3-Substituted xanthines as promising candidates for tetrad formation: synthetic, analytical and computational studies

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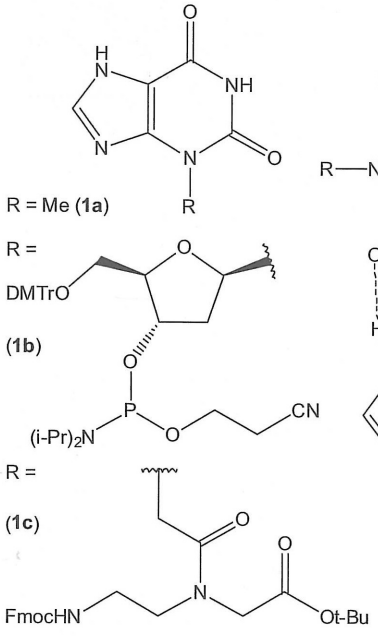
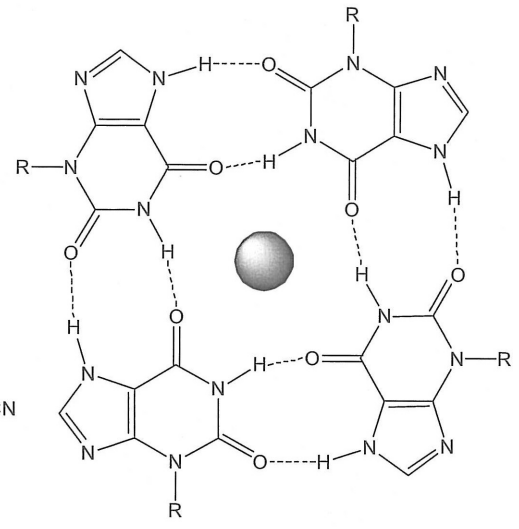
Xanthine derivatives play a decisive role in a variety of intracellular metabolic pathways as substrates and/or intermediates of numerous enzymes or enzyme systems.[1] To date no study has been devoted to investigate the properties of 3-substituted xanthine derivatives in higher ordered structures. It 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.[2,3]

3-Substituted xanthine derivatives (**1a-c**) have been synthesized starting from alkylation or glycosylation of 7-benzylxanthine[4] followed by high-pressure hydrogenation, to remove the benzyl group, and subsequent functional group transformations to obtain 3-methylxanthine (**1a**), 3-(2'-deoxy-□-D-ribofuranosyl)xanthine phosphoramidite (**1b**) and the xanthine PNA monomer (**1c**), respectively. The quadruplex-forming ability of 3-methylxanthine (**1a**) has been investigated directly by MS measurements while compounds (**1b**) and (**1c**) have been incorporated into oligonucleotides and PNA oligomers, respectively.





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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), with or without intercalating ions, lies between those of uric acid and guanine quartets.

References:

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