Solid-State NMR for Molecular Science

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Education
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In order to elucidate functions of molecules, characterization of the molecule is the first step. There are varieties of important molecules, which are insoluble to any solvents and functional at amorphous state. Solid-state NMR enables to obtain variety of information at atomic resolution without damages of molecules and significant restrictions. Thus solid-state NMR is one of the essential tools for the characterizations of those molecules.

We have been working on methodology and hardware developments of solid-state NMR and their applications for structural biology and material science. We study characterization of membrane proteins and peptides, organic materials, natural products and synthetic polymers. Characterizations of those molecules based on solid-state NMR are under investigations through collaborations with several research groups.

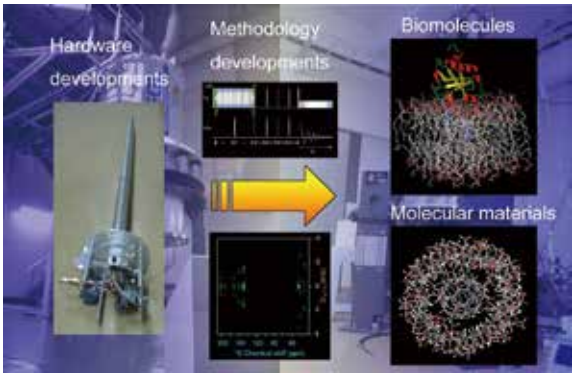

Figure 1. Outline of our studies.

Selected Publications

- N. Uekama, T. Aoki, T. Maruoka, S. Kurisu, A. Hatakeyama, S. Yamaguchi, M. Okada, H. Yagisawa, K. Nishimura and S. Tuzi, "Influence of Membrane Curvature on the Structure of the Membrane-Associated Pleckstrin Homology Domain of Phospholipase C-δ1," *Biochim. Biophys. Acta, Biomembr.* **1788**, 2575–2583 (2009).
- T. Iijima and K. Nishimura, "^{2}H Quadrupolar Carr-Purcell-Meiboom-Gill NMR for Paramagnetic Solids," *Chem. Phys. Lett.* **514**, 181–186 (2011).
- K. Yazawa, F. Suzuki, Y. Nishiyama, T. Ohata, A. Aoki, K. Nishimura, H. Kaji and T. Asakura, "Determination of Accurate ^{1}H Positions of Alanine Tripeptide with Anti-Parallel and Parallel β-Sheet Structures by High Resolution ^{1}H Solid State NMR and GIPAW Chemical Shift Calculation," *Chem. Commun.* **48**, 11199–11201 (2012).
- M. Tanio and K. Nishimura, "Intramolecular Allosteric Interaction in the Phospholipase C-δ1 Pleckstrin Homology Domain," *Biochim. Biophys. Acta, Proteins Proteomics* **1834**, 1034–1043 (2013).
- M. Yagi-Utsumi, K. Kato and K. Nishimura, "Membrane-Induced Dichotomous Conformation of Amyloid β with the Disordered N-Terminal Segment Followed by the Stable C-Terminal β Structure," *PLoS One* **11**, 0146405 (10 pages) (2016).
- N. Ousaka, F. Mamiya, Y. Iwata, K. Nishimura and E. Yashima, "'Helix-in-Helix' Superstructure Formation through Encapsulation of Fullerene-Bound Helical Peptides within a Helical Poly(methyl methacrylate) Cavity," *Angew. Chem., Int. Ed.* **56**, 791–795 (2017).

1. Extractions of Multiple Distance Information among Carbons Simultaneously from Uniformly ^{13}C Labeled Biomolecules Based on Solid-State NMR[1)]

There are number of organic materials, which are insoluble to any solvent. Solid-state NMR is one of the most powerful tools to provide molecular information for such samples at intact conditions. We have been carried out collaboration studies with many research groups for characterizations of those molecules. We have been collaborated with Prof. Tetsuro Asakura group in Tokyo university agriculture and technology during a couple of years for the characterizations of molecular structure and packing of silk fibroin using solid-state NMR and successfully reported several collaboration works at past.

In this study, applicability of a standard analysis approach developed for proton driven spin diffusion (PDSD) to dipolar assisted rotational resonance (DARR) experiment was verified to extract precise distance information simultaneously for uniformly ^{13}C labeled biomolecules. DARR spectra at several mixing times from 10 to 400 ms were acquired for [U-^{13}C] Ala tetra peptide microcrystal possessing antiparallel β-sheet structure whose atomic coordinates were determined from X-ray crystallography. Normalized cross peak intensities among coupled sites were plotted respect to the mixing times. Then the best fit curves were calculated based on two different approaches with and without considering experimentally obtained zero-quantum line shape function. The obtained distances were compared with the ones from X-ray crystallography. The obtained interatomic distances were well fit to the ones from X-ray crystallography in the range of 1.0–6.0 Å with the standard deviation of 0.244 Å, without considering the zero-quantum line-shape functions.

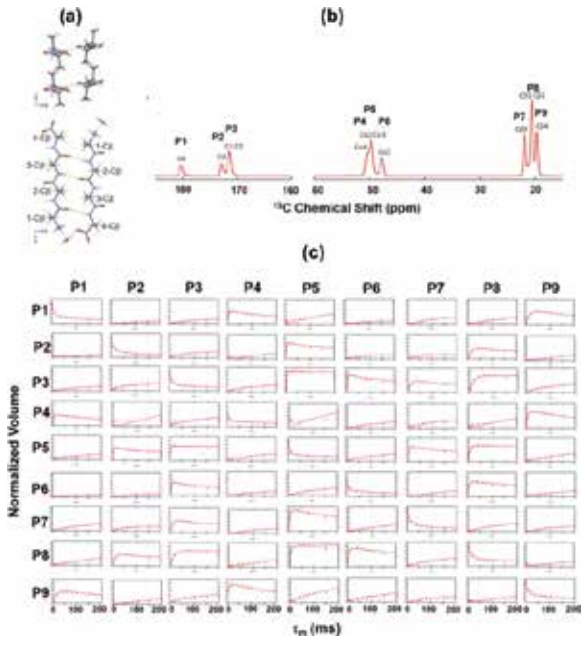

Figure 2. (a) X-ray crystallographic structure and (b) the ^{13}C CP/MAS spectrum of [U-^{13}C] AP-β-Ala_4. The bold numbers in (b) correspond to the numbers of the following matrix element numbers. (c) Build-up curves of AP-β-Ala_4 observed with DARR. The numbers shown for the peaks observed and labeled in (b).

Currently, we are also collaborating with several other research groups for characterizations of natural products, newly designed synthetic polymers, and new molecular materials, based on solid-state NMR.

2. Structural Characterization of Amyloid Peptide Oligomer Promoted on Lipid Bilayers Using Solid-State NMR

Amyloid β (Aβ) peptides exhibit random structures in solution, however after incubation, those conform insoluble amyloid fibrils, which are found in senile plaque as hallmark of Alzheimer's disease. Although, their structures have been characterized precisely, molecular mechanism of formation of the amyloid fibrils in human brain has not been clarified. Accumulated evidences strongly suggest that an initial stage of aggregation may be promoted on surface of neuronal membrane, and ganglioside GM1 specifically interacting with Aβ may play important roles for the binding of Aβ to the surface of neuronal membrane.

In current study, to clarify the contribution of GM1 in fibrillation process, we have been attempted to characterize oligomeric structure of Aβ(1-40) bound to lipid bilayers consisting of GM1 and DMPC. NMR measurements for sequential signal assignments have been completed. Currently, additional ^{13}C through space homonuclear correlation spectra are under measurements for the sample whose 4 types of amino-acid residues are selectively ^{13}C enriched to verify validity of signal assignments obtained from the analyses of various ^{13}C homonuclear and ^{13}C-^{15}N heteronuclar correlation spectra. In addition, correlation peaks among remote sites in ^{13}C through space homonuclear correlation spectra are under investigation to clarify intermolecular packing of Aβ (1-40).

Currently, we are also collaborating with other research groups for characterizations of amyloid fibrils using solid-state NMR.

Reference

1) A. Naito, K. Okushita, K. Nishimura, G. S. Boutis, A. Aoki and T. Asakura, *J. Phys. Chem. B* **122**, 2715–2724 (2018).