranges from 1.7 to 4.1 kcal/mol). It is likewise worth noting that this rotated isomer ($\phi = 158-176°$) is preferred for *Z* amides. The energy differences ($\Delta E = E_{E\text{-anti}} - E_{Z\text{-anti}}$) lie in the range from 2.1 to 2.6 kcal/mol.

Concerning the disposition around the $COCH_3$ group, the staggered conformation is the conformation of lowest potential energy for *Z* isomers, while an eclipsed conformation is reached for the energy minima encountered in the case of *E* isomers. The angle of torsion about the NCO−CH_3 bond (ψ) is denoted in Chart 3.

Moreover, it should be noted that X-ray crystal structures for a number of simple amides and peptides reveal a structural arrangement close to a *Z*-anti conformation.[30] Assuming that amides may be associated by hydrogen bonds in the solid state, the orientation of the methyl groups could result from such an intermolecular bonding rather than the conformational preference. Thus, conformations obtained in both the gas phase and solution cannot rigorously be inferred from results in the crystalline state.

N-Methylacetamide (**1**) offers an interesting situation as there are three hydrogen atoms at Cα, and this substance provides one of the simplest models for reproducing the conformational characteristics of the peptide bond in proteins. Energy calculations at the B3LYP/6-31G* level were carried out by rotating the torsion angle NH−CHα between 0° and 60° with a 5° step, while other geometrical parameters were freed, to obtain a complete conformational spectrum for this substance. The electronic energies resulting from such a computation have been collected in Supporting Information. As indicated by these values and Figure 1, the *Z* amide structure with a torsion angle ϕ close to 60° (or alternatively 180° referred to H-2) is the most stable structure.

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Table 1. Energy Differences (kcal/mol) for Amides 3, 4, and 6 in the Gas Phase at the B3LYP/6-31G* Level

isomer	ϕ	Ψ	isomer	ϕ	Ψ	ΔE (syn − anti)	ΔE ($E_{anti} - Z_{anti}$)
$\mathbf{3}E_{syn}$	15.85	17.23	$\mathbf{3}E_{anti}$	167.38	0.68	3.66	2.62
$\mathbf{3}Z_{syn}$	0.04	179.98	$\mathbf{3}Z_{anti}$	157.74	174.45	1.72	
$\mathbf{4}E_{syn}$	24.19	17.13	$\mathbf{4}E_{anti}$	142.26	4.03	3.87	2.12
$\mathbf{4}Z_{syn}$	332.99	169.93	$\mathbf{4}Z_{anti}$	175.91	173.92	1.98	
$\mathbf{6}E_{syn}$	30.00	11.23	$\mathbf{6}E_{anti}$	217.24	6.63	4.01	2.53
$\mathbf{6}Z_{syn}$	337.52	164.44	$\mathbf{6}Z_{anti}$	175.62	167.39	4.12	

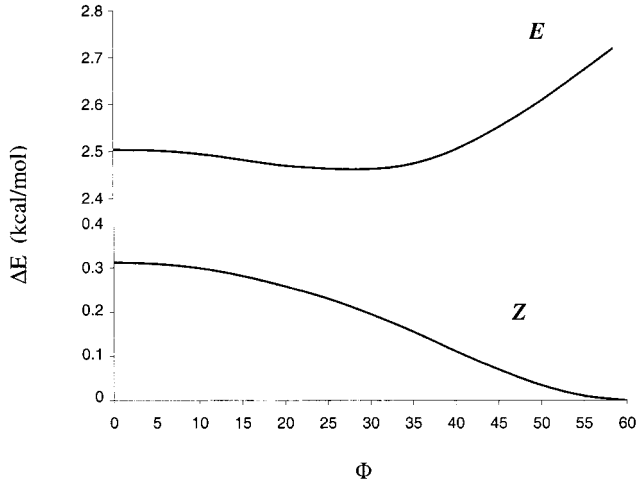

Figure 1. Computed variation in the energy for (*Z*)- and (*E*)-*N*-methylacetamide with the torsion angle ϕ (deg). Energy data have been arbitrarily referred (E = 0.00 kcal/mol) to a conformation of lowest potential energy (ϕ = 60°, E = −155 950.890 kcal/mol).

Chart 3. Eclipsed ($\psi = 0°$) and Staggered ($\psi = 180°$) Conformations around the O−C−C−H Bond

Table 2. Energy Differences (kcal/mol) and Torsion Angles (deg) for (*Z*)- and (*E*)-*N*-Methylacetamide

	E isomer		*Z* isomer		
model chemistry	ϕ	Ψ	ϕ	Ψ	ΔE ($E - Z$)
B3LYP/6-31G*	28.97	1.41	179.99	179.99	2.46
MP2/6-31G*	29.98	1.53	176.32	159.45	2.24
MP2/6-31+G**	29.68	3.69	179.97	179.99	2.06
HF/6-31G**	18.61	2.25	24.60	158.14	2.54

Finally, the most stable conformers of *E* and *Z* isomers were fully optimized without any constraints, and such data are gathered in Table 2. The most stable structure in the gas phase corresponds to a *Z*-anti arrangement (ϕ = 180°) that is lower in energy by ∼2.5 kcal/mol than other rotamers for the *E* amide structure. A further optimization of the maximum (ϕ = 0°) was performed to locate the saddle point consistent with a *Z*-syn conformation (ϕ = 0.27°, ψ = 179.86°), the difference in energy being 0.31 kcal/mol with respect to the *Z*-anti conformation. Such a transition structure was characterized by one and only one imaginary frequency corresponding to rotation around the CON−CH_3 bond. It should be noted that the greater stability of the *Z* isomer of *N*-methylacetamide (equivalent to the trans isomer)[31] has been previously documented, although the syn rotamer was postulated as the most favorable conformation by Hartree−Fock calculations.[12,13]

To shed light, we have recalculated the conformational spectrum at a higher level of theory (Table 2). Both MP2/6-31G* and MP2/6-31+G** calculations predict a *Z*-anti disposition, with the staggered conformation for the $COCH_3$ group, as the low-energy conformer for *N*-methylacetamide, whereas no local minimun could be found for the alternative syn conformation. In stark contrast, lower level calculations (HF/6-31G**) invariably suggest that an orientation close to a *Z*-syn conformer (ϕ = 24.6°) is about 2.5 kcal/mol more stable than the *E*-syn form. Furthermore, when the most stable geometry obtained at the HF/6-31G* level was fully optimized without any constraints at the B3LYP/6-31G* level, then the *Z*-anti conformation (with a staggered disposition for the $COCH_3$ group) was found anew to be the lowest in energy. On the contrary, the most stable conformation predicted by the B3LYP/6-31G* level, after its complete optimization at the HF/6-31G** level, results in the *Z*-syn disposition gathered in Table 2. Thus, it now becomes clear that Hartree−Fock methods do predict a single conformation but one different to that of higher level calculations, both DFT and Møller−Plesset calculations.

Table 3. Energy Differences (kcal/mol) and Torsion Angles (deg) for Amides 2 and 5 (B3LYP/6-31G* Level)

isomer	ϕ	Ψ	isomer	ϕ	Ψ	ΔE ($E_{anti} - Z_{anti}$)
$\mathbf{2}E_{anti}$	163.00	1.62	$\mathbf{2}Z_{anti}$	164.68	175.81	2.50
$\mathbf{5}E_{anti}$	191.11	1.63	$\mathbf{5}Z_{anti}$	169.50	173.89	3.23

In the cases of *N*-ethylacetamide (**2**) and *N*-benzylacetamide (**5**), bearing two hydrogen atoms at Cα in both structures, further optimizations were carried out at the B3LYP/6-31G* level following the procedure previously established for **3**, **4**, and **6**. The potential energy varies slightly with the torsion angle ϕ, with the sole exception of a sharp maximum observed for each *Z* or *E* isomer due to eclipsing arrangements. Thus, in the case of *E* isomers, the methyl group of the acetate function would be at the eclipsed position to the α-substituent on nitrogen, either methyl for **2** or phenyl for **5**. Likewise, for *Z* isomers, the local maximum occurs by an eclipsing of the carbonyl group of the acetate to the α-substituent on nitrogen.

For both amides, syn conformations occur at torsion angles ϕ = 0 and 120°, whereas anti rotamers are defined by ϕ values of 180 and 300°, each corresponding to a pair of enantiomeric rotational isomers. Table 3 summarizes the results of the conformational analysis of **2** and **5**. Moreover, in a comparison of *Z*-anti and *E*-anti structures, the former was more stable by about 2.5−3.2 kcal/mol at this level of theory. The torsion angles of the corresponding *Z*-anti amides **2** and **5** narrow from 164.7 to 169.5°, respectively.

Effect of Solvent. Simulation studies going from the gas phase to solution are especially important for amides

(31) Although rotation about the C−N bond in amides is generally referred to as cis-to-trans isomerization, the definition of cis and trans amides is ambiguous, and its use discouraged by the standard IUPAC nomenclature: *A Guide to IUPAC Nomenclature of Organic Compounds. Recommendations 1993*; Blackwell Scientific Publications: Oxford, 1993.

Table 4. Calculated Solvent Effects (kcal/mol) for *N*-(1-Methylbenzyl)acetamide at the B3LYP/6-31G* Level

solvent	isomer	ϕ	Ψ	isomer	ϕ	Ψ	ΔE (syn − anti)	ΔE ($E_{anti} - Z_{anti}$)
$CHCl_3$	$\mathbf{4E}_{syn}$	23.68	17.25	$\mathbf{4E}_{anti}$	141.36	4.22	3.75	1.92
	$\mathbf{4Z}_{syn}$	26.08	169.30	$\mathbf{4Z}_{anti}$	175.52	173.67	2.00	
CH_3OH	$\mathbf{4E}_{syn}$	23.43	15.72	$\mathbf{4E}_{anti}$	140.95	4.44	3.68	1.84
	$\mathbf{4Z}_{syn}$	25.60	169.59	$\mathbf{4Z}_{anti}$	175.34	174.50	2.01	
H_2O	$\mathbf{4E}_{syn}$	23.40	15.49	$\mathbf{4E}_{anti}$	140.87	4.49	3.68	1.83
	$\mathbf{4Z}_{syn}$	25.60	169.65	$\mathbf{4Z}_{anti}$	175.46	170.78	2.01	

in order to obtain reliable models of the backbones of proteins. In fact, elucidation of protein folding mechanisms represents an ongoing activity of theoretical biochemistry.[32]

Early experimental studies involving dynamic NMR[2,11a] have been supplemented by computational calculations during the past decade.[11b−g] Most of these studies concentrate on the effects of solvent parameters such as solvent polarity or hydrogen-bond donor ability on the rotational barrier. In general, amide bond rotation decreases as either the polarity or the hydrogen bond formation increases. Thus, it appears that the barrier for *N*,*N*-dimethylacetamide is higher in methanol than in acetonitrile by 1.0 kcal/mol, even though both solvents have similar dielectric constants.[11e] However, the energy differences calculated at different levels of theory are different, and, accordingly, caution should be paid to estimate solvent effects. Anyway, the inclusion of such effects is found to give barriers in good agreement with experiment, whereas gas-phase ab initio methods show a tendency to give smaller barriers than those observed experimentally.[11a]

A priori deductions cannot be invoked because calculations suggest that the transition state structures favored for simple amides in the gas phase and in aprotic solvents may be different from those found in an aqueous environment.[33] We have chosen *N*-methylacetamide (**1**) and *N*-(1-methylbenzyl)acetamide (**4**) and have redetermined the energy differences in three polar solvents, water ($\epsilon = 78.5$), methanol ($\epsilon = 32.7$), and chloroform ($\epsilon = 4.8$).[34,35] The inclusion of chloroform is justified by the fact that NMR spectra of numerous amides are often recorded in this deuterated solvent, thereby providing a feasible comparison with experimental data.

The self-consistent reaction field (SCRF) theory,[36] as implemented in the Gaussian 94 package, has been used with the B3LYP/6-31G* energies to model these amides in solution and to calculate the solvation energy using the simple, yet useful, Onsager dipole protocol.[37] Optimizations were performed without constraints starting from structures optimized previously in the gas phase at the same level of theory. The results obtained from applying the Onsager procedure to the four possible conformers of **4** (as determined by their torsional angles) are listed in Table 4. *E*-anti and *Z*-anti rotamers are invariably the most stable structures irrespective of the solvent considered, with energy differences between them ranging from 1.8 to 1.9 kcal/mol.

Table 5. Calculated Solvent Effects (kcal/mol) for *N*-Methylacetamide Rotamers at the B3LYP/6-31G* Level

solvent	isomer	ϕ	Ψ	isomer	ϕ	Ψ	ΔE ($E_{syn} - Z_{anti}$)
$CHCl_3$	**1*E***	19.42	2.34	**1*Z***	179.98	179.95	1.79
CH_3OH	**1*E***	16.53	2.43	**1*Z***	179.97	179.98	1.46
H_2O	**1*E***	16.13	2.43	**1*Z***	179.98	179.87	1.42

As expected, the conformational stability increases as bulk solvent polarity becomes larger. In the SCRF model, the stabilization energy reflects the interaction between the dipole moment of the amide ($\mu E > \mu Z$) and the dipole moment induced by solvation. Thus, the aqueous environment has a more pronounced effect on the *E* isomer than it has on the *Z* analogue with respect to the gas phase, albeit small variations are found anyway. Going from the gas phase to the water cage, the *E*-anti conformation is stabilized by 1.28 kcal/mol, while the same effect for the *Z*-anti conformer is 0.98 kcal/mol. It is fair to say, however, that although the energy change correlates well with solvent polarity, the effect of a hydrogen bonding solvent, by incorporating for instance, a water molecule hydrogen bonded to the oxygen atom, has not yet been studied. A similar behavior can be observed in the case of *N*-methylacetamide (**1**), although the torsional angle found after energy optimization without any constraints is close to that of an *E*-syn conformation (Table 5, see also Figure 1 above). The *Z*-anti conformation is preferred by about 1.4−1.8 kcal/mol in the range of solvents studied. Again, the stabilization obtained in water for the most stable conformation of the *E* isomer is greater than for its *Z* analogue (3.23 kcal/mol vs 2.19 kcal/mol).

Previous NMR spectroscopy studies indicated that *N*-methylacetamide exists as the cis isomer (*E* form) to a minor extent (1−3%) in water, not changing much in nonpolar solvents. The trans isomer (*Z* form) was found to be lower in energy by ∼2.5 kcal/mol. Computations also suggest that in the low-energy conformer of *N*-methylacetamide, the *N*-methyl group is oriented in such a way that one of its hydrogen atoms is eclipsed by the amide hydrogen atom, whereas the other methyl substituent is eclipsed by the carbonyl group.[38,39]

It should be noted that solvent effects have also been evaluated for stable *Z* and *E* conformers of secondary

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(35) Characterization of solvent polarity by means of the dielectric constant may be ambiguous as this parameter simply represents the ability of a solvent to separate charge and orient its dipoles, whereas the overall solvation ability depends on several interactions. The Dimroth−Reichardt transition energy parameter (E_T) more accurately reflects solvent polarity. The normalized E_T values for water, methanol, and chloroform are 1.000, 0.762, and 0.259, respectively; see ref 34, pp 363−371.

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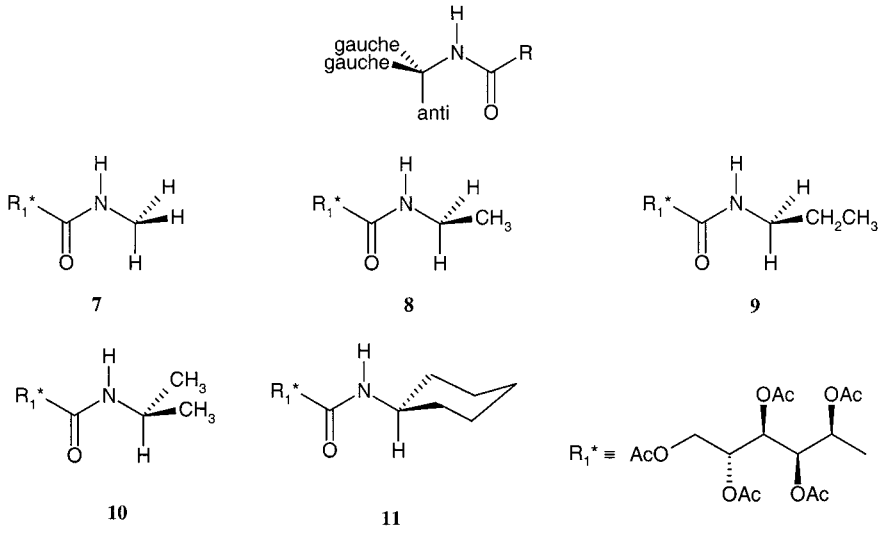
Chart 4



amides by measuring their enthalpies of solvation, as this parameter correlates well with the ability of the solvent to donate a hydrogen bond to the amide oxygen.[40] Such studies were focused on two limiting cases: *N*-methylpropianamide, which is known to exist almost exclusively in the *Z* conformation,[41] and 2-pyrrolidine in which ring formation leads to the adoption of the less favorable *E* conformation.[42] Only in polar protic solvents, where aggregation between two solutes should be minimal, the enthalpies of solvation were the same for both amides. Our results are, nevertheless, consistent with those reported by Wolfenden et al., who found the population of the *Z* conformer for *N*-methylacetamide to be 98.5%.[39] In addition, these authors observed that the population of the *E* isomer slightly increases in $CDCl_3$ and C_6D_{12} (2.8 and ~2%, respectively) with respect to D_2O (1.45%).

NMR Correlation Studies. The magnetic anisotropy induced by the amide function has been the subject of numerous NMR studies, and its application still represents a valuable tool for determining barriers to rotation as well as populations of *Z* and *E* isomers,[2] assuming that in most cases such an interconversion is slow on the NMR time scale. We have now envisaged that this anisotropic effect might equally be utilized to predict conveniently the preferential conformation around the N−Cα bond.

In determining the NMR chemical shift of a selected nucleus, several empirical correlations are presently available.[43] The Shoolery relationship has become the most popular correlation for calculating approximate chemical shifts for methylene protons in $CDCl_3$ solution.[44] The chemical shift for the deshielded methine proton can be evaluated by means of a modified Shoolery equation:[44d]

$$\delta_{CHXYZ} = 0.23 + \sigma_X + \sigma_Y + \sigma_Z \qquad (1)$$

where σ_X, σ_Y, and σ_Z represent constants for the substituents and the amide function. Accordingly, the observed chemical shift (δ_{obs}), experimentally measured on the NMR spectrum, can be utilized to roughly estimate the deshielding caused by the amide function (δ_{amide}) on a particular proton:

$$\delta_{amide} = \delta_{obs} - (0.23 + \sigma_X + \sigma_Y) \qquad (2)$$

If one assumes that a *Z*-anti conformation should be prevalent in solution, we can regard δ_{amide} as a reflection of the deshielding on anti and gauche hydrogen atoms. The substituent other than hydrogen will then occupy a gauche disposition.

$$\delta_{amide} = \delta_{anti}/n + (n-1)\delta_{gauche}/n \qquad (3)$$

where *n* represents the number of hydrogen atoms located at Cα. Obviously, the magnitude encountered for δ_{amide} is an average shift as hydrogen atoms at Cα rotate rapidly at room temperature. To obtain statistically significant deshielding values, besides **1**−**6**, we have also incorporated the acyclic carboxamides **7**−**11** (Chart 4)[45] to the present study.

Table 6 collects the chemical shifts measured in $CDCl_3$ for secondary amides **1**−**11** and the deshielding caused by the amide function on hydrogen atoms in anti and gauche arrangements. These chemical shifts lie in the range 2.36−2.47 and 1.63−1.74 ppm, respectively. Such figures, on average, are found to be similar by considering amides **1**−**6** only or the more extended set of amides **1**−**11**, albeit in the latter case the statistical deviation was slightly higher ($\delta_{anti} - \delta_{gauche} = 0.76$ ppm, having a statistical deviation of 5.30%).

Although the Shoolery equation is parametrized for numerical data obtained in $CDCl_3$, we have also applied this relationship to the corresponding chemical shifts obtained in D_2O and DMSO-d_6. In the latter cases, δ_{anti} and δ_{gauche} values were similar to those found in $CDCl_3$,

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Table 6. Magnetic Deshielding (ppm Scale) Caused by the Amide Function (δ_{anti}, δ_{gauche}) on CON−CHα Protons for Amides 1−11 in $CDCl_3$

compd	δ_{obs}	σ	δ_{amide}	δ_{anti}	δ_{gauche}	$\delta_{anti} - \delta_{gauche}$
1	2.80	(H,H)	1.89	2.42	1.63	0.79
2	3.28	(H,Me)	2.03	2.42	1.64	0.78
3	4.06	(Me,Me)	2.47	2.47[a]		
4	5.17	(Me,Ph)	2.43	2.43[a]		
5	4.43	(H,Ph)	2.03	2.42	1.64	0.78
6	6.25	(Ph,Ph)	2.36	2.36[a]		
Σ*n*/*n* (RSD)				2.42	1.64	0.78
(partial)				(2.30%)	(0.35%)	(0.74%)
7	2.82	(H,H)	1.91	2.42	1.66	0.76
8	3.29	(H,Me)	2.04	2.42	1.66	0.76
9	3.23	(H,Et)	2.08	2.42	1.74	0.68
10	4.05	(Me,Me)	2.46	2.46[a]		
11	3.75	$-(CH_2)_5-$	2.36	2.36[a]		
Σ*n*/*n* (RSD)				2.42	1.66	0.76
(total)				(2.20%)	(2.42%)	(5.30%)

[a] Values taken for the averaging calculation. RSD, Relative standard deviation.

albeit such data do not exhibit enough statistical confidence.

It has been known that chemical shifts can also carry useful information about the structure of proteins. Contributions from the peptide group are particularly noticeable for protons at the Cα position. It seems that Cα protons are predominantly shifted downfield in β-sheets and upfield in α-helices, although such shifts are likely influenced by hydrogen bonding both to carbonyl groups and to solvent.[46] Since most [ϕ] angles in proteins[47] lie in the region from −180° to −60°, one should expect a strong dependence of the Cα proton shift on this angle. Furthermore, helices will have mean [ϕ] values near −60° and sheets mean values close to −120°. With these considerations, Ösapay and Case were able to calculate the magnetic anisotropy of the peptide bond to the Cα proton by varying the [ϕ] angle (conversely, the dependence on the [ψ] angle is very weak).[46] Unfortunately, correlation between backbone conformers and chemical shifts can be established only for the α-helical and β-sheet regions of the Ramachandran surface.[48]

A large number of conformations may, however, be estimated by computation of NMR chemical shielding anisotropy tensors at the GIAO-RHF level with the 6-31+G* and TZ2P basis sets. Such chemical shifts correlate well with experimental results, a fact that reinforces the key idea of employing chemical shifts alone to establish a prevalent backbone folding.[49] It is equally worth mentioning the complete prediction of the proton NMR spectrum of organic molecules by DFT calculations of chemical shifts and spin−spin coupling constants.[50]

In closing this section, it should be mentioned that the search for a correlation between the chemical shift of the α-protons and a particular conformation has been a long-awaited assessment.[51,52] In their classical review, Stewart and Siddall pointed out that "the presence of moderately hindered rotation can lead to differences in the relative populations of the possible conformations. In this case, the chemical shift for the α-protons will be a *weighted* mean of those corresponding to each of the conformations".[2a]

A recent and thought-provoking report notes that the relation between fast-exchange chemical shift and conformer population is more complex than the situation outlined in classical NMR reviews and assumed by most experimentalists.[53] Thus, for methylcyclohexane, the inconsistency between the slow-exchange free-energy differences and the fast-exchange equilibrium constants, which were spread over a wide range for the various ^{13}C positions, has been demonstrated. Accordingly, Mueller and Weitekamp conclude from this study that any fit requires contributions to the chemical shift with a temperature dependence that is greater than that measured in slow exchange. These authors have introduced new terms in the spin Hamiltonian, referred to as ALBATROSS, which should be important for experimentally verifying the temperature dependence in other conformational issues. Such an extrapolation to our model should be taken with caution because variable-temperature measurements have not been performed and chemical shifts at ambient temperature are interpreted from the observed fast-exchange line positions. Whether or not the magnetic deshielding on gauche or anti protons may be different after linear extrapolation to different temperatures, it does not render invalid our results as evidenced by the small statistical deviations. Simply, we have established from experimental NMR data the prevalent existence of a particular conformer, albeit the conformational population cannot be determined with complete accuracy. Anyway, Mueller and Weitekamp clearly conclude in their final paragraph that "the new equations of motion give intermediate-exchange line widths that are very similar to those of the traditional theory, and therefore, previously reported conformer interconversion rates and activation barriers are not likely to be as significantly affected".[53]

Conclusions

The conformational analysis of simple acetamides, both in the gase phase and in solution, is well reproduced by theoretical calculations performed at the B3LYP/6-31G* level of theory, which predict a *Z*-anti arrangement as the most stable structure, also having a staggered conformation with respect to the dihedral angle O−C−C−H (ψ). The Cα−NH torsional angles (ϕ) widen from 157.7 to 180.0° in the gas phase, which is a reasonable variation assuming that the ground state is planar. Conformational minima have also been found for *E* amides with torsion angles corresponding to anti orientations (and an eclipsed conformation for the angle ψ),

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(47) Torsion angles for proteins have been labeled [ϕ] and [ψ] to avoid misinterpretation with the angles ϕ and ψ described for simple amides through the present manuscript. The conformation of a polypeptide, as far as the run of the backbone through the molecule is concerned (i.e., the secondary structure), is therefore described by a set of torsion angles for each amino acid residue. See inter alia: (a) *IUPAC−IUB Recommendations 1971*; IUPAC: Pergamon, 1971; IUPAC Information Bulletin No. 10. (b) *Amino Acids, Peptides and Proteins*; Young, G. T., Ed.; The Chemical Society: London, 1972; Vol. 4, p 455.

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which are less stable than the *Z* isomer by 2.1−3.2 kcal/mol. *N*-Methylacetamide (**1**) deviates slightly from this behavior because its most stable *E* conformer exhibits a torsion angle ϕ close to 30°. In any event, the latter is less stable than the corresponding *Z*-anti conformer by 2.5 kcal/mol. Similar conclusions were equally reached with the aid of higher levels of theory: MP2/6-31G* and MP2/6-31+G** methods. With respect to solvent effects, the relative stability of both rotational isomers increases in polar solvents, although there is a greater stabilization of the more polar *E* isomer. Thus, the simple SCRF model does reproduce for such amides dipole−induced dipole interactions leading to *Z*-anti structures as the preferred rotamers in solution. Assuming the prevalent existence of the latter orientation, we have also evaluated the magnetic deshielding generated by the amide function on the hydrogen atoms positioned at the adjacent carbon atom. Typical chemical shifts, having small statistical deviations, have been found at $\delta_{anti} = 2.42$ (2.30%) ppm and $\delta_{gauche} = 1.64$ (0.35%) ppm, with $\delta_{anti} - \delta_{gauche} = 0.78$ (0.74%) ppm. With a larger statistical basis, a similar $\delta_{anti} - \delta_{gauche} = 0.76$ ppm is found, although the statistical deviation raises to 5.30%. Such data should provide a useful guide to assigning amide rotamers in solution.

In addition, a simple estimation of populations from the corresponding energy differences shows that, for amides **3**, **4**, and **6**, the *Z*-anti conformation exists almost exclusively, ranging from 94.8 to 99.9%. In the cases of amides **2** and **5**, no minima attributable to a *Z*-syn orientation could be found. Again, the major conflict is found for *N*-methylacetamide (**1**), which has been the subject of numerous and controversial studies, due to a lower energy difference. Our DFT calculations, however, have allowed us the unequivocal characterization of its *Z*-syn and *Z*-anti conformations as a saddle point and the lowest conformational minimun, respectively, with a barrier to rotation of 0.31 kcal/mol around the CON−CH_3 bond. Because of the similar deshielding for the anti and gauche protons of **1** (and **7** as well) with respect to other secondary amides, one might suggest that deshieldings for the *Z*-anti and *Z*-syn conformers are the same, which might have led to the overestimation of the *Z*-anti geometry. This surmise, however, fully disagrees with the well-known model for the anisotropic effect of the amide group, which gives a greater deshielding for anti protons.[2,51]

As mentioned before, such results enable a further understanding of average reference shifts for Cα protons in proteins; sheets will have [ϕ] values of −120° (consistent with a *Z*-anti conformation), whereas mean [ϕ] values near 0° or +120° will correspond to *Z*-gauche conformations and values close to +60° indicate a *Z*-syn disposition.

Experimental Section

Materials and Methods. *N*-Methylacetamide (**1**) and *N*-ethylacetamide (**2**) were commercially available and used without further purification. Amides **3**,[54] **4**,[55] **5**,[56] **6**,[57] and **7**−**11**[45] were prepared according to procedures described in the literature. NMR spectra for the latter substances having concentrations in the range of 5−12 mg/0.5 mL of $CDCl_3$ were recorded at 20 °C using either a 200 or 400 MHz spectrometer. Chemical shifts were referred to tetramethylsilane (TMS) as the internal standard ($\delta = 0.00$ ppm). The statistical confidence of experimental data was analyzed using the Fischer method,[58] which utilizes the equation for the *F*-distribution that allows statistical tests on random variables that deviate from normal distributions. *F*-Values were obtained as the ratio of the variances.

All structures were fully optimized using procedures implemented in the Gaussian 94 MO package.[25] Preliminary semiempirical calculations were performed at the PM3 level,[24] whereas DFT refinements were carried out using the Becke three-parameter density functional theory with the Lee−Yang−Parr correlation functional (B3LYP)[26,27] and the internal 6-31G* basis set.[28] In the case of *N*-methylacetamide, supplementary calculations have also been performed using Hartree−Fock[59] and Møller−Plesset perturbation[60] theories. Solvent effects were evaluated with DFT calculation in the self-consistent reaction field theory (SCRF) using the standard dipole model of Onsager.[37]

Acknowledgment. This investigation was supported by grants from the Ministry of Science and Technology (PB98-0997) and the Junta de Extremadura-Fondo Social Europeo (IPR00-C021). J.L.B. and J.L.B. thank the Junta de Extremadura and the University of Extremadura, respectively, for predoctoral fellowships. Last, but not least, we thank the Editor and the reviewers for their useful comments and suggestions.

Supporting Information Available: Computed electronic energies for the rotational pathway for (*Z*)- and (*E*)-*N*-methylacetamide at the B3LYP/6-31G*, MP2/6-31G*, MP2/6-31+G**, and HF/6-31G** levels, characterization of the *Z*-syn conformation as the saddle point, and energies in Hartrees and optimized geometries for all the species described in Tables 1−5, in Z-matrix form. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0102361

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