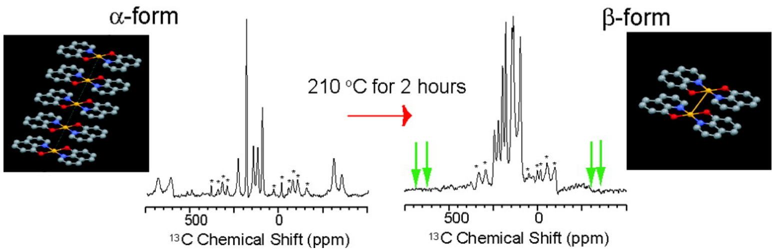
Communication

Characterization of Polymorphs and Solid-State Reactions for Paramagnetic Systems by C Solid-State NMR and ab Initio Calculations

Medhat A. Shaibat, Leah B. Casabianca, Nalinda P. Wickramasinghe,
Stephen Guggenheim, Angel C. de Dios, and Yoshitaka Ishii

J. Am. Chem. Soc., **2007**, 129 (36), 10968-10969• DOI: 10.1021/ja0703980 • Publication Date (Web): 18 August 2007



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Characterization of Polymorphs and Solid-State Reactions for Paramagnetic Systems by ^{13}C Solid-State NMR and ab Initio Calculations

Medhat A. Shaibat,[†] Leah B. Casabianca,[§] Nalinda P. Wickramasinghe,[†] Stephen Guggenheim,[‡] Angel C. de Dios,[§] and Yoshitaka Ishii*,[†]

Department of Chemistry and Department of Earth and Environmental Sciences, University of Illinois at Chicago, 845 W Taylor Street Chicago Illinois 60607, Department of Chemistry, Georgetown University, NW Washington, D.C. 20057

Received January 18, 2007; E-mail: yishii@uic.edu

Paramagnetic complexes have been widely used as drugs[1,2] and organic semiconductors[3] and as molecular devices.[4] In pharmacology, morphologies of a drug compound are known to alter the effectiveness of drugs as well as thermal stability.[5,6] In material science, polymorphs have distinctive optical and electronic properties.[7] Paramagnetic systems have been also utilized as building blocks of self-assembled nanomaterials; the supramolecular structures determine their unique properties.[8] Thus, distinguishing polymorphs or supramolecular structures in paramagnetic complexes is essential in characterizing drugs and advanced materials containing paramagnetic ions.

X-ray crystallography is the most useful technique to obtain structural information of paramagnetic systems in solids, but only for systems that can be crystallized. For noncrystalline samples, powder X-ray diffraction (PXRD) can distinguish between samples with different structures. However, the identification of polymorphs is often not trivial, especially if the PXRD patterns are similar or broad. Also, quantitative PXRD analysis can be difficult because the diffraction intensities depend on crystallite size, preferred orientations of crystallites, and other factors.[9]

Solid-state NMR (SSNMR) is a powerful method for characterizing polymorphs of diamagnetic systems including drugs.[5,10,11] In particular, ^{13}C chemical shifts obtained by magic angle spinning (MAS) are sensitive probes of molecular packing.[5,11,12] In contrast, applications of SSNMR to paramagnetic systems have been very limited, owing to large hyperfine shifts and associated line broadening. Despite previous excellent studies,[13] lack of effective methodologies has hindered high-resolution ^{13}C SSNMR for paramagnetic systems. Recently, our group developed a novel method using very fast MAS (VFMAS; spinning speed $\geq$20 kHz) to attain high-resolution ^{13}C and ^{1}H SSNMR spectra for paramagnetic systems,[14,15] and SSNMR of paramagnetic materials is gaining renewed attention in various interesting applications.[16,17]

In the present study, we discuss the possibility of distinguishing polymorphs of Cu(II) paramagnetic complexes by ^{13}C VFMAS SSNMR. We demonstrate that ^{13}C SSNMR spectra for polymorphs of paramagnetic complexes display unusually large differences in line widths and spectral positions. As an application, we demonstrate SSNMR characterization of solid-state reactions for paramagnetic systems for the first time.

To examine the possibility of distinguishing polymorphs for paramagnetic systems by ^{13}C SSNMR, we performed experiments on α- and β-forms of polycrystalline Cu(II)(8-quinolinol)$_2$ [CuQ$_2$]. CuQ$_2$ has been studied as an anti-leukemia agent,[2] and its β-form is thermally more stable.[18] As shown in the molecular structures in the insets of Figure 1a,b, the α-form exhibits an interesting molecular-chain-like supramolecular structure in (a), whereas the β-form has a dimerlike structure in (b). Figure 1a,b shows ^{13}C VFMAS SSNMR spectra of (a) α- and (b) β-CuQ$_2$. Assignments to chemical groups obtained by ^{13}C−^{1}H dipolar dephasing[14] are also displayed in (a) and (b) (see the Supporting Information (SI)). With the excellent resolution obtained by VFMAS, it is clear that the two polymorphs of this complex show significantly distinctive ^{13}C spectra. The α-form exhibits peaks displaying large hyperfine shifts at 683, 630, −301, −360 ppm, whereas the β-form has no corresponding peaks in these regions. In the region from 50 to 300 ppm, the α-form shows five lines (233, 187, 148, 124, 98 ppm), while the β-form shows seven lines (246, 222, 198, 179, 145, 137, 98 ppm). Because an α-CuQ$_2$ complex has a structure very similar to that of a β-CuQ$_2$ complex (rmsd = 0.179 Å), the significant difference in the spectral features should be attributed to paramagnetic effects. To confirm this, as shown in Figure 1c,d, we carried out ab initio calculations of the shifts[17] for six non-protonated ^{13}C (red bars) and 12 ^{13}CH (blue bars) in monomeric (c, top) α- and (d, top) β-CuQ$_2$. Although the calculated *diamagnetic* shifts show only small differences of 1.9 ppm in absolute values on average between the two forms, the two polymorphs clearly present distinctive calculated shifts of 35 ppm difference on average (see SI). This confirms that hyperfine shifts are exceptionally sensitive to small structural differences between the two polymorphs. We found that ab initio calculations for the tetramer (c and d, bottom) better reproduce the experimental shifts for α-CuQ$_2$ and for the 50−300 ppm region of β-CuQ$_2$; this indicates that intermolecular interactions notably influence the chemical shifts. In (d), more lines are predicted than in (c), reflecting that two Qs are equivalent in α-CuQ$_2$, but the symmetry is reduced in β-CuQ$_2$.[18] The calculations for the β-form (d top) monomer and (d bottom) tetramer predicted the presence of the peaks around 650 and −350 ppm, yet these

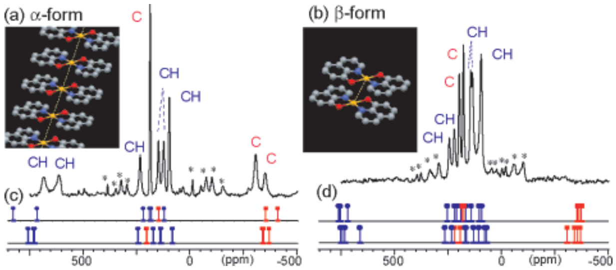


Figure 1. (a, b) ^{13}C MAS spectra of (a) α-form and (b) β-form Cu(8-quinolinol)$_2$ (CuQ$_2$) obtained at ^{13}C frequency of 100.6 MHz without decoupling under VFMAS at 20 kHz with corresponding X-ray structures.[18] The experimental time was (a) 21 min and (b) 42 min for 15 mg of the samples. Spinning sidebands are indicated by *. Atoms in the structures are color-coded: C (gray), N (blue), O (red), Cu (orange); the Cu−Cu distances are (a) 3.84 Å and (b) 3.44 Å. (c, d) Shift positions obtained by ab initio calculations for (c) α-CuQ$_2$ and (d) β-CuQ$_2$ in the (top) monomeric and (bottom) tetrameric forms. See the SI about the details of the experiments and the ab initio calculations.

[†] Department of Chemistry, University of Illinois at Chicago.
[‡] Department of Earth and Environmental Sciences, University of Illinois at Chicago.
[§] Department of Chemistry, Georgetown University.

10.1021/ja0703980 CCC: $37.00

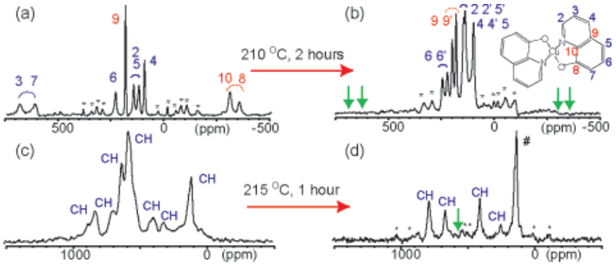


Figure 2. (a, b) ^{13}C MAS spectra of (a) α-CuQ_2 and (b) *β*-CuQ_2 obtained by heating α-CuQ_2 at 210 °C for 2 h, with ab initio-based assignments. *n* denotes the site indicated in the inset ($n = 2-10$); n' is the corresponding site in the nonequivalent Q in *β*-CuQ_2. (c, d) ^{13}C MAS spectra of (c) P-Cu(imidazole)$_2$ (Cu(Im)$_2$) and (d) B-Cu(Im)$_2$ obtained by heating P-Cu(Im)$_2$ at 215 °C for 1 h. The spinning speeds were (a, b) 20.0 kHz and (c, d) 25.0 kHz; the experimental time was (a) 21 min, (b) 86 min, and (c) 684 min, and (d) 68 min. # denotes a signal from a free imidazole.

peaks are not observed in Figure 1b presumably because of paramagnetic relaxation outlined below. Because in α-CuQ_2 the corresponding signals show considerably shorter T_2 (0.2−0.4 ms) than signals at 50−300 ppm (0.8−3.2 ms) and the *β*-form has shorter T_2 for the signals in the latter region (0.4−1.2 ms), the *missing* signals in *β*-CuQ_2 are likely to be quenched by enhanced paramagnetic relaxation. Therefore, we conclude that ^{13}C SSNMR under VFMAS provides a unique solution to distinguish polymorphs for paramagnetic systems through shifts and relaxation properties.

As an important application of the present method, we examine the possibility of characterizing solid-state reactions by ^{13}C SSNMR. Solid-state reactions of organic compounds have gained increasing attention.[19] However, characterization of solid-state reactions is often intractable, particularly when the products are not soluble or distinguishable in solution. Figure 2a,b show ^{13}C VFMAS SSNMR spectra of (a) α-CuQ_2 and (b) the product obtained by heating α-CuQ_2 for 2 h in a crucible in a sand bath maintained at 210 °C,[20] which leads to formation of *β*-CuQ_2. Comparison of Figure 2b with Figure 1b clearly suggests that the primary product of the reaction is *β*-CuQ_2. To quantify α-CuQ_2 remaining in the product, we examined the spectral regions around 650 and −350 ppm (arrows in Figure 2b), where lines affected by large hyperfine shifts are observed for α-CuQ_2. Using the spectrum in Figure 2a as a reference spectrum, we found that α-CuQ_2 in the product was under the detection limit ($\leq$5%) (see SI for additional data). Thus, the SSNMR analysis showed that the reaction yielded pure *β*-CuQ_2. Although PXRD can distinguish between two polymorphs, quantitative analysis is difficult as explained above. With the ab initio-based signal assignments, SSNMR also yields site-resolved information on chemical environments. Therefore, this SSNMR approach provides an excellent means that permits quantitative analysis of coexisting polymorphs or compounds if excitation efficiencies and relaxation effects are properly considered (see SI).

We applied this technique to characterize a solid-state reaction from amorphous-like *pink-form* (P-form) of Cu(II)(imidazole)$_2$ [Cu(Im)$_2$] to polycrystalline *blue-form* (B-form) Cu(Im)$_2$.[21] Cu(Im)$_2$ is an anticorrosion material,[22] and a model of imidazolate-bridged Cu(II) centers in the active site of superoxide dismutase (SOD).[21] Figure 2c,d shows ^{13}C VFMAS SSNMR spectra for (c) P-Cu(Im)$_2$ and (d) B-Cu(Im)$_2$ obtained by heating P-Cu(Im)$_2$ at 215 °C. On the basis of the isotropic shift positions and the line widths of ^{13}C SSNMR, one can distinguish between these two forms of Cu(Im)$_2$. The spectra span ~800 ppm, confirming that these compounds are paramagnetic materials. The line widths of P-Cu(Im)$_2$ in Figure 2c are considerably broader than those of B-Cu(Im)$_2$ in Figure 2d. The broad line widths in (c) presumably reflect disorder in the P-form, which displays broader PXRD. In (c), seven lines are identified; the line positions (822, 686, 623, 575, 387, 311, 104 ppm) are different from those in (d) (782, 661, 402, 247 ppm). The absence of the peak at 575 ppm in (d) clearly suggests that B-form is the primary product here.

In conclusion, we have demonstrated that ^{13}C SSNMR using VFMAS is a highly sensitive tool to distinguish different polymorphs or supramolecular structures of paramagnetic complexes. We also applied this technique to characterize solid-state reactions involving rearrangements of polymorphs for paramagnetic systems. Although only conversions of the polymorphs were demonstrated, it is likely that this method is applicable to other types of reactions and useful for characterization of various drugs and advanced materials.

Acknowledgment. We thank Prof. Cynthia Jameson at UIC for helpful discussion. This work was supported in part by the NSF CAREER program (CHE 449952), the Dreyfus Foundation Teacher-Scholar Program, and NIH RO1 Grant (AG028490).

Supporting Information Available: Details of sample preparation, experimental conditions, and ab initio calculations; complete ref 17b. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Farrell, N. P. *Uses of Inorganic Chemistry in Medicine*; Royal Society of Chemistry: Cambridge, 1999. (b) Zhang, C. X.; Lippard, S. J. *Curr. Opin. Chem. Biol.* **2003**, *7*, 481−489.
(2) Daniel, K. G.; Gupta, P.; Harbach, R. H.; Guida, W. C.; Dou, Q. P. *Biochem. Pharmacol.* **2004**, *67*, 1139−1151.
(3) Curry, R. J.; Gillin, W. P. *Curr. Opin. Solid State Mater. Sci.* **2001**, *5*, 481−486.
(4) Cao, Y. D.; Zheng, Q. Y.; Chen, C. F.; Huang, Z. T. *Tetrahedron Lett.* **2003**, *44*, 4751−4755.
(5) Byrn, S. R.; Pfeiffer, R. R.; Stephenson, G.; Grant, D. J. W.; Gleason, W. B. *Chem. Mater.* **1994**, *6*, 1148−1158.
(6) Datta, S.; Grant, D. J. W. *Nat. Rev. Drug Discovery* **2004**, *3*, 42−57.
(7) Curry, R. J.; Gillin, W. P.; Clarkson, J.; Batchelder, D. N. *J. Appl. Phys.* **2002**, *92*, 1902−1905.
(8) (a) Tsao, T. B.; Lee, G. H.; Yeh, C. Y.; Peng, S. M. *Dalton Trans.* **2003**, 1465−1471. (b) Zhou, H. C.; Groves, J. T. *Biophys. Chem.* **2003**, *105*, 639−648.
(9) Bish, D. L.; Reynolds, R. C. J. In *Modern Powder Diffraction*; Bish, D. L., Post, J. E., Eds.; Mineralogical Society of America: Washington, 1989.
(10) Schmidt-Rohr, K.; Spiess, H. W. *Multidimensional Solid-State NMR and Polymers*; Academic Press Inc.: San Diego, 1994.
(11) (a) Petkova, A. T.; Leapman, R. D.; Guo, Z. H.; Yau, W. M.; Mattson, M. P.; Tycko, R. *Science* **2005**, *307*, 262−265. (b) Kameda, T.; McGeorge, G.; Orendt, A. M.; Grant, D. M. J. *Biomol. NMR* **2004**, *29*, 281−288.
(12) Harper, J. K.; Facelli, J. C.; Barich, D. H.; McGeorge, G.; Mulgrew, A. E.; Grant, D. M. *J. Am. Chem. Soc.* **2002**, *124*, 10589−10595.
(13) (a) Chacko, V. P.; Ganapathy, S.; Bryant, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 5491−5492. (b) Walter, T. H.; Oldfield, E. J. *Chem. Soc., Chem. Commun.* **1987**, 646−647. (c) Brough, A. R.; Grey, C. P.; Dobson, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 7318−7327. (d) Liu, K.; Ryan, D.; Nakanishi, K.; McDermott, A. *J. Am. Chem. Soc.* **1995**, *117*, 6897−6906. (e) Crozet, M.; Chaussade, M.; Bardet, M.; Emsley, L.; Lamotte, B.; Mouesca, J. M. *J. Phys. Chem. A* **2000**, *104*, 9990−10000.
(14) Ishii, Y.; Chimon, S.; Wickramasinghe, N. P. *J. Am. Chem. Soc.* **2003**, *125*, 3438−3439.
(15) (a) Wickramasinghe, N. P.; Shaibat, M.; Ishii, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5796−5797. (b) Wickramasinghe, N. P.; Ishii, Y. *J. Magn. Reson.* **2006**, *181*, 233−243.
(16) (a) Zhang, X. M.; Zhang, C.; Guo, H. Q.; Huang, W. L.; Polenova, T.; Francesconi, L. C.; Akins, D. L. *J. Phys. Chem. B* **2005**, *109*, 19156−19160. (b) Jovanovic, T.; McDermott, A. E. *J. Am. Chem. Soc.* **2005**, *127*, 13816−13821. (c) Balayssac, S.; Bertini, I.; Lelli, M.; Luchinat, C.; Maletta, M. *J. Am. Chem. Soc.* **2007**, *129*, 2218−2219. (d) Oomomo, T.; Maruta, G.; Takeda, S. *Polyhedron* **2005**, *24*, 2431−2436.
(17) (a) Zhang, Y.; Sun, H. H.; Oldfield, E. *J. Am. Chem. Soc.* **2005**, *127*, 3652−3653. (b) Kervern, G.; et al. *J. Am. Chem. Soc.* **2006**, *128*, 13545−13552.
(18) Hoy, R. C.; Morris, R. H. *Acta Cryst.* **1967**, *22*, 476; Palenik, G. J. *Acta Crystallogr.* **1964**, *17*, 687−695.
(19) Tanaka, T.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025−1074.
(20) (a) Suito, E.; Sekido, E. *Proc. Jpn. Acad.* **1957**, *33*, 196−200. (b) Fanning, J. C.; Jonassen, H. B. *J. Inorg. Nucl. Chem.* **1963**, *25*, 29−35.
(21) Masciocchi, N.; Bruni, S.; Cariati, E.; Cariati, F.; Galli, S.; Sironi, A. *Inorg. Chem.* **2001**, *40*, 5897−5905.
(22) Gasparac, R.; Stupnisek-Lisac, E. *Corrosion* **1999**, *55*, 1031−1039.

JA0703980