Acta Cryst. (2002). A**58** (Supplement), C55

SPECTRAL MOMENTUM DENSITIES IN MATTER DETERMINED BY ELECTRON SCATTERING

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The spectral electron momentum density is an important and fundamental property of the ground state electronic structure of a solid. In the independent particle approximation it gives the probability that an electron in band i has the momentum q and energy omega (relative to the Fermi energy or vacuum). Electron correlations change this simple picture, introducing a width in the main feature, which varies as a function of q and omega and is the quasiparticle lifetime. It also introduces density at higher energies, which can be in the form of broad satellite structures (intrinsic plasmons) or broad tails to the main feature (i.e. quasiparticle band) or both. Using the (e,2e) technique (electron momentum spectroscopy) we have been successful in measuring the spectral densities for some simple crystalline, polycrystalline and amorphous materials with an energy resolution a little better than 1eV and momentum resolution better than 0.1au (0.05 $Å^{-1}$). The energy resolution of 1eV is generally much smaller than the lifetime broadening, except near the Fermi level where lifetime broadening can be quite small. The measured spectral densities provide a severe challenge to many-body theoretical descriptions of condensed matter. This will be demonstrated for the simple cases of graphite [1] and aluminium [2] as well as some more complex examples.

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Keywords: SPECTRAL MOMENTUM DENSITY ELECTRON CORRELATIONS QUASIPARTICLES

Acta Cryst. (2002). A**58** (Supplement), C55

COVALENT INCORPORATION OF SELENIUM INTO OLIGONUCLEOTIDES FOR X-RAY CRYSTAL STRUCTURE DETERMINATION VIA MAD

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Covalent derivatization of nucleic acids for crystallographic phasing is thus far limited to incorporation of 5-halogen-2'-deoxyuridine or 5-halogen-2'-deoxycytidine. MIR and MAD phasing have been performed on bromine-containing nucleic acid crystals. However, applications of either method with bromo-derivatives are often not successful in practice. Disruptions or alterations of base stacking and other structural perturbations due to bromine may hamper crystallization efforts. Often halogen derivatives cannot be crystallized under native conditions. A further potential problem associated with halogen derivatives is that the modified nucleotides are light sensitive.
We have incorporated selenium into oligonucleotides at the sugar 2'-position (2'-methylseleno-uridine) and in place of the non-bridging phosphate oxygens (phosphoroselenoates = PSe's). In combination with MAD or SAD these modification strategies open up a new route to rapid determination of crystal structures of DNA and RNA, nucleic acid analogs and protein-nucleic acid complexes. A major advantage of a derivatization strategy using selenium compared to 5-bromo U (C) or 5-iodo U (C) is that selenium can be incorporated in place of oxygen at a variety of sites in nucleic acids, including base, sugar and phosphate group. In the case of modification at the phosphate, the two resulting diastereoisomeric PSe's can be separated by ion-exchange HPLC. Although PSe-DNA was previously reported to decompose with a half-life of 30 days, oligodeoxynucleotides containing a single P-Se moiety per strand were stable in crystallization droplets for months. Subsequent structure determination using MAD or SAD revealed fully occupied selenium sites and excellent experimental maps.

Keywords: ANOMALOUS DISPERSION, DNA AND RNA, PHOSPHOROSELENOATES

Acta Cryst. (2002). A**58** (Supplement), C55

CRYSTAL STRUCTURES OF DAMAGED/MODIFIED DNAS AND MUTAGENESIS

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Methoxyamine attacks cytosine and adenine moieties of dna, and modifies them to produce N6-methoxyadenine (mo6A) and N4-methoxycytosine (Mo4c) residues, respectively. These modifications induce pyrimidine (T→C) and purine (G→A) transitions during DNA replication. Activated oxygen atoms such as those in hydroxyl radicals and in hydrogen peroxide and hydrogen superoxide anion radicals also give many damages on DNA. 5-Formyluracil (f5U), which is an oxidized form of thymine, induces purine transition mutation. To investigate the pairing property of these modified residues in B-form DNA, crystal structures of six different DNA dodecamers, d(CGCGmo6AATCCGCG), d(CGCGmo6AATTCGCG), d(CGCAAATTmo4CGCG), d(CGCGAATTmo4CGCG), d(CGCGAATf5UCGCG) and d(CGCGGATf5UCGCG), have been X-ray analyzed. These structures indicate that mo6A can form a pair with T and C, and mo4C can form a pair with A and G, all four in the Watson-Crick type geometry. These mis-pairing occur through tautomerization of amino groups between the amino and imino states. In the case of f5U derivatives, it has been revealed that f5U can form a pair with a in the Watson-Crick geometry, while f5U can form a shift-up wobble pair with G, which is a new type of pairing. To form the latter pair, the f5U residue must be chemically dissociated at N3. Structural modeling of DNA polymerase with DNA fragments containing modified bases suggest that all the observed non-complementary pairs are acceptable in DNA polymerase with no structural interference, which leads to explanation of their mutation mechanism.

Keywords: DAMAGED DNA MODIFIED BASES MUTAGENESIS

Acta Cryst. (2002). A**58** (Supplement), C55

CRYSTAL STRUCTURES OF ACRIDINE-4-CARBOXAMIDES COMPLEXED WITH THE DNA HEXANUCLEOTIDE d(CGTACG)2

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DNA-binding agents that intercalate into DNA and poison topoisomerases i and ii are important drugs in the treatment of cancer. Examples of this class of drug, developed at the Auckland Cancer Society Research Centre, are the acridine-4-carboxamides, which include daca (n-[2-(dimethylamino)ethyl]acridine-4-carboxamide), currently in clinical trial. Using x-ray crystallography we have solved the structures of 9-amino-daca and seven of its derivatives bound to the hexanucleotide d(cgtacg)2. Some of these compounds are biologically active anticancer agents and others are not. The complex structures fall into two groups, independent of biological activity. One set of complexes form 'normal' intercalation structures in which the ligand intercalates at each cpg step with its carboxamide sidechain lying in the major groove, and its dimethylamino group hydrogen-bonding with the o6/n7 atoms of g2. The carboxamide group lies in the plane of the acridine ring with its oxygen hydrogen-bonded to the n10, and its nh group bound to the g2 phosphate by a bridging water molecule. These findings enabled us to formulate a molecular rationale for how the 9-aminoacridine-4-carboxamides might poison topoisomerase ii. The second group of complexes form in the presence of cobalt and have a remarkably different structure. A novel intercalation complex is formed involving four dna duplexes and four ligand molecules which is reminiscent of the multiple-stranded dna helices seen in recombination, repair processes and g-quadruplexes, demonstrating that these intercalators can stabilize non b-dna structures of possible biological relevance.

Keywords: DNA-DRUG COMPLEXES OLIGONUCLEOTIDE-DRUG COMPLEXES INTERCALATION