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Effects of Hydrogen Bonding in the Calculation of ^{15}N Chemical Shift Tensors: Benzamide

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In a recent paper the principal values of the ^{15}N chemical shift tensor in benzamide have been reported.[1] The tensor principal values have been measured using the dynamic nuclear polarization (DNP) experiment and also by cross polarization (CP) in a static sample of ^{15}N-benzamide at room temperature. Both experimental approaches produce very similar principal values. The values obtained by fitting the CP static spectrum with the Powder method[2] are the following: $\delta_{11} = -176$ ppm, $\delta_{22} = -321$ ppm, and $\delta_{33} = -326$ ppm. These values are referenced to an external sample of nitromethane and yield an isotropic shift value of -274 ppm, which is close to the -271.5 ppm MAS (Magic Angle Spinning) value and the liquid values of -278.4 ppm in DMSO and -282 ppm in CDCl$_3$, from the literature.[3] Because the measurements were done in a disordered sample no information was available on the orientation of the principal components and only reliable quantum chemical calculations of the tensor would allow these assignments to be made.[4]

The near degeneracy of the δ_{22} and δ_{33} principal components (~5 ppm) in benzamide is difficult to explain *a priori*, and preliminary calculations failed to predict this trend in the principal values even though the predicted isotropic shift is near the experimental value. Relatively little is known about ^{15}N chemical shift tensors or their principal values,[5,6] but there are a number of principal tensor values in amines and amides that have been reported in the literature. Unfortunately the inspection of these values shows tensor patterns with sizable differences between the δ_{22} and δ_{33}. For instance the difference is 44 ppm in L-asparagine monohydrate and 41 ppm in *N*-acetylglycine. The solid state isotropic shift value in benzamide, which is close to the liquid values, also would indicate that intermolecular effects should not be a relevant factor in the determination of the ^{15}N chemical shift tensor. In this communication we present new quantum chemical calculations including the hydrogen bond (HB) interactions that explain the experimental measurements of the ^{15}N chemical shifts principal values in benzamide and provide a basis for the spatial assignment of the experimental principal components.

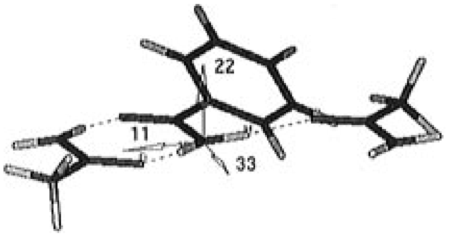

Figure 1. Molecular structure of benzamide showing the hydrogen bonding interactions with the first neighbors and the orientation of the principal axis of the ^{15}N chemical shift tensor according to the DFT calculations. The structure of benzamide and its first neighbors, where the phenyl group has been replaced by methyl groups, was taken from the neutron diffraction study.[12] The principal components of the shift tensor are labeled in rank order, see text and Table 1.

The HF (Hartree−Fock) and DFT (Density Functional Theory) calculations were performed with the Gaussian 94 computer program.[7] All calculations employed the GIAO[8] (Gauge Invariant Atomic Orbitals) method with Dunning D95** basis sets,[9] which include polarization functions. The DFT calculations use the BLYP exchange correlation functional[10] and a coupled perturbative scheme without including the magnetic field effects in the exchange correlation functional.[11] The HF and DFT calculations of the chemical shieldings on the isolated molecule were done for optimized geometries, completed with the same basis set, and for the 123 K experimental structure from the neutron diffraction study by Gao et al.[12] To include the effects of the HB in the calculations we have included in the molecular model the amide groups of the two first neighboring molecules of benzamide. This was done using the distances and angles between the benzamide and its first neighbors from the diffraction study and replacing the phenyl group by a methyl group to simplify the calculations. The corresponding structure is shown in Figure 1. The calculated chemical shieldings were converted to the shift scale by subtracting the shielding values from the absolute shielding value of nitromethane, -135.8 ppm, obtained from the literature.[13]

The calculated values for both the isolated molecule and the hydrogen bonded species are presented in Table 1. All the calculated values using the isolated molecule model fail to reproduce even the qualitative features of the experimental tensor pattern, but the DFT calculations for both the optimized and the neutron diffraction (ND) structures reproduce within reason (i.e. ~20 ppm) the isotropic value of the chemical shift. When the HB interactions are included in the calculations there is a dramatic effect of up to 30−40 ppm in the tensor components. This change exhibits similar trends when using both the HF and the DFT methods in the calculations and its magnitude is highly anisotropic. The change in the isotropic value is smaller than that in the individual components as a consequence of the component averaging as well as the opposing movement of individual components. While δ_{11} and δ_{33} increase, δ_{22} decreases with HB formation involving neighboring molecules.

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Table 1. Comparison of the Experimental and Calculated ^{15}N Chemical Shift Principal Values in Benzamide Using Different Computational Methods[a]

method	δ_{11}	δ_{22}	δ_{33}	δ_{iso}
optimized structure (HF)	−250	−330	−401	−327
optimized structure (DFT)	−227	−304	−367	−299
ND structure (HF)	−239	−324	−381	−315
ND structure (DFT)	−223	−302	−357	−294
ND structure + HB (HF)	−197	−334	−359	−297
ND structure + HB (DFT)	−180	−311	−322	−271
experimental[b]	−176	−321	−326	−274

[a] All values in ppm referenced to nitromethane (see text). According to the calculations the principal components are approximately oriented as follows: δ_{33} along the C−N bond, δ_{22} perpendicular to the C−NH_2 plane, and δ_{11} in the C−NH_2 plane and perpendicular to the C−N bond. Their actual orientation according to the DFT calculations using the ND structure with the corresponding HB is shown in Figure 1. [b] From ref 1.

Without more extensive corresponding data for other molecules it is difficult to establish any general rule for the HB effects on ^{15}N chemical shifts tensors; however it is noted that the components that become less shielded, δ_{11} and δ_{33}, are approximately in the plane of the HB interaction, while the component nearly perpendicular to this plane, δ_{22}, becomes more shielded. The opposing HB effect on δ_{22} and δ_{33} makes them nearly degenerate thereby explaining the experimental features unique to this tensor.

The results presented in this communication highlight the importance of including HB and, in general, intermolecular interactions in the calculation on ^{15}N chemical shifts tensors. This has been observed before in a previous study of the ^{15}N chemical shifts tensors of uracil[14] but it appears that the magnitude of the effect is greater for an amide nitrogen than for the aromatic nitrogens in uracil. Further evidence of the importance of including intermolecular interactions in the calculation of ^{15}N chemical shifts tensors can be found in a recent study of these tensors in a series of heterocycles.[15] For these compounds the RMS between experimental and calculated values, which do not include intermolecular effects, is approximately 30−40 ppm. The large RMS value is comparable with the values obtained here when the HB is neglected and almost one order of magnitude larger than the RMS obtained when the HB is included in the calculations. This may indicate that the findings presented here are not limited to benzamide, but are a general feature in the calculation of ^{15}N chemical shift tensors. The extreme sensitivity observed in the tensor components from HB indicates that the study of ^{15}N tensor components may be used to complement the determination of the tertiary structures of molecules of biological significance in solid state samples and/or in frozen solutions. It is well-known that the HB is the principal governing factor in the tertiary structure of biomolecules, therefore the extremely high sensitivity of the ^{15}N tensor components to these interactions makes ^{15}N tensors premier indicators of biomolecular structure and portends high value for these NMR methods. Finally, due to the high sensitivity and specificity of tensors, this work emphasizes some of the advantages of measuring tensor components instead of the traditional isotropic values.

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