## CHEMISTRY SEMINAR 291

# Studies of Protein Folding, Unfolding, and Misfolding by Rapid Pressure Jump NMR

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#### **Abstract**

The equilibrium between a protein's folded and unfolded state is strongly impacted by hydrostatic pressure. Many proteins can be unfolded by applying a modest amount (≤2.5 kbar) of hydrostatic pressure or can be mutated to generate small internal cavities, such that the volume difference between the folded and denatured states becomes sufficiently large to permit pressure-induced unfolding inside an NMR spectrometer. Rapidly and repeatedly dropping the pressure from denaturing conditions (i.e. 2.5 kbar) to 1 bar makes possible a range of experiments to monitor the actual folding process under native conditions. By building a device that allows such rapid (ms) and repeated (>100,000 times) switching, it is now possible to monitor directly the folding process by two- and three-dimensional NMR. Measurements on the model system ubiquitin show that the spectrum of the unfolded state disappears at a rate that is faster than the appearance of the folded spectrum, providing evidence of a meta-stable, NMR-invisible intermediate state. Its structure is investigated by pressure-jump NOE and pressure-jump RDC measurements. High pressure is also able to resolubilize peptides and proteins embedded in amyloid fibrils and, as demonstrated for the Alzheimer's related Abeta peptide, pressure-jump NMR experiments therefore can provide atomic information on the residues involved in the very initial steps of amyloid formation and on the growth of oligomers from less than 100 kD to larger than 1000 kD.

#### **About the Speaker**

Adriaan (Ad) Bax was born in 1956, in The Netherlands and became a US citizen in 1999. He received his Ph.D. in 1981 from Delft University of Technology, The Netherlands, for work related to the development of twodimensional nuclear magnetic resonance (NMR) techniques, which he carried out at Delft and Oxford Universities. His Ph.D. thesis was reprinted in book format and for many years served as a popular text, introducing students to the application of twodimensional NMR in chemistry. Bax joined NIH in 1983, where he has been working on the development and application of a wide variety of advanced multi-dimensional NMR techniques to problems of biochemical and biomedical interest. His group spearheaded the introduction of triple resonance NMR spectroscopy of 13C/15N-enriched proteins, developed the now standard joint analysis of 15N R1, R2, and NOE for characterizing protein backbone dynamics, and introduced the first methods for weakly aligning proteins in a magnetic field by the use of liquid

crystals. Bax's work has been recognized by numerous awards, including the Hans Neurath Award from the Protein Society and the 2018 Welch Award in Chemistry. In 2002, he was elected to both the National Academy of Arts and Sciences and the National Academy of Sciences.

