JOC Article

Conformation of Secondary Amides. A Predictive Algorithm That Correlates DFT-Calculated Structures and Experimental Proton Chemical Shifts†

Martín Avalos, Reyes Babiano,* José L. Barneto, Pedro Cintas, Fernando R. Clemente, José L. Jiménez, and Juan C. Palacios

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain

reyes@unex.es

Received November 12, 2002

The magnetic deshielding caused by the amido group on CON−CHα protons of secondary amides can easily be correlated with DFT-based structures at the B3LYP/6-31G* level of theory via a novel algorithm that refines previous models, such as the classical McConnell equation. The shift is given by $\delta = a + 2.16\cos^2(\alpha - 35)/d$, where α denotes the virtual dihedral angle resulting from linking the carbonyl and the α-carbons and d is the distance (Å) between the shifted proton and the carbonyl oxygen. Notably, in this equation a is a parameter that can be optimized for different solvents, namely, $CDCl_3$, DMSO-d_6, and D_2O. For the development of these correlations, the preferential conformation of amides is taken from the optimized structures in the gas phase obtained at the DFT level. The deshielding on anti and gauche protons in both rotamers of (*Z*)-acetamides and *E*/*Z* isomers of formamides has been evaluated. This methodology has proved to be highly reliable, allowing us to discard ab initio or DFT conformational arrangements when shifts calculated by the above-mentioned equation differ from the experimental values. Thus, the anti disposition between the CHα proton and the N−H bond appears to be the more stable conformation of simple amides. For amides bearing only one proton at Cα, a local syn minimum can equally be characterized. The rotational barriers around the CON−alkyl bond along with the pyramidalization of the amido group have also been reassessed. As the conformation is taken away from anti or local syn minima, the nonplanarity of the amido group appears to increase.

Introduction

The accurate description of the amide linkage is of utmost importance for understanding the conformation of peptide bonds and a series of fundamental in vivo processes such as protein−protein interactions and folding.[1,2] There are numerous studies aimed at elucidating the conformational preference of amides, and *N*-methylacetamide has largely been assessed for this purpose as this substance provides an appropriate mimicry of the peptide bond involving two rotational barriers, for the *C*-methyl and *N*-methyl groups. However, theoretical calculations often lead to contradicting results depending on the level of theory and basis sets, suggesting both syn and anti conformations. In general, Hartree−Fock-based methods give little conformational preference for the methyl group on the nitrogen atom, though favoring syn conformers.[3] Calculations by Krimm and associates of amide stretch vibrational frequencies in *N*-methylacetamide and small peptides indicate that the former adopts preferential *Z* and *E* geometries having a *C*-methyl hydrogen eclipsing the oxygen and an *N*-methyl hydrogen eclipsing the NH group.[4] Later on, studies carried out to ascertain the effect of hydrogen bonding on amide I and II vibrational frequencies by Tasumi et al.[5] and Kubelka and Keiderling[6] also suggest a preferential syn arrange-

* To whom correspondence should be addressed. Phone: +34-924-289380. Fax: +34-924-271149.

† Dedicated to the memory of Max Perutz (1914−2002). Nobody else understood so admirably the stereochemical matching and folding of peptide chains.

(1) *The Amide Linkage*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley: New York, 2000.

(2) (a) *Prediction of Protein Structure and the Principles of Protein Conformation*; Fasman, G. D., Ed.; Plenum Press: New York, 1989. (b) Wüthrich, K. *Science* **1989**, *243*, 45−50. (c) Creighton, T. E. *Curr. Opin. Struct. Biol.* **1991**, *1*, 5−16. (d) Wagner, G.; Hyberts, S. G.; Havel, T. F. *Annu. Rev. Biophys. Biomol. Struct.* **1992**, *21*, 167−198. (e) *Protein Folding*; Creighton, T. E., Ed.; Freeman: New York, 1992. (f) Matthews, B. W. *Annu. Rev. Biochem.* **1993**, *62*, 139−160. (g) Voet, D.; Voet, J. G. *Biochemistry*, 2nd ed.; Wiley: New York, 1995; pp 141−213. (h) Jaenicke, R.; Seckler, R. *Adv. Protein Chem.* **1997**, *50*, 1−59. (i) Craig, E.; Yan, W.; James, P. In *Molecular Chaperones and Folding Catalysts*; Bukau, B., Ed.; Harwood: Amsterdam, 1999; pp 139−162. (j) Walter, S.; Buchner, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1098−1113.

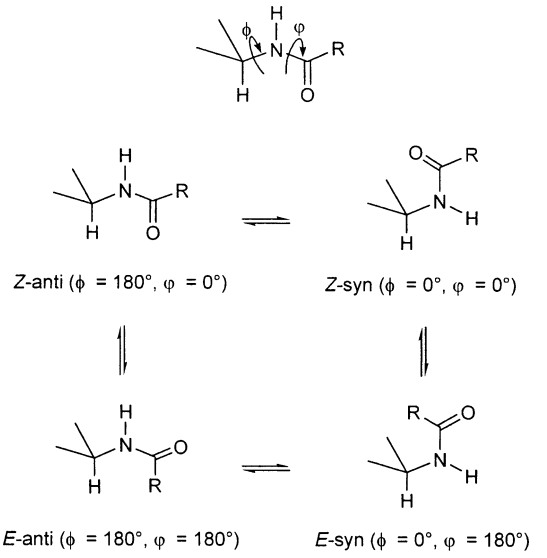
(3) (a) Jorgensen, W. L.; Gao, J. *J. Am. Chem. Soc.* **1988**, *110*, 4212−4216. (b) Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715−4720. (c) Guo, H.; Karplus, M. *J. Phys. Chem.* **1992**, *96*, 7273−7287.

(4) (a) Krimm, S.; Song, S.; Asher, S. A. *J. Am. Chem. Soc.* **1989**, *111*, 4290−4294. (b) Mirkin, N. G.; Krimm, S. *J. Am. Chem. Soc.* **1990**, *112*, 9016−9017. (c) Song, S.; Asher, S. A.; Krimm, S.; Shaw, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 1155−1163. (d) Mirkin, N. G.; Krimm, S. *J. Am. Chem. Soc.* **1991**, *113*, 9742−9747. (e) Chen, X. G.; Asher, S. A.; Schweitzer-Stenner, R.; Mirkin, N. G.; Krimm, S. *J. Am. Chem. Soc.* **1995**, *117*, 2884−2895. (f) Schweitzer-Stenner, R.; Sieler, G.; Mirkin, N. G.; Krimm, S. *J. Phys. Chem. A* **1998**, *102*, 118−127.

(5) Torii, H.; Tatsumi, T.; Kanazawa, T.; Tasumi, M. *J. Phys. Chem. B* **1998**, *102*, 309−314.

10.1021/jo026695z CCC: $25.00
Published on Web 02/04/2003

CHART 1. Syn and Anti Conformations for *Z* and *E* Isomers of Secondary Amides



ment. Calculations at B3LYP/6-31G*, MP2/6-31G*, and MP2/6-31+G** levels for a series of acetamides, including *N*-methylacetamide itself, invariably predict that the lowest energy conformer is the *Z*-anti conformer.[7] In particular, the use of methods involving electronic correlation and diffuse functions appears to be important for representing lone pairs and delocalized structures, thereby accounting for a greater charge distribution of the amide linkage than once thought as suggested by Wiberg and others.[8] Moreover, the *Z*-anti orientation could also be inferred from the chemical shifts of the N−CHα protons as a proton situated anti to the NH proton consistently resonates ∼0.8 ppm further downfield than a proton located in a gauche disposition.[7] As indicated in Chart 1 the conformational sphere of a secondary amide can be described, in an unambiguous fashion that clarifies obsolete cis and trans terms, by the torsion angles ϕ and φ defining the rotamer states about each of the two C−N bonds involved in the amide bonds (vide infra). NMR spectroscopy and computation are thus two methods which can be applied complementarily with considerable power to the conformational analysis.

The most reliable feature of NMR data as an experimental tool is the fact that chemical shifts do precisely reflect the magnetic anisotropy originated by the amide function and they are likewise sensitive to other local effects provided by solvents and substituents. Within this context it is fair to mention that Hα chemical shifts are repeatedly used as diagnostic probes of secondary structure in peptides and proteins. Therefore, some correlations between torsional angles and observed shifts have been proposed, although patterns cannot often be defined with accuracy.[9] Likewise, correlations based on amide proton[10] and carbon or nitrogen shift tensors have equally proved to be useful markers of local protein structure.[11]

A salient drawback of using *N*-alkylated acetamides as reduced models lies in the fact that experimental NMR data are only available for *Z* conformers owing to their greater stability. Complex acetamides such as those derived from amido sugars also exhibit a preferential or exclusive *Z*-anti geometry as revealed by both NMR studies in solution and X-ray crystallography.[12] *N*-Methylacetamide, however, is the only simple acetamide that allows one to study the *E* conformer by NMR spectroscopy.[13] In stark contrast, *N*-substituted formamides exist as mixtures of *Z* and *E* isomers, thereby enabling a direct comparison between calculated and experimentally available data. Formamide itself, the simplest model, has been the subject of extensive spectroscopic and computational studies.[14] The rotational barriers for *N*,*N*-dialkyl-substituted formamides have also been investigated theoretically, including the effect of a hydrogen-bonding solvent.[15] Detailed studies on hydrogen-bonding interactions have been provided for *N*-alkylformamides as well.[16] The rotational microwave spectrum, in the frequency range of 18−40 GHz, along with ab initio calculations of *N*-methylformamide suggests a conformer with the methyl group cis to the carbonyl oxygen, though the equilibrium

(6) Kubelka, J.; Keiderling, T. A. *J. Phys. Chem. A* **2001**, *105*, 10922−10928.

(7) Avalos, M.; Babiano, R.; Barneto, J. L.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **2001**, *66*, 7275−7282.

(8) (a) Wiberg, K. B.; Brenneman, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 4, 831−840. (b) Greenberg, A.; Thomas, T. D.; Bevilacqua, C. R.; Coville, M.; Ji, D.; Tsai, J.-C.; Wu, G. *J. Org. Chem.* **1992**, *57*, 7093−7099. (c) Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1995**, *117*, 2201−2209. (d) Wiberg, K. B. *Acc. Chem. Res.* **1999**, *32*, 922−929.

(9) (a) Dalgarno, D. C.; Levine, B. A.; Williams, R. J. P. *Biosci. Rep.* **1983**, *3*, 443−452. (b) Jiménez, M. A.; Nieto, J. L.; Herranz, J.; Rico, M.; Santoro, J. *FEBS Lett.* **1987**, *221*, 320−324. (c) Szilagyi, L.; Jardetzky, O. *J. Magn. Reson.* **1989**, *83*, 441−449. (d) Ösapay, K.; Case, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 9436−9444. (e) Wishart, D. S.; Sykes, B. D.; Richards, F. M. *Biochemistry* **1992**, *31*, 1647−1651. (f) Williamson, M. P.; Asakura, T. *J. Magn. Reson., Ser. B* **1993**, *101*, 63−71. (g) Ösapay, K.; Case, D. A. *J. Biomol. NMR* **1994**, *4*, 215−230. (h) Beger, R. D.; Bolton, P. H. *J. Biomol. NMR* **1997**, *10*, 129−142. (i) Sitkoff, D.; Case, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 12262−12273. (j) Sharman, G. J.; Griffiths-Jones, S. R.; Jourdan, M.; Searle, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 12318−12324.

(10) (a) Tjandra, N.; Bax, A. *J. Am. Chem. Soc.* **1997**, *119*, 8076−8082. (b) Tessari, M.; Vis, H.; Boelens, R.; Kaptein, R.; Vuister, G. W. *J. Am. Chem. Soc.* **1997**, *119*, 8985−8990. (c) Sharma, Y.; Kwon, O. Y.; Brooks, B.; Tjandra, N. *J. Am. Chem. Soc.* **2002**, *124*, 327−335.

(11) (a) Spera, S., Bax, A. *J. Am. Chem. Soc.* **1991**, *113*, 5490−5492. (b) Wishart, D. S.; Sykes, B. D.; Richards, F. M. *J. Mol. Biol.* **1991**, *222*, 311−333. (c) De Dios, A. C.; Pearson, J. G.; Oldfield, E. *Science* **1993**, *260*, 1491−1496. (d) Jiao, D.; Barfield, M.; Hruby, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 10883−10887. (e) De Dios, A. C.; Oldfield, E. *J. Am. Chem. Soc.* **1994**, *116*, 11485−11488. (f) Lee, D.-K.; Ramamoorthy, A. *J. Magn. Reson.* **1998**, *133*, 204−206. (g) Hong, M. *J. Am. Chem. Soc.* **2000**, *122*, 3762−3770. (h) Wei, Y.; Lee, D.; Ramamoorthy, A. *J. Am. Chem. Soc.* **2001**, *123*, 6118−6126. (i) Yao, X.; Hong, M. *J. Am. Chem. Soc.* **2002**, *124*, 2730−2738.

(12) (a) Avalos, M.; Babiano, R.; Durán, C.; Jiménez, J. L.; Palacios, J. C. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2205−2215. (b) Avalos, M.; Babiano, R.; Cintas, P.; Durán, C.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron* **1995**, *51*, 8043−8056. (c) Avalos, M.; Babiano, R.; Carretero, M. J.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron* **1998**, *54*, 615−628.

(13) Radzicka, A.; Pedersen, L.; Wolfenden, R. *Biochemistry* **1988**, *27*, 4538−4541.

(14) (a) Kirchhoff, W. H.; Johnson, D. R. *J. Mol. Spectrosc.* **1973**, *45*, 159−165. (b) Mohandas, P.; Singh, S. *J. Mol. Struct.: THEOCHEM* **1990**, *361*, 229−242. (c) Barszczewicz, A.; Jaszunski, M.; Jackowski, K. *Chem. Phys. Lett.* **1993**, *203*, 404−408. (d) Florian, J.; Johnson, B. G. *J. Phys. Chem.* **1994**, *98*, 3681−3687. (e) Kirby, C. W.; Lumsden, M. D.; Wasylishen, R. E. *Can. J. Chem.* **1995**, *73*, 604−613. (f) Neuefeind, J.; Zeidler, M. D.; Poulson, H. F. *Mol. Phys.* **1996**, *87*, 189−201. (g) Adalsteinsson, H.; Maulitz, A. H.; Bruice, T. C. *J. Am. Chem. Soc.* **1996**, *118*, 7689−7693. (h) Vaara, J.; Kashi, J.; Jokisaari, J.; Diehl, P. *J. Phys. Chem. A* **1997**, *101*, 5069−5081 and references therein.

(15) (a) Bloemendal, M.; Rouw, A. C.; Somsen, G. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 53−60. (b) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261−4270.

(16) (a) Engdahl, A.; Nelander, B.; Astrand, P.-O. *J. Chem. Phys.* **1993**, *99*, 4894−4907. (b) McGrady, J. E.; Mingos, D. M. P. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2287−2292. (c) Gao, J.; Pavelites, J. J.; Habibollazadeh, D. *J. Phys. Chem.* **1996**, *100*, 2689−2697.

conformation of the methyl group could not be found.[17] Two recent studies mainly focused on *N*-methylformamide and *N*-methylacetamide give evidence of similar arrangements of the methyl groups with respect to the CONH group to represent global minima. Thus, Nandini and Sathyanarayana describe ab initio calculations at the HF/6-31+G* level on the molecular geometry and the vibrational spectra of such amides,[18] whereas Wiberg and Roush have evaluated the methyl rotational barriers for various *N*-methylamides and thioamides at the MP2 level using a higher basis set, 6-311+G**.[19] For *N*-methylformamide *E*-anti and *Z*-syn conformations were found to be the most stable geometries by 0.88 and 0.33 kcal/mol with respect to the *E*-syn and *Z*-anti ones, respectively. Notably, the lowest energy conformer (*Z*-syn) exhibits a marked pyramidalization at the nitrogen atom (i.e., deviation of the alkyl group from the H−N−C−O plane). Similarly, the lowest energy conformation for both (*E*)- and (*Z*)-*N*-methylacetamide was found to be syn.[19] Such results disagree with experimental conformations based on proton chemical shifts and related DFT and ab initio methods which point to a preferential *Z*-anti arrangement.[7] We have judged that a step forward to clarify the structure of secondary amides is a further reassessment of theoretical and empirical data for *E* and *Z* isomers. Theoretical geometries and experimental magnetic deshielding can be correlated through a linear plot, and predictions appear to be quantitative within statistical confidence limits. This new correlation will afford a fresh approach to interpreting and predicting suitable conformations for amides, with putative extrapolations to amide linkage in larger molecules.

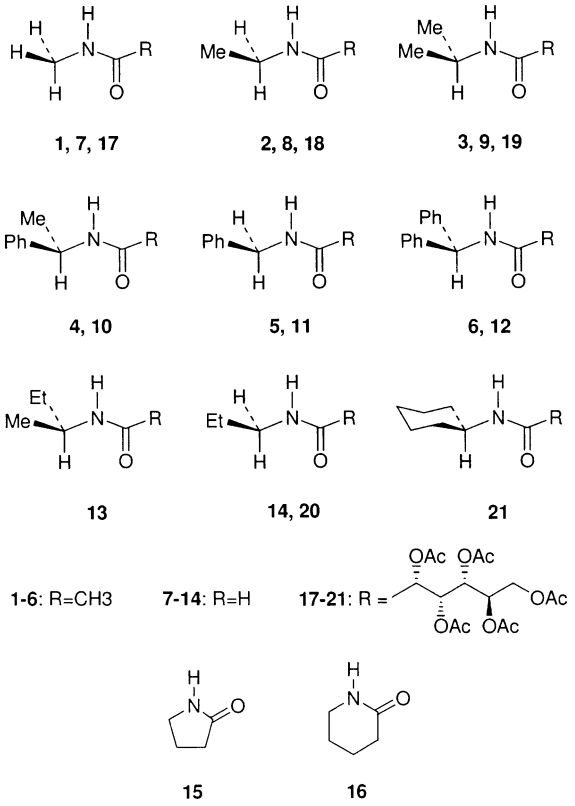
Materials and Methods

Acetamides **1** and **2**, formamide **7**, and cyclic amides **15** and **16** were obtained from commercial suppliers and used without further purification. Compounds **3**,[20a] **4**,[20b] **5**,[20c] **6**,[20d] and **9**[20a] were prepared and purified according to protocols described previously. Compounds **8**, **10**, **11**, **12**, **13**, and **14** were prepared by reaction of formic acid with the corresponding amine, as described for **9**.[20a] Formamides **10**, **11**, and **12** crystallized from diethyl ether, while **8**, **13**, and **14** were purified by vacuum distillation.

DFT and ab initio calculations were carried out using the Gaussian98 package.[21] The stationary points were characterized by frequency calculations to verify that minima and transition structures have zero and one imaginary frequency, respectively. Zero-point vibrational energies have been computed and scaled at the corresponding levels of theory, B3LYP/6-31G* (0.9806), HF/6-31G** (0.9181), MP2/6-31G* (0.9670), and MP2/6-31+G** (unscaled).[22]

All NMR data were collected at 400 MHz in perdeuterated solvents ($CDCl_3$, DMSO-d_6, and D_2O, 99.9% D) with chemical shifts referred to tetramethylsilane (TMS) as the internal standard ($\delta = 0.00$ ppm).

CHART 2. Set of Structures 1−21



Results and Discussion

As mentioned before, the configurational and conformational spectrum of simple amides can adequately be denoted as a function of two torsional angles, ϕ and φ. These angles are conceptually different from the torsion angles [ϕ] and [ψ], used to characterize the secondary structure of peptides and proteins, and should not be misused as equivalents at all.[23] Chart 1 depicts the limiting syn and anti conformers for both *E* and *Z* isomers.

Model compound studies have been undertaken on *E* and *Z* isomers of the acyclic formamides **7**−**14**, as well as on the cyclic derivatives 2-pyrrolidone (**15**) and δ-valerolactam (**16**), which can only be present as *E* isomers. Experimental data for acetamides **1**−**6**, the subject of a previous study,[7] and some chirally modified sugar amides, **17**−**21**, have also been included for parallel discussions and to enlarge the statistical basis (Chart 2).

One of the most classical methods for calculating proton shifts based on magnetic anisotropy was developed

(17) Fantoni, A. C.; Caminati, W. *J. Chem. Soc., Faraday Trans. 1* **1996**, *92*, 343−346.
(18) Nandini, G.; Sathyanarayana, D. N. *J. Mol. Struct.: THEOCHEM* **2002**, *579*, 1−9.
(19) Wiberg, K. B.; Rush, D. J. *J. Org. Chem.* **2002**, *67*, 826−830.
(20) (a) LaPlanche, L. A.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 337−341. (b) Nerdel, F.; Goetz, H.; Fenske, M. *Justus Liebigs Ann. Chem.* **1963**, *665*, 21−34; *Chem. Abstr.* **1963**, *59*, 12612d. (c) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longman and Wiley: New York, 1989; p 1269. (d) *Dictionary of Organic Compounds*; Eyre & Spottiswoode Publishers: London, 1965.
(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. W.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1998.
(22) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.
(23) *Amino Acids, Peptides and Proteins*; Young, G. T., Ed.; The Chemical Society: London, 1972; Vol. 4, p 455.

TABLE 1. B3LYP/6-31G* Torsional Parameters and Energy Differences (kcal/mol) for Formamides 7−9

	minimum			transition state			
isomer	ϕ	φ	pyram	ϕ	φ	pyram	ΔE
7 *E*	179.9	180.2	179.7	0.0	180.0	180.0	0.80
7 *Z*	179.2	0.0	179.9	0.0	0.0	180.0	0.07
8 *E*	185.3	178.0	183.2	57.8	180.0	180.0	3.09
8 *Z*	191.4	356.5	187.6	57.4	0.0	180.0	4.44
9 *E*	180.0	180.0	180.0	55.7	184.5	173.2	2.78
9 *Z*	157.9	3.6	170.8	61.3	0.4	179.3	4.26

by McConnell in the late 1950s.[24] Assuming that the atom whose shift is being considered and the anisotropic source are far apart, such a shift is given by

$$\delta_{\text{anis}} = (3L_oR^3)^{-1}\sum\chi_{ii}(3\cos^2\theta_i - 1) \qquad (1)$$

where L_o denotes Avogadro's constant, R is the distance between the shifted atom and the center of the group magnetic anisotropy, χ_{ii} is a component of the magnetic susceptibility tensor, and θ_i is the angle between the i axis ($i = x, y, z$) and the vector **R**. That relationship can be simplified in the case of an axially symmetric group such as the amide function:

$$\delta_{\text{anis}} = (3L_oR^3)^{-1}\Delta\chi(3\cos^2\theta - 1) \qquad (2)$$

where $\Delta\chi$ is the difference between magnetic susceptibilities along the axis of symmetry and within the plane of symmetry and θ is the angle between the vector **R** and the normal to the plane of axial symmetry.

The direct application of McConnell's equations meets a series of important limitations, as the center of the group anisotropy is often denoted arbitrarily and numerous chemical functions possess small magnetic susceptibilities. Delocalized structures, however, constitute a notable exception, and thus, Sitkoff and Case have found a good agreement between the DFT data and the susceptibility values in eq 1 or 2 for the alanine dipeptide.[9i]

Theoretical Calculations. In a preliminary screening of formamides **7**−**14** in the search of their energy profiles carried out at a semiempirical (PM3) level,[25] the anti disposition was invariably detected as the most stable conformer irrespective of which configuration (*E* or *Z*) was considered. Overall, however, the predictions were not reliable enough because *E* isomers were always found to be more stable than their *Z* counterparts and, in addition, geometries for both minima and maxima at the PM3 level were markedly different from those found in DFT or ab initio calculations.

At the B3LYP/6-31G* level we have first concentrated on models **7**−**9**, which contain three, two, and one proton, respectively, at the CO−NCHα moiety. In these formamides the anti conformation was significantly more stable for both rotamers with ϕ values between 157.9° and 191.4° (Table 1). In the case of (*E*)-**9** and (*Z*)-**9** it was also possible to characterize a local minimum that corresponds to a syn conformation (see the Supporting Information, Figure S1). Finally, the saddle points were determined to be a syn conformation ($\phi = 0.0°$) for both (*E*)-**7** and (*Z*)-**7**, a conformation having both methylenic protons in a gauche disposition for both rotamers of **8** ($\phi \approx 57°$), and a conformation placing the proton of (*E*)-**9** and (*Z*)-**9** in a gauche orientation ($\phi = 61°$ and 56°, respectively).

The calculated rotational barrier for the methyl group in the *E* rotamer of *N*-methylformamide (**7**) is higher than for its *Z* counterpart. This situation changes for *N*-ethyl- and *N*-isopropylformamides (**8** and **9**), and the barriers for their *Z* isomers are ∼1.4 kcal/mol higher in energy than those of the *E* isomers. Clearly, the increasing steric hindrance of the alkyl group contributes to increasing rotation barriers (Table 1, 0.80−0.07 kcal/mol in **7** versus 2.78−4.44 kcal/mol in **8** and **9**).

Since this work uses *N*-methylformamide as a probe molecule looking at structural effects on the proton shift, it was also convenient to check the reliability of DFT versus ab initio calculations. Data gathered in Table 2 reveal that both DFT (B3LYP/6-31G*) and MP2/6-31G* methods, and even an ordinary, but of lower accuracy, method such as the HF/6-31G** level provide similar results in terms of the ϕ and φ torsions, and energy differences between *E* and *Z* isomers ($\Delta E = 0.9-1.0$ kcal/mol). However, the use of diffuse functions at the MP2/6-31+G** level results in a substantially different structure for (*Z*)**-7** in which the amido group becomes less planar ($\varphi = 3.0°$) and the methyl group adopts a disposition close to a syn conformation ($\phi = 18.0°$). Thus, the amide nitrogen for this rotamer increasingly pyramidalizes in arrangements other than the preferred anti conformation.

For comparative purposes, the *E* isomer of *N*-methylacetamide (**1**) shows, in different theoretical models, ϕ torsion angles close to either 30° or 19° (Table 2), due to steric crowding between the methyl groups. Again, the nonplanarity of the nitrogen atom is consistently observed for conformations far from a syn or anti disposition ($\phi = 0°$ or 180°). For the *Z* rotamer ((*Z*)-**1**), calculations at the MP2/6-31+G** and HF/6-31G** levels give evidence of a clear-cut pyramidalization (∼170°) for ϕ torsion angles of 17.8° and 24.6°, respectively.

As discussed earlier for the rotamers of **9**, formamides **10**, **12**, and **13** bearing only one proton at the CON−CHα group, show syn local minima along with the minimum energy conformations which were found to be again the anti forms ($\Delta E_{\text{syn-anti}} = 1.64-4.05$ kcal/mol). In every case the *Z*-anti rotamers are also lower in energy ($\Delta E_{E\text{-anti}-Z\text{-anti}} = 0.74-1.36$ kcal/mol). Similarly to the structural situation encountered for the rotamers of **8**, the formamides **11** and **14** having two hydrogen atoms at the CON−CHα moiety exhibit minimum energy conformations that correspond to *Z*-anti arrangements at the B3LYP/6-31G* level of theory. Once again the pyramidalization bias takes place for conformations that deviate from anti as well as local syn conformations (Table 3).

A direct comparison between the set of formamides **8**−**14** with the series of acetamides **2**−**6**[7] indicates that the latter structures possess energy differences between their *E*-anti and *Z*-anti rotamers that are significantly higher (1.93−3.16 kcal/mol versus 0.69−1.36 kcal/mol for formamides; see the Supporting Information and Table 3). This result agrees with the coexistence of both rotamers in solution as the formyl proton lowers the congestion of the *E* isomer from what it would have been with

(24) McConnell, H. M. *J. Chem. Phys.* **1957**, *27*, 226−229.
(25) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220.

TABLE 2. Torsion and Pyramidalization Angles (deg) and Energy Differences (kcal/mol) for *E* and *Z* Rotamers of 1 and 7

		E isomer			*Z* isomer			
compd	model chemistry	ϕ	φ	pyram	ϕ	φ	pyram	ΔE_{E-Z}
1	B3LYP/6-31G*	29.0	188.8	165.6	180.0	0.0	180.0	2.47
	MP2/6-31G*	30.0	192.2	160.2	176.3	358.5	183.1	2.64
	MP2/6-31+G**	29.7	191.8	160.4	17.8	3.6	170.3	2.72
	HF/6-31G**	18.6	186.7	169.2	24.6	4.0	170.1	2.70
7	B3LYP/6-31G*	179.9	180.2	179.7	179.2	0.0	179.9	0.85
	MP2/6-31G*	180.2	179.6	180.7	178.7	0.4	179.0	0.98
	MP2/6-31+G**	180.0	180.0	180.1	18.0	3.0	172.2	1.23
	HF/6-31G**	180.2	180.0	180.0	179.3	0.1	179.8	1.02

TABLE 3. Torsion and Pyramidalization Angles (deg) and Energy Differences (kcal/mol) for the Formamides 8−14 in the Gas Phase at the B3LYP/6-31G* Level

isomer	ϕ	φ	pyram	isomer	ϕ	φ	pyram	$\Delta E_{\text{syn-anti}}$	$\Delta E_{E\text{-anti}-Z\text{-anti}}$
				8 *E*-anti	185.3	178.0	183.2		0.71
				8 *Z*-anti	191.4	356.5	187.6		
9 *E*-syn	7.4	183.0	174.8	**9** *E*-anti	180.0	180.0	180.0	2.43	0.74
9 *Z*-syn	0.1	0.0	179.9	**9** *Z*-anti	157.9	3.6	170.8	1.64	
10 *E*-syn	34.4	192.3	160.4	**10** *E*-anti	158.8	182.7	176.1	2.36	1.36
10 *Z*-syn	333.5	357.0	190.8	**10** *Z*-anti	229.1	4.1	170.7	2.01	
				11 *E*-anti	179.7	181.1	179.3		1.04
				11 *Z*-anti	190.9	355.6	193.1		
12 *E*-syn	311.0	170.9	194.3	**12** *E*-anti	161.7	177.1	186.2	1.95	1.03
12 *Z*-syn	12.6	354.2	182.5	**12** *Z*-anti	174.3	352.3	197.4	4.05	
13 *E*-syn	21.6	187.8	166.9	**13** *E*-anti	182.2	178.6	182.0	2.38	0.85
13 *Z*-syn	1.2	0.1	179.4	**13** *Z*-anti	202.9	356.8	188.3	1.71	
				14 *E*-anti	172.9	183.9	173.8		0.69
				14 *Z*-anti	166.2	4.0	171.4		

a methyl group. On the other hand, the energy differences between syn and anti conformations, irrespective of which *E* or *Z* rotamer is considered, are only slightly lower for the formamides **9**, **10**, and **12** ($\Delta E_{\text{syn-anti}}$ = 1.64−4.05 kcal/mol) than for the corresponding acetamides **3**, **4**, and **6** ($\Delta E_{\text{syn-anti}}$ = 1.86−4.33 kcal/mol) in which both conformational minima can be observed. It must be stressed that N−Cα rotational barriers are significant (Table 1 and the Supporting Information, Figure S1) with the sole exception of the *Z* rotamer of *N*-methylformamide ((*Z*)-**7**) in which the barrier is calculated to be similar to that of *N*-methylacetamide (∼0.07 kcal/mol). In contrast, the *E* rotamers for *N*-methylacetamide and *N*-methylformamide show different profiles in both conformational minima and transition structures, because *N*-methylacetamide exhibits little or no variation until $\phi = 30°$ whereas for torsion angles >30° the barrier rapidly increases due to the repulsion with the methyl group. The transition structure is reached at $\phi = 60°$ with a barrier of 0.27 kcal/mol[7] (see the Supporting Information).

Even though our DFT and ab initio studies do consistently predict a favorable anti arrangement for *E* and *Z* rotamers of simple acetamides and formamides, certain model cases are still the subject of controversy and have a somewhat confusing history as pointed out in our introductory remarks, especially in relation with the structure of the amido group. Numerous studies aimed at solving this situation simply reveal that the nitrogen inversion mode is very floppy with negligible barriers between planar and nonplanar configurations.[26−29] Our results at the B3LYP/6-31G* level give evidence of the existence of planar structures and that pyramidalization increases away from the canonical syn and anti conformations.

From the above results it appears that the B3LYP/6-31G* model does predict an anti conformation to be the favorable arrangement for both rotamers of formamides in the gas phase. Overall, there seems to be a pronounced preference to adopt that conformation in the case of the *E* isomers. Moreover, there are no significant deviations between simple formamides and acetamides with respect to their preferential conformation.

NMR Relationships. This follows our recent work on acetamides to test the reliability of quantum models to yield a good agreement between structure and experimental proton chemical shifts. It has been shown that primary acetamides do preferentially exist in a *Z*-anti disposition.[7] The population of the *E* isomer of *N*-methylacetamide is very low, which contrasts with the appreciable figures observed for the *E* isomers of formamides **7**−**14** in different solvents (Supporting Information, Table S4), thus extending this methodology to both amide conformers.

As shown by Shoolery and others,[30] through a simple empirical relationship, the chemical shifts for methylene

(26) Fogarasi, G.; Szalay, P. G. *J. Phys. Chem. A* **1997**, *101*, 1400−1408.

(27) Samdal, S. *J. Mol. Struct.: THEOCHEM* **1998**, *440*, 165−174.

(28) For a recent development of the MM4 force field for amides, see: Langley, C. H.; Allinger, N. L. *J. Phys. Chem. A* **2002**, *106*, 5638−5652.

(29) For experimental microwave values of rotational barriers, see: Kojima, T.; Yano, E.; Nakagawa, K.; Tsunekawa, S. *J. Mol. Spectrosc.* **1987**, *122*, 408−416.

(30) (a) Shoolery, J. N. *Varian Associates Technical Information Bulletin*; Palo Alto, CA; Vol. 2, No. 3. (b) Friedrich, E. C.; Gates Runkle, K. *J. Chem. Educ.* **1984**, *61*, 830−832. (c) Friedrich, E. C.; Gates Runkle, K. *J. Chem. Educ.* **1986**, *63*, 127−129. (d) Beauchamp, P. S.; Marquez, R. *J. Chem. Educ.* **1997**, *74*, 1483−1485.

TABLE 4. Magnetic Deshielding (ppm) Originated by the Amide Function on CON−CHα Protons for Amides 1−6 and 17−21 in $CDCl_3$

	$\sum n/n \pm$ SD		
compd	δ_{anti}	δ_{gauche}	$\delta_{anti} - \delta_{gauche}$
1−**6**	2.42 ± 0.06	1.64 ± 0.01	0.78 ± 0.01
17−**21**	2.41 ± 0.07	1.69 ± 0.05	0.72 ± 0.05
16 and **17**−**21**	2.42 ± 0.05	1.66 ± 0.04	0.76 ± 0.04

and methine protons in $CDCl_3$ solution can roughly be evaluated by eq 3,

$$\delta_{CH,XYZ} = 0.23 + \sigma_X + \sigma_Y + \sigma_Z \quad (3)$$

where σ_X, σ_Y, and σ_Z are constants for the different substituents. For the case of an amide group, that relationship can also be utilized to determine the deshielding caused by the amide function (δ_{amide}) on a particular proton (δ_{obsd}):

$$\delta_{amide} = \delta_{obsd} - (0.23 + \sigma_X + \sigma_Y) \quad (4)$$

In addition that deshielding is an average magnitude as anti and gauche hydrogen atoms at Cα rapidly interconvert at room temperature:

$$\delta_{amide} = \delta_{anti}/n + (n - 1)\delta_{gauche}/n \quad (5)$$

where n is the number of protons at Cα.

Table 4 briefly summarizes our previous results on the magnetic anisotropy found for three different sets of model compounds: acetamides **1**−**6**, *O*-acetylgluconamides **17**−**21**, and the entire range of both sets. Such data are consistent with a preferential *Z*-anti conformation for these substances.[7]

We have equally determined for the *Z* rotamers of formamides **7**−**14** the deshielding caused by the amide function on α-hydrogen atoms located in anti and gauche arrangements (Table 5). These figures lie consistently about 2.52, 1.69, and 0.83 ppm for δ_{anti}, δ_{gauche}, and $\delta_{anti}-\delta_{gauche}$, respectively, having very low statistical deviations. These chemical shifts are close to, though slightly higher than, those found for acetamides and chiral gluconamides. Therefore, the alkyl−CO group appears to have a small effect on the whole anisotropy. A direct comparison between data from Tables 4 and 5 enables deshielding on anti and gauche protons caused by the presence of a methyl group of 0.10 and 0.05 ppm, respectively, to be determined.

The dispersion of chemical shifts is nearly absent as demonstrated in the fit statistics (SD values) in Table 5. The latter result suggests the existence of a common and prevalent conformation which has, in turn, been assigned to be the *Z*-anti form. The magnetic deshielding found experimentally also agrees with the calculated DFT and ab initio structures.

The DFT values for the *E* rotamers of formamides **7**−**14** are equally consistent with an anti conformation, and Table 6 gives the magnetic anisotropies on anti and gauche protons of these substances. It must be recalled that the anti form appears to be the only conformational minimum for formamides bearing two and three hydrogen atoms at Cα (e.g., **7**, **8**, **11**, and **14**) which exhibit higher rotational barriers than their *Z* isomers. In the case of formamides having only one proton at Cα, both the anti and syn forms can be observed, although the former appears to be the most stable structure for the *E* rotamers (by about 1.95−2.43 kcal/mol). In addition, both the anti ($\delta_{anti} = 1.98$ ppm) and gauche ($\delta_{gauche} = 2.08$ ppm) protons are similarly affected by the magnetic anisotropy of the amide function as reflected by the low statistical deviation of the set ($\delta_{anti} - \delta_{gauche} = -0.10$ ppm).

At this point, it may be somewhat surprising that the local deshielding for gauche protons, which lie beyond the plane of the amide function, is found to be slightly higher than for the corresponding and otherwise coplanar anti protons. A preliminary estimation based on McConnell's relationship (vide supra)[24] reflects the direct dependence of amide magnetic anisotropy on the angle (θ) between the vector **R** (the distance between the amide and the shifted proton) and the normal to the plane of axial symmetry (i.e., the amide group). Accordingly, this angular contribution makes the protons out of the amide plane, such as gauche protons, much less deshielded. However, as pointed out earlier, quantitative predictions may be premature as data for the susceptibility tensor (χ) are scarce, although figures for formamide indicate that this tensor is approximately axially symmetric about the normal to the amide plane.[31]

To shed light on the magnetic anisotropy of the *E* isomers, a further computation has been accomplished on **15** and **16**, which are constrained in an *E* geometry.

Table 7 (see also Figure S2 in the Supporting Information) collects the results of the lowest energy structures for which the torsion angle values (with respect to the H_1 proton) are located at 55° for **15** and at 47° for **16**. Clearly, the angled structures remain anchored in a gauche conformation, and therefore, the magnetic deshielding (δ_{amide}) is equivalent to δ_{gauche}, which has been determined to be 2.26 and 2.17 ppm for **15** and **16**, respectively. These anisotropies are still greater than the δ_{gauche} values found for the acyclic series (Table 6). This fact can be partly explained by the conformational rigidity and steric congestion of these cyclic derivatives. The existence of such effects on shielding makes it impossible in practice to obtain a perfect model and hence a close correlation between chemical shifts. In fact, the literature cautions against applying chemical shift data from acyclic model compounds to cyclic derivatives.[32] In view of the unusually high magnetic anisotropy of 2-pyrrolidone, this substance has been removed from the data set that we shall discuss below. Its inclusion, however, would slightly modify (∼1%) the overall fit of the data. In contrast, **16** has been maintained as removal of its magnetic anisotropy contribution causes a negligible variation in the statistical fitting.

Having established a representative sampling of acetamide and formamide torsion angles at the B3LYP/6-31G* level and the corresponding magnetic deshielding

(31) (a) Pauling, L. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2293−2294. (b) Schmalz, T. G.; Norris, C. L.; Flygare, W. H. *J. Am. Chem. Soc.* **1973**, *95*, 7961−7967. (c) Flygare, W. H. *Chem. Rev.* **1974**, *74*, 653−687.

(32) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1972; p 160.

TABLE 5. Magnetic Deshielding (ppm Scale) Caused by the Amide Function on CON−CHα Protons for the *Z* Rotamers of Formamides 7−14 in $CDCl_3$

compd	δ_{obsd}	σ	δ_{amide}	δ_{anti}	δ_{gauche}	$\delta_{anti} - \delta_{gauche}$
7	2.86	(H, H)	1.95	2.52	1.67	0.85
8	3.36	(H, Me)	2.11	2.52	1.70	0.82
9	4.18	(Me, Me)	2.59	2.59[a]		
10	5.23	(Me, Ph)	2.49	2.49[a]		
11	4.49	(H, Ph)	2.09	2.52	1.66	0.86
12	6.34	(Ph, Ph)	2.45	2.45[a]		
13	4.02	(Me, Et)	2.53	2.53[a]		
14	3.28	(H, Et)	2.13	2.52	1.74	0.78
$\sum n/n \pm$ SD				2.52 ± 0.06	1.69 ± 0.04	0.83 ± 0.04

[a] Values taken for the averaging calculation.

TABLE 6. Magnetic Deshielding (ppm Scale) Caused by the Amide Function on CON−CHα Protons for the *E* Rotamers of Formamides 7−14 in $CDCl_3$

compd	δ_{obsd}	σ	δ_{amide}	δ_{anti}	δ_{gauche}	$\delta_{anti} - \delta_{gauche}$
7	2.94	(H, H)	2.03	1.98	2.06	−0.08
8	3.29	(H, Me)	2.04	1.98	2.10	−0.12
9	3.71	(Me, Me)	2.12	2.12[a]		
10	4.71	(Me, Ph)	1.97	1.97[a]		
11	4.42	(H, Ph)	2.02	1.98	2.06	−0.08
12	5.78	(Ph, Ph)	1.89	1.89[a]		
13	3.42	(Me, Et)	1.93	1.93[a]		
14	3.19	(H, Et)	2.04	1.98	2.10	−0.12
$\sum n/n \pm$ SD				1.98 ± 0.10	2.08 ± 0.02	−0.10 ± 0.02

[a] Values taken for the averaging calculation.

TABLE 7. Torsion Angles (deg) and Magnetic Deshielding (ppm) for Amides 15 and 16

compd	ϕ(CONH−CH_1)	ϕ(CONH−CH_2)	δ_{obsd}	$\delta_{amide} = \delta_{gauche}$
15	54.8	−65.7	3.41	2.26
16	47.3	−69.7	3.32	2.17
$\sum n/n \pm$ SD				2.22 ± 0.06

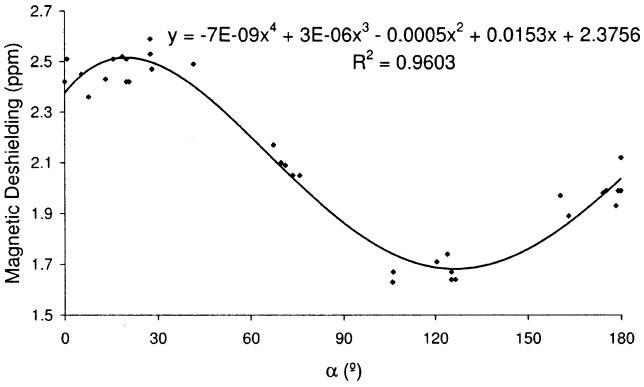
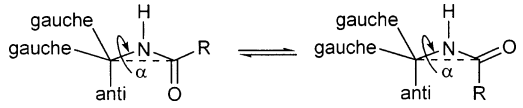


FIGURE 1. Magnetic deshielding (δ_{amide}) caused by the amide function (ppm scale) versus the virtual dihedral angle α (deg) for amides **1**−**14** and **16**.

for such structures, it is now possible to provide a schematic diagram (Figure 1) of the magnetic deshielding (δ_{amide}) as a function of the virtual torsion angle H−C−C−O (α) resulting from the bonding between the carbonyl carbon and the Cα atom as defined in Chart 3.

Experimental data can be fitted to a fourth-order polynomial plot that most resembles in profile the $\cos^2$ function with an approximate phase difference of 35° (Figure 1). The lack of symmetry as evidenced by the downward curvature suggests that not only the dihedral angle but also the distance between the shifted atom and any point of the anisotropy source should be involved. Looking at the graph, however, there are really only four clusters of data points, which correspond to the four possible *E*/*Z* and anti/gauche conformational combinations. Consequently, it seems appropriate to fit the data to an equation that has a few adjustable parameters. With these premises a plot of δ_{amide} versus $\cos^2(\alpha - 35)/d$, where *d* is the distance (Å) between the shifted proton and the carbonyl oxygen atom, with conventional least-squares optimization becomes linear with a regression coefficient of $r^2 = 0.94$ (eq 6, Figure 2).

CHART 3. Virtual Dihedral Angle (α) Defined for the *Z* and *E* Rotamers of Formamides and Acetamides



$$\delta = a + 2.16\cos^2(\alpha - 35)/d \qquad (6)$$

Remarkably, the angular function in eq 6 does reproduce the anisotropic effect as well. It might be argued that the latter correlation gives rise to anisotropies regardless of the distance between the given atoms. In fact, logical solutions can only be obtained for the typical O−CN−CHα distances encountered in amides. Moreover, eq 6 can be regarded as a convenient surrogate of the classical McConnell equation to calculate the magnetic anisotropy in amides and as having a series of inherent pluses. In particular, no magnetic susceptibilities are required, and geometrical parameters can be precisely determined.

Equation 6 can be parametrized in solvents other than $CDCl_3$, notably DMSO-d_6 and D_2O, two common solvent

TABLE 8. Experimental and Calculated (B3LYP/6-31G* Structures) Magnetic Deshieldings (δ_{amide}) for the *E* Rotamer of *N*-Methylacetamide in Deuterated Solvents

calcd			$CDCl_3$			DMSO-d_6			D_2O		
			calcd		exptl	calcd		exptl	calcd		exptl
ϕ	α	*d*	δ_H	δ_{amide}	δ_{amide}	δ_H	δ_{amide}	δ_{amide}	δ_H	δ_{amide}	δ_{amide}
29.0	32.5	4.340	2.19	1.92	1.99	1.99	1.72	1.75	2.09	1.82	1.94
147.0	150.1	3.997	1.79			1.59			1.69		
268.8	259.8	4.064	1.78			1.58			1.68		

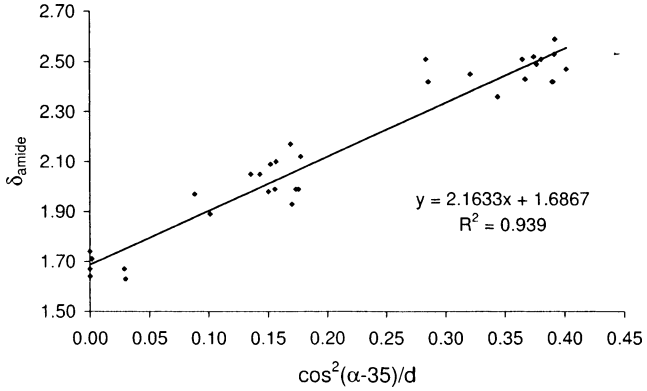


FIGURE 2. Correlation between δ_{amide} and the function $\cos^2(\alpha - 35)/d$ for amides **1**−**14** and **16**. Empirical shifts were taken from $CDCl_3$ solutions at 400 MHz.

systems employed in NMR studies of amides and peptides. To fit the amide anisotropies in these solvents, the intercept *a* for the corresponding linear plot has been recalculated using the same least-squares optimization as above to give the following values: 1.69 ± 0.08 ($CDCl_3$); 1.49 ± 0.14 (DMSO-d_6); 1.59 ± 0.16 (D_2O). The larger deviations (0.14−0.16) observed in DMSO-d_6 and D_2O with respect to those of $CDCl_3$ (<0.1) are logical assuming that the Shoolery equations have been parametrized for the latter solvent.

Accordingly, we have calculated δ_{anti} and δ_{gauche} shifts in DMSO-d_6 and D_2O using eq 6 and hence the theoretical δ_{amide} values by means of eq 5. The experimental δ_{amide} estimates have been obtained using the modified Shoolery equation (eq 4). In both deuterated solvents the difference between theory and experiment shows an RMS error of 0.12 and 0.14 ppm in DMSO-d_6 and D_2O, respectively, within a ±0.30 ppm interval (see the Supporting Information, Table S5 and Figure S3).

Nevertheless, the agreement between experimental and calculated anisotropies (δ_{amide}) should also be valid in the limiting cases, in which neither syn nor anti conformations can precisely be defined. Thus, our calculations for the *E* rotamer of *N*-methylacetamide, the less populated isomer in solution, suggest a preferred conformation when the ϕ dihedral angle is ∼29°. A likely reason for this torsion angle is a balance between a favorable anti conformation while the repulsion between methyl groups is kept at a minimum. For this rotamer, the CON−CH_3 protons can be observed in some deuterated solvents (Table 8). The application of eq 6 gives rise to a good agreement between the experimental and calculated deshieldings in the three solvents studied. Here, the calculated δ_{amide} is the average contribution of the three hydrogen atoms (δ_H) arising from eq 6.

TABLE 9. Experimental and Calculated Magnetic Anisotropies for Amides 1 *Z*, 7 *E*, and 7 *Z* at Different Theory Levels in Deuterated Solvents

		$CDCl_3$		DMSO-d_6		D_2O	
isomer	model chemistry	calcd δ_{amide}	exptl δ_{amide}	calcd δ_{amide}	exptl δ_{amide}	calcd δ_{amide}	exptl δ_{amide}
1 *Z*	B3LYP/6-31G*	1.94	1.89	1.74	1.63	1.84	1.66
	MP2/6-31G*	1.97		1.77		1.87	
	MP2/6-31+G**	**2.23**		**2.03**		**2.13**	
	HF/6-31G**	**2.18**		**1.98**		**2.08**	
7 *Z*	B3LYP/6-31G*	1.94	1.95	1.74	1.67	1.84	1.83
	MP2/6-31G*	1.94		1.74		1.84	
	MP2/6-31+G**	**2.21**		**2.01**		**2.11**	
	HF/6-31G**	1.93		1.73		1.83	
7 *E*	B3LYP/6-31G*	2.02	2.03	1.82	1.80	1.92	1.96

As pointed out earlier (Table 2), DFT, HF, and MP2 model chemistries offer different results for the *Z* isomers of **1** and **7**. Table 9 summarizes again the experimental and calculated δ_{amide} values using the α (deg) and *d* (Å) parameters generated by these models. Irrespective of which model chemistry or solvent was adopted, there is a good agreement between theory and experiment, notably in $CDCl_3$, with the exception of the structures obtained at the HF/6-31G** and MP2/6-31+G** levels, which show large deviations (such figures are given in bold). These discrepancies result from the wrong conformer being predicted as the lowest in energy. Thus, it is relevant to conclude that only theoretical models predicting anti conformations are consistent with the experimental anisotropies encountered for simple amides. As a final illustration, no discrepancies were found either for the *E* rotamer of *N*-methylformamide, as every ab initio or B3LYP method predicts the anti arrangement to be the most stable conformer (Table 9 and the Supporting Information).

Conclusions

In this paper we describe a primarily computational study of the conformational behavior of secondary formamides with respect to rotation about the CON−alkyl bond. At the B3LYP/6-31G* level the anti conformation appears to be the most stable structure for both *E* and *Z* rotamers. Local minima corresponding to syn arrangements have only been detected for formamides containing only one proton at the CON−CHα position. The barrier heights for CON−alkyl rotation increase as the bulkiness of the alkyl group increases, although an almost negligible barrier is found for the *Z* rotamer of *N*-methylformamide (and *N*-methylacetamide as well). Magnetic shieldings are also calculated for the CHα protons in anti and gauche arrangements for both *E* and *Z* rotamers, and it is shown that there is a significant and systematic dependence of the experimental chemical shift on the

torsion angle and the distance between the shifted proton and the oxygen atom, via the optimized expression $\delta = a + 2.16 \cos^2(\alpha - 35)/d$. The latter empirical relationship allows the measured chemical shift to serve as an experimental proof of structure. As concluding remarks, the B3LYP/6-31G* method used for the majority of the calculations presented has been shown again and again to yield high-quality results at low computational cost, and so is quite appropriate for the present application to the conformational analysis of ordinary amides.

Acknowledgment. Financial support from the Ministry of Science and Technology (Grant PB98-0997) and the Junta de Extremadura-Fondo Social Europeo (Grant IPR00-C021) is gratefully acknowledged. J.L.B. and F.R.C. thank the Junta de Extremadura and the University of Extremadura, respectively, for their scholarships. Finally, we thank the reviewers for their valuable comments and suggestions that have largely improved the first draft.

Supporting Information Available: Figures of computed variation in the energy profile (kcal/mol) for *E* and *Z* rotamers of formamides **7**−**9**, torsional curves for formamides **15** and **16**, and a plot of the observed values in three different solvents versus $\cos^2(\alpha - 35)/d$, Tables of B3LYP/6-31G* torsional parameters and energy differences (kcal/mol) for *N*-methylacetamide, acetamides **3**, **4**, and **6**, and acetamides **2** and **5**, populations (%) of the *E* rotamer for **1** and formamides **7**−**14** in different solvents, experimental and calculated (eq 6) deshieldings on CON−CHα protons in DMSO-d_6 and D_2O, and experimental and calculated (eq 6) magnetic anisotropies for amides (*E*)-**1** and (*E*)-**7** at different theory levels in deuterated solvents, and Cartesian coordinates of calculated minimum energy and saddle point structures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026695Z