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Departmental Seminar

The conformation of Congo-red ligand bound to amyloid fibril HET-s(218-289)

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Amyloid fibrils are aggregates of repetitive β-sheets. They are related to prion diseases and diseases such as the Alzheimer's, and they also play a role in normal physiological function. Small dye molecules such as Congo red (CR) and Thioflavin are used to detect the presence of amyloid fibrils. HET-s (218-289) is an amyloid-fibril forming protein from the fungus Podospora anserina. Recently, by means of ^{13}C chemical shift perturbations it has been demonstrated that CR binds at specific sites in HET-s and causes no changes in the fibril structure.[1] The sulfonate and the amide groups on the CR molecule are proposed to form favorable electrostatic and hydrogen bonding interactions with amino acid residues on the fibril surface thus facilitating the binding.[1] However the structural changes in the conformation of CR upon binding have not been studied. The CR molecule comprises of a central biphenyl moiety, which, in the free molecule, has a rotational degree of freedom along the bond connecting the two phenyl rings. The biphenyl rings are known to adopt various torsion angles in liquids, gases and solids, which result from a cumulative effect of π−π conjugation of the rings, steric interactions and weak σ-π and π−π interactions. The torsion angle of biphenyl moieties is reported to be approximately 40° in the gas phase and 20–30° in solution.[2] The unit cell of the crystal lattice of the calcium salt of CR contains two molecules in which the biphenyl rings adapt two different torsion angles of 25° and 0°.[3] Modifications of CR at the central group or at the naphthyl rings showed lowered binding affinities to amyloids. It has been also demonstrated that CR has better affinity to amyloid staining and is also more specific to amyloids, when compared to other ligand derived from CR. The conformation of CR is crucial for complete understanding of the binding geometry and interactions of CR in HET-s(218-289). Earlier HADDOCK docking studies show a torsion angle of ~5° for the biphenyls in the CR bound to HET-s(218-289).[1] We have used solid-state NMR spectroscopy in order to directly measure the torsion angle ϕ around the central single bond between the phenyl rings in CR bound to HET-s(218-289). The angle ϕ can be inferred from anisotropic NMR interactions such as chemical shift anisotropy (CSA) and dipolar coupling. In this study we use the 2D-MAS rotor-synchronous spin-diffusion experiment to determine the torsion angle ϕ.[4-6]

References:

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(3) Ojala, W. H.; Ojala, C. R.; Gleason, W. B. Antiviral Chemistry and Chemotherapy 1995, 6, 25.
(4) A. Kentgens, E. De Boer, W. S. Veeman, J. Chem. Phys. 1987, 87, 6859–6866.
(5) R. Tycko, A. E. Berger, J. Magn. Reson. 1999, 141, 141–147.
(6) A. Hagemeyer, K. Schmidt-Rohr, H. W. Spiess, in Waugh Conference on High Resolution NMR in Solids (Ed.: S.W. Warren), MIT, Cambridge, MA, 1989, pp. 85–130

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11:30 AM (Tea/Coffee at 11:15 AM)

Seminar Hall, TCIS