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Carbonyl Carbon and Nitrogen Chemical Shift Tensors of the Amide Fragment of Acetanilide and *N*-Methylacetanilide

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Abstract: Both carbon-13 and nitrogen-15 solid-state NMR spectroscopy have been employed to characterize the carbonyl carbon and nitrogen chemical shift (CS) tensors of the amide fragment of (*Z*)-acetanilide (**I**) and (*E*)-*N*-methylacetanilide (**II**). These two related compounds exhibit very different structural features in the solid state, as shown by previous X-ray diffraction studies. The orientation of the principal axis system (PAS) of both the carbon and nitrogen CS tensors has been determined using dipolar-chemical shift NMR spectroscopy in conjunction with IGLO chemical shielding calculations. For **I** and **II**, the carbon CS tensors are found to be very similar. In each, the most shielded direction is perpendicular to the amide plane while the intermediate component lies approximately along the carbonyl bond. Unlike the carbon results, the three principal components of the nitrogen CS tensor reveal striking variations which can be attributed predominantly to differences in the orientation of the *N*-phenyl substituent with respect to the amide plane. The orientation of the PAS of the nitrogen CS tensor has been unambiguously determined for **I** and **II** from the results of two separate dipolar-chemical shift NMR experiments for each compound. The intermediate component of the nitrogen CS tensor lies perpendicular to the amide plane in both compounds while the most shielded direction lies close to the C–N bond, toward C_α. Although the shielding calculations adequately reproduce the experimental shielding trends, they are less successful in determining the absolute magnitudes of the principal components of the experimental shielding tensors, which, in the case of **I**, can be partly attributed to the neglect of intermolecular N–H- -O=C hydrogen bonding in the calculations.

Introduction

Both carbon-13 and nitrogen-15 solid-state NMR spectroscopy have found widespread application in structural studies of small peptides and proteins. The chemical shielding interaction has been found to be a sensitive probe of structural features such as peptide backbone conformation, secondary structure, and hydrogen bonding. This has resulted in numerous studies focusing on the relationship between carbon[1] and nitrogen[2] chemical shift (CS) tensors and these structural characteristics. Carbon and nitrogen CS tensors have also been exploited in the characterization of polypeptide structure and dynamics in lipid bilayers.[3] As well, *ab initio* chemical shielding calculations have been utilized recently in an effort to better understand the relationship between the amide carbon and nitrogen chemical shielding tensors and polypeptide structure.[4]

Due to the significance of the chemical shielding interaction in the study of polypeptide structure and dynamics, the characterization and understanding of the carbon and nitrogen CS tensors of the amide fragment is essential. To this end, several reports have appeared in the literature with emphasis on the characterization of the amide carbon[3h,5–15] and nitrogen[5,11,16–28] CS tensors using a variety of solid-state NMR techniques.

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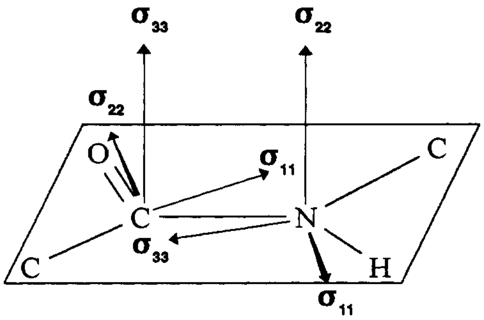
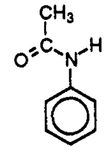


Figure 1. Typical orientation of the principal axis system for both the carbon and nitrogen CS tensors of the amide fragment.

Although the principal components of both the amide carbon and nitrogen CS tensors are sensitive to subtle structural changes, it has been found that these CS tensors show marked similarities throughout the wide range of polypeptides examined.[5] This can be attributed to similarities in the molecular and electronic structure of the amide fragment as well as to the fact that the chemical shielding interaction is fundamentally a local phenomenon. In addition, it is well-established that for the carbonyl carbon chemical shielding tensor, the most shielded direction is perpendicular to the amide plane while the intermediate component lies approximately along the carbonyl bond (Figure 1). For the amide nitrogen, the most shielded direction is approximately along the C–N bond with the intermediate component perpendicular to the amide plane (Figure 1).

In the present study, ^{13}C and ^{15}N solid-state NMR spectroscopy have been used to determine the carbon and nitrogen CS tensors in two amides, acetanilide (**I**) and *N*-methylacetanilide (**II**). The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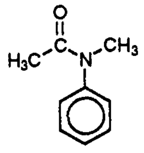
II

impetus for this study is 2-fold. First, the characterization of both the carbon and nitrogen CS tensors of the amide fragment of these two species will contribute to our understanding of the chemical shielding interaction in this class of compounds. Obviously, the study of amides and simple peptides is important as such systems can be used as models to gain insight into the chemical shielding interaction in proteins. Secondly, and not unrelated to the first, is a more specific interest related to the very different structures of acetanilide and *N*-methylacetanilide in the solid state. In Table 1, the various bond lengths and bond angles involving the amide fragment of **I** and **II**, as determined by X-ray diffraction studies,[29-32] have been compiled for comparative purposes. Acetanilide (orthorhombic, space group *Pbca*) exists in the *Z* conformation in the solid state which places the carbonyl oxygen *cis* to the phenyl ring. As well, it is found that the acetamide plane is twisted out of the phenyl ring plane by 17.6°. *N*-Methylacetanilide (orthorhombic, space group *Pnma*), however, exists in the *E* conformation in the solid state (carbonyl oxygen *trans* to the phenyl ring) with the phenyl ring plane orthogonal to the *N*-methylacetamide plane. Similar differences in amide conformation have been found to exist in the amino acids L-phenylalanine anilide and L-phenylalanine-*N*-methylanilide which have been exploited, recently, in molecular imprinting techniques for the design of polymers possessing "custom-made" recognition sites.[33] These structural differences are presumably a consequence of the increased steric interactions that result upon moving from the secondary to tertiary amide, and it will be interesting as well as informative to examine how this affects the carbon and nitrogen CS tensors.

Table 1. Interatomic Distances and Angles in the Amide Fragment of I and II As Determined by X-ray Diffraction

(*Z*)-acetanilide[29,32]		(*E*)-*N*-methylacetanilide[30]	
	Bond Distance (Å)		
N–C(O)	1.354	N–C(O)	1.344
N–C_{ipso}	1.413	N–C_{ipso}	1.481
C–O	1.219	C–O	1.263
C–CH_3	1.495	C–CH_3	1.503
		N–CH_3	1.467
	Angle (deg)		
C_{ipso}–N–H	115	C_{ipso}–N–CH_3	118.7
C_{ipso}–N–C(O)	127.6	C_{ipso}–N–C(O)	119.6
C(O)–N–H	117	C(O)–N–CH_3	121.7
N–C–O	123.1	N–C–O	117.0
N–C–CH_3	115.3	N–C–CH_3	118.5
CH_3–C–O	121.6	CH_3–C–O	124.5

We have used dipolar-chemical shift NMR spectroscopy to characterize the amide carbon and nitrogen CS tensors of **I** and **II**.[34-38] This technique, which relies on the presence of a dipolar coupled, isolated spin pair, has been used extensively in our laboratory.[39] It is well-known that the results from this experiment are often not unambiguous because of the axially symmetric nature of the dipolar interaction.[38] Traditionally, these shortcomings have been at least partially alleviated by making use of local symmetry arguments and comparisons with CS tensors determined in related systems, as well as performing *ab initio* chemical shielding calculations for the species under experimental investigation and/or related model systems. In the present study, we have followed these conventional approaches. The *ab initio* chemical shielding calculations have been performed using the IGLO (*I*ndividual *G*auge for *L*ocalized Molecular *O*rbitals) method[40-42] for both the amide carbon and nitrogen of **I** and **II** as well as the GIAO (*G*auge-*I*ncluding *A*tomic *O*rbitals) method[43]

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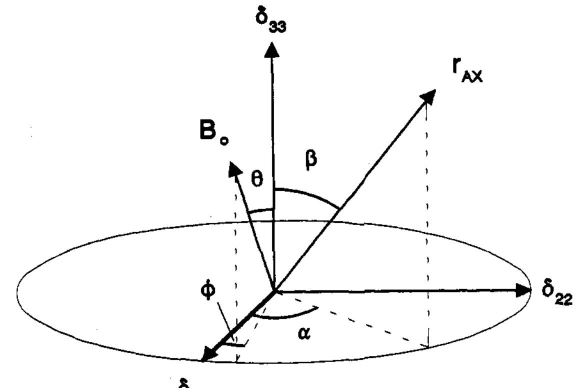
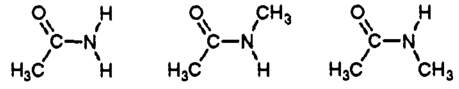


Figure 2. The orientation of the magnetic field vector in the principal axis system of the CS tensor is defined by the polar angles θ and ϕ. The relative orientation of the dipolar tensor and the CS tensor is defined by the Euler angles α and β.

Chart 1



III IV V

for several small amides (**III**, **IV**, and **V**) (Chart 1). These calculations not only help to alleviate the ambiguity associated with the experimental findings but also facilitate directly our understanding of the experimental CS tensors. The effects of intermolecular hydrogen bonding on the carbonyl carbon and nitrogen chemical shielding tensors for the amide fragment have also been explored by performing GIAO shielding calculations for the acetamide (**III**) dimer. It should be mentioned that, to the best of our knowledge, the calculations performed here represent only the third such report involving the *ab initio* calculation of the complete carbon and nitrogen chemical shielding tensors in the amide fragment.[4b,44] Also, the nitrogen CS tensors of **I** and **II** have been unambiguously experimentally determined by utilizing a second dipolar interaction reference frame from which to define the CS tensor. This was made possible by preparing several isotopically labeled spin pairs of **I** and **II**.

Theory

Solid-State NMR. The perturbation of the Zeeman energy levels of a nuclear spin by the chemical shielding interaction results from induced electronic motions in the presence of an external magnetic field which in turn generates secondary magnetic fields that alter the strength of the applied field "felt" by the nuclear spin. The Hamiltonian governing this interaction for a nuclear spin, *A*, can be written as

$$\mathcal{H}_{CS} = \hbar\gamma_A \mathbf{I}_A \cdot \sigma \cdot \mathbf{B}_o \tag{1}$$

where $\mathbf{I}_A$ is the nuclear spin angular momentum vector and σ is the chemical shielding tensor, with all other terms having their standard meaning. The chemical shielding interaction is described by a second rank Cartesian tensor which, in general, is determined by nine independent components. However, to first order, only the symmetric part of the chemical shielding tensor contributes to the NMR spectrum[45,46] and consequently only six independent quantities need be determined. These are normally specified with reference to an axis system in which the chemical shielding tensor is diagonal, known as the principal axis system (PAS), and are given as the three principal components, σ_{11}, σ_{22}, and σ_{33} (the diagonal elements), which designate the direction of least, intermediate, and greatest shielding, respectively, and three Euler angles which orient the PAS of the chemical shielding tensor in a molecular reference frame. For a single crystallite with an arbitrary orientation with respect to the external magnetic field, the magnitude of the chemical shielding interaction will be a function of the three principal components of the chemical shielding tensor as well as the orientation of the magnetic field in the PAS of the chemical shielding tensor (Figure 2) which can be specified by the polar and azimuthal angles θ and ϕ, respectively. Consequently, the orientation-dependent resonance frequency for a nuclear spin, *A*, can be written as

$$\nu(\theta,\phi) = \nu_L - \nu_{CS} \tag{2}$$

where

$$\nu_L = \frac{\gamma_A}{2\pi}\mathbf{B}_o \tag{3}$$

$$\nu_{CS} = \nu_L(\sigma_{11}\sin^2\theta\cos^2\phi + \sigma_{22}\sin^2\theta\sin^2\phi + \sigma_{33}\cos^2\theta) \tag{4}$$

where ν_L represents the A spin Larmor frequency. In a powder sample, all possible orientations (θ,ϕ) will be present which gives rise to a characteristic line shape known as a powder pattern. Calculation of the NMR line shape due to a static powder sample involves summation of $\nu(\theta,\phi)$ over all values of θ ($0° \leq \theta \leq 180°$) and ϕ ($0° \leq \phi \leq 360°$).

The magnitude of the chemical shielding interaction is referenced with respect to the bare nucleus. In conventional NMR experiments, however, one measures chemical shifts, δ, which quantify the difference in resonance frequency between a nuclear spin in the species under investigation and the same isotope in a standard reference compound. The chemical shift of a nuclear spin, A, can be converted to an absolute chemical shielding scale provided the magnitude of the absolute shielding in the experimental reference compound is known:

$$\delta_A \simeq \sigma_{Ref} - \sigma_A \tag{5}$$

The convention used here for the three principal components of the chemical shift tensor, δ_{ii}, is $\delta_{11} \geq \delta_{22} \geq \delta_{33}$. From eq 5, it is clear that a large chemical shift corresponds to a small absolute shielding; δ_{11} and σ_{11} refer to the least shielded component of the chemical *shift* (CS) and chemical *shielding* tensor, respectively. The isotropic CS, δ_{iso}, is defined as one-third of the trace of the CS tensor:

$$\delta_{iso} = {}^1/_3(\delta_{11} + \delta_{22} + \delta_{33}) \tag{6}$$

The three principal components of the CS tensor can be obtained experimentally from the analysis of an NMR CS powder pattern and are defined as the points of inflection (δ_{11} and δ_{33}) and discontinuity (δ_{22}), respectively. However, information regarding the orientation of the PAS in the molecular reference frame is generally unavailable from such an experiment and is much more difficult to obtain experimentally. One solution is to perform a single-crystal NMR study[47] which unfortunately is time-consuming and places stringent requirements on the size and quality of the crystal. A second and often more viable experiment for extraction of this orientation information involves analysis of the NMR spectrum of a static powder sample under conditions where a nucleus, A, is spin–spin coupled to a second nucleus, X, with all other spin–spin interactions in the sample being negligibly small or experimentally eliminated. For two spin-${}^1/_2$ nuclei, the

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NMR spectrum of a static powder sample for either of the nuclei in such an isolated spin pair[34-39] will be sensitive to not only the chemical shielding interaction but also both the direct dipolar and indirect J coupling between the two spins. Under such conditions, eq 2 must be modified as follows:

$$\nu_m(\theta,\phi) = \nu_L - \nu_{CS} - m\nu_D - mJ_{iso} \qquad (7)$$

where

$$\nu_D = R_{eff}[1 - 3(\sin\beta\sin\theta\cos(\phi - \alpha) + \cos\beta\cos\theta)^2] \qquad (8)$$

$$R_{eff} = R - \frac{\Delta J}{3} \qquad (9)$$

$$R = \left(\frac{\mu_0}{4\pi}\right)\frac{\gamma_A\gamma_X\hbar}{2\pi}\langle r_{AX}^{-3}\rangle \qquad (10)$$

$$\Delta J = J_{\parallel} - J_{\perp} \qquad (11)$$

where R is the direct dipolar coupling constant, ΔJ is the anisotropy in the indirect spin–spin coupling interaction, and the angles α and β define the orientation of the unique component of the dipolar interaction tensor (the AX internuclear vector) in the PAS of the CS tensor (Figure 2). Note that the above equations are strictly valid only for a heteronuclear spin pair ($\gamma_A \neq \gamma_X$), as in the present study; for homonuclear spin pairs the situation is more complex.[39,48] For each orientation defined by θ and ϕ, the A-spin NMR spectrum will show a resonance signal for each allowed spin state of the X-spin, defined by the quantum number m. The difference in frequency between these signals is a function of the magnitude of the dipolar and J coupling interactions, which are both, in principle, anisotropic, while the average of the resonances is dependent upon the chemical shielding interaction. The NMR spectrum for a static powder sample will thus consist of a series of subspectra for each spin state of nucleus X with characteristic splittings about each of the three principal components of the CS tensor. These splittings can be used to obtain information concerning the relative orientations of the dipolar and CS interaction tensors (Figure 2). Note that because the isotropic indirect spin–spin coupling between ^{13}C and ^{15}N is generally small for the amide fragment,[49] this interaction has been neglected in the analysis of the experimental NMR spectra obtained in this study and will not be considered further. With the magnetic field vector aligned with each of the three principal components of the CS tensor, it is easy to show that the magnitude of the splittings at each of these positions, $\Delta\nu_{ii}$, is given by:

$$\Delta\nu_{11} = |R_{eff}(1 - 3\sin^2\beta\cos^2\alpha)|$$

$$\Delta\nu_{22} = |R_{eff}(1 - 3\sin^2\beta\sin^2\alpha)|$$

$$\Delta\nu_{33} = |R_{eff}(1 - 3\cos^2\beta)| \qquad (12)$$

The above expressions are only strictly valid when the differences in the principal components of the chemical shielding tensor are much greater than the direct dipolar interaction. Deviations can occur depending upon the relative magnitudes of these two interactions as well as the orientation of the dipolar vector in the PAS of the CS tensor.[15,38] Because the unique axis of the dipolar tensor corresponds to an internuclear vector in the chemical species under observation, information concerning the orientation of the PAS of the CS tensor in the molecular reference frame can be established.

***Ab Initio* Chemical Shielding Calculations.** Amide carbon and nitrogen chemical shielding tensors have been calculated using the IGLO method[40-42] for **I** and **II** and the GIAO method[43] for **III**, **IV**, and **V**. Because of the size of the molecules involved in the IGLO calculations, we have used a recently developed variant of IGLO, DIGLO (*D*irect IGLO),[50] which avoids the storage of the two-electron repulsion integrals in a manner similar to that found in direct SCF programs[51] and, in its data-flow optimized version, reduces the amount of additional peripheral storage to a minimum.

Physically, the chemical shielding tensor, σ, describes the electronic effect on the Zeeman energy levels of magnetic nuclei, due to the response of the electrons to a static external magnetic field, $\mathbf{B}_0$. In closed-shell molecules, this leads to a second-order change in the molecular energy:

$$E = E_0 + \mathbf{B}_0\cdot\chi\cdot\mathbf{B}_0 + \sum_{i=1}^{N}\mu_i\cdot\sigma_i\cdot\mathbf{B}_0 + \ldots \qquad (13)$$

where the summation is taken over the N nuclei in the system. Here, we are not interested in the magnetic susceptibility, χ, but only in the bilinear response property, σ_i. Hence, the components of the σ tensor of nucleus i are defined as:

$$\sigma_{\alpha\beta_i} = \left(\frac{\partial^2 E}{\partial\mu_{\alpha_i}\partial\mathbf{B}_\beta}\right)_{\mu_i=\mathbf{B}\rightarrow 0} \quad ; \quad \alpha, \beta = x, y, z \qquad (14)$$

The σ tensor can be considered to arise from a sum of diamagnetic and paramagnetic contributions; $\sigma_i = \sigma^d{}_i + \sigma^p{}_i$. Only the diamagnetic part depends on the ground state wave function alone; the determination of the paramagnetic term requires knowledge of the first-order wave functions which have to be calculated through some form of perturbation theory. For an in-depth analysis of the calculation of nuclear magnetic shielding tensors, the reader is referred elsewhere.[52]

Experimental Section

Acetanilide Isotopomers. Acetanilide-^{15}N and acetanilide-^{15}N,^{13}C(CO) were prepared by adding a solution containing 0.99 g (12.6 mmol) of acetyl chloride or 1.00 g (12.6 mmol) of acetyl chloride-^{13}C(CO) (99%, MSD Isotopes, Montreal, Canada) in 10 mL of chloroform to a mixture of 1.19 g (12.6 mmol) of aniline-^{15}N (99%, MSD Isotopes) and 4.00 g of sodium carbonate in 25 mL of chloroform.[53] The addition was performed over a period of 15 min such that the temperature was maintained below 50 °C. The solution was stirred for 1 h and, after filtration, concentrated on a rotary evaporator to yield white crystals of acetanilide-^{15}N or acetanilide-^{15}N,^{13}C(CO).

Preparation of acetanilide-^{15}N,^{2}H was performed by dissolving acetanilide-^{15}N in ethyl acetate and adding D_2O. This mixture was shaken vigorously for several hours. The organic layer was then separated, dried over $MgSO_4$, and concentrated on a rotary evaporator to yield white crystals of acetanilide-^{15}N,^{2}H. Subsequent analysis by ^{15}N solution NMR revealed that the deuteration had occurred to an extent of approximately 90%.

***N*-Methylacetanilide Isotopomers.** *N*-Methylacetanilide-^{15}N,^{13}C(CO) and *N*-methylacetanilide-^{15}N,^{13}C(*N*-CH_3) were prepared *via* the acetylation of *N*-methylaniline-^{15}N or *N*-methylaniline-^{15}N,^{13}C(*N*-CH_3). These two aniline derivatives were first synthesized according to a standard literature procedure[54] with the exception that aniline-^{15}N and iodomethane-^{13}C (99%, MSD Isotopes) were used as starting reagents. The acetylation was carried out by refluxing for 1 h a mixture of 1.07 g (9.9 mmol) of *N*-methylaniline-^{15}N or 1.09 g (9.9 mmol) of *N*-meth-

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ylaniline-^{15}N,^{13}C(N-CH$_3$) with an excess of acetic anhydride-$^{13}C_2$(CO) (99%, MSD Isotopes) or acetic anhydride (1.5 equivalents) in glacial acetic acid. The mixture was then poured over crushed ice and neutralized with 5% NaOH (aq) to precipitate white crystals of *N*-methylacetanilide-^{15}N,^{13}C(CO) or *N*-methylacetanilide-^{15}N,^{13}C(N-CH$_3$).

Solid-State NMR Spectroscopy. ^{13}C and ^{15}N solid-state NMR spectra were acquired at 50.3 and 20.3 MHz, respectively, with a Bruker MSL 200 spectrometer ($\mathbf{B}_0$ = 4.7 T) and at 100.6 and 40.6 MHz, respectively, with a Bruker AMX 400 spectrometer ($\mathbf{B}_0$ = 9.4 T). The spectra were obtained using Bruker double-air-bearing MAS probes and zirconium oxide rotors (7-mm o.d. at 4.7 T and for the ^{15}N spectra at 9.4 T, 4-mm o.d. for the ^{13}C spectra at 9.4 T). Cross-polarization (CP) under the Hartmann–Hahn matching condition was used to enhance the sensitivity of all the spectra with typical ^{1}H 90° pulse widths of 4.4 (4.7 T) and 4.7 μs (9.4 T) for the ^{15}N NMR spectra and 3.0 (4.7 T) and 3.8 μs (9.4 T) for the ^{13}C NMR spectra. For the acetanilide isotopomers, typical CP times were 3.5 (^{15}N NMR spectra) and 5.0 ms (^{13}C NMR spectra), while for the *N*-methylacetanilide isotopomers, 7.0 (^{15}N NMR spectra) and 5.0 ms (^{13}C NMR spectra) were typical contact times. Following CP, all spectra were acquired with high-power ^{1}H decoupling. Due to the long proton spin–lattice relaxation times in these systems, the FLIPBACK pulse sequence[55] was used with a typical recycle delay of 30 s. It is worth mentioning at this point that considering the difficulty experienced by others in obtaining high-quality ^{15}N solid-state NMR spectra of peptides and proteins, the calibre of the spectra obtained here is comparatively high. The problem of obtaining high-quality spectra can be predominantly related to line broadening effects due to the large dipolar interaction between the secondary amide nitrogen and the directly bonded proton. In the case of the ^{15}N NMR powder pattern of acetanilide-^{15}N,^{13}C(CO), we have observed a rapid deterioration in the resolution of the dipolar splittings due to the ^{13}C nucleus with decreasing proton decoupling power. Nitrogen NMR spectra were referenced to NH$_3$ (l, 25 °C) by setting the observed nitrogen signal of solid ^{15}NH$_4$NO$_3$ to 23.8 ppm. Carbon chemical shifts were referenced to tetramethylsilane by setting the carbon signals of solid adamantane to 38.56 (CH$_2$) and 29.50 ppm (CH).

Calculations. Calculations of ^{13}C and ^{15}N NMR line shapes were performed with a 486 microcomputer using a FORTRAN-77 program that incorporates the POWDER routine of Alderman *et al.*[56] Preliminary values of the angles α and β as well as R_{eff} required for the line shape calculations were obtained from the dipolar splitting ratio method.[38]

Calculation of the carbonyl carbon and nitrogen chemical shielding tensors of **I** and **II** was performed on Convec C210 and IBM RS6000/560 workstations using a recently developed direct version of the IGLO method.[50] The atomic orbital basis set used for the calculations was the standard basis II[41] which can be represented as [51111,2111,1] for first-row atoms (d exponent 1.0 for C, N, and O) and [311,1] for hydrogen (p exponent 0.7). Geometries used in the calculations were obtained from the X-ray structures described in the text. The carbonyl carbon and nitrogen chemical shielding tensors of amides **III**, **IV**, and **V** were calculated on an IBM RS6000/580 workstation using an efficient implementation of the GIAO method[57] incorporated in the TEXAS 90 *ab initio* program package.[58] A 6-311G basis set was used for each of the calculations involving **III** (monomer), **IV**, and **V**, augmented with two sets of polarization functions on all atoms. For the acetamide dimer, we have employed an attenuated basis set[59] in which a 6-311G(2D,2P) set was used for the atom of interest and directly bonded atoms, while a 4-31G set was used for the remaining atoms. The geometry of **III** used in the shielding calculations was obtained from a previous neutron diffraction study[60] while the structures of **IV** and **V** were obtained from a molecular mechanics study by Schnur *et al.*[61]

Results and Discussion

(a) Characterization of the Carbonyl Carbon CS Tensor in Acetanilide and *N*-Methylacetanilide. (i) Results for Acetanilide-^{15}N,^{13}C(CO).

The 50.3-MHz ^{13}C NMR spectrum obtained for a static powder sample of acetanilide-^{15}N,^{13}C(CO) is shown in Figure 3 along with the calculated spectrum which best fits the experimental data. Splittings due to dipolar coupling to the adjacent ^{15}N nucleus are clearly evident at the δ_{11} and δ_{33} regions of the powder pattern while at the δ_{22} region the splitting is too small to be resolved, implying that the dipolar vector lies close to the magic angle, 54.7°, with respect to the intermediate component of the carbon CS tensor. In analyzing the experimental spectrum, we have used a value for this splitting, $\Delta\nu_{22}$, such that the dipolar interaction was ensured to be traceless. The calculated spectrum was obtained using the following parameters (see Table 2): δ_{11} = 248 ± 2 ppm, δ_{22} = 175 ± 1 ppm, δ_{33} = 90 ± 2 ppm, and R_{eff} = 1230 ± 40 Hz. As well, the angles α and β were determined to be 30 ± 5° and 90 ± 3°, respectively, which places the most shielded component, δ_{33}, perpendicular to the amide plane and the least shielded component, δ_{11}, 30° off the ^{13}C–^{15}N bond axis. From Figure 2, this orientation of the PAS of the carbon CS tensor requires that the intermediate component, δ_{22}, lies at an angle of 60° with respect to this bond axis. We have also obtained the ^{13}C NMR spectrum of this compound at 9.4 T and have found excellent agreement between the experimental spectrum and that calculated using the same parameters derived from the analysis at 4.7 T. The isotropic ^{13}C CS obtained here (171.5 ppm) agrees well with that reported previously in solution, 168.3 ppm.[62] This result is not surprising in light of earlier ^{1}H NMR studies in pyridine solution[63] which found the acetanilide molecule to exist in the *E* conformation to an extent of only 0.1%.

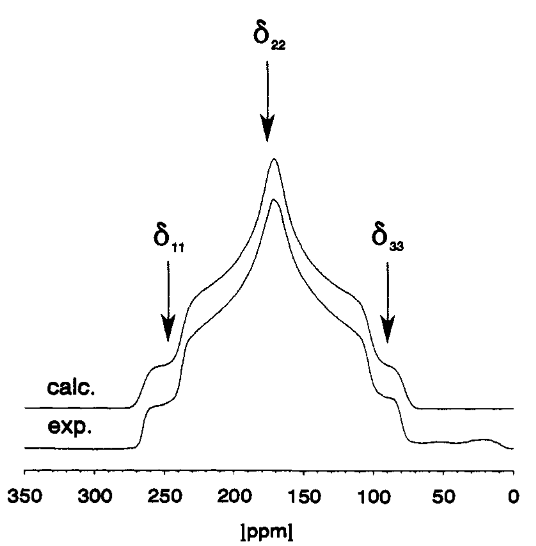

Figure 3. The experimental (bottom) and calculated (top) ^{13}C NMR spectra for a static powder sample of acetanilide-^{15}N,^{13}C(CO) obtained at 4.7 T. The three principal components of the carbon CS tensor are labeled.

Table 2. Principal Components and Orientation of the Carbonyl Carbon CS Tensor in Amides

	δ_{11} (ppm)	δ_{22} (ppm)	δ_{33} (ppm)	δ_{iso}[a] (ppm)	α[b] (deg)	β[b] (deg)	ref
acetanilide	248(2)	175(1)	90(2)	171.5	30	90	this work
N-methyl-acetanilide	243(2)	175(1)	93(2)	170.2	32	90	this work
typical peptides	243(4)	178(7)	93(4)	171(2)			c

[a] Obtained from CP/MAS solid-state NMR spectra. [b] α and β are defined with respect to the ^{15}N–^{13}C(CO) dipolar vector; see text for details. [c] From ref 5; the typical shielding parameters are the average obtained from 23 different reference spectra of the amide fragment in peptides. The standard deviation reflects the diversity of the peptides and the experimental error in the data.

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(ii) **Results for *N*-Methylacetanilide-^{15}N,^{13}C(CO).** The experimental ^{13}C NMR spectrum obtained for *N*-methylacetanilide-^{15}N,^{13}C(CO) at 4.7 T was very similar to that obtained for the analogous isotopomer of **I**. The agreement between the observed and calculated spectra was maximized using the following parameters (see Table 2): $\delta_{11} = 243 \pm 2$ ppm, $\delta_{22} = 175 \pm 1$ ppm, $\delta_{33} = 93 \pm 2$ ppm, and $R_{\rm eff} = 1250 \pm 30$ Hz. The angles α and β were determined to be $32 \pm 5°$ and $90 \pm 2°$, respectively.

(iii) **Discussion.** The carbonyl ^{13}C chemical shift tensors of **I** and **II** exhibit a remarkable similarity to one another. This finding is consistent with the sensitivity of the chemical shielding interaction to predominantly local influences. The structural differences between **I** and **II** are more focused in the vicinity of the amide nitrogen nucleus which is therefore anticipated to be more sensitive to these changes; the electronic structures of the carbonyl groups in these two systems appear to be quite similar. Unfortunately, due to the diverse multitude of structural variations that exist for **I** and **II**, it is difficult to isolate the origin of the small difference in isotropic chemical shifts, 1.3 ppm. The result that the isotropic chemical shift of **II** is more shielded than in **I** is consistent with both the magnitude and direction of *N*-methyl substituent effects for amides, which has the effect of increasing the average shielding at the carbonyl carbon nucleus. For example, the carbonyl ^{13}C isotropic chemical shift for formamide is 165.5 ppm while in the (*Z*)-*N*-methyl derivative it is 163.4 ppm.[62] Likewise, for acetamide, the ^{13}C isotropic chemical shift is 172.7 ppm whereas in (*Z*)-*N*-methylacetamide it is 171.6 ppm.[62]

With the requirement that one of the three principal components of the carbon CS tensor lies perpendicular to the amide plane, the values for α and β determined for **I** and **II** are consistent with two possible orientations of the ^{13}C CS PAS, corresponding to a 180° rotation about the ^{13}C–^{15}N dipolar vector. For example, in **I**, the most shielded direction is fixed perpendicular to the amide plane. Therefore, the least shielded component can lie 30° off the ^{13}C–^{15}N bond in a direction toward the *N*-phenyl substituent (placing the intermediate component approximately along the carbonyl bond as in Figure 1) or in a direction toward the amide hydrogen. Although the correct solutions are unavailable from the experimental results, it is possible to resolve this ambiguity by making use of the well-established connection between the orientation of the carbonyl ^{13}C CS PAS and the electronic structure of the carbonyl fragment.[64] Invariably, it is found that the most shielded direction lies perpendicular to the carbonyl plane, originating from high-energy $\sigma \rightarrow \sigma^*$ transitions, while the least shielded direction is approximately perpendicular to the carbonyl bond, arising from $\sigma \rightarrow \pi^*$ type excitations. The intermediate principal component of the carbonyl ^{13}C chemical shift tensor therefore lies approximately along the carbonyl bond and is dictated by $n \rightarrow \pi^*$ transitions. On the basis of this information, we conclude that an analogous orientation of the ^{13}C CS PAS exists for **I** and **II**, which is depicted in Figure 4. Note that the angle between the intermediate component and the carbonyl bond in **I** is 3°, based on the X-ray determined N–C–O bond angle of 123.1° (Table 1).[29] In **II** this angle is calculated to be 5° on the opposite side of the carbonyl bond as compared with **I**, based on the N–C–O bond angle of 117.0° (Table 1).[30]

In Table 2, we have presented the results of a literature survey pertaining to the experimental data available for the principal components of ^{13}C CS tensors for the amide fragment. With the exception of one compound, acrylamide,[7] all literature values included in this survey pertain to peptides. The results obtained here for the ^{13}C CS tensors of **I** and **II** are very similar to the corresponding average values obtained from the literature survey, which reflects the invariance of the electronic structure of the carbonyl fragment not only in **I** and **II** but also in the range of peptides previously studied. The largest variation within each of the three principal components exists in the intermediate component, δ_{22}. Previous studies have suggested that this component is sensitive to hydrogen bonding effects.[1c,10,14] Since intermolecular N–H- -O=C hydrogen bonding is thought to be important in **I**, but impossible for **II**, it is surprising that the magnitudes of the intermediate component in **I** and **II** are identical within experimental error. However, it should be emphasized that the magnitude of this component may be intrinsically different for isolated molecules of **I** and **II** and it is possible that the experimental equivalence arises from the effects of intermolecular hydrogen bonding present in the crystal lattice of **I**. We will explore this possibility further in the next section when discussing the results of the carbon chemical shielding calculations. Finally, in each of these investigations where information concerning the orientation of the PAS of the CS tensor was obtained,[7-12,14] it was concluded that the intermediate component invariably lies near the carbonyl bond direction, with the most shielded component perpendicular to the amide plane, as depicted in Figure 1 and in agreement with the results obtained here for **I** and **II**.

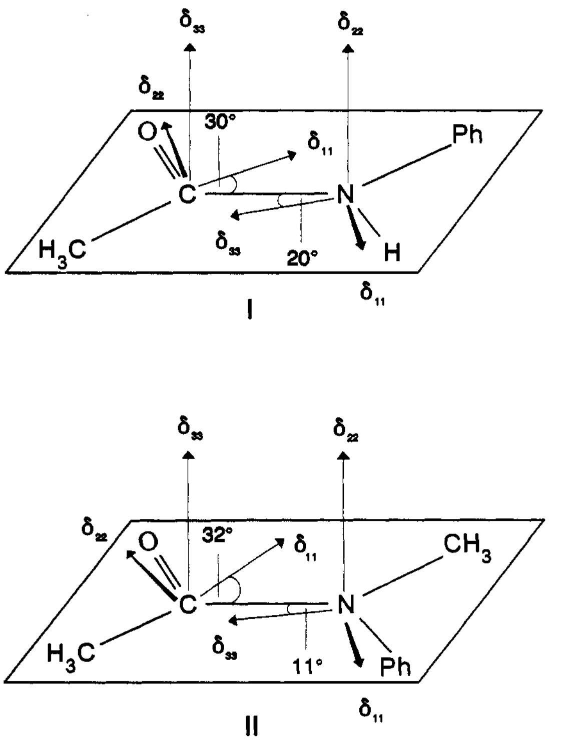

Figure 4. Orientation of the PAS of the carbon and nitrogen CS tensors for **I** and **II** as determined from dipolar-chemical shift NMR spectroscopy.

In Table 3, we have tabulated the results obtained from the *ab initio* carbon chemical shielding calculations for the amide carbon of both **I** and **II** and also for several small amides (**III**, **IV**, and **V**). As well, we have converted the experimental carbon CS tensors for **I** and **II** to an absolute shielding scale based on the absolute carbon chemical shielding for tetramethylsilane (186.0 ppm),[65] to facilitate comparison with the calculated results. The major conclusion from these results is that each calculation determines the orientation of the PAS of the ^{13}C CS tensor to be analogous to that depicted in Figure 1, with the intermediate component lying close to the carbonyl bond direction and the most shielded component perpendicular to the amide plane. This provides further conclusive evidence that the orientation of the PAS in **I** and **II** is as displayed in Figure 4. Note that the calculated isotropic shielding for the carbonyl carbon of **IV** and **V** is more shielded than that in **III**, in agreement with the trend observed experimentally that *N*-methyl substitution leads to an increase

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Table 3. Calculated Principal Components and Orientation of the Carbonyl Carbon Shielding Tensor of the Amide Fragment in Several Amides[a]

compd		σ_{11} (ppm)	σ_{22} (ppm)	σ_{33} (ppm)	σ_{iso} (ppm)	Ω (deg)[b]
(*Z*)-acetanilide (I)	calc[c]	−86	32	110	19	3
	exp	−62	11	96	15	3[d]
(*E*)-*N*-methylacetanilide (II)	calc[c]	−79	14	116	17	1
	exp	−57	11	93	16	5[d]
acetamide (III) monomer	calc[e]	−101	14	113	9	2
acetamide (III) dimer	calc[e]	−92	0	114	7	2
(*Z*)-*N*-methylacetamide (IV)	calc[e]	−79	22	109	18	1
(*E*)-*N*-methylacetamide (V)	calc[e]	−82	25	106	16	0

[a] The principal components of the experimental carbon CS tensors of I and II have been converted to chemical shielding values based on the experimental absolute carbon shielding in tetramethylsilane; 186.0 ppm.[65] [b] Ω represents the angle between the intermediate principal component (σ_{22}) and the C=O bond axis. In all cases, the most shielded direction lies perpendicular to the amide plane. [c] IGLO calculations using 274 and 308 basis functions for I and II, respectively (standard basis II). [d] These angles have been calculated based on the experimental N–C–O bond angles obtained from X-ray diffraction results (Table 1). [e] Calculated using the GIAO method.

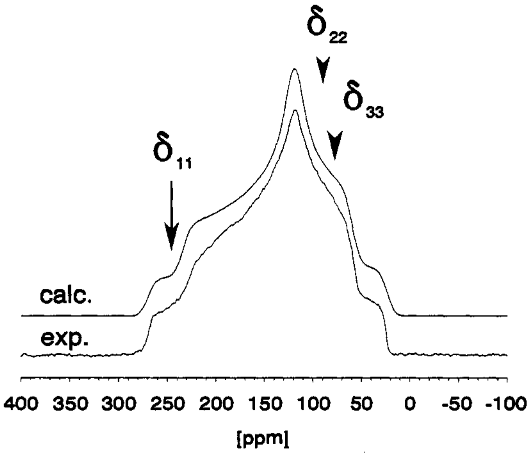

Figure 5. The experimental (bottom) and calculated (top) ^{15}N NMR spectra for a static powder sample of acetanilide-$^{15}N,^{13}C$(CO) obtained at 4.7 T. The three principal components of the nitrogen CS tensor are labeled.

in isotropic shielding,[62] although the magnitude of this effect is calculated to be somewhat larger than is observed experimentally. Also, the calculations involving **IV** and **V** predict that the *Z* to *E* conformational change involving the *N*-methyl substituent has a minimal influence on the carbonyl carbon shielding tensor.

The calculated results for **I** and **II** are in satisfactory agreement with the experimental shielding tensors, considering the size of the systems calculated. It is interesting that despite significant deviations between experiment and theory in the magnitudes of the principal components, the calculated isotropic shielding values are in very good agreement with experiment which illustrates the importance of studying the shielding tensor rather than simply its trace. Unfortunately, a direct comparison between the experimental and theoretical results is difficult as the calculations correspond to an isolated molecule in the gas phase at 0 K whereas intermolecular interactions, particularly hydrogen bonding, as well as rovibrational averaging and librational motion influence the experimental shielding results.[66] In light of this argument and the fact that δ_{22} has been suggested to be sensitive to hydrogen bonding, it is interesting to note the excellent agreement between experiment and theory in the intermediate component of the carbon shielding tensor of **II**, where intermolecular hydrogen bonding is absent, compared with the large deviations found for this component in **I**, where hydrogen bonding is thought to be important. This result implies that the intermediate component in an isolated molecule of **I** may be intrinsically more shielded than that in **II** and that the equivalence observed experimentally can be partly attributed to hydrogen bonding within the crystal lattice of **I**, which results in a deshielding of the intermediate component. In order to further examine the influence of intermolecular N–H- -O=C bonding, the carbonyl carbon chemical shielding tensor has been calculated for the acetamide (**III**) dimer (see Table 3), which can be readily compared with the results for the monomeric species. It is found that although the orientation of the PAS is relatively insensitive to hydrogen bonding, there are significant changes in the magnitudes of both the least shielded and intermediate components, with σ_{11} more shielded and σ_{22} more deshielded in the hydrogen bonded species. The most shielded component remains relatively invariant to the effects of hydrogen bonding. Since σ_{11} and σ_{22} move in opposite directions with a slightly larger shift in the intermediate component, the isotropic shielding shows only a slight deshielding upon hydrogen bonding. The fact that the intermediate component is calculated to be more deshielded in the hydrogen bonded species is consistent with the aforementioned rationalization of the experimental equivalence observed in the intermediate principal component of the carbonyl carbon CS tensors of **I** and **II**. Also, based on these results, it appears that inclusion of hydrogen bonding effects in the calculation of the carbon chemical shielding tensor of **I** would bring the magnitudes of both σ_{11} and σ_{22} into closer agreement with experiment. Finally, it should be mentioned that the results of the *ab initio* calculations are consistent with the experimental observations of Asakawa *et al.*,[1c] who found that both δ_{11} and δ_{22} are sensitive to hydrogen bonding, with δ_{22} moving downfield and δ_{11} upfield with decreasing hydrogen bond length in a series of peptides containing L-alanine residues.

(b) Characterization of the Amide Nitrogen CS Tensor in Acetanilide and *N*-Methylacetanilide. (i) Results for Acetanilide-$^{15}N,^{13}C$(CO). The 20.3-MHz ^{15}N NMR spectrum obtained for a static powder sample of acetanilide-$^{15}N,^{13}C$(CO) is shown in Figure 5 along with the calculated spectrum. Although the effects due to dipolar coupling to the ^{13}C nucleus are clearly evident in the experimental spectrum, analysis of this powder pattern is difficult since the magnitude of this dipolar interaction comprises a much larger fraction of the anisotropic ^{15}N chemical shielding interaction than it does the anisotropic ^{13}C chemical shielding interaction. This, combined with the fact that the ^{15}N CS tensor is nearly axially symmetric ($\eta = 0.12$), makes it difficult to extract the magnitudes of $\Delta\nu_{22}$ and $\Delta\nu_{33}$ from the powder pattern. To help circumvent this problem, we have independently determined the three principal components of the ^{15}N CS tensor from an analysis of the ^{15}N CS powder pattern obtained for acetanilide-^{15}N (see Table 4): δ_{11} = 247 ppm, δ_{22} = 90 ppm, and δ_{33} = 77 ppm. The errors in these values are estimated to be 1 ppm. Combining these with the value of the effective dipolar coupling constant obtained from analysis of the corresponding ^{13}C spectrum, the combination of α and β consistent with the experimental spectrum was determined to be $\alpha = 0°$ and $\beta = 20°$, with an estimated error in α between 5° and 10° and in β of 2°. This orientation of the PAS places the intermediate principal component perpendicular to the amide plane with the most shielded direction 20° off the ^{15}N–^{13}C bond axis. The ^{15}N NMR spectrum

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Table 4. Principal Components and Orientation of the Nitrogen CS Tensor in Amides

	δ_{11} (ppm)	δ_{22} (ppm)	δ_{33} (ppm)	δ_{iso}[a] (ppm)	α (deg)	β (deg)	ref
acetanilide	247(1)	90(1)	77(1)	138.0	0[b]	20[b]	this work
					0[c]	83[c]	this work
N-methyl-acetanilide	220(2)	95(2)	58(2)	124.8	0[b]	11[b]	this work
					0[d]	53[d]	this work
typical peptides	223(7)	79(8)	55(9)	119(6)			e

[a] Obtained from CP/MAS solid-state NMR spectra. [b] α and β are defined with respect to the ^{15}N–^{13}C(CO) dipolar vector; see text for details. [c] α and β are defined with respect to the ^{15}N–^{2}H dipolar vector; see text for details. [d] α and β are defined with respect to the ^{15}N–^{13}C(*N*-CH$_3$) dipolar vector; see text for details. [e] From ref 5; the typical shielding parameters are the average obtained from 36 different reference spectra of the amide fragment in peptides. The standard deviation reflects the diversity of the peptides and the experimental error in the data.

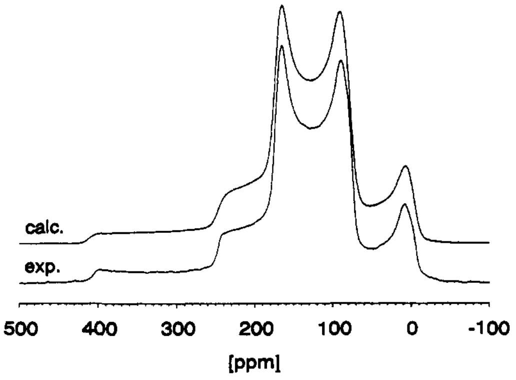

Figure 6. The experimental (bottom) and calculated (top) ^{15}N NMR spectra for a static powder sample of acetanilide-$^{15}N,^{2}H$ obtained at 4.7 T.

of this sample was also acquired at 9.4 T and showed very good agreement with the calculated spectrum obtained using the parameters derived from the analysis of the 4.7-T spectrum. It should be mentioned that in analyzing the ^{15}N NMR spectra for both acetanilide-^{15}N and acetanilide-$^{15}N,^{13}C$(CO), significant intensity distortions in the NMR line shape have been observed.[67] Such distortions are apparent in the experimental spectrum shown in Figure 5, occurring in the region between the δ_{11} and δ_{22} components. Similar distortions have been reported in the ^{15}N NMR spectra of several polypeptides[12,25] and are the result of anisotropy in the ^{15}N cross-polarization efficiency caused by the large dipolar interaction with the directly bonded proton.

(ii) **Results for Acetanilide-$^{15}N,^{2}H$.** The ^{15}N NMR spectrum for a static powder sample of acetanilide-$^{15}N,^{2}H$ (see Figure 6) consists of three subspectra corresponding to each of the allowed spin states of the quadrupolar deuterium nucleus ($I = 1$). In general, the theory of dipolar-chemical shift NMR spectroscopy where the dipolar coupled nucleus is quadrupolar is more complex.[15] Qualitatively, the effect of the quadrupolar interaction is to "tip" the axis of quantization of the quadrupolar spin away from the magnetic field vector which results in spin states that are a mixture of the pure Zeeman states. Under such conditions, the dipolar Hamiltonian is non-secular; the dipolar splittings given by eq 14 are no longer valid. Fortunately, the magnitude of the deuterium quadrupolar interaction is small compared with the Larmor frequency at 4.7 T (30.7 MHz) so that the quadrupolar-induced mixing will be minimal.[68] Consequently, the high-field approximation is valid and the theory presented here can be used in the analysis of the NMR spectrum. The calculated spectrum shown in Figure 6 was obtained using an effective dipolar coupling constant of 1690 ± 40 Hz with the angles α and β being 0 ± 3° and 83 ± 3°, respectively (see Table 4). This result places the intermediate component perpendicular to the amide plane (in agreement with the ^{15}N–^{13}C(O) analysis) and the least shielded component 7° off the ^{15}N–^{2}H bond axis. Again, we have also acquired the ^{15}N NMR spectrum of this sample at 9.4 T and have found very good agreement with the calculated spectrum obtained using the parameters derived from the analysis at 4.7 T. It is worth mentioning that if the anisotropy in the one bond J coupling between ^{15}N and ^{2}H is assumed to be negligible, the value of the dipolar coupling determined here yields a ^{15}N–^{2}H bond length of 1.034 Å, somewhat shorter than the findings of two previous NMR studies involving peptides.[21,25] This result indicates that motional averaging of the ^{15}N–^{2}H dipolar interaction is small, the rigidity of which is presumably a consequence of hydrogen bonding in the acetanilide crystal lattice.[31]

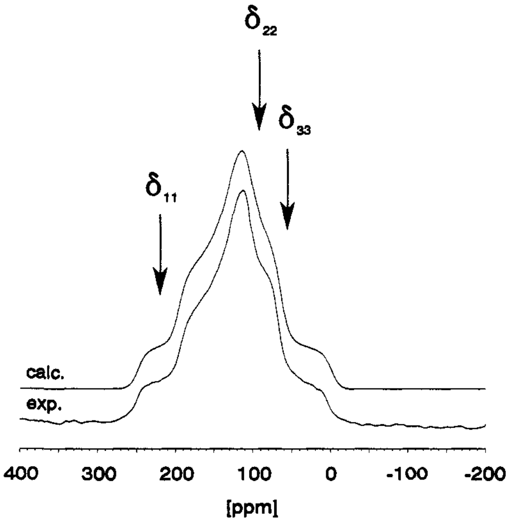

Figure 7. The experimental (bottom) and calculated (top) ^{15}N NMR spectra for a static powder sample of *N*-methylacetanilide-$^{15}N,^{13}C$(*N*-CH$_3$) obtained at 4.7 T. The three principal components of the nitrogen CS tensor are labeled.

(iii) **Results for *N*-Methylacetanilide-$^{15}N,^{13}C$(CO).** The experimental and the calculated spectra obtained for a static powder sample of *N*-methylacetanilide-$^{15}N,^{13}C$(CO) at 4.7 T are shown in Figure 7. The calculated spectrum was obtained using the following parameters (see Table 4): $\delta_{11} = 220 \pm 2$ ppm, $\delta_{22} = 95 \pm 2$ ppm, $\delta_{33} = 58 \pm 2$ ppm, $R_{eff} = 1250 \pm 30$ Hz (as determined in the ^{13}C NMR study for this compound), $\alpha = 0°$, and $\beta = 11°$. The estimated error in α is between 5 and 10° while for β the estimated error is 2°. This orientation of the ^{15}N CS PAS is similar to that determined for acetanilide in that the intermediate component is perpendicular to the amide plane and the most shielded component is close to the ^{15}N–^{13}C(CO) dipolar vector, making an angle of 11° in **II**.

(iv) **Results for *N*-Methylacetanilide-$^{15}N,^{13}C$(*N*-CH$_3$).** From the experimental spectrum for a static sample of this isotopomer of **II** at 4.7 T, an effective dipolar coupling of 900 ± 40 Hz and values for α and β of 0 ± 5° and 53 ± 2°, respectively, were obtained. This result again places the intermediate component perpendicular to the amide plane and the most shielded component 53° off the ^{15}N–^{13}C(*N*-CH$_3$) dipolar vector. Note that the value determined for the effective dipolar coupling obtained here yields a ^{15}N–^{13}C(*N*-CH$_3$) bond length of 1.504 Å (assuming $\Delta J = 0$), somewhat longer than that determined by X-ray diffraction (1.467 Å) (Table 1).[30] This result suggests motional averaging of this dipolar interaction and may possibly result from the presence of

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[67] Eichele, K.; Lumsden, M. D.; Wasylishen, R. E. Nitrogen-15 NMR Spectra of Powder Samples of Acetanilide Obtained by ^{1}H, ^{15}N Cross-Polarization, paper No. 483 presented at the 76th Canadian Chemical Conference and Exhibition, Sherbrooke, Quebec, May 31–June 4, 1993.

[68] See for example: Gerald, R., II; Bernhard, T.; Haeberlen, U.; Rendell, J.; Opella, S. *J. Am. Chem. Soc.* **1993**, *115*, 777–782. The magnitude of the amide ^{2}H quadrupolar coupling constant in *N*-acetyl-D,L-valine was found to be 212.6 kHz.

anisotropic motion of the methyl group, as implied in the X-ray diffraction study.[30]

(v) Discussion. The values of α and β obtained from analysis of the ^{15}N dipolar-chemical shift NMR spectra for I and II (Table 4) are consistent with two possible orientations of the ^{15}N CS PAS in I and II, keeping the intermediate principal component fixed in a direction perpendicular to the amide plane. For example, from the calculation of the ^{15}N spectrum of acetanilide-^{15}*N*,^{13}*C*(CO), β was determined to be 20°. Consequently, the most shielded direction can lie 20° off the ^{15}N–^{13}C dipolar vector in a direction toward the α carbon, placing the least shielded direction close to the N–H bond (as in Figure 1), or it can lie 20° off the ^{15}N–^{13}C bond on the opposite side, toward the carbonyl bond. To determine which of these possible orientations is correct, the results of the analysis of the dipolar-chemical shift NMR spectrum involving the ^{15}N–^{2}H spin pair must be utilized. To do so, it is necessary to reference each of the above solutions with respect to the ^{15}N–^{2}H dipolar vector. For the former solution (as in Figure 1) one can calculate the angle between the least shielded component and this vector to be 7°, based on the X-ray determined C(O)–N–H bond angle of 117° (Table 1).[32] For the latter solution, the corresponding angle is 47°. The fact that the ^{15}N–^{2}H dipolar-chemical shift NMR spectrum was calculated using $\alpha = 0°$ and $\beta = 83°$ is consistent with only the former of these two solutions, which is depicted in Figure 4. In an analogous manner, one can use the results obtained from the analysis of the ^{15}N NMR spectra of both *N*-methylacetanilide-^{15}*N*,^{13}*C*(CO) and *N*-methylacetanilide-^{15}*N*,^{13}*C*(*N*-CH_3), combined with the C(O)–N–CH_3 bond angle (Table 1), to fix the orientation of the ^{15}N CS PAS for II (Figure 4).

Unlike the carbon CS tensors, a comparison of the experimental nitrogen CS tensors for I and II reveals considerable differences in both the magnitudes of the principal components and the orientation of the PAS (see Table 4). As expected, the nitrogen chemical shielding interaction is clearly a more sensitive probe of the structural variations in I and II than is the carbonyl carbon chemical shielding interaction. The fact that the isotropic nitrogen shielding in I is significantly more deshielded than in II is consistent with the effects of conjugation with an *N*-phenyl substituent. For example, the isotropic nitrogen chemical shift of neat formamide is 112.4 ppm while for (*Z*)-*N*-phenylformamide in $CDCl_3$ solution it increases to 138.4 ppm.[69] Likewise, the isotropic nitrogen chemical shift for acetamide is 103.4 ppm (0.5 M, $CHCl_3$) while for I in DMSO solution it is 133.2 ppm.[69] In II, such a delocalization is prohibited due to the orthogonality of the phenyl ring with respect to the amide plane, resulting in an increased isotropic nitrogen chemical shielding. Note that conjugation with the phenyl ring in I is reflected in a shorter N–C_{ipso} bond length, as compared to II (Table 1). It should also be mentioned that *N*-methyl substitution has a comparatively insignificant effect on δ_{iso}(N). For example, the nitrogen isotropic shift of acetamide can be compared with that of (*E*)-*N*-methylacetamide, 106.0 ppm,[69] a difference of only 2.6 ppm. Clearly, this result isolates the dependence of the nitrogen chemical shielding interaction on the orientation of the *N*-phenyl substituent as the dominating effect controlling the difference in nitrogen shielding tensors present in I and II.

An examination of the individual nitrogen CS tensor components in these two systems (Table 4) supports this argument. It can be seen from these results that the smaller isotropic nitrogen shielding in I results from a greater deshielding when the magnetic field is aligned with both the least and most shielded directions in I and II. In agreement with the results presented here, the least shielded component of the nitrogen CS tensor of the amide fragment has been found to invariably lie approximately perpendicular to the C(O)–N bond direction, within the amide plane. As well, the most shielded component consistently lies approximately parallel with the C(O)–N bond direction, also within the amide plane. Since σ_{11} and σ_{33} are both in-plane components, the paramagnetic shielding contribution to each of these must be governed by out-of-plane $\sigma \leftrightarrow \pi$ excitations (*i.e.*, $\sigma \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$). Consequently, the greater nitrogen deshielding in I can, in part, be rationalized by invoking conjugation arguments. Specifically, delocalization to the *N*-phenyl substituent in I leads to a stabilization of the π^* antibonding framework and a destabilization of the π bonding system. Therefore, the existence of lower-energy $\sigma \leftrightarrow \pi$ excitations results in a larger paramagnetic shielding contribution and hence a greater deshielding of the nitrogen in-plane shielding tensor components of I, compared with II where such a delocalization is prohibited. As well, it is worth mentioning that more extensive delocalization in I could also increase the paramagnetic shielding contribution by increasing the effective nitrogen nuclear charge. Such an increase would lead to a contraction of the nitrogen p atomic orbitals involved in the electronic excitations controlling the paramagnetic shielding term, thereby decreasing the radius of these charge circulations and increasing the strength of the resulting induced magnetic fields. The intermediate component of the nitrogen CS tensor appears to show the least sensitivity to the structural variations present in I and II, arising from high-energy in-plane $\sigma \rightarrow \sigma^*$ excitations. However, it is important to be aware of the possibility that this component may be affected in different directions by the various structural differences present in I and II, therefore resulting in an overall small difference between the two compounds.

In Table 4, the results of a literature survey concerning experimental data on nitrogen CS tensors in the amide fragment of peptides are tabulated. Unlike the results from the carbon study (Table 2), there exist significant deviations between the nitrogen CS tensors of I and II and the average values obtained from the literature. Interestingly, both the least shielded and most shielded components of II are very similar to the average values in peptides while in I these components are more deshielded. This can be understood in light of the prototypical environment of the amide nitrogen in peptides, which is bonded to a four-coordinate carbon nucleus. In this respect, despite the absence of hydrogen bonding, II can be justified to more accurately represent a model peptide in terms of electronic structure considerations as delocalization to the phenyl ring is forbidden while in I, as mentioned, it appears that conjugation with the phenyl ring deshields the nitrogen nucleus, which is reflected in both the least and most shielded principal components. The origin of the greater deshielding of the intermediate component in I and II with respect to the average literature values is obscure.

Unlike the results obtained from the carbon study, there exists considerable deviation within each of the average values of the three principal components of the nitrogen chemical shift tensor in peptides. This result is indicative of the sensitivity of the nitrogen chemical shielding interaction to local structural features. For example, the out-of-plane intermediate component of the nitrogen CS tensor is thought to reflect comformational features and peptide secondary structure.[2b] Also, a recent study by Kuroki *et al.*[2c] indicates that all three components of the nitrogen CS tensor are sensitive to the geometry of N–H- -O=C intermolecular hydrogen bonding. Finally, it is worth mentioning that in all studies where information concerning the orientation of the PAS of the nitrogen CS tensor was obtained,[11,16,19–23,25,26] the results were analogous to the findings in the present study.

In Table 5 the results of nitrogen *ab initio* chemical shielding calculations using the IGLO method for I and II and the GIAO method for III, IV, and V are presented. In order to facilitate comparison of the calculations with experiment, the experimental nitrogen CS tensors determined for I and II have been converted

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(69) (a) Witanowski, M.; Stefaniak, L.; Webb, G. A. *Annu. Rep. NMR Spectrosc.* **1993**, *25*, 167. (b) Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; John Wiley & Sons: New York, 1979; p 59.

Table 5. Calculated Principal Components and Orientation of the Nitrogen Shielding Tensor of the Amide Fragment in Several Amides[a]

compd		σ_{11} (ppm)	σ_{22} (ppm)	σ_{33} (ppm)	σ_{iso} (ppm)	Ω (deg)[b]
(*Z*)-acetanilide (I)	calc[c]	31	163	215	137	8
	exp	−2	155	168	107	20
(*E*)-*N*-methylacetanilide (II)	calc[c]	46	166	234	149	1
	exp	25	150	187	121	11
acetamide (III) monomer	calc[d]	77	165	252	165	10
acetamide (III) dimer	calc[d]	70	169	247	162	8
(*Z*)-*N*-methylacetamide (IV)	calc[d]	71	178	264	171	9
(*E*)-*N*-methylacetamide (V)	calc[d]	71	169	279	173	13

[a] The principal components of the experimental nitrogen CS tensors of I and II have been converted to chemical shielding values based on the experimental absolute nitrogen shielding in ammonia; 244.6 ppm.[70] [b] Ω represents the angle between the most shielded principal component (σ_{33}) and the C–N bond axis. In all cases, the intermediate component lies perpendicular to the amide plane. [c] IGLO calculations using 274 and 308 basis functions for I and II, respectively (standard basis II). [d] Calculated using the GIAO method.

Table 6. Calculated Principal Components of the Nitrogen Chemical Shielding Tensor in (*Z*)-Acetanilide as a Function of Orientation of the *N*-Phenyl Substituent with Respect to the Acetamide Plane

$C-N-C_{ipso}-C2$ torsion (deg)	σ_{11} (ppm)	σ_{22} (ppm)	σ_{33} (ppm)	σ_{iso} (ppm)
0	38	172	215	142
45	50	168	227	148
90	58	170	233	154

to a chemical shielding scale based on the absolute nitrogen chemical shielding in ammonia (244.6 ppm at 20 °C).[70] For each of the amides studied, the calculations predict an orientation of the nitrogen chemical shielding PAS analogous to that depicted in Figure 1, in agreement with the experimental results obtained here. Notice that the calculated isotropic nitrogen shielding for III is determined to be 28 ppm more shielded than in I, in agreement with experimental chemical shift differences for these two compounds.[69] Furthermore, an examination of the individual tensor components reveals that the greater deshielding in I is reflected in both the least shielded and most shielded components of the nitrogen chemical shielding tensor; the intermediate component is calculated to differ by only 2 ppm. This result supports the argument presented earlier concerning the effects of conjugation on the in-plane tensor components, which partially accounts for the greater deshielding of the nitrogen nucleus in I with respect to II. Also, a comparison of the calculated nitrogen chemical shielding tensor in III with those of IV and V indicates that *N*-methyl substitution leads to a greater isotropic nitrogen shielding, although the calculated differences are somewhat larger than those found experimentally. This result may also help to partially account for the larger nitrogen isotropic shielding in II, compared with that in I. Finally, in order to gain some insight into the influence of N–H- -O=C hydrogen bonding, the nitrogen chemical shielding tensor in the acetamide (III) dimer has been calculated and can be compared with the results of the calculation involving the monomeric species (Table 5). In agreement with the work of Kuroki *et al.*,[2c] the calculations indicate that each of the three principal components of the nitrogen chemical shielding tensor is sensitive to such hydrogen bonding effects, with the result that the isotropic nitrogen shielding experiences a small deshielding effect upon hydrogen bonding. Undoubtedly, inclusion of hydrogen bonding effects into the calculation of the nitrogen shielding tensor in I would bring the calculated results into closer agreement with experiment. As well, it may be that a small part of the greater nitrogen deshielding in I, with respect to II, can be attributed to the presence of intermolecular hydrogen bonding in the crystal lattice of I.

Although the calculated principal components of the nitrogen chemical shielding tensors for I and II lack quantitative agreement with experiment, the results are satisfactory considering the size of the calculations involved as well as the well-known difficulty associated with the *ab initio* calculation of the paramagnetic contribution to nitrogen chemical shielding tensors at the Coupled Hartree Fock (CHF) level of theory when the nitrogen atom is involved in multiple bonding or contains a lone pair.[71] However, it is interesting that the largest deviation between experiment and theory is in the most shielded component, where the paramagnetic contribution is the smallest, in contrast to the usual difficulty involving the calculation of the least shielded component.[72] The calculations adequately reproduce the trend in shielding observed experimentally. For example, both σ_{11} and σ_{33} are calculated to be much less shielded in I than in II, while the intermediate component shows little variation, in agreement with the experimental results. Also, the most shielded component is calculated to lie closer to the C–N bond in II, also in agreement with experiment. In an effort to gain a further understanding of the differences in nitrogen chemical shielding between compounds I and II, IGLO calculations of the nitrogen shielding tensor in I have been performed using three different orientations of the *N*-phenyl ring with respect to the acetamide plane (0°, 45°, and 90°), the results of which are presented in Table 6. In performing these calculations, the $C-N-C_{ipso}-C2$ torsion was fixed at the desired angle, with the rest of the molecule optimized using the TRIPOS force field.[73] The results show that as the *N*-phenyl substituent rotates from within the acetamide plane to an orthogonal conformation, both the least shielded and most shielded components become progressively more shielded, while the intermediate component is much less sensitive and appears to pass through a minimum. Also, the difference in shielding between the planar and orthogonal conformations in both σ_{11} and σ_{33} is approximately 20 ppm, leading to a change in the isotropic nitrogen shielding of 12 ppm. These results are in agreement with the experimental nitrogen shielding patterns for I and II and provide firm evidence that the difference in nitrogen shielding in these two species is predominantly related to the difference in orientation of the *N*-phenyl substituent with respect to the amide plane.

Conclusions

The carbon and nitrogen chemical shift tensors in acetanilide (I) and *N*-methylacetanilide (II) have been characterized using both solid-state NMR spectroscopy and *ab initio* chemical shielding calculations. The experimental results obtained for the carbon chemical shift tensors in I and II are very similar and are consistent with both *ab initio* chemical shielding calculations and previous experimental determinations in peptides. The nitrogen chemical shift tensors in I and II have been unambiguously determined by utilizing two different dipolar-chemical

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(70) Jameson, C. J.; Jameson, A. K.; Oppusunggu, D.; Wille, S.; Burrell, P. M.; Mason, J. *J. Chem. Phys.* **1981**, *74*, 81–88.

(71) (a) Bouman, T. D.; Hansen, Aa. E. *Chem. Phys. Lett.* **1992**, *197*, 59–66. (b) van Wüllen, Ch.; Kutzelnigg, W. *Chem. Phys. Lett.* **1993**, *205*, 563–571. (c) Gauss, J. *J. Chem. Phys.* **1993**, *99*, 3629–3643.

(72) See for example: (a) Schindler, M. *J. Am. Chem. Soc.* **1987**, *109*, 5950–5955. (b) Bouman, T. D.; Hansen, Aa. E. *Int. J. Quantum Chem.* **1989**, *23*, 381–396.

(73) *SYBYL Molecular Modelling Software*; Tripos Associates Inc., St. Louis, MO, 1989.

shift NMR experiments for each species. Both the experimental and theoretical results reveal considerable variations in both the orientation of the nitrogen CS PAS in **I** and **II** and the magnitudes of the three principal components. These variations appear to originate primarily from differences in the orientation of the *N*-phenyl substituent with respect to the amide plane, thereby affecting the extent of nitrogen π-electron delocalization in these systems. IGLO calculations of the nitrogen chemical shielding tensor in **I** as a function of orientation of the aromatic ring plane with respect to the amide plane reinforce this argument. These findings are in concordance with the well-known nitrogen deshielding effect that results from *N*-phenyl substitution in amides and provide further insight into the origin of this effect. Finally, the results of the present study illustrate the significance of intermolecular N–H- -O=C hydrogen bonding on both the carbonyl carbon and nitrogen chemical shielding tensors of the amide fragment. Clearly, it is imperative that the influence of this interaction be modeled when employing theoretical techniques to supplement solid-state NMR measurements of these shielding tensors.

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