A Solid-state ^{17}O NMR Study of β-Glycine: High Sensitivity of ^{17}O NMR Parameters to Hydrogen-bonding Interactions

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We will present a solid-state ^{17}O NMR study of β-glycine and demonstrate that ^{17}O NMR parameters are highly sensitive to the local molecular structures, in particular, hydrogen-bond environments, indicating that, potentially, solid-state ^{17}O NMR is a powerful tool for investigating the polymorphs of drugs.

Solid-state ^{17}O NMR spectroscopy has attracted the attention of researchers for biological applications.[1–4] One of the advantages using solid-state NMR is that NMR parameters are generally described by second-rank tensors, which are tightly related to the local electronic structures. In biological solids, the obtained ^{17}O NMR parameters are chemical shielding (CS) and electric-field-gradient (EFG) tensors. More specifically, ^{17}O CS tensor components (δ_{11}, δ_{22}, and δ_{33}), quadrupole coupling constant (C_Q) and asymmetry parameter (η_Q), and the Euler angles (α, β, and γ) can be extracted from the analysis of stationary ^{17}O NMR spectra. The Euler angles represent the relative orientations between the ^{17}O CS and EFG tensors.[5] In particular, ^{17}O NMR tensors are attractive since the range of ^{17}O CS tensors, for example, are distibuted around ca. 1500 ppm from urea to aldehyde, which makes it possible to probe the local molecular strctures in details. In this communication, we will present a solid-state ^{17}O NMR study of β-glycine and demonstrate that, compared to the ^{17}O NMR tensors for γ-glycine previously determined,[6] ^{17}O NMR parameters are highly sensitive to hydrogen-bond environments. This work is part of a systematic investigation of amino acids, peptides, and proteins by solid-state ^{17}O NMR performed at RIKEN Genomic Sciences Center.

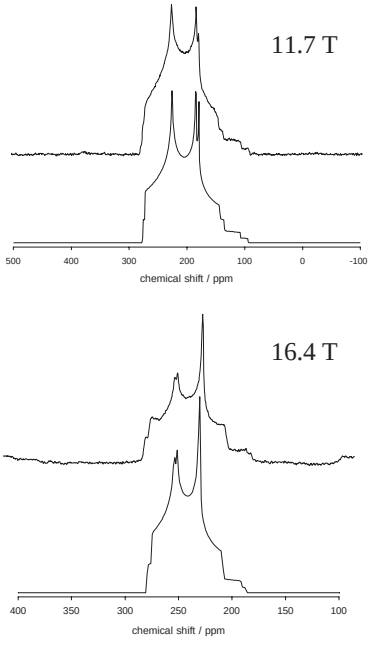

Figure 1. Experimental and theoretical ^{17}O MAS NMR spectra for [^{17}O]-β-glycine, observed at (upper) 11.7 and (lower) 16.4 T with sample spinning frequencies of 12.40 ± 0.04 and 13.34 ± 0.01 kHz, respectively.

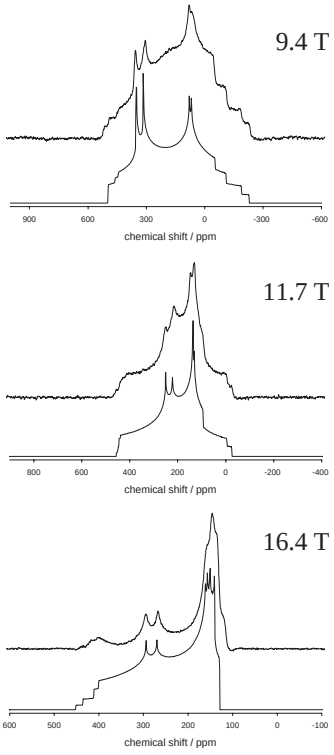

Figure 2. Experimental and theoretical ^{17}O stationary NMR spectra for [^{17}O]-β-glycine, observed at (upper) 9.4, (middle) 11.7, and (lower) 16.4 T.

Detailed procedures for preparing [^{17}O]-glycine have been described elsewhere.[7] $H_2{}^{17}O$ (90 atom %, purchased from TAIYO NIPPON SANSO) was used for the present enrichment procedure. Before and after ^{17}O NMR experiments, powder X-ray diffraction was run on a Rigaku RINT 2200V diffractometer using Cu Kα radiation. From the diffraction patterns (data not shown) recorded from $2\theta = 3.00^\circ$ to $2\theta = 50.00^\circ$, the space group of the present compound was confirmed to be $P2_1$ ($Z = 2$, $a = 5.0932$, $b = 6.272$, $c = 5.3852$ Å, $\beta = 113.19^\circ$). All the ^{17}O NMR experiments were performed on a Chemagnetics Infinity-400 spectrometer and JEOL ECA 500 and 700 spectrometers operating at frequencies of 54.24, 67.80, and 94.91 MHz, respectively. The pulse power for ^{17}O was typically

Table 1. Experimental ^{17}O CS, EFG tensors, and Euler angles for β-glycine and γ-glycine[a]

	δ_{11}	δ_{22}	δ_{33}	δ_{iso}	C_Q	η_Q	α	β	γ
β-Glycine									
Site-A	470(8)	318(8)	67(8)	285(2)	7.48(8)	0.48(4)	0(4)	90(4)	154(4)
Site-B	468(8)	318(8)	54(8)	280(2)	7.10(8)	0.50(4)	0(4)	90(4)	147(4)
γ-Glycine[b]									
O1	465(5)	310(5)	65(5)	280(2)	7.3(1)	0.42(4)	0(4)	90(4)	145(4)
O2	460(5)	285(5)	71(5)	272(2)	6.7(1)	0.62(4)	0(4)	90(4)	149(4)

[a]Errors in the last digits are given in parentheses; chemical shift in ppm, C_Q in MHz, angle in degrees. [b]Ref 6. Note that the errors are re-estimated.

180–220 kHz. An external sample of liquid water was employed for chemical shift referencing. The number of scans for the MAS and the stationary NMR experiments were approximately 1200 and 12000–30000, respectively. Spectral simulations were performed on a Pentium IV personal computer (3.00 GHz, 1 Gb memory, 200 Gb disk space) using the program developed by the authors on MATLAB (The MathWorks, Inc.). Figure 1 shows the experimental and simulated ^{17}O MAS spectra for [^{17}O]-β-glycine recorded at (upper) 11.7 and (lower) 16.4 T. In the spectral simulations, it was assumed that there are two carboxylate oxygen sites (sites A and B) since it exists in the zwitterionic form, and each simulated spectrum was a sum of sites A and B subspectra. The analysis of the ^{17}O MAS spectra yielded the following parameters: site A, $\delta_{iso} = 285 \pm 2$ ppm, $C_Q = 7.48 \pm 0.08$ MHz, $\eta_Q = 0.48 \pm 0.04$; site B, $\delta_{iso} = 280 \pm 2$ ppm, $C_Q = 7.10 \pm 0.08$ MHz, $\eta_Q = 0.50 \pm 0.04$. Figure 2 shows the experimental and calculated ^{17}O stationary NMR spectra for the [^{17}O]-β-glycine recorded at (upper) 9.4, (middle) 11.7, and (lower) 16.4 T. Generally, ^{17}O stationary NMR spectra of biological solids exhibit so complicated line shapes. In the present work, however, ^{17}O NMR tensors can be unambiguously obtained from the analysis of line shapes recorded at multiple magnetic fields simultaneously. All the ^{17}O NMR parameters obtained are summarized in Table 1.

It is interesting to compare the present results with the ^{17}O NMR tensors previously reported for γ-glycine[6] together with the intermolecular hydrogen bonds (see Table 1 and Figure 3). At a glance, it can be seen that the local H-bonding interactions are different between the glycine polymorphs. It has been established that the values of both ^{17}O δ_{iso} and C_Q tend to decrease when the oxygen atoms are involved in stronger H-bonding environments, from which spectral assignments can be achieved. Unfortunately, however, the crystal structure of β-glycine[8a] indicates that O1 and O2 have similar H-bonding environments, and the experimental error bars are relatively large. As a result, it is dangerous to conclude the spectral assignment at the present time. Nevertheless, it is important to point out that the values of δ_{iso} and C_Q, for example, are still different between the two oxygen atoms. Moreover, it can be clearly observed from Table 1 that there are differences in the ^{17}O NMR parameters between the glycine polymorphs. Therefore, it is different molecular structures including H-bonding environments and intramolecular interactions such as the electric charges of NH_3^+ groups that exhibit significant variations for the magnitudes of ^{17}O NMR tensors.

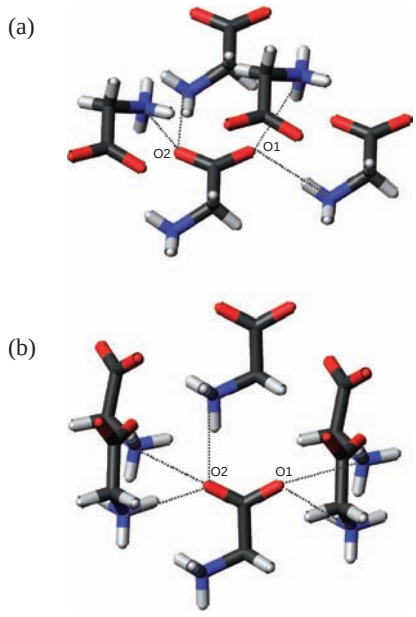

Figure 3. Hydrogen-bonding structures and atomic labels for (a) β-glycine[8a] and (b) γ-glycine.[8b]

In summary, we have presented the first experimental determination of the ^{17}O NMR tensors for β-glycine, which are different from those of γ-glycine. The magnitudes of ^{17}O CS and EFG tensors are sensitive to the local molecular structures. It is expected that the present results for carboxylate functional groups in amino acids are also relevant to the situations in other functional groups, which will establish a foundation for future solid-state ^{17}O NMR studies for polymorph studies.

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