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The research was supported by National Science Center in Poland (Grant SONATA BIS 6 NCN, 2016/22/E/ST4/00461).

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Keywords: amines, alcohols, ring-puckering

MS10-P08

A novel salt of antidiabetic drug metformin resulting from a proton transfer reaction: Synthesis, characterization, crystal structure and solution studies

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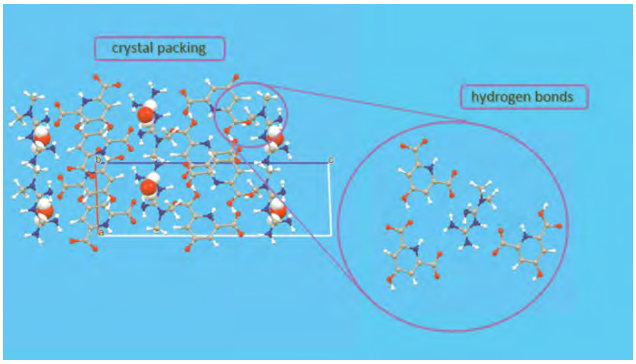
The product of proton transfer reactions between donors and acceptors in which the proton from one species is transferred to the basic center has been designated by different names such as “proton transfer compound” (PTC), “charge transfer complex” (CT-complex) and “H-bonded complex”. These are equivalent and merely emphasize different aspects of the same phenomenon. In recent years, the design and development of new active pharmaceutical ingredients (APIs) based on the proton transfer reactions have been widely developed [(1)]. *N*,*N*-dimethylbiguanide (known as metformin), is the first line drug of choice to treat non-insulin dependent mellitus, which contains the guanidine moiety that can easily forms strong hydrogen bonds with the acidic functionalities like acids and phenols [(2)]. Metformin can be administered in the form of one of its pharmaceutically acceptable salts of various organic and inorganic acids. As part of our studies on proton transfer compounds and their metal complexes of biological interest, here-in, we report new proton transfer compound, [($MetH_2$)(HO-dipic$H)_2 \cdot H_2O$], metformin with 4-hydroxy-2,6-pyridinedicarboxylic acid. The proton transfer compound was synthesized and characterized by FTIR, ^1H and ^{13}C NMR, and single crystal X-ray studies (Fig 1). The solution potentiometric studies provided additional evidences of interaction between HO-dipicH_2 and metformin, supporting the results obtained from the solid state studies. We gratefully acknowledge the support of this work by the Sistan and Baluchestan University. Financial support from Spanish Ministerio de Economía y Competitividad (MAT2013-40950-R and MAT2016-78155-C2-1-R), Factoría de Cristalización—Consolider Ingenio 2010).



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Keywords: Proton transfer, X-ray structure.

MS11- Hot structures in biology

Chairs: Prof. Maria Joao Romao, Prof. Fred Antson

MS11-P01

Neanderthal adenylosuccinate lyase: insights in catalysis and link with disease-causing mutation

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Adenylosuccinate lyase is a conserved enzyme involved in purine metabolism for which several mutations in the human enzyme (hADSL) are known to affect intelligence and behaviour. During evolution modern humans acquired a specific substitution (Val429Ala) in ADSL distinguishing it from the ancestral variant present in Neanderthals (nADSL). I will present a structural, biophysical and biochemical comparison of hADSL and nADSL aimed at determining whether this substitution is functionally relevant and could be responsible for phenotypical differences between these species. This work shows that hADSL and nADSL differ in thermal stability but not in enzymatic activity. Similar observations are made when comparing native hADSL with hADSL containing the nearby disease-causing Arg426His substitution hinting towards a phenotypical effect. In addition the combined X-ray crystallography and SAXS data reveals that ADSL undergoes conformational changes during catalysis which together with the structure of a hitherto undetermined product bound conformation helps explain the effect of several human disease-causing substitutions.

Keywords: Neanderthal, Human disease.