MS10-O4 Targeting transthyretin amyloidosis: Joint neutron and X-ray diffraction analysis of a pathogenic protein

Ai Woon Yee[1,2], Martine Moulin[1,2], Matthew Blakeley[3], Edward Mitchell[2,4], Michael Haertlein[1], Jonathan Cooper[5], Trevor Forsyth[1,2]

1. Life Sciences group, Institut Laue-Langevin, Grenoble, France
2. EPSAM, Keele University, UK
3. Large Scale Structures group, Institut Laue-Langevin, Grenoble, France
4. European Synchrotron Radiation Facility, Grenoble, France
5. Laboratory of Protein Crystallography, Drug Discovery Group, Wolfson Institute for Biomedical Research, UCL, UK

email: yee@ill.fr

Transthyretin (TTR) amyloidosis is the most common hereditary form of amyloidosis that is characterised by extracellular deposition of insoluble amyloid fibrils derived from misfolded protein in one or more organ systems in the body.[1] It is an irreversible and progressive disease and is fatal within 10 years of onset. Autosomal dominant mutations[2] in the TTR gene alter the protein stability leading to tetramer dissociation and favouring an abnormal monomeric structure, which in turn polymerises into unknown intermediates and finally into amyloid fibrils.[3]

Up to date, more than 200 X-ray crystal structures are available for TTR, but there is no consistent model to conclude the molecular assembly of the fibril building blocks and the triggering factors for this process. Neutron protein crystallography is a powerful tool that strongly complements X-ray structural studies by revealing key details of hydrogen atom interactions within the protein. Looking at the differences in hydrogen bonding, protonation states and hydration of two TTR mutants – S52P and T119M, which play opposite roles in the protein stability,[4,5] will provide key insights into how they destabilise the tetramer and promote amyloidotic aggregation.

References:

1. Planté-Bordeneuve V, Said G. *Lancet Neurol.* 2011;10(12):1086-1097.

2. Saraiva MJM. Database on Transthyretin Mutations. 2013:1-24.

3. Damas AM, Saraiva MJ. *J Struct Biol.* 2000;130(2-3):290-9.

4. Mangione PP, Porcari R, Gillmore JD, et al. *Proc Natl Acad Sci U S A.* 2014;111(4):1539-44.

5. Sebastião MP, Lamzin V, Saraiva MJ, Damas a M. *J Mol Biol.* 2001;306:733-44.

Keywords: amyloid, transthyretin, neutron, x-ray

MS10-O5 Bond Formation, Interactions and Reactions in *Peri*-Substituted Naphthalenes.

John D. Wallis[1], Amelie Wannebroucq[1], Gizem Saritemur[1], Nerea Mercadal[1], Laura Nomen Miralles[1], Mateusz B. Pitak[2], Simon J. Coles[2]

1. School of Science and Technology, Nottingham Trent University, Clifton Lane, Nottingham NG11 8NS, UK
2. National Crystallography Service, School of Chemistry, University of Southampton SO17 1BJ, UK.

email: john.wallis@ntu.ac.uk

Crystal structures of *peri*-naphthalenes containing a dimethylamino group and an alkene, e.g. **1**-**4**, show either attractive interactions or bond formation between the *peri*-substituents depending on the electrophilicity of the alkene. Charge density measurements have been used to characterise these interactions and bonds. Using the "Atoms in Molecules" approach, the values of the electron density and the Laplacian at the (3,-1) critical monitor the progress of bond formation. It is of note that the inter-group bond in zwitterion **3** (1.647 Å) is not fully formed.

In naphthalene **5** the neighbouring dimethylamino group modifies the properties of the aldehyde group which can be protonated or acylated on oxygen. A series of related ketones also protonate on oxygen, though for the t-butyl and phenyl ketones protonation on nitrogen with formation of a hydrogen bond to the carbonyl pi system is preferred.

Initial investigations show two types of interaction between *peri*-oriented carboxylate and aldehyde groups in anion **6**: either a Bürgi-Dunitz type interaction of carboxylate oxygen with the aldehyde carbonyl group, or direction of the aldehyde hydrogen atom at the face of the carboxylate group.

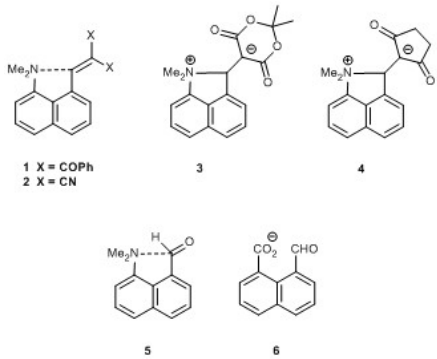

Figure 1. Structures of *peri*-naphthalene derivatives.

Keywords: Interactions, charge density measurements, long bonds.