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Review

Structural characterization, recognition patterns and theoretical calculations of long-chain N-alkyl substituted purine and pyrimidine bases as ligands: On the importance of anion–π interactions

Juan J. Fiol*, Miquel Barceló-Oliver, Andrés Tasada, Antonio Frontera, Àngel Terrón, Ángel García-Raso

Departament de Química, Universitat de les Illes Balears, Palma E-07122, Spain

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ABSTRACT

Long-chain N-alkyl substituted purine and pyrimidine bases are very interesting ligands for studying interaction motifs of biological relevance. The understanding of new types of recognition patterns between bases like RNA quartets combined with C–H/π, lone pair–π and anion–π interactions is necessary to study and control many biological processes. These interactions are essential for the packing of the crystals, and some studies have already proved their importance in biology. One of the major revelations is the importance of anion–π interactions with both pyrimidine and purine rings. In many studies, anion–π interactions with biologically relevant anions like chloride or bromide have been shown, anticipating that these interactions are likely present in biological systems.

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Abbreviations: DNA, deoxyribonucleic acid; Z-DNA, double helical structure of DNA, Z type; RNA, ribonucleic acid; tRNA, transfer RNA; ATP, adenosine-5′-triphosphate; Ade, adenine, 6-aminopurine; AdeH, adeninium, protonated form of Ade; N^6AdeC_n, N^6-alkyladenine; N^6AdeC_{10}, N^6-decyladenine; $(N^6AdeH)C_{10}$, N^6-decyladeninium, protonated form of N^6AdeC_{10}; $(N^9Ade)_2C_3$, N^9,$N^{9\prime}$-trimethylene-bisadenine; $(N^9AdeH)_2C_3$, N^9,$N^{9\prime}$-trimethylene-bisadeninium, diprotonated form of $(N^9Ade)_2C_3$; $(N^9AdeH)C_3(N^9Ade)$, monoprotonated form of $(N^9Ade)_2C_3$; $(N^6Ade)_2C_3$, N^6,$N^{6\prime}$-trimethylene-bisadenine; $(N^6AdeH)_2C_3$, N^6,$N^{6\prime}$-trimethylene-bisadeninium, diprotonated form of $(N^6Ade)_2C_3$; $(N^9AdeH)C_4(N^3AdeH)$, N^9,$N^{3\prime}$-tetramethylene-bisadeninium; $(N^6Ade)N(9)$, N^6-substituted adenine presenting a hydrogen bond with N^9 as acceptor; $(N^9Ade)N(6)$-H, N^9-substituted adenine presenting a hydrogen bond with N^6 as donor; $(N^6Ade)N(3)$-H, N^6-substituted adenine presenting a hydrogen bond with N^3 as donor; $(N^9Ade)N(7)$, N^9-substituted adenine presenting a hydrogen bond with N^7 as acceptor; Hyp, hypoxanthine, 1*H*-purin-6(9*H*)-one; HypH, hypoxanthinium, protonated form of Hyp; $(N^9Hyp)_2C_3$, N^9,$N^{9\prime}$-trimethylene-bishypoxanthine; $(N^9HypH)_2C_3$, N^9,$N^{9\prime}$-trimethylene-bishypoxanthinium; $(N^9Hyp)_2C_4$, N^9,$N^{9\prime}$-tetramethylene-bishypoxanthine; $(N^9HypH)_2C_4$, N^9,$N^{9\prime}$-tetramethylene-bishypoxanthinium; Cyt, cytosine, 4-amino-1*H*-pyrimidine-2-one; CytH, cytosinium, protonated form of Cyt; N^1CytC_6, N^1-hexylcytosine; $(N^1CytH)C_6$, N^1-hexylcytosinium, protonated form of $CytC_6$; CHC^+, [(N^1-hexylcytosinium)·(N^1-hexylcytosine)] hydrogen bonded base pair; Ura, uracil, 2,4-dihydroxypyrimidine; N^1UraC_6, N^1-hexyluracil; N^1UraC_6-κO^4, N^1-hexyluracil coordinated through O^4 atom; FUra, 5-fluorouracil, 5-fluoro-2,4-dihydroxypyrimidine; $FUraC_6$, N^1-hexyl-5-fluorouracil.

* Corresponding author. Tel.: +34 971172306; fax: +34 971173426.
E-mail address: jfa950@uib.es (J.J. Fiol).

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CH/π
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1. Introduction

Nucleobase–metal ion interactions have been studied for more than 60 years and are still in the focus of today's research interests because of the important role of metal ions in the biochemistry of nucleic acids. Solution and solid state studies have provided a wealth of information on the metal ion binding patterns to DNA [1,2]. Methyl or ethyl N^9-substituted purines and N^1-substituted pyrimidines have been used as biological models, owing to the poor solubility properties in water of the natural bases, to study metal ion interactions and recognition patterns [1–3]. However, fewer studies deal with other modified purine or pyrimidine bases and their coordinating properties [4,5].

The biological interest of natural substituted nucleobases is based on different aims. For instance, methylated forms of adenine and cytosine occur at some stage in DNA and many modified bases are found in tRNAs. The use of those derivatives in medical treatment as antiviral or anticancer drugs has been described [6], a classical example is the acyclovir [9-(2-hydroxyethoxymethyl)guanine] and its derivatives used for antiviral therapy, as they are extremely selective and low in cytotoxicity [7]. In addition, the use of non natural nucleosides as inhibitors of enzymes is an important line of research [8]. Another very interesting aspect to highlight is the research on purine riboswitches present in RNA, which are a class of riboswitches that selectively recognize guanine and adenine [9]. As a matter of fact the purine riboswitch is the only one so far that has been mutated to respond to non-natural ligands, opening up possibilities to use riboswitches as novel gene-expression tools [10]. Moreover, the affinity of N^6-substituted purines for cytokinin receptors in plants has recently been demonstrated [11] showing important cytokinin activity for several alkyl-and benzyl-alkylaminopurines in *Amaranthus*. Finally, some N^1-substituted fluorouracil derivatives occur as natural products in certain sponge species [12], some of them present interesting antitumor properties and they have the peculiarity of being the first reported fluorine-containing natural products from marine source.

The theoretical interest in these synthetic ligands and its chemistry features is mainly devoted to understand the different roles played in the recognition processes, which are crucial to control genetics and enzymatic action [13]. Not only the normal or metal mediated hydrogen bonds of base pairs are involved [14], π–π stacking, hydrophobic interactions, C–H/π interactions and also anion–π converge in a unique complexity [15–17]. The increasing amount of X-ray structural data and theoretical calculations in this field show the relevance of these recognition patterns. In the particular case of anion–π interactions, they are gaining significant recognition in this field since their pivotal role in some biological processes has been recently demonstrated [18,19]. Moreover, the closely related lone pair–π interaction has been observed in several biological systems. For instance, Egli and Sarkhel have reported an interesting case of O–π interactions involving an RNA pseudoknot [20]. In addition Gámez et al. have demonstrated the importance of anion–π interaction in DNA bases, since they are electron-deficient arenes. A thorough Cambridge Structural Database search shows several hits for halide–nucleobase interactions. As an example, they reported a close contact (3.271 Å) between the six-membered ring centroid of a coordinated adenine and the fluorine of a lattice tetrafluoridoborate cobalt complex [21]. Similar interactions were also found for guanine and thymine [20]. These crystallographic cases of halide–nucleobase supramolecular associations clearly illustrate the ability of natural arenes to participate in anion–π binding contacts [21]. More recently, Mooibroek and Gámez have shown that anion–π and lone pair–π interactions present remarkable directional character [22,23].

Other areas of interest where nucleobases have an important role include, for instance, the utilization of adenine synthetic derivatives for tailoring metal organic frameworks [24]. Furthermore, tethered nucleobases are also used as supramolecular motifs [25,26] to construct more or less complicated molecular architectures [27]. In addition, the molecular recognition properties of DNA molecules can be utilized for the construction of nanodevices, with applications ranging from nanoconstruction to intelligent drug delivery [28]. The construction of machinelike devices that are capable of motion (rotational and unidirectional), pulling and stretching, is now possible with the help of DNA. Another interesting research field is the introduction of reactive functional groups in modified nucleotides since it provides vast opportunities for extending the functions and properties of these biomolecules. This is a good strategy for providing nucleic acids with catalytic properties by incorporating strategic chemical modifications in the heterocyclic nucleobases [29]. Finally, the formation of efficient catalytic silver nanoparticles on carbon nanotubes by adenine functionalization has been recently reported [30]. Interestingly, adenine covalently attached to the carbon nanotube surface is able to facilitate the formation of catalytic nanoparticles with controlled sizes. This material is able to promote the oxidation of hydroquinones.

2. Long-chain alkyl N-substituted purine and pyrimidine bases as ligands

A nice review has recently been published that presents an overview regarding the utilization of chelate-tethered nucleobases as models for metal ion–DNA interactions. In addition, it deals with the analysis of the molecular architecture of metal complexes capable of base-pair hydrogen bonding [4,24]. Some interesting supramolecular complexes synthesized from these ligands include dimeric and tetrameric assemblies, as well as hydrogen-bonded chains [4].

Normally, functional groups as sulfonic or carboxylic groups, are added to maximize the coordination chemistry of the tethered nucleobase ligands. The present review is centered specially in the N-substituted alkyl nucleobases, focusing on the chemistry and coordination properties of derivatives of natural nucleobases.

2.1. Purine bases

Different types of substituted purine nucleobases have been obtained, including (i) N^9,$N^{9'}$-polymethylene-bisadenines or bishypoxanthines (ii) N^6,$N^{6'}$-polymethylene-bisadenines, (iii) N^9-alkyladenines and (iv) N^6-alkyladenines [31–42]. Moreover, X-ray structures of the ligand or metal complexes are known (see Fig. 1). A brief description for each type of ligand is detailed below.

2.1.1. Polymethylene-bispurine ligands

The interest of N^9,$N^{9'}$-polymethylene-bispurine is related to its stacking ability in the nucleic acids. Polymethylene-bispurine ligands are good models of dinucleotide analogs for studying stacking interactions avoiding the influence of other factors like hydrogen bonding and electrostatic interactions that involve the sugar

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