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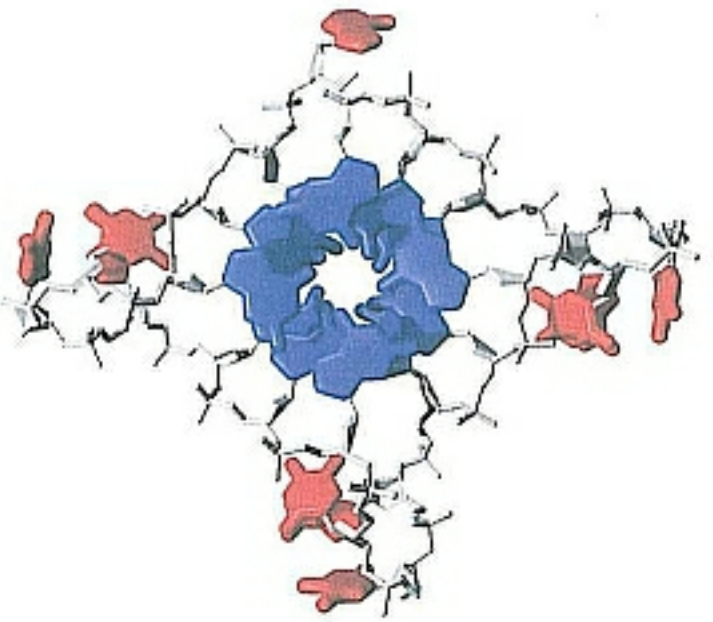
GUANOSINES AND QUADRUPLEXES

Programme and Book of Abstracts



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Higher-ordered structures based on purines: towards expanding the alphabet – computational, synthetic and analytical studies

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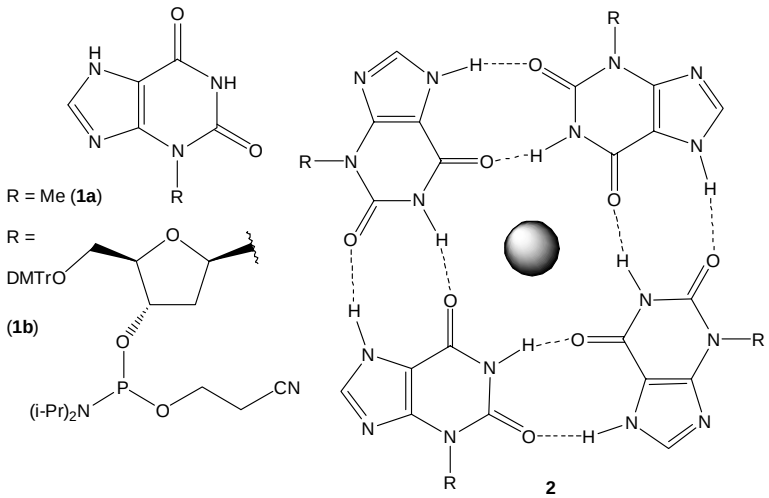
New tetramer structures, based on 9-methylxanthine (Xa),[1] 9-methylxanthine protonated at N7 (XaH^+) and 9-methyluric acid (Ua), were investigated by high level density functional calculations. We have found that homo- and heterotetrads can be formed by low barrier hydrogen bond possessing positive charges [$(XaH^+)_4$, $(XaH^+\text{-}Xa)_2$, $(XaH^+\text{-}Ua)_2$]. Systems with zero charge [$(Xa)_4$, $(Xa\text{-}Ua)_2$, $(Ua)_4$] were also constructed, investigated and compared to guanine quadruplex [$(G)_4$]. It was shown that the new tetramers can bind cations and anions without the necessity of stacking interactions. Application of the calculated systems in higher ordered structures (*e.g.* quadruplexes)[2-4] are very promising with or without intercalating ions.

Xanthine derivatives play a decisive role in a variety of intracellular metabolic pathways as substrates and/or intermediates of numerous enzymes or enzyme systems.[1] To date no study has been devoted to investigate the properties of 3-substituted xanthine derivatives in higher ordered structures. It is anticipated that the dominant 7*H* tautomeric form of 3-substituted xanthines would facilitate the formation of tetrads similary to the formation of guanine quadruplexes.[2-4]

3-Substituted xanthine derivatives (**1a, 1b**) have been synthesized starting from alkylation or glycosylation of 7-benzylxanthine[5] to obtain 3-methylxanthine (**1a**) and 3-(2'-deoxy-β-D-ribofuranosyl)xanthine phosphoramidite (**1b**), respectively. The quadruplex-forming ability of 3-methylxanthine (**1a**) has been investigated directly by MS and NMR measurements while compound (**1b**) has been incorporated into oligonucleotides.



In addition, high-level computational studies have also been performed to the same end. The total binding energy of 3-methylxanthine monomers in tetrads (**2**, R = Me) and the analogous octamers, with or without intercalating ions, lies between those of uric acid and guanine quartets.

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