Frequency-swept solid-state ^{33}S NMR of an organosulfur compound in an extremely low magnetic field

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ABSTRACT.

Frequency-swept solid-state ^{33}S nuclear magnetic resonance (NMR) spectra of a ^{33}S -enriched organosulfur compound, $[^{33}\text{S}]$ -diphenyl disulfide, are presented. The NMR spectra were acquired at extremely low magnetic fields, 0.06 and 0.10 T, which correspond to Larmor frequencies of 0.1959 and 0.3265 MHz, respectively. The quadrupole coupling constant, C_Q , and the asymmetry parameter, η_Q , for $[^{33}\text{S}]$ -diphenyl disulfide were found to be $C_Q = 43.3 \pm 1.9$ MHz and $\eta_Q = 0.70 \pm 0.20$, respectively. T_1 measurements of $[^{33}\text{S}]$ -diphenyl disulfide were performed between 60 and 300 K using nuclear quadrupole resonance signals, and a compromise observation temperature was found to be 300 K. Quantum chemical calculations were performed and the results demonstrated that the quadrupole frequencies and C_Q values were highly sensitive to the changes in dihedral angles of disulfide bonds.

INTRODUCTION

Sulfur is essential for life and it is well known [1] that organosulfur compounds play important roles in a variety of biological activities. For example, sulfur-containing methionine and cysteine are two of the twenty common amino acids in the human body, and a family of organosulfur compounds such as penicillin are used as marketed and developing drugs throughout history. Organosulfur compounds are also significant in industrial chemistry [2]. Sulfuric acid has a wide range of applications including chemical synthesis, mineral processing, oil refining, and so on. Petroleum and natural gas, which are formed from ancient decomposed organisms, contain many kinds of organosulfur compounds, and their efficient removal is an urgent topic in chemical engineering.

Solid-state sulfur-33 (^{33}S) nuclear magnetic resonance (NMR) is expected to become one of the most powerful tools for investigating the chemical properties of organosulfur compounds. However, despite this importance, there has been little research concerning solid-state ^{33}S NMR of organosulfur compounds. This is not surprising because the unfavorable nuclear properties of ^{33}S ($I = 3/2$, natural abundance = 0.75 %, $g = 2.055 \cdot 10^7 \text{ rad T}^{-1} \text{ s}^{-1}$, $Q = -5.5 \cdot 10^{26} \text{ m}^{-2}$) have made ^{33}S NMR experiments rather difficult. Although low sensitivity problems, which arise from the low Larmor frequency and natural abundance, may be overcome by ^{33}S -isotope enrichment using organic synthesis, the large quadrupole interactions, which depend on the molecular symmetry, potentially preclude NMR measurement. In general, inorganic compounds, in which molecular symmetry is high, tend to have relatively small quadrupole interactions, while organosulfur compounds have much larger interactions, which broaden the spectral width.

Traditionally, there have been two ways to record broadened NMR spectra, i.e., frequency- and field-swept types of NMR experiments. Recently, our group reported a field-swept solid-state ^{33}S NMR method for a compound forming covalent bonds. The merit of this method is that there is no limitation of spectral width [3]. This implies that almost all of the quadrupole nuclei in the periodic table could be measured as long as a sensitivity issue is resolved. Conversely, O'Dell *et al* [4] demonstrated the usefulness of a frequency-swept NMR method combined with a higher magnetic field, 21.1 T. Although it was proven that solid-state ^{33}S NMR spectra with extremely wide spectral widths could be successfully recorded, the authors stated in their conclusion: *It seems probable that other experimental NMR approaches, such as the indirect detection of ^{33}S via more amenable spin-1/2 nuclei such as ^1H or ^{13}C , could provide a more realistic route to the study of sulfur in organic or biological molecules.* For organosulfur compounds, the spectral width of solid-state ^{33}S NMR spectra is typically expected to be more than several megahertz even when using the highest magnetic field that is currently commercially available (~ 23.5 T). Because it may be difficult to constantly adjust the tuning and matching of the LC circuit over a wide range of observation frequencies, it is much better, in a practical sense, for spectral width to be narrower in order to avoid line-shape distortions. In this paper, we present, as an alternative to the current methods of solid-state ^{33}S NMR for organosulfur compounds, a new type of frequency-swept solid-state ^{33}S NMR that uses an extremely low magnetic field (~ 0.10 T). The advantage of the present method is that spectral width is expected to be much narrower than that at higher magnetic fields; that is, the experimental conditions become much closer to those of quadrupole nuclear resonance (NQR) experiments where a sharp signal is generally observed. The ^{33}S -enriched organosulfur compound, [^{33}S]-diphenyl disulfide, is newly synthesized and we briefly discuss the relation

between ^{33}S NMR parameters and the dihedral angles in disulfide bonds on the basis of quantum chemical calculations.

Experimental

Samples: We followed literature procedures [5,6] for the synthesis of ^{33}S -enriched diphenyl disulfide and its precursor, thiophenol. For thiophenol, phenylmagnesium chloride (2 mol/L in THF, 10.0 mL, 20.0 mmol) was added to a suspension of powdered sulfur $\alpha\text{-S}_8$ (0.40 g, 12.5 mmol) in dry THF (15.0 mL) at 0 °C, and the reaction mixture was stirred for 3 h at 60 °C. The solution was again cooled in an ice bath, and an aqueous solution of HCl (1 N, 25 mL) was added. The organic layer was washed with water and then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The obtained thiophenol (1.16 g, 10.5 mmol) was used in the subsequent step without further purification. For diphenyl disulfide, a round-bottom flask was charged with 1.5 mL of 30% H_2O_2 (13.2 mmol) and tetrabutylammonium iodide (10.0 mg, 0.27 μmol). The thiophenol (1.16 g, 10.5 mmol) was added to this solution at room temperature. After 1 h of vigorous stirring, the products were extracted with ethyl acetate. The combined organic phases were then dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the corresponding disulfides. The crude product was further purified by column chromatography eluting with EtOAc/hexane (1/1, v/v), to obtain diphenyl disulfide (784 mg, 3.59 mmol, 57.6%) as a yellow crystal. m.p. 50 °C–51 °C (lit. 59 °C–61 °C); ^1H -NMR (400 MHz, CDCl_3 , 298 K): δ (ppm), 7.20–7.40 (*m*, 6H), 7.48–7.57 (*d*, $J = 7.58$ Hz, 4H).

^{33}S NMR measurements: Approximately 20 mg of ^{33}S -enriched diphenyl disulfide was packed into a polypropylene tube (4.4 mm o.d.) and both ends were sealed with an epoxy-based adhesive under shaded conditions. The sample was then analyzed in ^{33}S NMR and NQR experiments with NMR equipment constructed in-house that used a super-heterodyne pulsed NMR spectrometer with a quadrature amplitude modulation (QAM) modulator. This equipment has been reported previously [3]. Solid-state ^{33}S NMR experiments were carried out at 0.06 and 0.10 T, which

correspond to the Larmor frequencies of 0.1959 and 0.3265 MHz, respectively. The error range of the strength of the external magnetic field was estimated to be ± 0.01 T. The ranges of spectral width used in the present ^{33}S NQR and NMR experiments at 0.06 and 0.10 T were from 23.05 to 23.60 MHz, from 23.0 to 23.7 MHz, and from 22.85 to 23.85 MHz. T_1 measurements were performed from 60 to 300 K using the standard inversion recovery method using NQR signals. For example, T_1 values at 60 and 300 K were found to be 1.24 s and 34.6 ms, respectively. As a compromise experimental condition, all the solid-state NMR experiments were performed at 300 K. Spectral simulations were performed using QUEST [7] and/or the program written by the authors of MATLAB (The Math Works, Inc.).

Quantum chemical calculations: All the quantum chemical calculations for the ^{33}S chemical shielding (CS) and electric-field-gradient (EFG) tensors were performed at the B3LYP[8-10]/6-31+G**, 6-311++G**, and/or cc-pVTZ level using the Gaussian03W program package [11] on a laptop PC. The gauge-induced atomic orbital approach [12,13] was used for the CS calculations, and $Q = -6.78 \text{ fm}^2$ [14] was employed in all EFG calculations. The geometry of diphenyl disulfide, as determined by X-ray diffraction [15], was used for all the calculations, and the two inequivalent sulfur sites in the compound were treated as a single sulfur site in this work since the differences in the calculated NMR parameters were very small.

Results and discussion

A typical ^{33}S NQR or zero-field NMR spectrum of diphenyl disulfide, acquired at 300 K, is shown in Figure 1. Two peaks, which arise from the two inequivalent sulfur atoms in the molecule, can clearly be observed in the spectrum. In general, the observed NQR frequency or quadrupole frequency, ν_Q , is expressed by

$$\nu_Q = 3C_Q \sqrt{1 + \eta_Q^2/3} / 2I(2I - 1) \quad [1]$$

and

$$C_Q = eV_{zz}Qh^{-1} \quad [2]$$

$$\eta_Q = (V_{xx} - V_{yy})/V_{zz}, \quad [3]$$

where C_Q and h_Q are the quadrupole coupling constant and the quadrupole asymmetry parameter, respectively, and V_{ii} ($i = X, Y$, and Z) is one of the three principal components of the electric-field-gradient (EFG) tensor ($|V_{xx}| < |V_{yy}| < |V_{zz}|$). The difference in the observed quadrupole frequency between the two peaks (less than approximately 55 kHz) was negligible; therefore, the following discussion focuses on a single sulfur site. The averaged quadrupole frequency was obtained as 23.361 MHz, which is close to those reported for $\alpha\text{-S}_8$ [3,4,16]. Note that h_Q cannot be determined by analyzing the NQR signals for nuclei with a spin number of 3/2, and the ^{33}S NMR measurements are essentially required to obtain h_Q . Recently, O'Dell *et al* [4] reported the usefulness of frequency-swept solid-state ^{33}S NMR combined with a higher magnetic field, 21.1 T, demonstrating that ^{33}S NMR parameters can be obtained for organic compounds or

compounds forming covalent bonds. As an alternative method, we propose frequency-swept solid-state ^{33}S NMR experiments at an extremely low magnetic field. The advantage of this methodology is that the spectral width of ^{33}S NMR spectra is expected to become narrow (less than a few megahertz), potentially offsetting any sensitivity issues caused by the lower Larmor frequencies.

Figure 2 shows the theoretical ^{33}S NMR spectra at 0.10 T with a quadrupole frequency of 23.361 MHz as a function of quadrupole asymmetry parameters. According to Equation (1), when a quadrupole frequency is experimentally determined, only one ^{33}S EFG parameter, C_Q or h_Q , is required for the spectral simulation, *e.g.*, when h_Q is zero, the value of C_Q becomes 46.723 MHz in the present case. The characteristic line-shapes, in which a doublet peak appears in the central region with a single peak on either side, can be observed without shifting the resonance frequencies. Apparently, the depth and shape of the valley in the doublet of the central region depend on h_Q , from which ^{33}S EFG parameters can potentially be determined.

The experimental and best-fit calculated ^{33}S NMR spectra of [^{33}S]-diphenyl disulfide observed at (a) 0.06 and (b) 0.10 T, which correspond to the Larmor frequencies of 0.1959 and 0.3265 MHz, respectively, are shown in Figure 3. The spectral width was experimentally limited so that only the central regions were observed for both cases. Unfortunately, the two sulfur sites could not be distinguished in the present experimental NMR spectra due to poor spectral resolution. Assuming that there was a single sulfur site, the analysis of the NMR spectra combined with quantum chemical calculations (which will be discussed later) yielded the following parameters: $C_Q = 43.3 \pm 1.9$ MHz and $h_Q = 0.70 \pm 0.20$. Note that the peaks on both

sides at 0.06 T could not be observed. This may be because tuning and matching of the NMR probe were imperfect in these frequency ranges.

Figure 4 shows the molecular structure of diphenyl disulfide determined by X-ray diffraction [ref] with atomic labeling as used in this study. The present calculated results for the ^{33}S CS tensors indicated that the span of the CS tensor, $|\mathbf{d}_{11} - \mathbf{d}_{33}|$, was approximately 320 ppm, which is safe to neglect in the spectral simulations when compared to the magnitude of the quadrupole interactions [ref]. Those for the ^{33}S EFG tensors yielded the following parameters: $C_Q = 44.9 \pm 2.7$ MHz and $h_Q = 0.73 \pm 0.02$, which were consistent with the results for the above spectral simulations. The calculated ^{33}S EFG tensor orientations, with respect to the molecular frame for diphenyl disulfide, are also shown in Figure 4. The orientations of the ^{33}S EFG tensors were essentially the same at both sulfur sites. For S1, the largest EFG tensor component, V_{zz} , was approximately perpendicular to the molecular plane (C3–S1–S2), and the smallest component, V_{xx} , was approximately 40° off the C3–S1 bond.

Note that ^{33}S EFG tensors are strongly related to the electronic properties of the ground state [17]. Therefore, there may be a strong correlation between local molecular structures, such as the dihedral angle of disulfide bonds, and the ^{33}S EFG parameters, which will be of importance for the future applications of solid-state ^{33}S NMR to biological systems or the analyses of cross-linked rubber structures. To investigate the dihedral angle dependence of ^{33}S EFG parameters, we constructed a simple model of an isolated diphenyl disulfide in which the torsion angle of C3–S1–S2–C9, ϕ , was artificially adjusted from 60° to 180° in steps of 20° . The quantum chemical calculations were performed at the B3LYP/6-31+G** level of theory and the experimental geometry [ref] was initially used for these calculations. Figure 5 indicates the

dependence of (a) quadrupole coupling constants and (b) quadrupole asymmetry parameters on the torsion angles. The EFG tensor orientations, which were consistent with those in Figure 4, were unchanged in all the cases. It can be observed that, with an increase in the torsion angles, the values of both C_Q and η_Q (data not shown) varied drastically, *e.g.*, a range in C_Q values of approximately 3 MHz. Conversely, a slight dependence of η_Q on the dihedral angles was observed. Apparently, the C_Q and η_Q values of ^{33}S are strongly related to the local molecular structures, from which the dihedral angles may be estimated. This indicates that the ^{33}S NQR experiments are potentially useful for investigating the conformation of S-S bonds in proteins or cross-linked structures of natural and synthetic rubbers since the experimental conditions of the ^{33}S NQR experiments were less stringent than those of solid-state ^{33}S NMR. Such studies are in progress in our group.

Conclusions

We presented a frequency-swept solid-state ^{33}S NMR spectra of a ^{33}S -enriched organosulfur compound, diphenyl disulfide, using low magnetic fields. The results demonstrated that the frequency-swept NMR spectra could be acquired and analyzed for the organosulfur compound at 0.06 and 0.10 T, which correspond to the Larmor frequencies of 0.1959 and 0.3265 MHz, respectively, at a temperature of 300 K. The quantum chemical calculations proved that quadrupole frequencies and quadrupole coupling constants were highly sensitive to changes in the dihedral angles of disulfide bonds. It is evident that the NMR method presented here can be applied to any ^{33}S -enriched organosulfur compounds, and the implication of the present study is that solid-state ^{33}S NMR and NQR experiments are, in addition to conventional NMR such as ^1H , ^{13}C , and ^{15}N , potentially useful as a new nuclear probe in the study of organosulfur compounds.

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FIGURE CAPTIONS

- Figure 1** A typical ^{33}S NQR spectrum of diphenyl disulfide, acquired at 300 K.
- Figure 2** Theoretical solid-state ^{33}S NMR spectra at the magnetic field of 0.10 T for the quadrupole frequency of 23.361 MHz, as a function of the quadrupole asymmetry parameter. The corresponding quadrupole coupling constant can be calculated from Equation [1].
- Figure 3** Experimental (upper trace) and best-fitted calculated (lower trace) frequency-swept ^{33}S NMR spectra of [^{33}S]-diphenyl disulfide, acquired at (a) 0.50 and (b) 0.10 T. Analyzing the NMR spectrum assuming that there was a single sulfur site gave $C_Q = 43.3 \pm 1.9$ MHz and $h_Q = 0.70 \pm 0.20$.
- Figure 4** Molecular structure of diphenyl disulfide with the atomic labeling used in this study. The ^{33}S EFG tensor orientations are also given: the V_{ZZ} component is approximately perpendicular to the molecular plane (C3–S1–S2), and the V_{XX} component is approximately 40° off the C3–S1 bond.
- Figure 5** Calculated ^{33}S quadrupole coupling constant (a) and quadrupole asymmetry parameter (b) versus the dihedral angles, C3–S1–S2–C9, for the model of diphenyl disulfide.

Figure 1. Yamada et al.

Figure 2. Yamada et al.

Figure 3. Yamada et al.

Figure 4 Yamada et al.

(a)

(b)

Figure 5. Yamada et al.

Graphical Abstract

^{33}S NMR spectra of $[^{33}\text{S}]$ -diphenyl disulfide