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A NOVEL RESONANT X-RAY DIFFRACTION METHOD TO STUDY THERMAL MOTION AND POINT DEFECTS IN CRYSTALS

J. Kokubun[1] K. Ishida[1] V.E. Dmitrienko[2] A. Kirfel[3] E.N. Ovchinnikova[4]
[1]Tokyo University of Science, Noda, Chiba 278-8510, Japan [2]Institute of Crystallography, 117333, Moscow, Russia [3]Mineralogisch-Petrologisches Institut der Universitat Bonn, D-53115 Bonn, Germany [4]Physical Department, Moscow State University, Russia

After an introductory survey of the X-ray resonant anisotropy, we present a resonant X-ray method to observe the thermal-motion-induced (TMI) and point-defect-induced (PDI) distortion of electronic states of atoms. This novel method uses an idea that, in general, the local atomic environment becomes less symmetric owing to point defects and/or thermal vibrations of atoms in crystals.

It is shown that, as a result of this phenomenon, an additional anisotropy of the resonant scattering factors can occur and the 'forbidden' Bragg reflections can be excited near the X-ray absorption edges (for details see Dmitrienko and Ovchinnikova, Acta Cryst. A56, 340 (2000)). Examples of crystals are presented (Ge, K_2CrO_4, C-15 type, and others) where such thermal-motion-induced and point-defect-induced reflections can be found. The tensor structure factors and unusual polarization properties of both types of reflections are computed.

The TMI reflections in germanium were recently observed by Kokubun et al. (Phys. Rev. B64, 073203 (2001)), Colella et al. (in press), and Kirfel et al. (in press) in accordance with this prediction. It was shown that the intensity of the 006 TMI reflection grows of about 30 times with temperature growing from 30 to 735 K and further growth of about 50 times is predicted up to the melting temperature of germanium. Owing to their resonant character, the PDI reflections allow to study separately both impurity atoms and host atoms of different types. The considered phenomena can provide a very sensitive method to study point defects because only the atoms distorted by defects produce contribution to the PDI reflections.
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Keywords: RESONANT DIFFRACTION FORBIDDEN REFLECTIONS THERMAL VIBRATIONS

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THREE-DIMENSIONAL STRUCTURE OF THE COMPLEXIN/SNARE COMPLEX

D.R. Tomchick[1] X. Chen[1,2] E. Kovrigin[1,2] D. Arac[1,2] M. Machius[1] T.C. Sudhof[3,4,5] J. Rizo[1,2]
[1]University of Texas Southwestern Medical Center Biochemistry, Rm. L4.250 5323 Harry Hines Blvd. DALLAS TX 75390-9038 USA [2]Dept. of Pharmacology, University of Texas Southwestern Medical Center [3]Dept. of Molecular Genetics, University of Texas Southwestern Medical Center [4]Center for Basic Neuroscience, University of Texas Southwestern Medical Center [5]Howard Hughes Medical Institute, University of Texas Southwestern Medical Center

During neurotransmitter release, the neuronal SNARE proteins synaptobrevin/VAMP, syntaxin, and SNAP-25 form a four-helix bundle known as the SNARE complex, which pulls the synaptic vesicle and plasma membranes together possibly causing membrane fusion. Complexin binds tightly to the SNARE complex and is essential for efficient Ca^{2+}-evoked neurotransmitter release. A combined X-ray and TROSY-based NMR study now reveals the atomic structure of the complexin/SNARE complex. Complexin binds in an antiparallel α-helical conformation to the groove between the synaptobrevin and syntaxin helices. This interaction stabilizes the interface between these two helices, which bears the repulsive forces between the apposed membranes. These results suggest that complexin stabilizes the fully assembled SNARE complex as a key step that enables the exquisitely high speed of Ca^{2+}-evoked neurotransmitter release.

Keywords: COMPLEXIN, SNARE COMPLEX, NMR DURING NEUROTRANSMITTER RELEASE

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METAL IONS AND THE CONFORMATION OF PEPTIDES FORMING AMYLOID DEPOSITS IN ALZHEIMER AND PRION DISEASE

G. Menestrina[1] M Comai[1] C Potrich[1] M Dalla Serra[1] G Guella[2] R Frassanito[2] C Meneghini[3] S Mobilio[3] S Morante[4]
[1]ITC-CNR Centre of Physics of the Aggregated States, Institute of Biophysics, Povo (Trento) Italy [2]Laboratory of Bioorganic Chemistry, Department of Physics, University of Trento, Povo (Trento), Italy [3]INFM-GILDA and University of RomaTre, Roma, Italy [4]INFM and University of Rome 'Tor Vergata', Roma, Italy

Distinct in clinical and neuropathological aspects, Alzheimer's and prion disease may descend from a similar molecular event: the formation of an altered protein conformer that triggers self-aggregation of long β -sheet fibers. In both cases, metal ions, in particular Cu(II), may play a role either in normal function and in degeneration of the involved proteins. Indeed, Alzheimer's amyloid β peptide (Ab), and prion protein (PrP), both contain histidines that may specifically bind metals like Cu, Zn and Mn. In human PrP, binding occurs on four sequential copies of an octarepeat present in the N-terminal region. In Ab peptides the binding site is at the N-terminus of pathogenic forms, Ab40 and Ab42. Synthetic Ab40, Ab42 and peptides containing a variable number of PrP octarepeats (1, 2 or 4 in the peptides called PrP-P1, -P2 and -P4) were obtained. The appearance of β -sheet, monitored by the shape of the amide-I absorption in the infrared spectrum (FTIR), preceded the growth of amyloid fibrils, seen by quasielastic light scattering (QLS). The binding of a maximum of one Cu per repeat of PrP-Pn peptides was determined by electrospray ionization mass spectroscopy (ESI-MS). The geometry of the Cu binding site was investigated under nearly physiological conditions by X-ray absorption spectroscopy (XAS), providing chemical selectivity and short-range order discrimination. XAS spectra of Cu(II) in solution and with peptides PrP-Pn were collected. Preliminary analysis shows that one Cu atom is coordinated by one histidine in PrP-P1, and by two histidines in PrP-P2 providing possible models of the molecular arrangements.

Keywords: XANES EXAFS COPPER BINDING AMYLOIDOSIS

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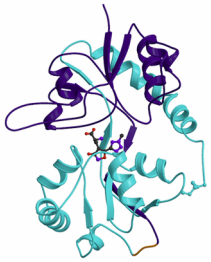
ELUCIDATION OF THE ACTIVATION AND DEACTIVATION MECHANISMS OF THE AMPA RECEPTOR GluR2 BY X-RAY CRYSTALLOGRAPHY AND ELECTROPHYSIOLOGY

J. Kastrup[1] A. Hogner[2] M.L. Lunn[3] C. Kasper[4] I.K. Larsen[5]
Royal Danish School of Pharmacy Department of Medicinal Chemistry Universitetsparken 2 COPENHAGEN Ø 2100 DENMARK

Glutamate is the principal excitatory neurotransmitter within the mammalian central nervous system (CNS), playing an important role in many different functions in the brain such as learning and memory. However, glutamate and glutamate receptors are also involved in neurodegenerative diseases and CNS disorders, e.g. Alzheimers disease and epilepsy. Glutamate receptors exist as G-protein coupled metabotropic receptors and as ligand-gated ionotropic receptors. One class of iGluRs is the AMPA receptors, consisting of homo- or heteromeric combinations of the subunits GluR1-4.

We have focused on X-ray structure determinations of the ligand-binding core of GluR2 in complex with different AMPA receptor agonists and antagonists. The structures of more than 10 complexes have been determined, and have provided a wealth of information on ligand binding modes and receptor activation/deactivation. In addition, the structures disclose different degrees of domain movements, which are correlated to the biological activities. The structural results, combined with functional studies on the full-length receptor, form a powerful platform for the design of new subtype selective agonists and antagonists.
The work is performed in collaboration with Prof. E. Gouaux, University of Columbia, USA and assoc. Prof. J. Egebjerg, University of Aarhus, Denmark.



Keywords: IONOTROPIC GLUTAMATE RECEPTORS LIGAND INDING CORE RECEPTOR LIGAND COMPLEXES