France, [6]BioMoCeTi, SMBH-UMR 7033 CNRS, 74 rue M. Cachin, 93017 Bobigny Cedex, France, E-mail：thierry.prange@univ-paris5.fr

How life emerged on Earth remains one of the great Mysteries for mankind. Molecules with backbones forming stable double helices, held by self-association, and capable of auto-replication - and more precisely nucleotides held by Watson-Crick base pairings - were considered as the seminal building blocks of life. Many scenarios involving extreme conditions were described, all of them dealing with the extreme pressure conditions of the "primary soup" that was present on earth at prebiotic stages. High-pressure molecular crystallography (HPMX) investigation of DNA was undertaken using crystals of the d(GGTATACC) octamer, in the range 0.2-2 GPa. This sequence crystallizes in the hexagonal P61 space group and is particularly interesting because it includes in a A-DNA crystal matrix, the B-form of DNA, leading us to simultaneously monitor the two forms of DNA under pressure. The 3D structure of d(GGTATACC) was recorded at ambient pressure, 0.55, 1.09 and 1.39 GPa and refined at 1.6 Å resolution. Fiber diagrams of the embedded B-DNA that superpose to the diffraction pattern of the A-DNA were analyzed from ambient pressure to up 1.9 GPa. A large axial compression of the DNA is observed (11 % at 1.39 GPa). The average base-step varies in A-DNA from 2.92 down to 2.73 Å, and in B-DNA from 3.40 to 3.10 Å. Surprisingly, in the case of A-DNA, the geometry of Watson-Crick base parings remains essentially invariant in the domain of pressure up to 1.39 GPa. Above 1.4 GPa, the crystal structure irreversibly deteriorates while the B-DNA fiber diagram still persists above 2 GPa. The remarkable stability and adaptation of d(GGTATACC) to high pressure is clearly associated with the base-paired double helix topology of the molecule by which it behaves as a molecular spring.

Keywords: DNA, high pressure,, macromolecular crystallography

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Conformational flexibility of cyclohexene residues

Luc Van Meervelt, Koen Robeyns
Katholieke Universiteit Leuven, Chemistry Department, Celestijnenlaan 200F - box 2404, Leuven (Heverlee), BE, 3001, Belgium, E-mail：Luc.VanMeervelt@chem.kuleuven.be

Cyclohexene nucleic acids (CeNAs) are developed as antisense drugs, which selectively bind with the messenger RNA to inhibit protein synthesis in human cells. CeNAs have proven to interact more effectively with RNA than its natural DNA and RNA analogues, and are able to introduce RNaseH activity. The flexibility of the cyclohexene moiety allows incorporation of the CeNA residues in both A- and B-type DNA, as the ring can adopt the $^2H_3$ or the $^3H_2$ half-chair conformations. We present here the structure of a fully modified CeNA duplex GTGTACAC (space group *R*32, 1.53 Å resolution, R = 15.8%). All CeNA residues adopt the $^3H_2$ conformation mimicking the C3'-endo conformation of natural A-DNA. In a second structure a CeNA residue is incorporated in the Dickerson dodecamer (space group $P222_1$, 1.9 Å resolution, R = 22.7%). To maintain the global B-type helix of the dodecamer, the C3' atom of the CeNA sugar ring is pushed into the ^2E envelope conformation, close to the expected $^2H_3$ conformation. In addition three $Co(NH_3)_6$ complexes stabilise the CeNA residue and crystal packing. These two recent structures indeed prove the flexibility of the CeNA ring making these CeNA building blocks ideal candidates for antisense therapy.

Keywords: nucleic acid crystallography, antisense, cyclohexene nucleic acid

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Structural insight on the mechanism of regulation of the MarR family of proteins

Dea Shahinas[1], Vivian Saridakis[2], Dinesh Christendat[1]
[1]University of Toronto, Cell and Systems Biology, 7 Jackes Ave. Apt 2601, toronto, ON, M4T 1E3, Canada, [2]York University, Department of Biology, 4700 Keele Street, Toronto, ON, M3J 1P3, E-mail：dea.shahinas@utoronto.ca

MarR transcription factors are diverse in nature and some of them are known to regulate multiple antibiotic resistance (MAR) in bacteria. They make up a large family of proteins characterized by a winged-helix DNA binding domain. Organic solvents and antibiotics can trigger an antibiotic resistant state which ultimately results in limited influx and increased efflux of these compounds into the cell. The multiple antibiotic resistance (mar) operon is regulated by a MarR transcriptional regulator and the products of this operon are known to mediate the MAR phenotype via regulation of more than 60 genes. Antibiotics and organic compounds bind to the MarR protein and induce a conformational change, a known mechanism of its regulation. Salicylate is a common inducer of MAR and inhibitor of MarR. This study presents for the first time the structure of a MarR family member from Methanobacterium thermoautotrophicum in the presence of salicylate. Salicylate binding revealed a large conformational change in its DNA binding lobe that renders it inactive to bind DNA. Salicylate binds two asymmetric sites on the M. thermoautotrophicum MarR non-cooperatively, as will be shown here through DNA binding and thermal denaturation assays. This provides insight into how transcription factors of the MarR family regulate the effective amount of multiple antibiotic resistance inducers. Understanding of this inactivation mechanism and comparative analysis with E.coli MarR can improve our understanding of multiple antibiotic resistance and can open the road to the development of new antimicrobial agents.

Keywords: transcription factor structure, antibiotic resistance, bound ligand interactions

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Activity regulation of the transcription factor Ets-1 by DNA-mediated homo-dimerization

Ekaterina P Lamber[1], Laurent Vanhille[2], Larissa Textor[3], Galina S Kachalova[4], Michael H Sieweke[2], Matthias Wilmanns[3]
[1]Ohio State University, 960 BRT, 460 West 12th Avenue, Columbus, OH, 43210, USA, [2]Centre d'Immunologie de Marseille-Luminy, Universite de la Mediterranee, Case 906, 13288 Marseille, Cedex 09, France, [3]EMBL-Hamburg c/o DESY, Notkestrasse 85, D-22603 Hamburg, Germany, [4]Max-Plank Unit for Structural Molecular Biology, c/o DESY, Notkestrasse 85, D-22607 Hamburg, Germany, E-mail：ekaterina.lamber@osumc.edu

The Ets-1 (E26 transforming specific sequence) proto-oncoprotein is a member of the Ets family of transcription factors that share a unique DNA binding domain termed ETS domain which recognizes specifically a GGAA/T core element. The function of the Ets-1 transcription factor is regulated by two autoinhibitory regions that flank ETS domain. Previous data revealed the mechanism for auto-inhibition of a monomeric Ets-1 on DNA response elements with a single Ets-1 binding site. Here, we present the X-ray structure of the Ets-1/DNA/Ets-1 complex formed on the sromelysin-1 promoter element containing two palindromic head to head Ets1-binding