

### ARTELINIC ACID FOR TREATMENT OF SEVERE MALARIA FORMS WATER-LINKED DIMERS

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The artemisinins are important antimalarials due to their efficacy against drug resistant parasites. They reduce parasitemia, fever, and coma time in patients faster than other available medications. Most artemisinins are too water insoluble for intravenous use. Sodium alpha-artesunate is water soluble and is currently used in a number of nations to treat severe malaria, but is chemically unstable in solution. *beta*-Arteminic acid was designed and synthesized as a chemically stable alternative to artesunate that can be formulated for intravenous use. A substantial preclinical effort is underway to develop arteminic acid for clinical use in severe malaria. Arteminic acid itself is not very water soluble and must be converted to salt form to be sufficiently water soluble. Both the crystal structure (monoclinic,  $P2_1$ ,  $a=9.260\text{\AA}$ ,  $b=12.572$ ,  $c=19.200$ ,  $\beta=92.27^\circ$ ,  $Z=2$ ,  $R1=0.065$ ,  $wR2=0.176$ ) and elemental analysis show that crystalline arteminic acid is a hemihydrate. The water molecule links two arteminic acid molecules by forming hydrogen bonds to the carboxyl group and the ring ether oxygen atom of separate molecules. QM calculations show that the most negative electrostatic potential on the surface of arteminic acid is by these oxygen atoms. The ether group conformation of the two arteminic acid molecules differs with the phenyl group either perpendicular or close to parallel with the artemisinin ring system. The perpendicular conformation is more consistent with proton nmr. The axial position of the ether group and the peroxide bond length are consistent with crystal structures of other *beta*-artemisinins. These experimentally determined geometries are important for developing accurate computational models for studying mechanism of action and structure-activity relationships.

**Keywords:** MALARIA ARTELINIC ACID ARTEMISININS

### THE STRUCTURE OF WATER NANOWIRE

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Two kinds of 'water nanowire' (Wire-I and -II) have been found in the polyhydrated crystal structure of tetrahydro-beta-carboline derivative. 'Wire' we report here means the isolated and infinite column structure of having nanoscale dimension in the length, formed by the hydrogen-bonded linkage (network) of water molecules, thus constituting one-dimensional structure of associated water molecules. The compound is a cyclised Schiff base of L-tryptophan and pyridoxal 5-phosphate, and forms a single crystal of space group  $R3$  ( $Z=9$ ) with 48 water molecules, in which the unit cell contains three Wire-I (diameter=1.642 nm) and Wire-II (diameter=0.639 nm). In Wire-I, the planes constituted by ten hydrogen-bonded water molecules are stacked with an interval of 0.473 nm perpendicular to the three-fold axis running to the  $c$ -direction. The neighboring planes are connected with each other by six hydrogen bonds of three water molecules. There are five kinds of hydrogen bonds in this wire. These intra-wire O...O distances are 0.267, 0.269, 0.279, 0.289 and 0.296 nm, and the hydrogen-bonded O-O-O angles range from 88 to 137 degree. In Wire-II, the water molecules form an infinite helical structure around the three-fold screw axis, in which three water molecules per one turn participate. The intra-wire O...O distance and O-O-O angle are 0.259 nm and 93 degree, respectively. These unusual, but exciting, structures are the first example of water nanowire existing in the crystal structure and thus provide the structural parameters of creating the one-dimensional structure of water molecules. In this congress, we would like to discuss the structural and hydrogen-bonding requisites of water molecules for constructing the nanowire structure.

**Keywords:** WATER NANOWIRE ONE-DIMENSIONAL

### SYSTEMATIC NEUTRON DIFFRACTION STUDY ON VARIABLE STRENGTH OHN HYDROGEN BONDS IN PHENOL – PYRIDINE ADDUCTS

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Very strong hydrogen bonds play important roles in chemical and enzymatic interaction and are, therefore, subject of great current interest. There are many examples of OHN hydrogen bonds, but most are of relatively moderate strengths. Only in so-called "transition region" or "critical region" characterized by a narrow range of dpka very short and strong ohn bridges can be formed. In these strong hydrogen bonds, the proton can be located closer to the o or closer to the n atom but also in the center of the bridge. The exact position of the proton can only be determined by neutron diffraction.

We have determined seven low-temperature neutron diffraction structures with different O...N bond length and different proton location in the hydrogen bridge. In 3-cyanopyridine – pentachlorophenol adduct proton is located at oxygen atom, in 2,4,6-trimethylpriridium 2,6-dichlo-4-nirtrophenolate is shifted to nitrogen. Other complexes characterized by stronger and shorter hydrogen bonds show systematic proton moving along the bridge caused by the DpKa change. The hydrogen bond in 4-methylpyridine – pentachlorophenol complex is characterized by one of the shortest OHN hydrogen bond known so far. The structure of 3,4-dimethylpyridine – 2,6-dichloro-4-nitrophenol adduct contains two symmetry independent adducts with significantly different geometries. The results are compared with earlier neutron diffraction studies of OHN hydrogen bonds. The change of hydrogen bond strength is reflected in the electron density of the complexes calculated using *ab initio* methods.

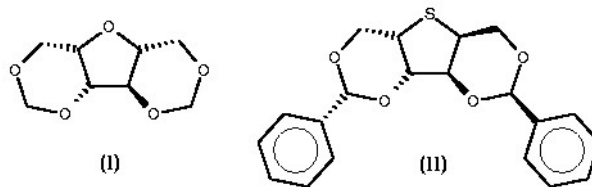
**Keywords:** NEURTON DIFFRACTION, HYDROGEN BOND, PHENOL - PYRIDINE COMPLEX

### 2,5-ANHYDRO-D-GLUCITOL AND 2,5-ANHYDRO-L-THIO-IDITOL DERIVATIVES: CONFORMATION AND POLYMORPHISM

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Compound (I), 2,5-anhydro-1,3:4,6-di-O-methylene-D-glucitol, has its furanoid ring in a  $C_2$  twist conformation with  $C_3$  on the twist axis. The 2,5-anhydro-L-thio-iditol derivative (II) exists in both monoclinic and tetragonal polymorphs. In the monoclinic polymorph, the inherent  $C_2$  molecular symmetry is only approximate, while in the tetragonal polymorph, the molecule lies on a crystallographic twofold axis. The conformations of the molecule in the two polymorphs differ mainly in the rotations of the phenyl groups of the benzylidene substituents. The absolute configuration of the tetragonal polymorph of (II) was determined. I has  $Z = 4$  in  $P2_12_12_1$ ,  $R = 0.076$  at 100 K; II (monoclinic) has  $Z = 2$  in  $P2_1$ ,  $R = 0.043$  at 296 K; II (tetragonal) has  $Z = 4$  in  $P4_12_12$ ,  $R = 0.039$  at 297 K.



**Keywords:** GLUCITOL, THIO IDITOL, POLYMORPHISM