Solid-State NMR for Molecular Science

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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 characterization 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.

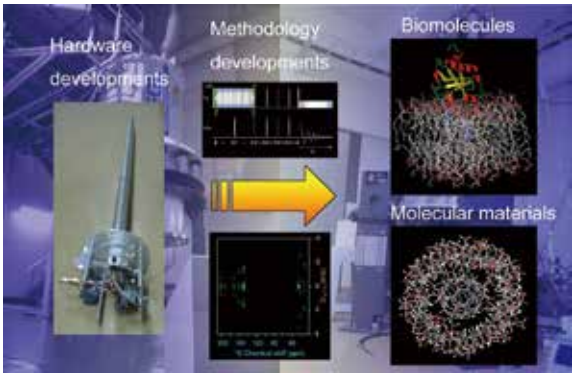

Figure 1. Outline of our studies.

Selected Publications

- J. Hu, R. Fu, K. Nishimura, L. Zhang, H. X. Zhou, D. D. Busath, V. Vijayvergiya and T. A. Cross, "Histidines, Heart of the Hydrogen Ion Channel from Influenza A Virus: Toward an Understanding of Conductance and Proton Selectivity," *Proc. Natl. Acad. Sci. U.S.A.* **103**, 6865–6870 (2006).
- 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).

1. Membrane Induced Dichotomous Conformation of Amyloid β (1-40) Bound to Lipid Bilayers[1)]

Various neurodegenerative disorders are ascribed to pathogenic molecular processes involving conformational transitions of amyloidogenic proteins into toxic aggregates characterized by their β-structure. Accumulating evidence indicate that neural cell membranes provide platforms for such conformational transitions of pathogenic proteins. Amyloid β (Aβ) is a major player in the onset and developments of Alzheimer's disease. Prof. K. Kato group in IMS has successfully determined monomeric structure of Aβ (1-40) bound to glycolipid GM1 embedded in micelles using solution NMR. However the membrane bound Aβ are not accessible with solution NMR techniques, because of its slow molecular tumbling. So we collaborate with Prof. K. Kato group to characterize Aβ oligomers induced on the surface of lipid bilayers composed of neutral lipids prior to formation of amyloid fibril using solid-state NMR.

Fully hydrated uniformly ^{13}C-, and ^{15}N isotope enriched Aβ (1-40) bound to DMPC vesicles were lyophilized immediately after preparation of sample in order to capture oligomeric state of Aβ and used for solid-state NMR measurements. Sequential signal assignments were carried out using solid-state NMR techniques of ^{13}C homonuclear scholar coupling based homonuclear correlation experiment of *constant time uniform cross peak COSY* (CT-UCCOSY) under magic angle spinning (MAS), in conjunction with ^{13}C observed *double cross polarization* (DCP) based NCO and NCA heteronuclear correlation experiments. All of observed signals were successfully assigned to C-terminal segment of Aβ (1-40) from Val_{24} to Val_{39}. Through the inspection of conformational dependent isotropic chemical shifts using TALOS-N, the conformation of C-terminal segment of Aβ (1-40) was identified to as β-structure. In order to clarify intermolecular packing of the C-terminal segment of Aβ (1-40), dipolar coupling based through-space homonuclear correlation experiments of *dipolar assisted rotational resonance* (DARR) were carried out with various mixing times up to 400 ms to obtain correlation among carbons up to 6 Å apart. The DARR spectra exhibited correlation peaks among carbons in same and adjacent residues. Therefore, intermolecular arrangement of the C-terminal segments of Aβ (1-40) was identified to as parallel β-sheet structure. The obtained structure of Aβ (1-40) bound to DMPC bilayers differs from any of reported ones such as monomer on lipids and fibrils conformed in the absence and the presence of lipids. The oligomeric structure of Aβ on DMPC bilayers suggests structural transition of Aβ from α to β is occurred at oligomeric state on lipid bilayers.

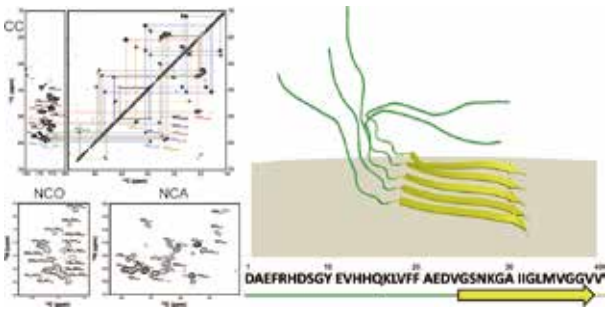

Figure 2. ^{13}C- homonuclear and ^{13}C-^{15}N heteronuclear correlation spectra of [U-^{13}C, ^{15}N] Aβ (1-40) bound to DMPC lipid bilayers acquired by solid-state NMR (right side). The proposed topology model of Aβ (1-40) bound to DMPC lipid bilayers (left side).

2. Characterizations of Organic and Inorganic Materials Based on Solid-State NMR through Observations of Natural Abundant Isotopes[2,3)]

There are a number of organic materials, which are insoluble to any solvents. Solid-state NMR is one of the most powerful tools to provide molecular information for such samples at intact conditions. Especially, for small organic molecules and polymers consisting of repeated local structures, ^{1}H and ^{13}C solid-state NMR spectra through the observations of those natural abundant isotopes retain reasonable spectral sensitivities. Combination of ultra high-field and ultra high-speed MAS also enables high-resolution spectra for ^{1}H as demonstrated in the past collaboration works.

We have been collaborated with several research groups to characterize molecular structures of various types of materials using solid-state NMR. During a year, our group contributed to provide molecular information of several molecular materials such as newly designed synthetic polymers[2)] for collaboration with Prof. Jiang group in JAIST and also inorganic materials[3)] for collaboration with Prof. Iijima group in Yamagata Univ.

Currently, we are also collaborating with several other research groups for characterization studies of natural products, newly designed synthetic polymers, functional materials and *etc.* based on solid-state NMR.

References

1) M. Yagi-Utsumi, K. Kato and K. Nishimura, *PLoS One* **11**, 0146405 (10 pages) (2016).
2) N. Huang, L. Zhai, D. E. Coupry, M. A. Addicoat, K. Okushita, K. Nishimura, T. Heine and D. Jiang, *Nat. Commun.* **7**, 12325 (12 pages) (2016).
3) T. Iijima, T. Yamase and K. Nishimura, *Solid State Nuc. Magn. Reson.* **76–77**, 15–23 (2016).