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Coordination Chemistry Reviews 251 (2007) 1973–1986
COORDINATION CHEMISTRY REVIEWS
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Review

Biological recognition patterns implicated by the formation and stability of ternary metal ion complexes of low-molecular-weight formed with amino acid/peptides and nucleobases/nucleosides

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Received 15 November 2006; accepted 10 March 2007
Available online 14 March 2007

Contents

Abstract

Metal–peptide or metal–nucleoside complexes may be used as models to identify recognition patterns for nucleic acids and peptides. Zinc fingers or *mer* and *fur* proteins are also examples of ternary systems with non-direct covalent bonds towards DNA.

In low-molecular-weight ternary complexes some recognition patterns are repeatedly observed. This recognition tackles with the complexity of the systems and is responsible for the extra stabilization of such complexes.

Abbreviations: acac, acetylacetonate; ACV, acyclovir: 9-[(2-hydroxyethoxy)methyl]guanine; ade, adenine; ADP^{3-}, adenosine 5′-diphosphate; L-ala-gly, L-alanylglycinate; L-arg, L-arginine; L-tyr-gly, L-tyrosylglycinate; AMP^{2-}, adenosine 5′-monophosphate; ATP^{4-}, adenosine 5′-triphosphate; bmp, 2,2′-bipyrimidine; bpy, 2,2′-bipyridine; bzim, benzimidazole; creat, creatinine; cyd, cytidine; cyt, cytosine; $dGMP^{2-}$, 2′-deoxyguanosine 5′-monophosphate; 7,9-dimehypox, 7,9-dimethylhypoxanthine; dmade, 1,9-dimethyladenine; en, ethylenediamine = 1,2-diaminoethane; gly, glycinate; glyH–N, glycine coordinated through the nitrogen atom; gly-gly, glycylglycinate; gly-L-his, glycyl-L-histidinate; gly-L-met, glycyl-L-methioninate; gly-L-metH, glycyl-L-methionine; gly-L-tyr, glycyl-L-tyrosinate; GMP^{2-}, guanosine 5′-monophosphate; gua, guanine; Hdmade, protonated 1,9-dimethyladenine; Hhip, hippuric acid; Hip, hippurate; HMG, high-mobility-group proteins; HMG1, high-mobility-group type 1 protein; Hmgua, protonated 9-methylguanine; icyt, isocytosine; I-hip, *ortho*-iodohippurate; im, imidazole; IRE, iron-responsive element; made, 9-methyladenine; mcyt, 1-methylcytosine; met, methioninate; mgua, 9-methylguanine; micyt, 1-methylisocytosine; mura, 1-methyluracil; mura-N3, 1-methyluracil coordinated through the N3 atom; ox, oxalate; phen, 1,10-phenanthroline; terpy, 2,2′,2″-terpyridine; thy, thymine; trp, tryptophanate

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0010-8545/$ – see front matter
doi:10.1016/j.ccr.2007.03.006

Some of these recognition patterns are:

(a) long bonds between metal ions and nucleobases;
(b) hydrogen bonds between the amino group of amino acids and a carbonyl group of the nucleobases and vice versa;
(c) hydrogen bonds between a coordinated water molecule and one of the ligands;
(d) stacking between nucleobases and aromatic ring or hydrophobic residues of amino acids;
(e) possible direct d–π interactions between metal ions and aromatic rings, as well as CH···π interactions and other odd recognition patterns that can still be rationalized.

Keywords: Recognition patterns; Ternary complexes; Hydrogen bonding; Stacking; Amino acids; Peptides; Nucleosides; Purine and pyrimidine nucleobases

1. Introduction

Ternary metal ion complexes formed by amino acids (or peptides) and nucleobases (or nucleosides) (Fig. 1) may be used to understand more complex biological interactions. Until now, two major reviews have been published [1,2] and two more are devoted only to palladium [3] and platinum [4]. The discrimination and selectivity in such systems have been also studied by Sigel and co-workers [5–9].

There is a good agreement between the Lippert classification of ternary complexes into three different types and their biological relevance [1,2,10,11] (Fig. 2):

(a) Direct metal-mediated interactions between nucleosides and proteins. For example, platinum cross-linking between histones and DNA.
(b) Metal ion promotion of indirect interactions, where the metal ion is bound to a peptide and this complex then recognizes DNA or nucleotides. Good biological examples are zinc finger or metallo-regulatory proteins.
(c) Metal ions promoting indirect interactions, where the metal ion is bound to a nucleotide or nucleic acid sequence and this complex recognizes a protein. The interaction of cisplatin with DNA that is recognized by the HMG protein is a standard example.

Types b and c of this Lippert classification [10,11] can offer relevant subtypes if the metal ions interact through water molecules with the pertinent ligands.

2. Recognition patterns

From the literature [1–4] it is becoming clear that the formation of ternary metal–amino acid–nucleoside compounds depends on different recognition patterns. These patterns are repeated in different compounds and have become strategies for the synthesis of desired complexes. Considering all the available data, X-ray structures [10,12–28] (Table 1), solid state studies [1,2,29–32] and solution studies [1,2,5–9,33–55], we can summarize some of the driving forces for recognition reactions. A possible list of them, with selected examples, is indicated below in Table 1.

2.1. Long bonds between metal ions and nucleobases

From known X-ray structures of ternary complexes [10,12–28], a long metal–O(2) bond (about 280 pm) for cytosine (cyt) and cytidine (cyd) derivatives [12–16] is found in compounds of Cu(II), Pt(II) and Cd(II). These ancillary bonds support the main metal-N(3) (or N(1)) short bond (Fig. 3). A similar situation occurs with the dimethylhypoxanthine ligand (7,9-dimehypox) where copper(II) is coordinated to N(1) with a normal bond length and to the C(6)=O carbonyl group in a long ancillary bond that reinforces the main Cu(II)–N(1) primary bond [17].

In other cases, as for instance in the complexes *trans*-[$(CH_3–NH_2)_2$Pt(gly-*N*)(mcyt-N^3)]$(NO_3)\cdot 2H_2O$ [18] and [Pd(gly-L-his)(mcyt)]$\cdot 3.5H_2O$ [10], only a Pt(II)–N(3) bond with cytosine is present (Table 1).

Ligands like cytidine offer for metal ions the N(3) and the C(2)=O sites, and depending on the metal ion (either side may be the primary one) both sites may coordinate giving rise to four-membered chelates. With the metal ions considered here, these four-membered rings are of course distorted, less with Cd(II), but significantly with Cu(II) or Zn(II). The point is that these four-membered rings are found in the solid state but in aqueous solution they will hardly persist. There, most likely six-membered semi-chelates are formed which involve a water molecule [56,57].

2.2. Intramolecular hydrogen bonds

2.2.1. Hydrogen bond between the amino group of an amino acid and a carbonyl group of the nucleobase or vice versa

Two coordinated ligands within the coordination sphere of the same metal ion can "recognize" each other. In some cases, as in [Cu(gly-gly)(creat)] [58], even two recognition patterns are present (Fig. 4).

Also, in the [Pd(gly-L-tyr)(cyd)]$\cdot 6.5H_2O$ complex [22], mediated by the metal ion, two intramolecular recognition hydrogen bonds between the oxygen of the coordinated carboxylate group and the cytidine amino group (dist. O···H–N = 230 pm[1]), and between the coordinated amino

[1] All the hydrogen bond distances are given between the acceptor and the hydrogen atoms.

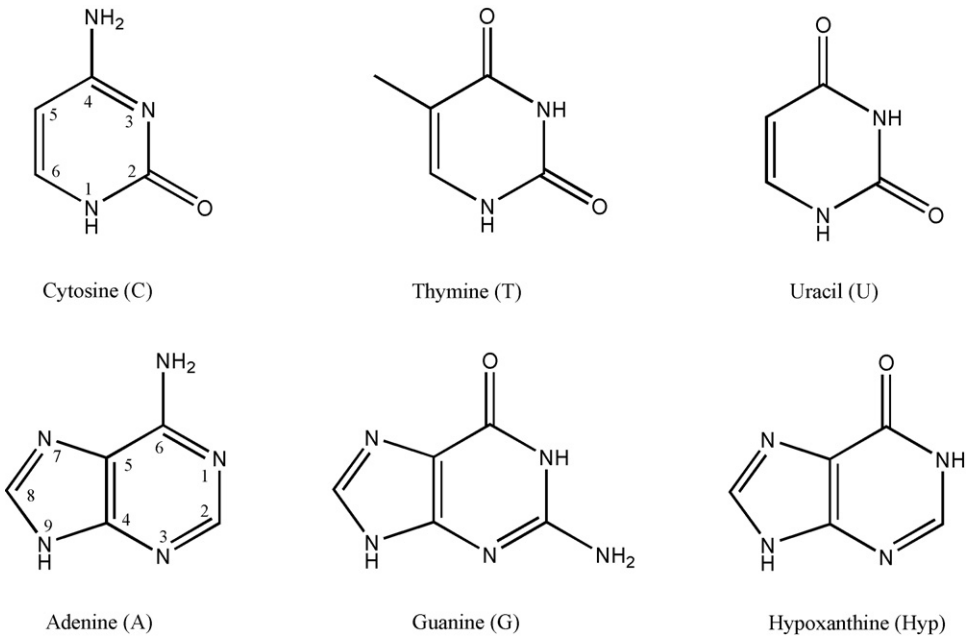

Fig. 1. Chemical structures and atom numbering of purine and pyrimidine nucleobases.

group of the dipeptide and the O(2) atom of cytidine (dist. O···H–N = 234 pm) are present.

In other cases, using ligands like acetylacetonate (acac) [59], the recognition pattern forms between the amino moiety of adenine and a coordinated carbonyl group (C=O). In further cases, a N atom of cytosine recognizes a NH_2 group of ethylenediamine (en) [60] forming a N–H···N bond, or a NH_2 group of ethylenediamine is recognized by the O(2) atom of 5-chlorouracil forming a C=O···H–N hydrogen bond [61]. In the case of the [Pd(gly-L-metH)(Hmgua)]$(NO_3)\cdot H_2O$ [25] complex (Fig. 5) there is a hydrogen bond between the terminal amino group of glycine and the O(6) of protonated 9-methylguanine (Hmgua) which is responsible for the tilting of the base towards the plane defined by the square planar coordination sphere of Pd(II).

The above pattern is also repeated with pyrimidine bases as for instance in the [Cu(gly-gly)(micyt)] complex (Fig. 6) [24]. Added to an ancillary long Cu(II)–O(4) bond, a hydrogen bond

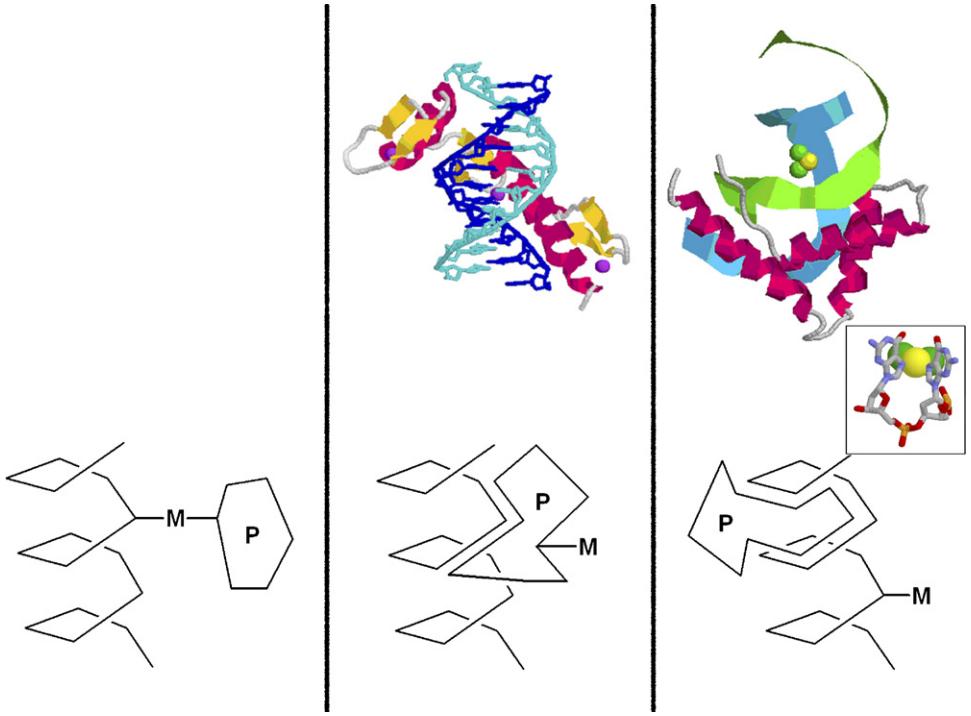

Fig. 2. Metal–peptide–nucleotide classification. Examples: (a) left, no real example is found in the literature; (b) middle, zing finger recognizing a DNA sequence (PDB: 1ZAA); (c) right, cisplatin bound to a DNA sequence recognizing HMG1 (PDB: 1CKT).

Table 1
X-ray structures for metal–amino acid (or peptide)–nucleobase (or nucleoside) ternary complexes

Complex	Coordination metal geometry	Amino acid (or peptide) bond	Nucleobase bond	Intramolecular bonds	Reference
[Cu(gly-gly)(ade)(H_2O)]	Square pyramidal	O_{car}, N_{ami}, N_{pep}	N(9)	–	[19]
[Cu(gly-gly)(made)(H_2O)]·4H_2O	Square pyramidal	O_{car}, N_{ami}, N_{pep}	N(7)	*Hydrogen bond* NH_2(ade)···OH_2 d = 234.7 pm	[21]
[Cu(gly-gly)(cyd)]·2H_2O	Square planar	O_{car}, N_{ami}, N_{pep}	N(3)	Cu···O(2)(cyd) d = 274 pm	[12,13]
[Cu(gly-gly)(cyt)]·2H_2O	Square planar	O_{car}, N_{ami}, N_{pep}	N(3)	Cu···O(2)(cyt) d = 281.9 pm	[14]
[Cu(gly-gly)(7,9-dimehypox)]·4H_2O	Square planar	O_{car}, N_{ami}, N_{pep}	N(1)	Cu···O(6)(7,9-dimehypox) d = 297.0 pm	[17]
[Cu(gly-gly)(icyt)]·2H_2O	Square planar	O_{car}, N_{ami}, N_{pep}	N(3)	*Hydrogen bond* C(4) = O(icyt)···HN_{pep} d = 287 pm	[24]
[Cu(gly-gly)(micyt)]·H_2O	Square planar	O_{car}, N_{ami}, N_{pep}	N(3)	*Hydrogen bond* C(4) = O(micyt)···HN_{pep} d = 280 pm	[24]
[Cu(L-ala-gly)(icyt)(H_2O)]·H_2O	Square planar	O_{car}, N_{ami}, N_{pep}	N(3)	–	[26]
[Cu(L-tyr-gly)(icyt)]·3H_2O	Square planar	O_{car}, N_{ami}, N_{pep}	N(3)	Cu···O(4)(icyt) d = 274.7 pm. *Hydrogen bond* C(4) = O(icyt)···HN_{pep} d = 259.0 pm	[26]
cis-[$(NH_3)_2$Pt(gly)(mcyt)](NO_3)·2H_2O	Square planar	N_{ami}	N(3)	Pt···O(2)(mcyt) d = 298.7 pm	[16]
trans-[$(CH_3$–$NH_2)_2$Pt(gly)(mcyt)](NO_3)·2H_2O	Square planar	N_{ami}	N(3)	–	[18]
cis-[Pt(glyH–N)(mura-N3)$(NH_3)_2$]	Square planar	N_{ami}	N(3)	–	[23]
[Pd(gly-L-his)(mcyt)]·3.5H_2O	Square planar	$N(3)_{im}$, N_{ami}, N_{pep}	N(3)	–	[10]
[Pd(gly-L-tyr)(cyd)]·6.5H_2O	Square planar	O_{car}, N_{ami}, N_{pep}	N(3)	*Possible N–H···π interaction*. d–π *interaction. Hydrogen bonds* NH(gly)···O(2)(cyd) and O(tyr)···N(4)(cyt)	[22]
[Pd(gly-L-metH)(Hmgua)](NO_3)·H_2O	Square planar	N_{ami}, S_{thioet}, N_{pep}	N(7)	*Hydrogen bond* C(6) = O···NH(gly) d = 265 pm	[25]
[Cd(hip)$_2$(cyt)(H_2O)$_2$]	Distorted trigonal bipyramid	O_{car}	N(3)	Cd···O(2)(cyt) d = 268.7 pm. *Stacking. Hydrogen bonds* N–C = O(cyt)···H_2O_{coord} and –OC = O···H_2O_{coord}	[15]
[Co,Ni,Zn(I-hip)$_2$(ACV)(H_2O)$_3$]	Octahedral	O_{car}	N(7)	*Stacking. Hydrogen bonds* C(6) = O(gua)···OH_{2coord} and –OC = O···OH_{2coord}	[27]
[Pt(bmp)(L-arg)](GMP)·5H_2O	Square planar	O_{car}, N_{ami},		*Stacking*. d–π *interaction. Hydrogen bond* N(arg)–O(Phosphate)	[28]

car = carboxylate; ami = amine; pep = peptide bond; thioet = thioether; d–π, see Section 2.4.3.

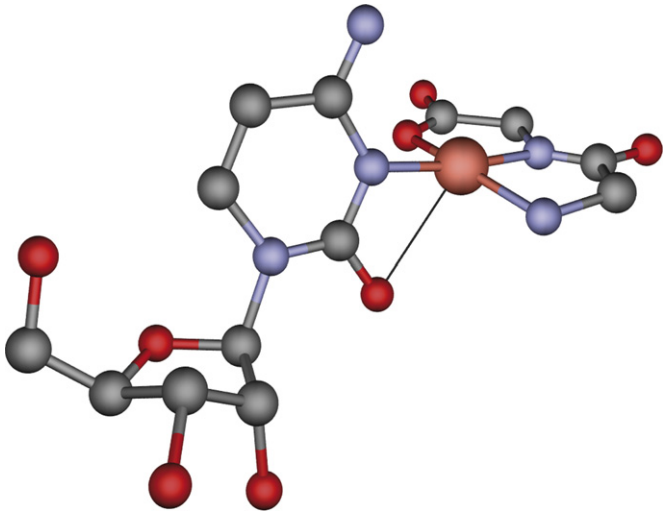

Fig. 3. Ancillary bond in the [Cu(gly-gly)(cyd)]·2H_2O complex [12,13]. Ancillary distance Cu(II)–O(2) = 280 pm (from Mercury) or 274 pm (according to the authors). CCDC code: GLCYCV.

between the O(4) atom of isocytosine and the NH_2 group of the dipeptide is present.

In some cases, as for instance in [Cu(gly-gly)(bzim)] and [Cu(L-ala-gly)(bzim)] complexes [62,63], a nearly coplanar arrangement of the Cu(II)–peptide plane and that of the benzimidazole ring is observed, showing a twisting of 20.8° from the coordination plane which favors the intramolecular C(8)–H···O–C hydrogen bond interaction (dist. C–H···O = 229 pm) (Fig. 7). This is amazing, but similar complementary recognition patterns can be found in DNA thymine–adenine pairs where, in addition to the two normal hydrogen bonds, also a C_{thy}=O···H–C_{ade}(2) bond is formed [64].

Very recently the role of these intramolecular bonding recognitions between amino–nucleobase or nucleobase–nucleobase coordinated to platinum(II) has been indicated as an indirect role for a metal ion in acid–base catalysis of nucleic acids pointing to a stabilization in solution and thus promoting catalytic activity [65].

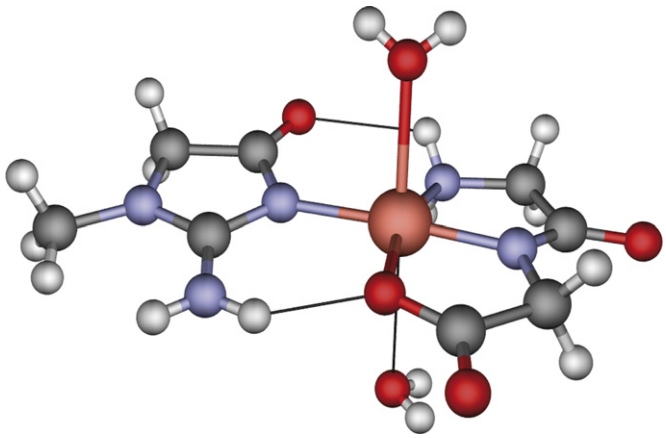

Fig. 4. Hydrogen bond recognition in [Cu(gly-gly)(creat)(H_2O)]·1.5H_2O [58]. Distances: O(creat)–NH_2(gly-gly) = 232 pm; NH_2(creat)–O(coordinated carboxylate group) = 197 pm. CCDC code: ZEBNID.

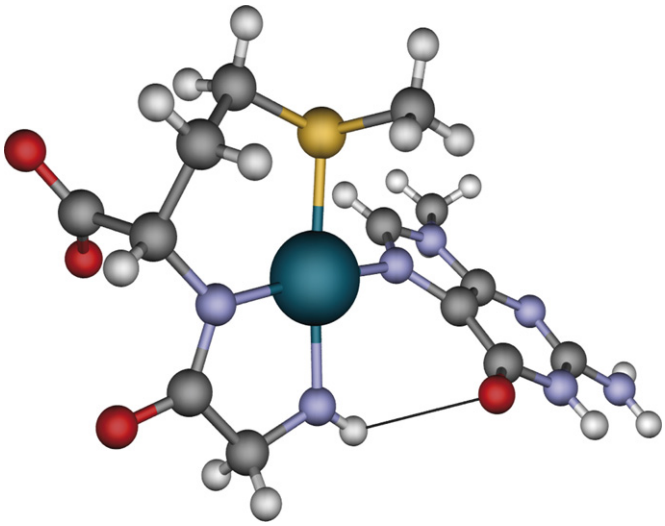

Fig. 5. Hydrogen bond recognition between a coordinated terminal NH_2 group of a peptide and the O(6) atom of an N(7)-coordinated 9-methylguanine; dist. = 265 pm in [Pd(gly-L-metH)(mgua)](NO_3)·H_2O [25]. CCDC code: RIMJIG.

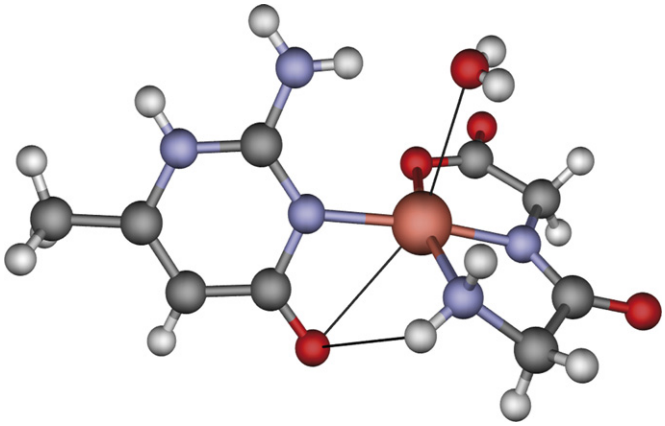

Fig. 6. Recognition in the [Cu(gly-gly)(micyt)] complex [24]. Added to an ancillary long bond (dist. = 278 pm) is a hydrogen bond between the O(4) atom from the isocytosine and the NH_2 group of the peptide (dist. = 280 pm). CCDC code: PULPUH.

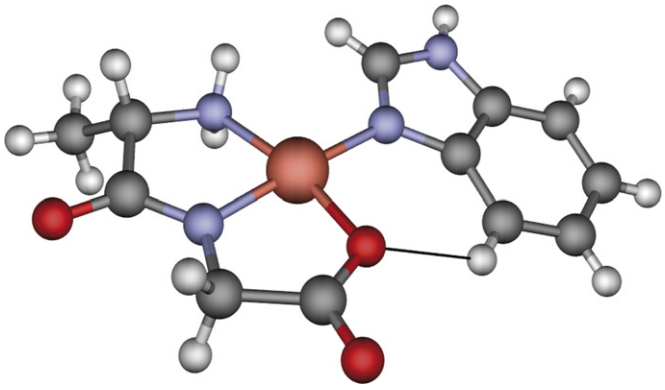

Fig. 7. In [Cu(L-ala-gly)(bzim)]·3H_2O [63] exists an intramolecular recognition with a hydrogen bond between the C_{arom}(8)–H···O (coordinated carboxylate); dist. = 229 pm. CCDC deposition no. 183541.

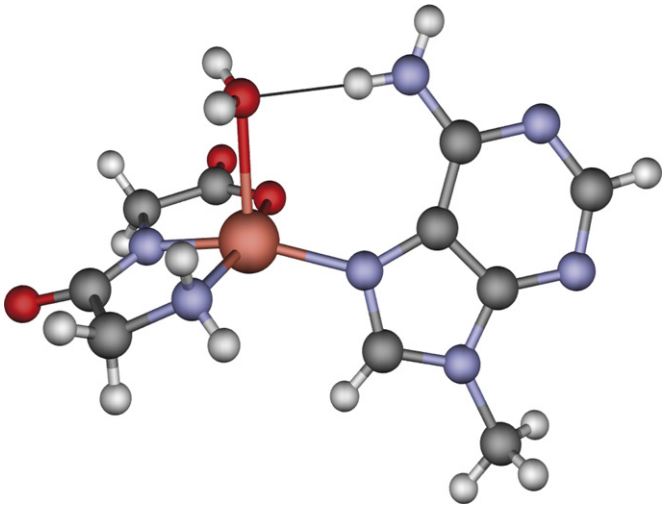

Fig. 8. In the [Cu(gly-gly)(made)(H_2O)] complex the coordinated water molecule recognizes the amino group of the N7-coordinated 9-methyladenine (dist. O(w)–N(6-amino) = 196 pm) [21]. CCDC code: GLMACU.

Kimura and Kikuta [66] have used the recognition between oxygen atoms of cytosine and NH groups of macrocycles in order to design selective DNA–nucleobase recognition systems.

2.2.2. *Hydrogen bond between a coordinated water molecule and a ligand*

Water molecules in the coordination sphere of a metal ion can interact with ligands through hydrogen bonds. This outer sphere interaction appears widely in the literature, i.e. not only in X-ray diffraction studies but it is also detected in solution by NMR.

Depending on the nucleobase, such an interaction can occur, e.g., with the 6-amino moiety of adenine as in [Cu(gly-gly)(made)(H_2O)] (Fig. 8), where the distance between $H_2O\cdots HN_{ade}(6)$ is only 196 pm [21].

For guanine derivatives, normally the hydrogen bonds are formed between the coordinated water and guanine O(6) (Table 1). This trend is repeated for guanine and acyclovir (ACV) derivatives in binary and ternary compounds [27,67–70] (Fig. 9).

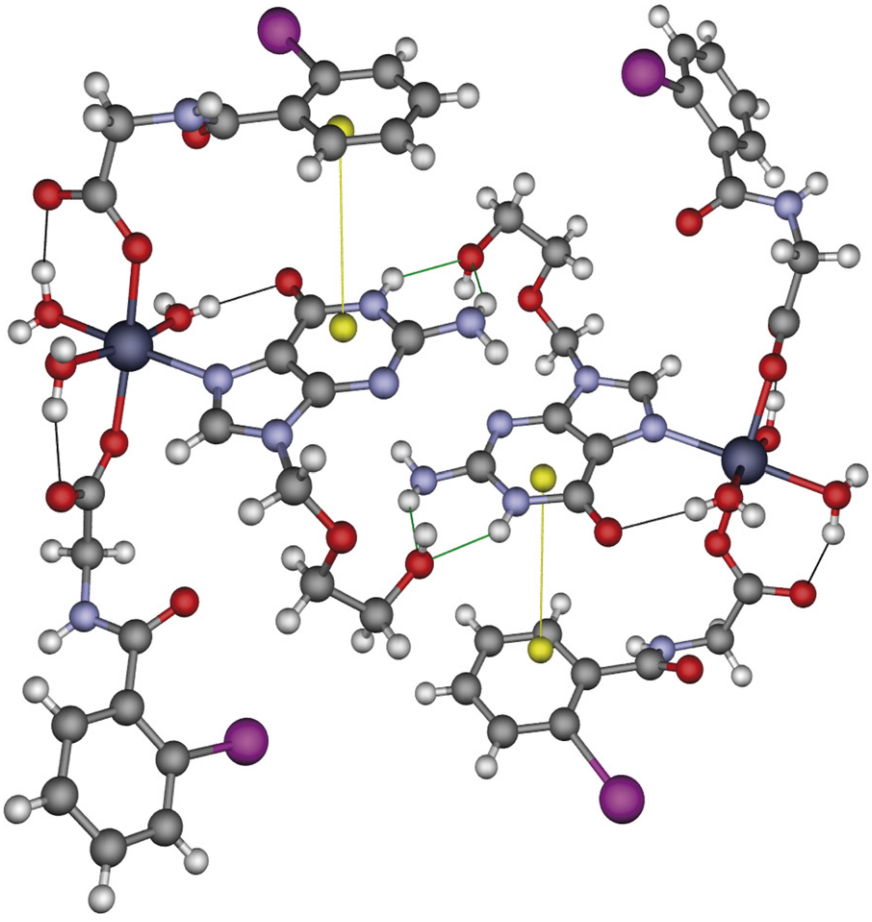

Fig. 9. Intramolecular recognition patterns in [(Co, Ni or Zn)(I-hip)$_2$(ACV)(H_2O)$_3$] [27]: (a) a coordinated water molecule recognizes O(6) of the guanine moiety (dist. H(w)–O(6) = 194 pm) (black thin lines); (b) hydrogen bonds between two coordinated water molecules and coordinated carboxylate groups (dist. H(8w)–O(car) = 175 and 179 pm) are formed (black thin lines); (c) a stacking interaction occurs between the guanine ring of ACV and the aryl ring of *ortho*-iodohippuric acid (indicated by yellow centroids) at 350 pm. The coordinated metal ion refers to Zn(II) or Co(II) because the two compounds are isostructural. CCDC deposition nos. 237827 (the zinc complex) and 237828 (the cobalt complex). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

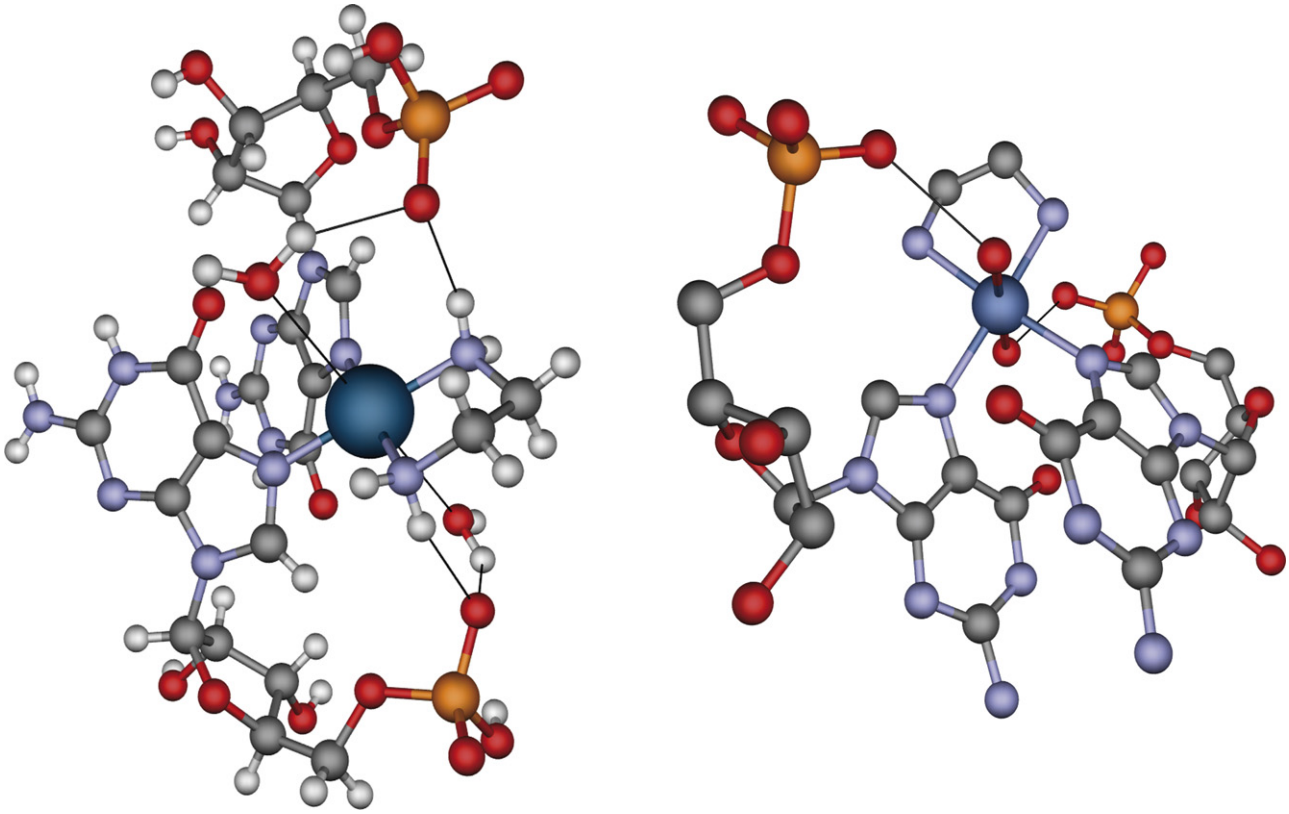

Fig. 10. (On the right) Hydrogen bond recognition between a phosphate group and water in $[Ni(en)(H_2O)_2(GMPH)_2]$ [69] (dist. O(w)···O(phos) = 262 pm). (On the left) The phosphate group of GMP and the amino group of ethylenediamine (dist. N–H···O(phos) = 206 pm) interact in $[Pt(en)(H_2O)_2(GMPH)_2]$ [71]. CCDC codes: SAZPAK01 and ZACGEP, respectively.

Albeit the recognition of purine–base residues is extremely important, but other ligand groups can also interact with water molecules of the coordination sphere. A well-known example is the interaction of the phosphate group in nucleoside 5′-monophosphates [68,69], for instance in the $[M(H_2O)(5\text{-NMP})]$-type complexes or also in the $[Ni(en)(H_2O)_2(GMPH)_2]$ complex (Fig. 10) [69].

In other examples, like in the square plane complexes $[(Pt \text{ or } Pd)(en)(GMPH)_2]\cdot 9H_2O$ these intramolecular interactions can occur between an ethylenediamine amino group and an oxygen atom from the phosphate group. Electrostatically bonded axial water molecules play key roles in a network of hydrogen bonding involving the phosphate O, ethylenediamine NH and C(6)O of the purine ring [71]. NMR shows that macrochelation involving NH···O(phosphate) is present in solution at pH 7, where the coordinated nucleotide is the dianionic form. This macrochelation also exists at low pHs where the nucleotide is the monoanionic form (as in the crystal).

Finally, a water molecule in the coordination sphere of a metal ion can interact with the carboxylate group of an amino acid in ternary complexes or with the carboxamide group of a peptide bond (Figs. 9 and 11) [15,27]. For instance, in the dimeric $[Cd(hip)_2(cyt)(H_2O)]_2$ complex [15] a coordinated water molecule recognizes a coordinated carboxylate group (dist. CO–O···H–OH = 212 pm) while another coordinated water molecule interacts with the carboxamide group of the hippurate moiety (dist. C=O···H–OH = 199 pm).

2.2.3. Hydrogen bond between the phosphate group of a nucleotide and amino groups

There exists also the possibility of an interaction between an amino acid residue (for instance the guanidinium group of an arginine) and a phosphate group as in the [Pt(bmp)(L-arg)]·GMP·5H$_2$O complex (Fig. 12) [28] (dist. N–H···O = 187 and 192 ppm). The hydrogen bond with the coordinated amino group (dist. N–H···O = 198 pm) further contributes to fixing the phosphate molecule. It is remarkable that one [Pt(bmp)(L-arg)] complex unit interacts with one GMP unit by means of a combination of a stacking interaction, possibly a d–π interaction, and hydrogen bonds to form a discrete adduct in the crystal structure.

2.3. Intermolecular hydrogen bonds

In crystal structures different intermolecular hydrogen bond interactions can be detected between carboxylate and peptide groups like those depicted in Figs. 9 and 13 [27].

In addition, special intermolecular interactions with recognition between nucleobases that are different from those described as Watson–Crick and Hoogsteen pairs, can be also found [27,28,65,70,72]. One example is shown in Fig. 13 where a tandem of hydrogen bonds between the exocyclic amino groups and

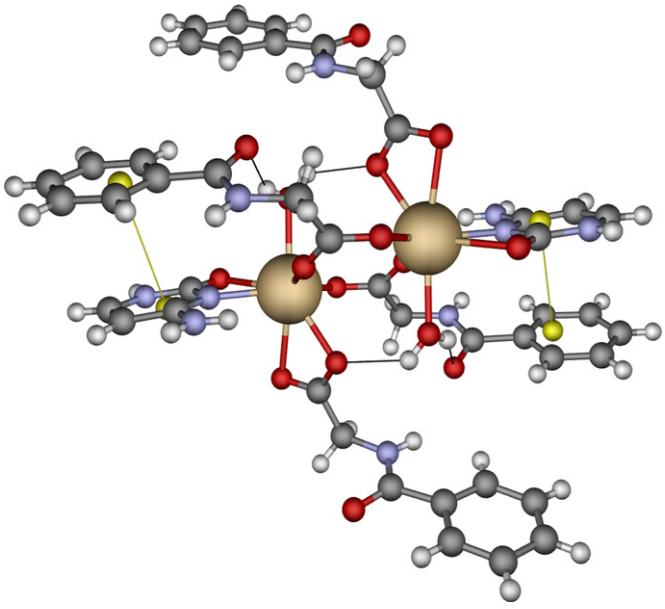

Fig. 11. Intramolecular recognition patterns in $[Cd(hip)_2(cyt)(H_2O)]_2$ [15]: (a) a coordinated water molecule recognizes a coordinated carboxylate group (dist. CO–O···H–OH = 212 pm); (b) a coordinated water molecule recognizes a coordinated carboxamide group (dist. C═O···H–OH = 199 pm); (c) a long ancillary metal–O(2) of cytosine bond occurs (dist. = 230 and 235 pm); (d) stacking between cytosine and the benzene residue is seen. Note, the ring planes are not strictly parallel, there is a tilting angle of approximately 10°, the closest (336 pm) and largest (360 pm) distances are indicated by yellow centroids. CCDC deposition no. 145108. {The color code follows the IUPAC recommendations and the Mercury program standards.}

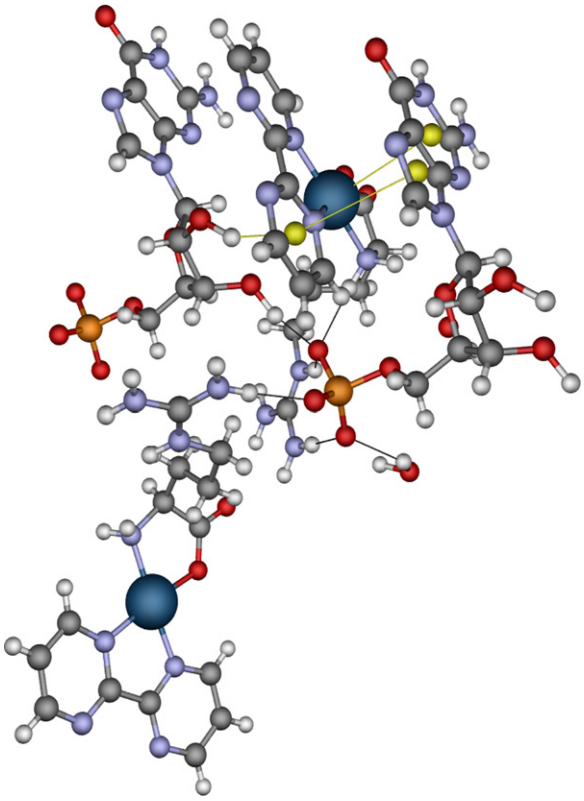

Fig. 12. The [Pt(bmp)(L-arg)]·GMP·$5H_2O$ complex [28] contains several recognition patterns. Depicted in black thin lines: (a) hydrogen bonds between the coordinated amino group of arginine and the phosphate group of the nucleotide (dist. = 198 pm); (b) further recognition occurs with the non-coordinated guanidine moiety and the phosphate group (dist. = 191, 186 and 184 pm) and one 3′-OH sugar group of another GMP molecule (dist. O(phos)···H–O(sugar) = 168 pm). Depicted with yellow centroids and connected by yellow thin lines is a stacking interaction between the guanine and bmp rings of *ca.* 348 pm; also, a possible d–π interaction between Pt(II) and the stacked guanine ring may occur with a distance between the centroids of 349 pm; finally there is an interaction of the 2′-OH group of the ribose ring with the bmp ring (dist. O–H···ring = 192 pm). CCDC deposition no. 201008.

N(3), corresponding to two guanine moieties, are observed. Similarly, the N(1) of a 9-methyladenine recognizes the exocyclic amino group of another 9-methyladenine ligand and vice versa in the *trans*-$[Pt(NH_3)_2(Hdmade)(made)](ClO_4)_3\cdot 3H_2O$ complex [65].

Although it is very important in biological systems, not many examples exist in the literature for intermolecular interactions between peptides and nucleobases. In the Schiff base [Cu(N-salicylideneserinato)(cyt)]·$2H_2O$ complex [73] a bond between the NH_2 group of cytosine and the serine carboxylate group is present (282 pm, between donor and acceptor atoms).

On the other hand, it is known that molybdenum enzymes and Mg-ATP dependent kinases show this type of recognition which is essential for the chemistry of these enzymes. In adition, zinc finger interactions with DNA or RNA interactions with IRE-binding proteins are based on this kind of recognition [74]. It would be relevant to measure with models the thermodynamic parameters of such hydrogen bonds.

An unprecedented solid state characterization of a minor tautomer of adenine, as a free molecule stabilized through non-covalent interactions, is found in the complex {[Mn(μ-ox)$(H_2O)_2$]·(7H-adenine)·H_2O}, where the 7H-adenine tautomer is present owing to hydrogen bond interactions [75]. A different way of stabilizing tautomers is through the coordination of metal ions to nucleobases; in this way even rare tautomers of purines [76] or pyrimidines [77] may be stabilized.

2.4. Stacking between nucleobases and aromatic residues of amino acids and other hydrophobic forces

The so-called π–π stacking interactions between two aromatic ring systems are relevant in the recognition between nucleotides and side chains of the peptide-backbone of enzymes. As more X-ray structures are known, this kind of patterns becomes more relevant as for instance for ATP-binding proteins which were reviewed recently [78]. A great amount of work has been done with ternary models both in solution [2,7–9,33,34,36,38–40] and in the solid state [15,27,28] as well as with related systems [78–101].

An important point is that π–π interactions could have implications in kinetics and bioregulation. Together with common π–π stacking interactions, cationic d–π, C–H···π, C–I···π (for thyroxine derivatives) or other hydrophobic factors should also be considered.

Metal ion-assisted stacking interactions: (i) facilitate the hydrolysis of nucleoside 5′-triphosphates [100], (ii) promote

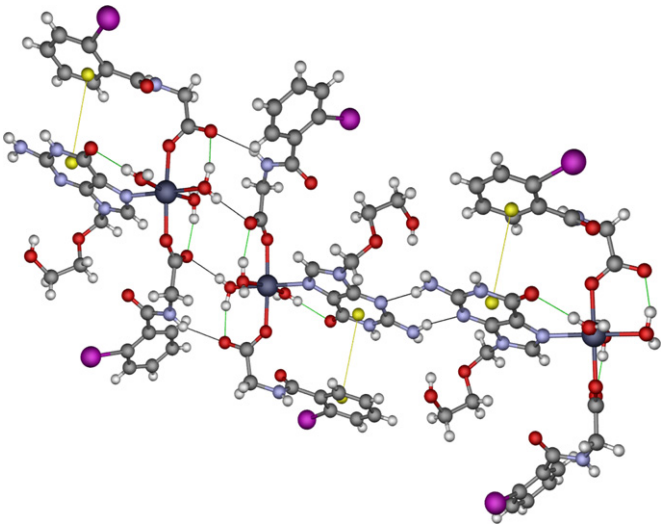

Fig. 13. Some of the intermolecular recognition patterns present in [(Co, Ni or Zn)(I-hip)$_2$(ACV)(H$_2$O)$_3$] complexes [27]: on the right side there is a tandem of recognitions between two guanine rings of ACV molecules depicted in black thin lines that is not a Watson–Crick nor Hoogsteen recognition pattern (N(3)···H–N(2) and vice versa). On the left side there are two recognitions between coordinated water molecules and the non-coordinated O atoms from carboxylate of I-hip and there are also two more recognitions between the other two non-coordinated O atoms of the carboxylate group and the N–H moiety from the peptide bond. CCDC deposition nos. 237827 (zinc complex) and 237828 (cobalt complex).

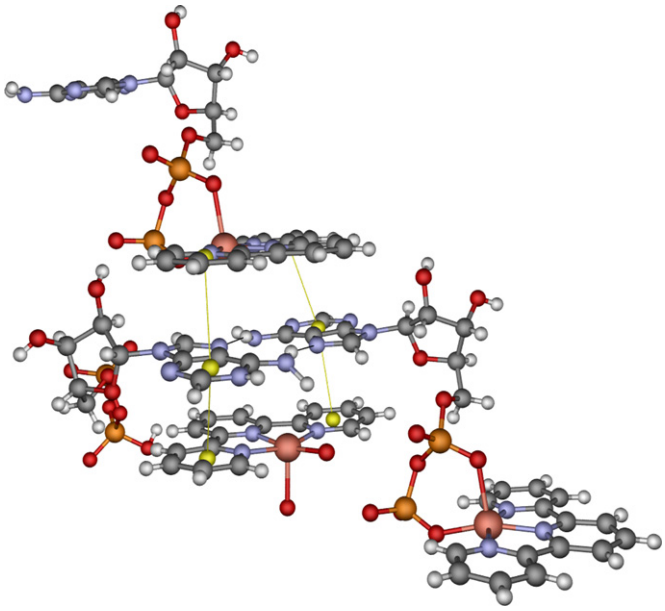

Fig. 14. [Cu(terpy)(H$_2$O)$_2$][Cu(terpy)(ADP)][H$_2$ADP]·16H$_2$O [72]: Stacking is indicated by yellow centroids between the adenine rings and the coordinated terpy ligands (dist. = 346–350 pm); it stabilizes the supramolecular aggregate. In the middle of the stacking cluster, two adenine moieties [one belonging to a coordinated ADP molecule (on the right) and the other to a free ADP molecule (on the left)] stack with two terpy moieties; one comes down from ([Cu(terpy)(H$_2$O)$_2$]$^{2+}$ and the other up from ([Cu(terpy)(ADP)]$^{2-}$; there are also two hydrogen bonds present (dist. N(6)–H···N(7) = 209 and 219 pm); recognition is further facilitated by the π–π interactions. CCDC code: BAZROJ.

special intermolecular interactions with recognition between the nucleobases different from the Watson–Crick and Hoogsteeen pairs (see for instance Figs. 14 and 15) [27,70,72], (iii) permit drug intercalation in DNA [101], (iv) induce chirality [27,85,102–104], and (v) modulate electron transfer [105].

For these reasons, the different types of non-covalent forces had been reviewed in the field of organic chemistry [106–108]. Also, quantum mechanical methods had been used to understand a special type of metal ligand aromatic cation–π interaction in which the cation is a part of a metal complex [109]. Moreover, semi-quantitative thermodynamic models of molecular recognition events have been proposed [110] to detect new recognition patterns, like anion–π interactions [111].

Experimentally, close contacts between halogen atoms and the carbon atoms of an aromatic ring have been observed in a halogen substituted phenylalanine with 2,2′-bipyridine [112] or

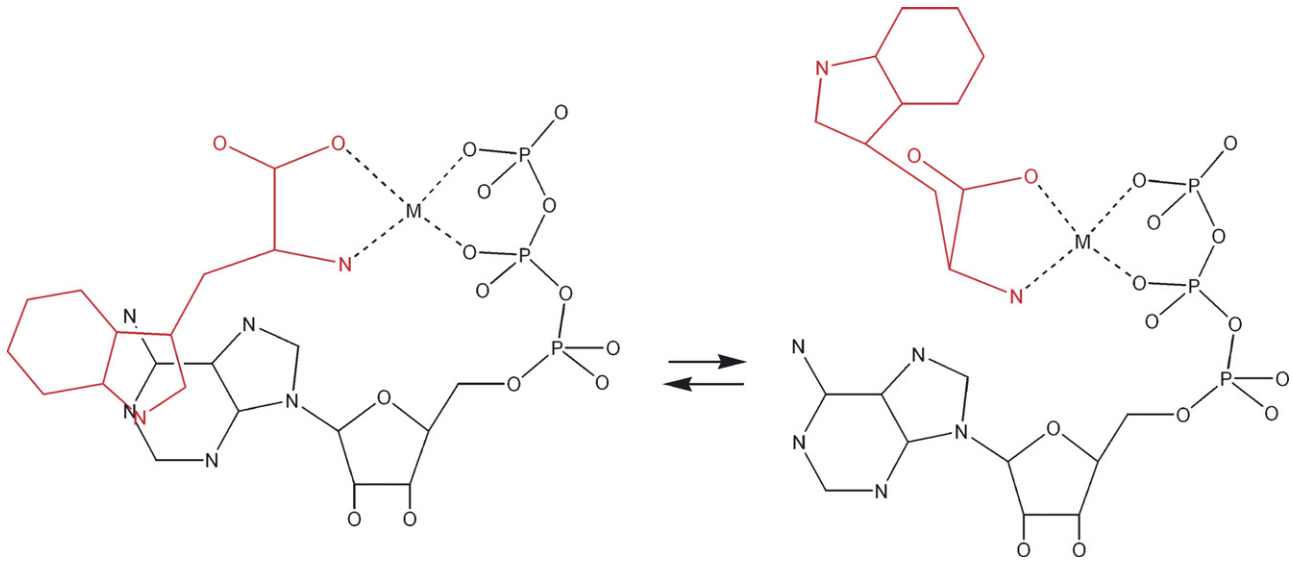

Fig. 15. Equilibrium between the open and closed forms with the stacking recognition in the M(ATP)(trp)$^{3-}$ complex [8,9].

other iodine contacts like I···I, I···H and I···C [113]. Also, interligand NH···π interactions are observed in solution by NMR spectroscopy [114].

Simple hydrophobic interactions must be also considered [2,29,37,115,116].

2.4.1. Stacking between nucleobases and aromatic ring residues of amino acids

Good examples for intramolecular stacks in ternary metal–aromatic amino acid residue–nucleobase systems are seen in the X-ray structures depictured in Figs. 9, 11 and 14. Moreover, good examples can be found in related systems where the nucleobase is normally substituted by phen- or bpy-type ligands like in Fig. 12 [9,72,79,80,83,85–95]. Fig. 14 depicts one of the related compounds, $[Cu(terpy)(H_2O)_2][Cu(terpy)(ADP)][H_2ADP]\cdot 16H_2O$, where stacking between the adenine rings and the coordinated terpy ligands stabilizes the supramolecular aggregate. In this example a recognition by hydrogen bonds between two adenine molecules that stack with two terpy molecules [down: $[Cu(terpy)(H_2O)_2]^{2+}$ ion, and up: $[Cu(terpy)(ADP)]^{2-}$ ion] is facilitated by π–π interactions (Fig. 14).

The stacking interactions are also well documented in solution by different techniques as potentiometry [2,36], NMR [34] or calorimetry [28,38–40]. Considering only the data that are related to amino acid residues and nucleobases or nucleosides the available literature is not overwhelming [1,2,7–9,33,34,36,38–40,44,46]. The equilibrium constant for the stacking interaction between CMP^{2-} and $H(trp)^{\pm}$ is only $0.77 \pm 0.70\,M^{-1}$; it increases with AMP^{2-} and $H(trp)^{\pm}$ to $6.83 \pm 1.62\,M^{-1}$ and with ATP^{4-} and $H(trp)^{\pm}$ it equals $6.2 \pm 1.2\,M^{-1}$ ($I = 0.1$ M) [9,36]. These stability constants confirm the natural trend that the purine nucleobases better interact than the pyrimidine ones. These data also indicate that the indole moiety of tryptophan forms somewhat less stable stacks with nucleobases than bpy or phen [4,7–9].

The percentages of the intramolecular stacks (Fig. 15) present in solution somewhat depend on the metal ion [7,9,34,36]. For instance, for the $M(ATP)(Trp)^{3-}$ complexes their values obtained by potentiometry oscillate between 35 ± 14 [Cu(II)] or 52 ± 12 [Mn(II)] and 74 ± 3 [Zn(II)] per cent; the NMR data indicate a value of 40 ± 15 [Zn(II)] per cent.

Calorimetry shows that the enthalpic interaction is very exothermic whereas the entropic factors are not favorable. For this reason, high enthalpic values of ΔH are compatible with very low equilibrium constants [9,38–40].

Stacking is also related with the dielectric constant of the solvents [8,9]. For the system Cu(II)/phen/ATP [8], the percentage of complex in the closed form with stacking is 90% for the $[Cu(phen)(ATP)]^{2-}$ complex in water, and shifts to only 46% if the solvent is a mixture of 50% (v/v) 1,4-dioxane–water. Formation of a metal–ion bridge between the individual parts of a stacking adduct favors the stability of this adduct strongly in comparison with the stacks in the pure organic-ligand system phen/ATP. The promotion factor in water is about 25 while in the dioxane–water mixture it is about 250. Sigel points out that these data indicate that the selectivity is much more pronounced under conditions with a reduced polarity [8]. There are also a number of cases where the addition of an organic solvent to an aqueous solution initially enhances the stacking/hydrophobic interaction, meaning that only at high concentrations of the organic solvent the interaction is diminished; consequently, the interaction passes through a maximum [8].

It is now well established that the "effective" dielectric constants in the active-site cavities of enzymes are reduced compared to that in bulk water due to the presence of aliphatic and aromatic amino acid side chains at the protein interface; the solvent dependent metal ion–nucleobase recognition and the extent of macrochelate formation is also affected in binary metal ion–nucleotide complexes. For example [117], the extent of the degree of macrochelation for Cu(5′-AMP) in different 1,4-dioxane–water mixtures passes through a minimum at about 10% using a 30% (v/v) dioxane–water solution. The degree of macrochelation recovers to a level of about 50% in 50% dioxane–water. Whereas it is also clear that addition of dioxane to an aqueous solution of the $Cu(ATP)^{2-}$ complex decreases the degree of macrochelation with increasing dioxane concentrations [117]. Macrochelation within the binary nucleotide–metal ion complexes and stacking interactions are opposing each other [118]. The change in conformation can also be recognized with other ligands; this fact indicates a role of the phosphate site for specific metal–fragment–nucleotide recognitions [119].

2.4.2. Common hydrophobic interactions

Amino acids with hydrophobic side chains like leucine, valine, proline, etc., show in solution studies an increase of the stability constants for their 2:1 complexes [1,2,29]. Usually, this stability enhancement is smaller than that observed for stacking. It should be added that hydrophobic interactions have also been proved to occur in ternary $M(ATP)(leucinate)^{3-}$ complexes in aqueous solution [9,37].

2.4.3. Cationic d–π interactions

Cationic d–π interactions have also been proposed to stabilize ternary complexes containing d-metal ions [41].

To our knowledge, only a few structures are known with an indicated cationic d–π interaction for a ternary peptide–nucleoside–metal ion complex; examples are $[Pd(gly\text{-}L\text{-}tyr)(cyd)]\cdot 6.5H_2O$ [22] (Fig. 16) and [Pt(bmp)(L-arg)]·GMP·$5H_2O$ (Fig. 12) [28]. More examples are known for related systems like $[Cu(trp)(bpy)]^+$ where the interaction occurs with the amino acid residue instead of a nucleobase moiety [81,93]. The problem in all these cases is that the close proximity of the aromatic ring to the metal ion does not necessarily mean that an interaction occurs; this proximity could be driven by the fact that the nearby ring reduces the intrinsic dielectric constant and that this strengthens the "ionic" interactions within the coordination sphere [93].

2.4.4. C–H···π and N–H···π interactions

Okawa first recognized the importance of C–H···π interactions in the stereoselective formation of several metal complexes [104]. A general survey of C–H···π interactions in the crystal

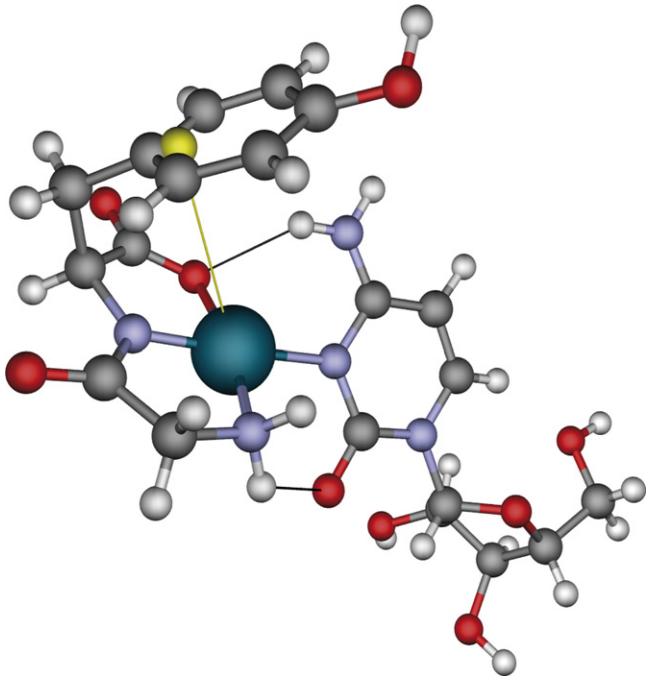

Fig. 16. The cationic d–π interaction is indicated by one yellow centroid connected to the metal ion by means of a yellow thin line (dist. Pd(II)-tyrosine ring = 372 pm) in the [Pd(gly-L-tyr)(cyd)]·6.5H_2O complex [22]. There are also two recognition hydrogen bonds present: one between the oxygen of the coordinated carboxylato group and the cytidine amino group (dist. O···H–N = 230 pm) and another one between the coordinated amino group of the dipeptide and the O(2) of cytidine (dist. O···H–N = 234 pm). CCDC code: BUCBUW. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

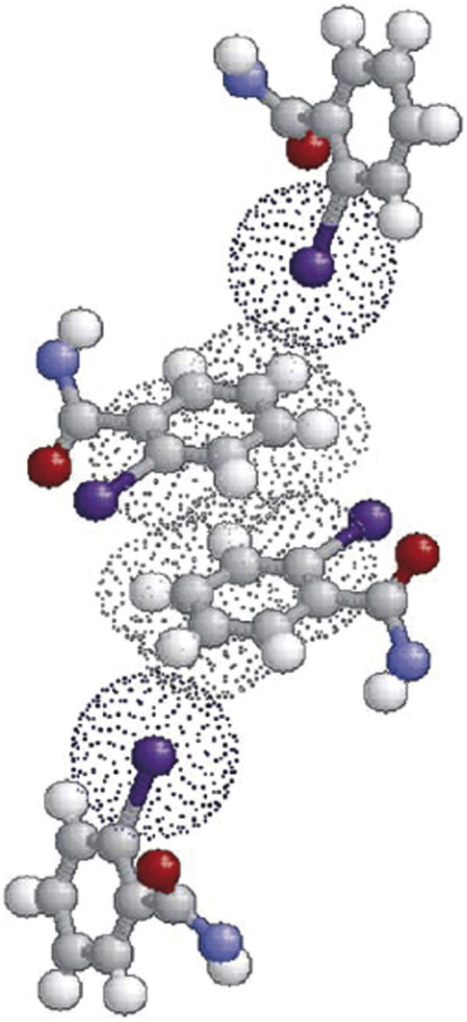

Fig. 17. C–I···π···π···I–C interaction in the [Cu(I-hip)$(phen)_2$]$^+$(I-hip$^-$)·7H_2O complex [123,125]. CCDC deposition no. 285763. (Reproduced with permission from the original publication [123].)

structure of transition metal compounds was made by Nishio and co-workers [120]. Nishio and co-workers defined different parameters for surveying this type of interaction in which a C–H (or N–H) interacts with an aromatic ring in regions where the hydrogen atom is offset out of the π-plane; the interaction distance must be shorter than the sum of the Van der Waals radii for the presence of these types of short contacts. The C–H···π interaction (or the N–H···π one) is the weakest extreme of non-conventional hydrogen bonds. Though weak, the C–H···π hydrogen bond plays significant roles, even in solution, such as the conformation of molecules as well as in chiral recognition [120].

Although to our knowledge there are no X-ray structures of a metal–amino acid–nucleoside ternary compound with a C–H···π (nor N–H···π) interaction, such interactions cannot be ruled out. Nevertheless, in case of the [Pd(gly-L-tyr)(cyd)]·6.5H_2O complex [22] depicted in Fig. 16, the NH_2 moiety of cytidine is 287 pm from the aromatic ring of tyrosine (whereas the sum of the Van der Waals radii of H and C calculated by Bondi is 290 pm [121]) which could correspond to a N–H···π interaction. On the other hand, related compounds like [Cu(gly-L-trp)(phen)]·2H_2O [122] show this type of interaction between phenanthroline and the trp residues as in other related complexes with bpy or phen [94,123]. In other cases of very similar complexes this interaction is not present [79,83]. On the N–H···π interactions side, they stabilize the most hindered rotamer of the (s)-tyrosinato side group in bis-[(s)-tyrosinato(diamine)cobalt(III)] complexes [114].

These kinds of interactions could be hypothetically also present in ternary systems in solution.

2.4.5. C–I···π interactions

The C–I···π interaction is a special case of the C-halogen···π interactions [124] as defined by Guru Row in organic molecules. They may be related also to C–H···π and N–H···π interactions as just defined and they could be relevant to understand thyroxine [3:5,3′:5′-tetraiodothyronine, T4)]-peptide recognition [123].

For tyrosine derivatives, which contain iodine atoms, different patterns related to I···I, I···H interactions must be considered [86,87,112,113]. Recently [123,125] in a related compound [Cu(I-hip)$(phen)_2$](I-hip)·7H_2O, a C–I···π interaction was described (Fig. 17).

3. Concluding remarks

Quite often the described recognition patterns appear in groups. For instance, the molecules depicted in Figs. 9, 11 and 12, encompass different intermolecular recognition patterns including stacking and hydrogen bonding. This means that the summarized recognition patterns facilitate the formation of ternary complexes as it is shown by some of the examples listed in Table 1.

This review uses mostly solid state data (some of them very recent) to infer structures for biological molecules in comparison with solution data when such are available in the existing literature. Although there is not a total warranty that the solid state structures persist in solution, some of the patterns could perhaps be found in solution in the future.

Despite the complexity of biological ligands, together with experimental problems like low solubility, it is clear that these type of ligands own molecular recognition patterns and are thus involved in binding and selection of substrate(s) by a given receptor molecule; this may also give rise to specific functions [126]. We are at present at the advent of discovering many more of such recognition phenomena, induced by different interactions, similar to those defined in this review with low-molecular-weight ligands.

Acknowledgements

One of us, Miquel Barceló-Oliver, is grateful to the "Conselleria d'Economia, Hisenda i Innovació" of the Government of the Balearic Islands for a PhD fellowship [FPI05-34068589T]. The authors also thank the "Vicerectorat de Investigació i Política Científica" of the University of the Balearic Islands (project no. UIB2005/5), the "Conselleria d'Economia, Hisenda i Innovació" (competitive groups grant) of the Government of the Balearic Islands, and the "Dirección General de Investigación Científica y Técnica" of the Spanish authorities (project no. CTQ2006-09339) for their generous financial support.

The authors acknowledge the Cambridge Crystallographic Data Center (CCDC) and its Senior Scientific Editor Mrs. G. Heale for helping us to obtain all the crystallographic material used in this review. The software used to generate the figures and to calculate the distances and angle values are Mercury 1.4.1 [127] which can be obtained free of charge from CCDC.

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