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Influence of Intermolecular Interactions on the ^{13}C NMR Shielding Tensor in Solid α-Glycine

Vladimir G. Malkin,*,[†] Olga L. Malkina,[‡] and
Dennis R. Salahub

Département de Chimie et Centre d'Excellence sur la
Dynamique Moléculaire et Interfaciale
Université de Montréal, C.P. 6128 Succursale centre-ville
Montréal, Québec, Canada H3C 3J7
Centre de Recherche en Calcul Appliqué, 5160, boulevard
Décarie, bureau 400, Montréal, Québec, Canada H3X 2H9

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NMR is currently one of the most powerful tools for investigating biological structures both in the solid state and in solution. One of the necessary conditions for future progress in the field is theoretical insight into the nature of the dependence of NMR shielding tensors on the geometrical and electronic structure of the system. Despite significant recent progress in this direction,[1−3] pertinent applications have been made at the Hartree−Fock (HF) level of theory only and did not include the effects of electron correlation. Even at the HF level, the study of a system with more than about 400 basis functions is impractical (see ref 2) and, taking into consideration electron correlation using post-HF approaches, would impose even stricter limitations on the size of the system.

The cheapest way to include electron correlation is via density functional theory (DFT).[4] A sum-over-states density functional perturbation theory (SOS-DFPT) approach to NMR shielding tensor calculations has recently been developed and applied to a wide variety of systems.[5] The SOS-DFPT approach (using the Loc.1 approximation) is superior to the conventional uncoupled DFT method for calculating NMR chemical shifts[5−7] (in ref 5 we call the uncoupled DFT method the zero-order approximation) for systems with double and triple bonds and other systems where the HOMO−LUMO gap is rather small.

In this Communication, we illustrate the potential of the SOS-DFPT approach in a biochemical context by calculating the influence of intermolecular interactions on the shielding tensor of solid glycine. For complex systems such as this, the use of DFT may allow one to reduce the risk associated with the use of restricted physical models and/or the neglect of correlation, which is included in DFT as a matter of course, through the exchange correlation function.

We have chosen to study solid α-glycine because its structure is well established by neutron diffraction[8] and it has been the subject of intensive experimental NMR investigations.[9−11] Hence, direct comparisons with experiment can be made, without questions of solvent effects, etc., that cloud recent studies[2] of protein structure (in solution). In solid α-glycine, the molecule is in the zwitterion form.[8] The crystal structure is formed by double layers of glycine molecules connected by hydrogen bonds involving the charged subunits of the zwitterions. The dipolar glycine molecules are connected by short O···H bonds (1.728 and 1.832 Å) within a layer and relatively long hydrogen bonds (2.121−2.453 Å) between layers.

The main purpose of our work was to elucidate the influence of these hydrogen bonds on the components of the glycine carboxyl ^{13}C chemical shift tensor. Although we will also give results for the methylene carbon and for the nitrogen nucleus, we focus on the carboxyl carbon since it provides the most sensitive probe of the intermolecular interactions. We have calculated the principal components of the glycine carboxyl ^{13}C chemical shift tensor for a single molecule (Figure 1a) and for model clusters containing a central glycine molecule and fragments of zwitterions (or whole zwitterions) involved in hydrogen bonding with it (Figure 1b−d). In contrast to the study of de Dios, Laws, and Oldfield,[3] we have chosen to retain the molecular structure in the zwitterion fragments, rather than to use point charges. The goal of our work was not to examine the longer range interactions, where point charges would clearly be adequate, but rather to examine a series of models which elucidate the effects of the most important local interactions.

The clusters in Figure 1b,d simulate the hydrogen bonding within one layer of the crystal, whereas the cluster in Figure 1c includes two glycine molecules from the same layer and two fragments $(NH_4)^+$ simulating the NH_3^+ groups of glycine molecules in the layers above and below. For all the clusters we used the experimental geometries of solid α-glycine[8] (except for the additional "dummy" hydrogen atoms in NH_4^+ and O_2CH^-, simulating the rest of the molecule and positioned along the N−C or C−C bond at distances $R_{N-H} = 1.04$ Å and $R_{C-H} = 1.09$ Å, respectively.

All the calculations have been carried out with the deMon NMR program, which uses the SOS-DFPT approach[5] in conjunction with the deMon Kohn−Sham program.[12] The Loc.1 approximation,[5] the Perdew−Wang-91 exchange correlation potential,[13] and the IGLO-II[14] basis set were used. The calculated principal components of the ^{13}C chemical shift tensor δ_{ii} are given relative to liquid benzene by the formula $\delta_{ii} = \sigma_{ii} - \sigma_{iso}(C_6H_6)$. The value $\sigma_{iso}(C_6H_6)$ was obtained from the calculated ^{13}C shielding constant in an isolated benzene molecule, 62.9 ppm, by adding the gas−liquid shift of ca. 1 ppm.[15]

Chemical shift tensors were calculated for all the atoms of the structures a−d. As mentioned above, the carboxyl ^{13}C chemical shift tensor is very sensitive to intermolecular interactions, and it changes dramatically from structure a to d. Since the methylene ^{13}C chemical shift tensors vary relatively little (compared with the variations for the carboxyl carbon) in structures a−d ($\delta_{iso} = 86.9$, $\delta_{11} = 66.4$, $\delta_{22} = 81.3$, and $\delta_{33} = 112.9$ ppm for structure a; $\delta_{iso} = 79.1$, $\delta_{11} = 54.6$, $\delta_{22} = 79.2$, and $\delta_{33} = 103.4$ ppm for structure d; experimental values are $\delta_{iso} = 82.3$, $\delta_{11} = 61.6$, $\delta_{22} = 83.7$, and $\delta_{33} = 101.7$ ppm[9]) and the difference in the calculated nitrogen chemical shifts for structures a and d is also relatively small (8.8, 9.5, 11.0, and 5.9 ppm for δ_{iso}, δ_{11}, δ_{22}, and δ_{33}, respectively), only the results

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[†] Present address: Institute of Inorganic Chemistry, Slovak Academy of Sciences, SK-84236 Bratislava, Slovakia.

[‡] Present Address: Computer Center, Faculty of Science, Comenius University, Mlynska dolina CH-1, SK-84215 Bratislava, Slovakia.

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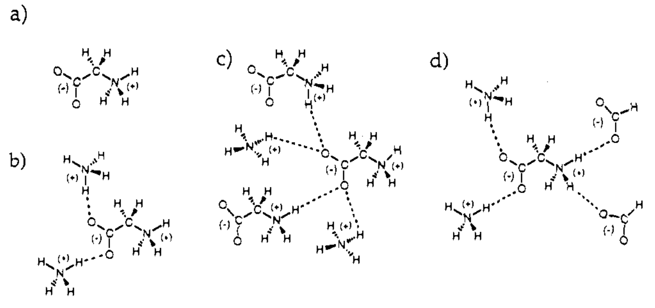

Figure 1. Glycine molecule and the clusters simulating the hydrogen bonding of the glycine molecule with its neighbors. For more details, see explanation in the text.

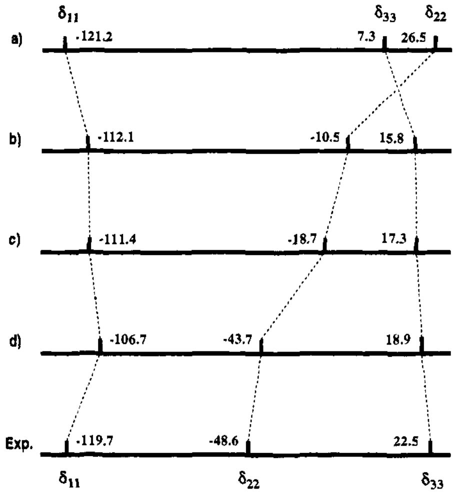

Figure 2. Comparison between the principal components of the glycine carboxyl ^{13}C chemical shift tensor (ppm with respect to liquid benzene) calculated with the SOS-DFPT approach and experimental data.[9]

for the carboxyl carbon are discussed below. The principal components of the glycine carboxyl ^{13}C chemical shift tensor (in ppm with respect to liquid benzene) are compared with experimental data[9] in Figure 2. The principal axes were labeled as in the experimental work[9] (δ_{11} is close to the bisector of the OCO angle, δ_{33} is close to perpendicular to the CO_2 plane, and δ_{22} is orthogonal to δ_{11} and δ_{33}).

The calculated values of δ_{iso}, δ_{11}, δ_{22}, and δ_{33} for a single glycine zwitterion (Figure 2a) (−29.1, −121.2, 26.5, and 7.3 ppm) are in poor agreement with their experimental counterparts (−48.6, −119.7, −48.6, and 22.5 ppm). The wrong order of δ_{33} and δ_{22} components is especially noticeable. The lack of agreement is not surprising; one expects that intermolecular hydrogen bonds involving ionic groups could have a large effect on the electronic structure of such a dipolar molecule.

As a first step on the way from a single molecule to a model appropriate for the description of the local properties of the carboxyl carbon in the solid, it is natural to include the nearest zwitterions (or at least models for their important parts) involved in the strong hydrogen bonds with the oxygen atoms of the carboxyl group. The simplest model which includes these interactions (Figure 1b) leads to significant improvement of the results and, in particular, to the correct order of the principal components (Figure 2b) ($\delta_{iso} = -35.6$, $\delta_{11} = -112.1$, $\delta_{22} = -10.5$, $\delta_{33} = 15.8$ ppm). However, the second component of the chemical shift tensor, δ_{22}, is still far from the correct value.

One might expect that a model with a more detailed description of the interactions involving these two oxygens could lead to further significant improvement of the results. Such a model has to include all hydrogen bonds touching these oxygens, that is, the two hydrogen bonds within the same layer (which were included in Figure 1b), and two hydrogen bonds with the neighboring glycine molecules from the layers above and below. As such a model we use the cluster in Figure 1c, where two entire zwitterions from the same layer and two fragments NH_4^+ from layers above and below were included.

As is seen from Figure 2, these expectations are not borne out; the results of the calculations with cluster c ($\delta_{iso} = -37.6$, $\delta_{11} = -111.4$, $\delta_{22} = -18.7$, $\delta_{33} = 17.3$ ppm) are only slightly better than those with cluster b. The "minimum" model b, which includes only the two NH_4^+ groups involved in the strongest hydrogen bonds, appears to be adequate to simulate such interactions. Moreover, these results indicate that the range of the influence of hydrogen bonding on the carboxyl ^{13}C chemical shift tensor includes the shorter hydrogen bonds (1.728 and 1.832 Å). The longer ones (2.121−2.453 Å) have a much smaller influence.

The final cluster considered here, cluster d, contains all the strongest hydrogen bonds of the "central" glycine molecule with neighboring molecules including those influencing the NH_4^+ group at the other end of the molecule. The results of our calculations for this cluster ($\delta_{iso} = -43.8$, $\delta_{11} = -106.7$, $\delta_{22} = -43.7$, $\delta_{33} = 18.9$ ppm), presented on Figure 2d, show a remarkable improvement of the principal components of the carboxyl ^{13}C chemical shift tensor relative to the previous clusters, and now good agreement with experimental data (−48.6, −119.7, −48.6, and 22.5 ppm) is obtained. We emphasize that the effects of strong intermolecular interactions can have a considerable range within the molecule; in this case the electronic perturbation is transmitted through three bonds to the carboxyl carbon: C−C−N−H! Of course, the other atoms in this pathway are also affected, but their shielding tensors are much less sensitive than those for the carboxyl carbon (the largest shift in principal components does not exceed 5 ppm between models b and d for the methylene carbon. Negative ions are typically more polarizable than neutral or positively charged fragments). The orientations of the principal components also agree well with experiment: the angle between δ_{11} and the bisector of the O−C−O angle is 3.7°, 0.2°, 8.0°, and 7.3° for structures a−d, respectively (the experimental value is ~3°[9]; the deviation of δ_{33} from the perpendicular to the O−C−O plane is 5.5°, 4.2°, 3.4°, and 2.1° for these structures (the experimental value is ~3.3°[9]).

The above analysis clearly demonstrates the influence of the various intermolecular interactions on the shielding tensor components. The overall agreement is compelling and approaches quantitative accuracy. For example, the error in δ_{iso} is 4.6 ppm for the carboxyl carbon and 3.2 ppm for the methylene carbon. As a point of comparison, an average discrepancy of 19 ppm was found in the recent HF study[3] of models of L-threonine and L-tyrosine. It is possible that correlation effects[16] and/or the point charge model may contribute to the error, in addition to the small basis set (as noted by the authors).

Although our results for cluster d are in pleasant agreement with experimental data, there remains some discrepancy between the calculated and experimental values. This is not surprising since solid α-glycine contains dipolar molecules, and hence, the long-range electrostatic fields could have a noticeable effect on the principal components of the chemical shift tensor. Taking such effects into account is straightforward (see refs 2 and 3 and references cited thereby) but is left for future study. However, our present results indicate that the electrostatic field effects beyond those included in our zwitterion model d are unlikely to have an overriding effect. The dominant effects are due to the shortest, and therefore strongest, hydrogen bonds at both ends of the molecule.

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