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Multiplicity of metal ion binding patterns to nucleobases

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Dedicated to Professor Dr H.P. Fritz, TU Munich, on the occasion of his 70th birthday

Contents

Abstract

The systematic study of interactions between metal ions and nucleobases, the constituents of nucleic acids, as well as nucleic acids in general started some 50 years ago, around 1950.

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This review is an attempt to recall the developments in this field, to list metal binding patterns as established today, and to examine prospects for the future. The focus of this survey will be on the coordination chemistry of metal species with the heterocyclic parts of nucleobases.

Keywords: Metal ions; Nucleobases; Binding patterns; X-ray crystallography

1. Introduction

The origin of nucleic acid chemistry is generally attributed to Friedrich Miescher, when he started in the 1860s to isolate what he called 'nuclein' from human pus cells. This material later proved to be a mixture of nucleic acids and proteins. It took until 1910–1930 to clearly identify the composition of RNA and DNA constituents (nucleosides, nucleotides) and until the 1940s to conclusively establish the hereditary function of DNA. Yet another decade later, in 1954 James D. Watson and Francis H.C. Crick came up with their model of B-DNA [1].

The systematic study of metal ion-nucleic acid interactions has many roots. In addition to the ones related to the above observations, several others deserve mentioning. The realization that nucleic acids are strong acids and for this reason require cations, hence metal ions or protonated amines, was among the earliest. In 1924 Einar Hammarsten, in a rather comprehensive paper of 83 pages had stated that 'Na^+ and other available metal cations' would be required in the cell nucleus to balance the negative charge of (what was later called) DNA [2]. Some 20–30 years earlier Alfred Werner had formulated essentials of coordination chemistry [3] which also provided the basis for understanding metal–nucleic acid complex formation in general.

Barnett Rosenberg's seminal discovery of Cisplatin (*cis*-$[Pt(NH_3)_2Cl_2]$) being a potent antitumor agent [4] and subsequent work strongly suggesting that Pt–DNA binding was responsible for triggering tumor cell killing, proved a climax in the field. Ever since then metal-nucleic acid studies have burgeoned.

The turn of the century is a timely occasion to reflect on the development of the field and to summarize as to where we stand at present and to define challenges for the future.

2. Nucleic acid composition and structures

Nucleic acids [5] are composed of nucleotides which are joined through phosphodiester linkages. Each nucleotide consists of a cyclic sugar (β-D-ribose in RNAs, β-D-2′ deoxyribose in DNA), which is phosphorylated in the 5′ position of the sugar and carries a heterocyclic ring at the C1′ position (β-glycosyl C1′-N bond). The heterocycles are, in general, the purine bases guanine (G) and adenine (A) and the pyrimidine bases cytosine (C) as well as thymine (T, DNA) or uracil (U, RNA).

Methylated forms of C (5-methylcytosine) and A (N6-methyladenine) occur at some stage in DNA, and many (> 30) modified bases are found in tRNAs. DNA usually occurs as an antiparallel double helix with base pairing through H bond formation between the complementary bases G and C. In addition, numerous other forms (e.g. triple-stranded DNA, four-stranded DNA, parallel stranded DNA, etc. [6]) have been established and there is every reason to believe that new forms await discovery. RNA is a single-stranded nucleic acid molecule, which by folding back on itself, can form double-stranded or triple-stranded structures in addition to single stranded regions. RNA structures are extremely complex, and the short tRNAs are just simple examples of how complicated RNA structures may be. tRNA structures were determined by X-ray crystallography earlier than DNA [7], with $tRNA^{phe}$ reported in 1973 [8].

3. Historical review of metal–nucleic acid interactions

3.1. Early history

The systematic binding studies of DNA with a metal ion — Hg^{2+} — started in the early 1950s, when Katz demonstrated that reversible changes in physico-chemical properties of DNA occurred upon addition of Hg^{2+} ions [9]. At the same time it was recognized that a minimum electrolyte concentration is required to maintain DNA in its double-stranded structure [10], but it took another 10 years to quantify the relationship between melting temperature T, and ionic strength [11]. In 1954 Thomas was able to demonstrate that Hg^{2+} ions indeed attach to the nucleobases of DNA [12], as further established by other groups in the years to come [13]. Complexation studies of Ag^{+} with RNA were initiated in the late 1950s [14], and by the mid 1960s numerous papers on the nucleic acid binding patterns of other metal entities such as CH_3Hg^{+} [15], Cu^{2+} [16] and Zn^{2+} [17] had been published. It was during this time that Beer and Moudrianakis made the suggestion that heavy metal labels exhibiting a specificity for the heterocyclic entities of the four common nucleobases (as opposed to typical phosphate binding, which does not lead to base specificity) might be useful for sequencing purposes of single-stranded DNA and RNA molecules [18]. Undoubtedly this idea provided a major impetus to this new field. A short review article by Weser [19], possibly the first one in the field, had appeared in 1968, summarizing stability constants of metal–nucleobase complexes and discussing metal binding patterns. By then it had also been recognized that metal ions frequently bind to both the phosphate groups of the nucleotides and to the heterocyclic parts in a concentration-dependent manner [20]. As a consequence, there was a marked influence of the metal ion and its concentration on T_m of a particular DNA, with low concentrations of the metals leading to thermal stabilization of DNA with all $+2$ metal ions studied (Mg, Co, Ni, Mn, Zn, Cd, Cu), but high concentrations of Cd^{2+} and Cu^{2+} causing unwinding due to increased binding of these ions to the heterocyclic bases.

The advent of routine single crystal X-ray crystallography in the 1960s eventually led to a large body of detailed structural information on metal–nucleobase interactions. The first X-ray structure of a metal–nucleobase complex, of a dicopper(II) compound containing four bridging (N3, N9) adenine anions and two axial aqua ligands, was reported by Sletten in 1967 [21]. The composition of this compound had already been correctly predicted by Weiss and Venner 4 years earlier [22]. Because of the use of the adenine parent compound rather than a N9-blocked derivative, the Cu^{II} complex above was not a good model for a Cu-nucleic acid interaction, but it was a start. Only one year later the X-ray structure of a complex of $CuCl_2$ with unsubstituted cytosine was published [23], with the metal binding to N3 and thus making it a better model. It did not take long before even better model bases, with the N1 (pym) and N9 (pu) positions carrying alkyl groups were employed, followed by the corresponding nucleosides and nucleotides. It appears that until the mid 1970s Cu^{II} compounds were among the most studied examples [24], although crystal structure analyses of other metal complexes with nucleobases also existed [25–27].

The elucidation of the three-dimensional structure of tRNAs, the smallest biologically relevant nucleic acids containing between 75 and 90 nucleotides, in the early 1970s provided a wealth of structural information not only as far as folding and nucleobase interactions were concerned, but also on metal binding. The crucial role of tightly bound Mg^{2+} ions for maintaining its characteristic was established beyond doubt [28].

3.2. The platinum era

In 1969, Rosenberg reported on the antitumor activity of *cis*-$[Pt(NH_3)_2Cl_2]$ (Cisplatin) [4], following an earlier paper on the filamentous growth of *Escherichia coli* bacteria in the presence of trace amounts of certain Pt coordination compounds [29].Observations by Harder and Rosenberg that the inhibitory effects of antitumor Pt compounds on mammalian cells in vitro was most pronounced on DNA synthesis whereas RNA and protein synthesis were less affected [30], soon shifted interest to interactions between DNA and Pt species as the most likely cause of activity. By 1971, as evident from the papers presented within a symposium on 'Coordination Complexes in Cancer Chemotherapy' at the Seventh International Chemotherapy Congress held in Prague, Pt–nucleobase interactions were intensively discussed. The groups of Rosenberg at Michigan State University, Drobnik from Prague and Roberts from the Chester Beatty Research Institute in the UK were among the first to conduct DNA binding studies, soon joined by others. In retrospective it is clear that the field of metal-nucleic acid interactions was dominated by Pt over the last three decades, which does not exclude progress in the understanding of the chemistry of other metals with these biomolecules, however (see also Section 3.3).

Within several years following the discovery of Cisplatin and its reactivity toward DNA, the principal binding patterns — DNA interstrand cross-linking [31], DNA intrastrand cross-linking [32], and DNA–protein cross-linking [33] — were iden-

tified or had at least been proposed. Proof of the significance of intrastrand cross-link formation between adjacent guanines and adjacent guanine and adenine nucleobases were achieved around 1980 and a few years later the major adducts of DNA had been quantified [34,35].

X-ray structural work on Pt-nucleobase complexes set in, with a lag phase of several years following Rosenberg's discovery, around 1975 (early reviews [25–27,36–38]). Two reports from this period are particularly noteworthy, that on $[(en)Pt(guanosine\text{-}N7)_2]^{2+}$ by Gellert and Bau [39], which provided the first structural insight in a G,G crosslink (even though the head–tail orientation of the two bases did not correspond to that occurring in the intrastrand adduct of Cisplatin, which is head–head), and that of *cis*$[Pt(NH_3)_2(5'\text{-}IMP)_2]^{2-}$ (IMP = inosine-monophosphate) by Goodgame et al. [40], where, in passing, an anchoring function of the guanine 06 site for Cisplatin was suggested. This comment subsequently spurred a very controversial discussion on the possible role of a N7,O6 chelate of guanine as a unique lesion of Pt^{II} complexes having a *cis* geometry (for a discussion, see [41]). Today it is generally agreed upon that for Pt^{II} compounds and in the presence of water, no such chelate forms but rather that a $Pt\text{–}OH_2$ group is H bonded to 06 of guanine. From X-ray crystal structures of Pt^{II} complexes containing other model nucleobases such as 9-methyladenine [42] and 1-methylcytosine [43], it was evident at an early stage, that Pt binding can also take place at other bases, not just guanine. The first crystal structure analysis of a Pt^{II} complex of a pyrimidine-2,4-dione nucleobase, that of 1-methylthymine, was published in 1978 by Lock, Rosenberg and coworkers [44], thereby completing the first round of X-ray structure determinations of Pt^{II} complexes of the four common DNA bases.

It took until 1984/85 before 'real' model compounds (showing the head–head arrangement of isolated guanine bases) of the major Cisplatin adduct were reported [45]. In 1985, structural information of this adduct with the more relevant d(pGpG) dinucleotide adduct also became available [46], and more recently X-ray crystal structure analyses of Cisplatin adducts of DNA fragments (intrastrand G,G adduct [47]; interstrand G,G adduct [48]) were achieved. Except on a model nucleobase level [49,50], there exist presently no X-ray data on proven (e.g. A,G) or feasible (e.g. G,C; A,C) minor DNA adducts of Cisplatin.

Parallel to X-ray crystallography, ^{1}H-NMR spectroscopy became a major tool in identifying Pt binding sites both in model systems and, at a later stage, in more complicated oligonucleotides and DNA fragments. For example, Pt^{II} binding to N7 of a guanine nucleobase, whether isolated or part of an oligonucleotide, unambiguously can be established on the basis of the downfield shift of the H8 resonance and its pH dependence: Since Pt^{II} prevents protonation of this site (pK_a of N7 protonated guanine is around 2–3, depending on the substituent at the 9-position), the insensitivity of the H8 chemical shift over a wide pH range (0–6) is a clear indication of Pt binding to this site. On the other hand, the acidification of N(1)H of guanine as a consequence of Pt^{II} coordination at N7 ($pK_a \cong 7.8\text{–}8.3$ [51]) is reflected by the sensitivity of the H8 signal to pH in the range $6 < pH < 10$ and the sigmoidal upfield shift with increasing pH. Moreover, coupling of the ^{195}Pt isotope with ^{1}H nuclei of nucleobases has frequently been applied as a means of identifying

Pt binding sites. This technique was particularly helpful with low field NMR spectrometers (60–200 MHz) in use, as was generally the case in the 1970s. Thus Pt coordination to N7 of guanine was usually evident from the ^{195}Pt satellites of the H8 resonance and the characteristic ^{3}J coupling of 20–32 Hz [50,52]. The advent of high field NMR spectrometers has led to a loss of this particular information, a disadvantage outweighed by many other advantages provided by these new instruments, however. Among these, the use of inverse detection of ^{15}N nuclei and combined detection of ^{1}H and ^{15}N in HSQC or HMQC NMR experiments are particularly noteworthy in that they have led to a sensitivity unprecedented a decade ago [53]. Although still time-consuming, the determination of solution structures of Pt adducts of DNA fragments by NMR techniques is rapidly moving to a routine stage, and fine details of dynamic processes of Pt-guanine cross-links are emerging [54].

3.3. Other metals

In the aftermath of the discovery of Cisplatin and the studies of Pt–nucleic acid interactions initiated by Cisplatin, the field of metal–nucleic acid complex formation in general has received considerable attention [55]. (en)Pd^{II}, a close relative of *cis*-$(NH_3)_2Pt^{II}$, yet much faster reacting (10^4–10^5) than the latter, has been intensively studied in particular by Martin's group [56] and has provided invaluable information concerning binding patterns or relative preferences for binding sites, and has allowed stability constants for Pt^{II}–nucleobase complexes to be estimated. $(CH_3)Hg^{II}$ binding to DNA and model nucleobases has been studied by various groups, among others those of Beauchamp [57] and Tobias [58]. A particularly striking feature of this work is the observation of multiple binding of this electrophile to nucleobases and the ease of displacement of nucleobase protons by $(CH_3)Hg^{II}$.

The development of an organometallic chemistry with nucleobases — chemistry leading to metal–C(nucleobase) bonds (as opposed to related chemistry that applies organometallic metal species for reactions with nucleobases giving N- or O-bonded compounds with common coordinative bonds [50]) — started in the early 1970s with the discovery of mercuric acetate reacting with uracil and cytosine nucleobases at the C5 position [60]. This finding was a surprise in that these reactions took place under very mild reaction conditions in water and occurred despite the presence of numerous N and O donor sites of the polynucleotides. There have been scattered reports on organometallic nucleobase complexes since then (for a brief review see [61]), but it took more than 20 years before X-ray structures of relevant model compounds of Hg^{II} became available [61,62].

Studies of $(NH_3)_5Ru^{III}$ binding to nucleobases had been initiated by Clarke and coworkers in the 1970s [63] and are still going on [64]. Interest in these reactions stems, among others, from potential applications of Ru coordination compounds in several pharmacentical areas, including the treatment of malignant tumors [65], and redox disproportionation leading eventually to scission of the glycosidic bond in N7 metalated guanosine [66].

In recent years interest in interactions of dinuclear, frequently acetato bridged metal species of Mo, Re, Ru, and in particular Rh with nucleobases has regrown [67,68] following early reports on striking antitumor effects of dirhodium(II) carboxylates [69]. From X-ray crystallography it is evident that the 'bite' provided by the dimetal entities is well suited to bind purine nucleobases through their N7 and X6 positions (X = NH for adenine; X = O for guanine) [67,68]. It is worth mentioning that with Pt dinuclear nucleobase complexes form spontaneously from mononuclear precursors, but usually the bridging donor atoms are from the pyrimidine entity of a nucleobase (e.g. N3 and O4 in uracil and thymine bases; N3 and N4 in cytosine bases [59]; N1 and N6 of adenine [70]) rather than from the pyrimidine and imidazole parts of a purine base, as observed in the cases mentioned above.

Among the many different metal ions that have been studied and are undergoing studies with nucleic acids and nucleobases, Zn^{II} always has occupied a special position. Being a redox-inactive metal ion and having a balanced affinity for N and O donors as present in nucleic acids, this metal ion is well suited as a partner of nucleobases (for a brief review see [71]). Lately Kimura and coworkers have demonstrated how auxiliary ligands, in their case macrocyclic polyamines, can lead to a highly selective binding pattern at a single nucleobase (N3 of uracil or thymine) [72], a feature potentially useful also for the control of genetic processes. Zn^{II} binding to a site normally not considered a primary donor atom for metal ions — N3 of pyrimidine-2,4-dione ligands — is remarkable and exemplifies the enormous potential lying in the design of metal compounds capable of binding in a highly selective manner.

4. Modes of metal binding

4.1. General aspects

With nucleic acids being polyanions at physiological pH and beyond (one negative charge per phosphate diester entity), they require cations for charge neutralization. These can be metal ions, protonated amines (spermine, spermidine) or protonated amino acid side chains (lysine, arginine). Non-coordinating alkali ions lead to a partial charge neutralization in the case of double-stranded DNA by condensing around DNA in a cylindrical fashion. Despite this partial charge neutralization (76% for + 1 cations according to Manning's theory), DNA still has a pronounced affinity for cationic metal entities. Metal species can interact with DNA or nucleic acids in either of the two following ways: First, directly via coordination to phosphate oxygen atoms, sugar oxygen atoms, atoms of the heterocyclic bases (N, C, O), or combinations thereof. Second, indirectly via its other ligands. This latter possibility includes H bond formation, e.g. between aqua or amine ligands and suitable acceptors of the nucleic acid, which can be considerable if multiple H bonds **1d** are possible, or $\pi-\pi$ interactions between the nucleic acid and the metal entity (intercalation; groove binding), if the metal carries

heteroaromatic auxiliary ligands. Again, combinations of all possibilities are feasible.

The present review represents a survey of direct metal-nucleobase binding motifs and will not consider interactions which exclusively occur through H bonding or π stacking. These aspects have been reviewed elsewhere [73]. Before going into a more detailed discussion of individual metal coordination patterns, a few general rules can be summarized:

1. Of all direct coordination modes, binding to the phosphate group is probably most important in the case of alkali and alkaline earth metal ions, which represent 'natural' counter ions of nucleic acids in cells.
2. The N7 positions of the purine bases G and A, which are well accessible in the major groove of duplex DNA and, of course, in single-stranded DNA as well as many RNAs, are major binding sites of metal ions, irrespective of the nature of the metal ion. Thus, examples for this mode are known both for hard Mg^{2+} ions and soft Pt^{II} species.
3. The floor of the minor groove of double-stranded DNA also presents metal binding sites. Among these, the combination of A-N3 and T-O2 is particularly efficient.
4. In single-stranded DNA, in RNA, and likewise with the isolated bases (model bases, nucleosides, nucieotides) virtually any site of the heterocyclic base can be metalated, including C atoms.
5. Metal binding to sites normally carrying protons (NH, NH_2, CH sites) is possible and does not necessarily require strongly basic reaction conditions, as might be anticipated from pK_a considerations.
6. Multiple metalation reactions at nucleobases are quite common and facilitated by initial nucleobase deprotonation. Frequently metal binding sites are sufficiently close to permit metal–metal interactions.
7. Metal complexes of protonated, hence cationic nucleobases (e.g. of A and G) are possible.
8. Exocyclic amino groups (of C, A, G) are metal binding sites only following the removal of one or both protons, hence after deprotonation, or after a shift of a NH_2 proton to another site of the base, which corresponds to a change in tautomer structure.
9. Metal chelates with nucleobases are possible, yet are relatively rare.
10. Nucleobase atoms normally involved in (Watson–Crick) pairing in double-stranded DNA can become metal binding sites as a consequence of an *anti*→*syn* switch of the nucleobase about the glycosidic bond, or DNA breathing.

In the following, metal binding sites will be discussed which in most instances have been established by X-ray crystallography. By and large, and in particular in cases with model systems applied, metal binding patterns have been studied, which involve a single nucleobase. Studies of mixed nucleobase complexes, hence cross-links of different bases, are relatively rare [49,50,74]. There are, however, now novel theoretical approaches available (Brownian-dynamics; simulations) which, even with complicated folding of nucleic acid strands, permit prediction of metal binding sites [75].

4.2. Metal binding to phosphate group

Binding of hard metal cations to the oxygen atoms of the phosphate groups in (isolated) mononucleotides or oligonucleotides is well established and not really surprising. A considerable number of X-ray crystal structure studies exist [76], in particular for alkali and alkaline earth metal ion binding to such sites, occasionally in conjunction with other sites (see Section 4.5).

4.3. Metal binding to sugar entity

The O2′ and O3′ hydroxyl groups of ribonucleotides are capable of chelating both main group metal ions, e.g., Na^+ [77], and transition metal ions, e.g. Cu^{2+} [78], Sn^{IV} [79], or Os^{IV} [80]. Of all metal binding modes, it is the least frequent one.

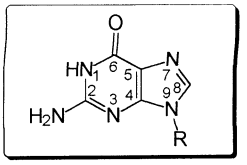
4.4. Metal binding to heterocyclic part of nucleobase

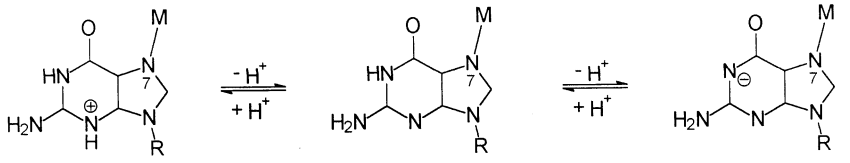
By far the most versatile metal binding patterns exist for the heterocyclic bases. In the early days of metal-nucleic acid chemistry, even up to 1970, few binding sites were considered, and some misconceptions existed concerning possible metal binding sites. X-ray crystallography and NMR spectroscopy (for diamagnetic metal ions) has changed the picture dramatically. It is by no means overexaggerated to state today that as far as binding sites are concerned, 'virtually anything is possible'. Not surprisingly, a substantial number of all established patterns refer to Pt complexes.

4.4.1. Guanine and related 6-oxopurines

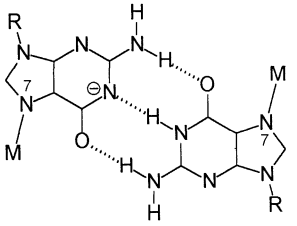
Metal coordination to the N7 site of guanine undoubtedly is a, possibly even the major metal binding pattern to nucleic acids or isolated bases [24,37,38,41,50,55]. A number of factors [56] favor binding to this site, e.g. ready accessibility in the major groove of DNA, non-involvement in base pairing (at least in the common Watson–Crick pairing scheme), possibility of H bonding between O6 and auxiliary ligands of the metal, a somewhat higher basicity of guanine-N7 as compared to adenine-N7, and most importantly a favorable electrostatic potential at this site [81]. The large dipole moment of guanine (> 7D) and its orientation [82] is indeed 'directing' any positively charged metal entity to this site (Scheme 1).

At physiological pH the N7 metalated guanine residue (N9 position blocked as in nucleosides and nucleotides) is neutral (**1a**). If the metal complex behaves kinetically inert, as is generally the case with $M = Pt^{II}$, both protonation (at N3 and/or O6 (**1b**) and deprotonation (at N1) (**1c**) of the guanine base is possible without (fast) metal migration. Examples exist for both situations [83,84]. With kinetically labile species, a pronounced competition between the metal ion and the proton exists, and a metal bound at acidic pH at N7 will 'cross over' to N1 if the pH is raised [56]. A special case is realized in hemideprotonated complexes 1d, hence species consisting of 1:1 mixtures of **1a** and **1c**, which give rise to three strong intermolecular H bonds **1d** [85]. Metal binding to O6 (**2**) has been reported to take

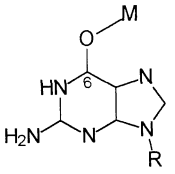




1b 1a 1c



1d



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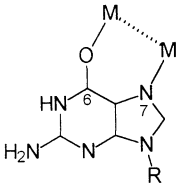

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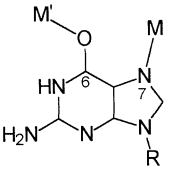

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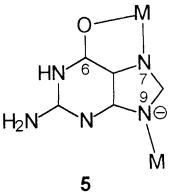

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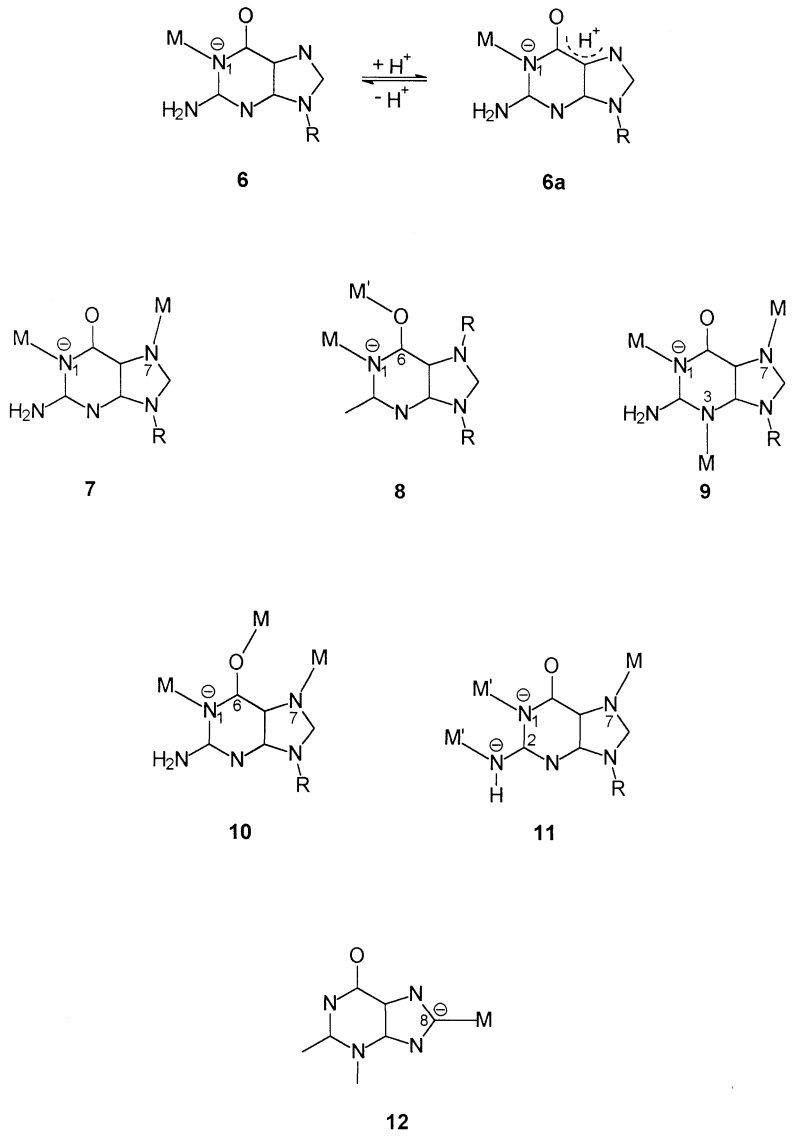
Scheme 1.



Scheme 1. (*Continued*).

place with $[(PPh_3)_2(CO)Rh]^+$ [86a,b], among others. Alkali metal ion binding to O6 is essential in maintaining guanine quartet structure as present in the telomeres, for example [86c,d]. Involvement of both N7 and O6 can take place in either a bridging (**3**, **4**) or a chelating fashion (**5**) with the latter realized in a cyclic, hexanuclear theophyllinato complex of $(CH_3)_3Pt^{IV}$ only [87]. In the case of bridge formation, both identical metal ions M (with M…M interactions, **3**) [68] and different metal

ions (e.g. $M = Pt^{II}$, $M' = Na'$, **4**) [88] have been realized. Deprotonation at the N1 position gives the corresponding anionic guanine species, e.g., **3c**, **4c** (not shown).

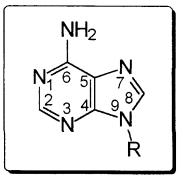
Metal binding to the N1 position following deprotonation of this site, opens a large array of different patterns. The following situations have been verified by X-ray analysis. Coordination to N1 (**6**) [89], with the possibility of reprotonation at N7 and/or O6 to give a metalated form of a rare guanine tautomer (**6a**); twofold metal binding either through N1 and N7 simultaneously (**7**) [90] or through N1 and O6 (in a heteronuclear 7,9-dimethy1hypoxanthine complex, **8**) [50]; threefold metal binding through N1,N7,N3 (**9**) [91]; threefold metal binding through N1,N7,O6 (**10**) [92]. In the last case, a Cu^{II} complex of inosine monophosphate, a phosphate oxygen atom is additionally involved in Cu^{II} binding. Very recently the first example of threefold metal coordination to a dianionic guanine nucleobase (**10**) has been reported by us [93]. In this complex, which is a planar, cyclic nucleobase quartet cross-linked by six metal ions, binding to the exocyclic amino group at the 2-position has been proven for the first time by X-ray structure analysis.

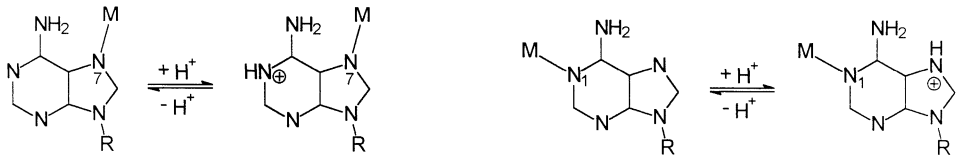
Finally, metal–carbon bond formation at C8 (**10**) has been observed with a number of different transition metal ions (e.g. Pd, Ru, Os, Hg) [94].

4.4.2. Adenine

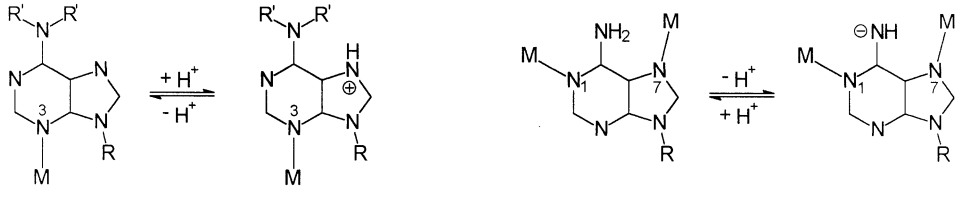
Adenine provides three at physiological pH unprotonated endocyclic nitrogen atoms (N1, N3, N7), all of which are potential metal binding sites. The basicity order (affinity for H^+) is N1 > N7 > N3. While in duplex DNA the N7 site is preferred as a metal binding site, with isolated adenine bases a pronounced dichotomy exists for metal binding at N1 and N7 [56,95]. Only in strongly acidic pH, when the N1 site is fully protonated, is metal binding preferentially through N7. Alkali metal ion binding to the N3 position of adenine (in conjunction with O2 of thymine) in the minor groove of DNA has lately received attention. There appears to be a consensus now that what has originally been termed the 'spine of hydration' in B-DNA in fact also contains alkali metal ions [96]. Na^+ binding to these sites in a d(ApT) minihelix was observed in 1976 [97] and the metal ion binding capacity of the 'ApT pocket' was noted in 1985 [98]. In isolated nucleobases N3 metal binding has also been realized if for steric reasons — e.g. complete methylation of the 6-amino group — blockage of N1 and N7 for metal binding is achieved [99]. In principle, a similar situation could be envisaged if for other reasons, e.g. protein binding and duplex formation, metal binding to the preferred sites is prevented. Examples of all three cases, **13a** [50,100], **14a** [101] and **15a** [96–99] are available. The existence of (Scheme 2) protonated forms of these compounds **(13b, 14b, 15b)** is well documented for transition metal ions, both by X-ray analysis (e.g. for **13b** [42]), UV and ^{1}H-NMR spectroscopy [99,102].

Twofold metal binding, to N1 and N7 (**16a**) is likewise quite common [103]. As a consequence, the 6-amino group undergoes a considerable acidification (> 4 log units) and anion formation (**16c**) is accomplished in moderately alkaline medium. N1,N7 binding gives rise to two mutually perpendicular M–N vectors which permit construction of molecular rectangles and meanders with 90°-angles [104]. Threefold metal binding to a neutral, 9-blocked adenine via N1, N3 and N7 has recently been observed in a polymeric, helical complex (**17**) [105].

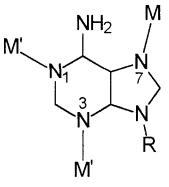




13a 13b 14a 14b



15a 15b 16a 16c



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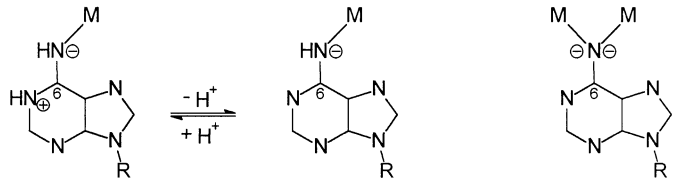
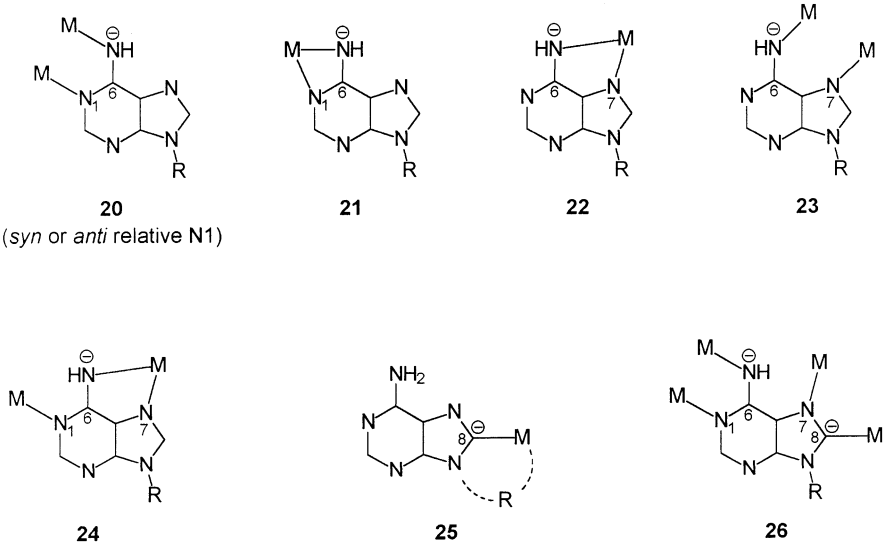


18a (*syn* or *anti* relative N1) 18c (*syn* or *anti* relative N1) 19

Scheme 2.



Scheme 2. (*Continued*).

Metal binding to the exocyclic amino function of adenine (and similarly in cytosine and guanine) requires deprotonation of this group. Unlike in aliphatic or aromatic amines, there is no lone electron pair available at the N atom for metal complexation, but rather this pair is delocalized into the heteroaromatic ring. Early suggestions on metal binding to the (intact) exocyclic NH_2 groups of nucleobases were erroneous, even though recent ab initio calculations and a structural database search strongly suggest that exocyclic amino groups can indeed be markedly non-planar and that some residual basicity permits it to act occasionally as a H bond acceptor [106]. However, this situation is insufficient for metal ion binding. Deprotonation of the exocyclic amino group prior to metal complexation does, however, not necessarily imply that the nucleobase becomes anionic. Rather, metal binding to this group can be accompanied by a shift of an amino proton to another site, e.g. N1 (**18a**), therefore generating a metalated form of a rare adenine tautomer [107]. Consequently, no strongly alkaline reaction conditions are required for such binding modes, certainly no pH conditions that might be anticipated from pK_a considerations (pK_a values for exocyclic groups are > 16). Of course, at higher pH the neutral ligand can be deprotonated (**18c**). As to the formation of N6 metalated species, initial metal coordination to N1 or N7 is likely to take place, followed by metal migration. Arpapahti [107b] has demonstrated such a process in the case of (dien)Pt^{II} migrating from N1 to N6. Once the metal resides at N6, it may adopt two different orientations, either *syn* to N1 or *anti*. Examples exist for both cases [107a–107c]. As far as consequences for the H bonding ability of a N6 metalated adenine nucleobase are concerned, the relevance to metal mutagenicity is an obvious one [108].

Beauchamp et al. [57] have demonstrated that for $M = CH_3Hg^{II}$ species **18c** can disproportionate to some extent into the disubstituted species **19** and free base.

Bidentale metal binding to N1 and N6 occurs in either a bridging (**20**) (*syn* [70, 109a,b]; *anti* [109c]) or chelating fashion (**21**) [110]. For $M = (Cp)_2Mo^{IV}$, (**21**) has been demonstrated as the kinetic product, which converts into the thermodynamic product **22**, which is a N6, N7 chelate [110]. A bidentate bridging mode (**23**), with metals at N6 and N7 has likewise been realized [67].

There are several reports on binding mode **24** with simultaneous metal binding to N1, N6, N7 [111,112], leading to trinuclear, cyclic metal complexes with remarkable receptor properties.

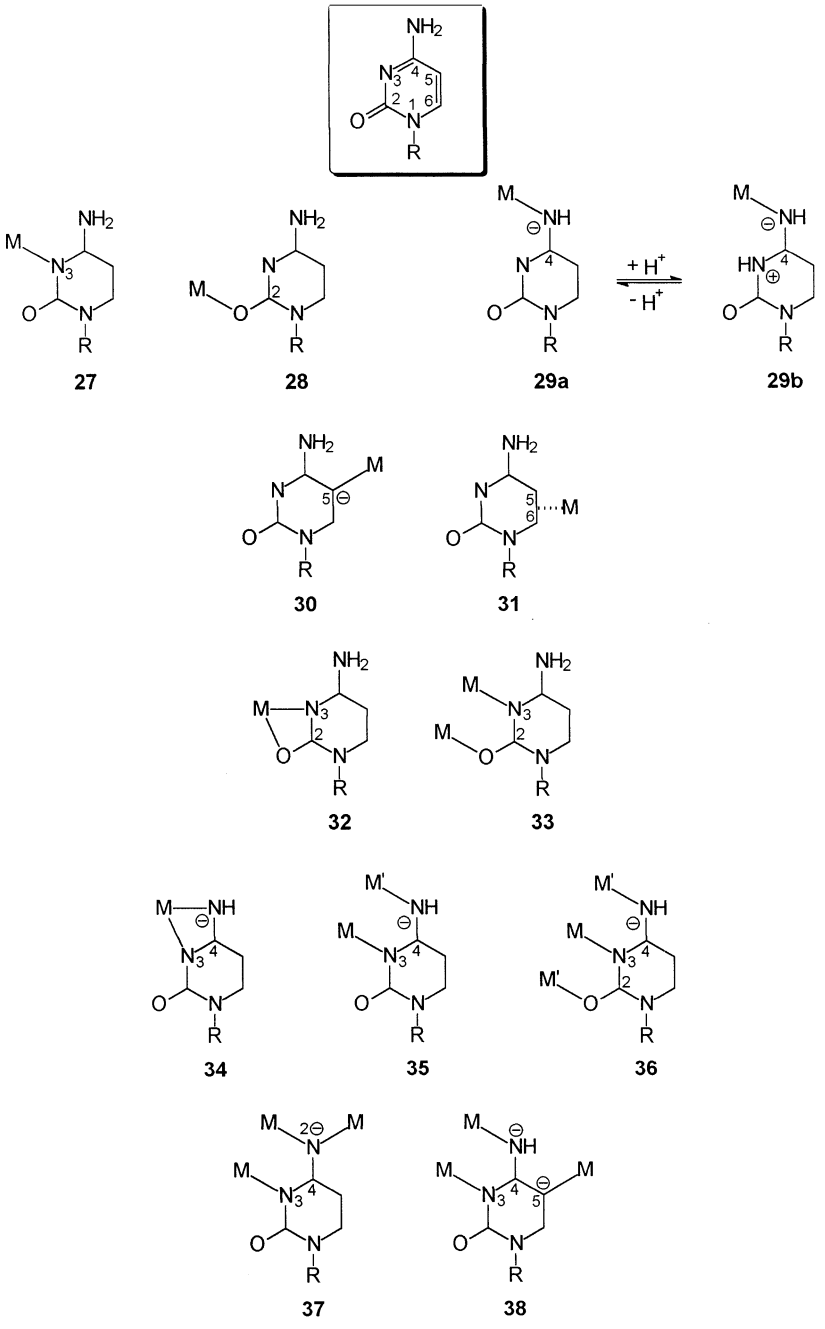
Ru binding to C8 of adenine (**25**), reinforced by a chelating residue at the 9-position, has been reported [113]. Finally, a record fourfold metalation of a 9-methyladenine dianion has been observed with $M = (trpy)Pd^{II}$ (**26**) with metal entities simultaneously bound to N1, N6, N7, and C8 [114].

4.4.3. Cytosine

Monodentate metal binding to N1 blocked cytosine nucleobases can occur in any of the following ways (review [115]): Through N3 (**27**) [116], O2 (**28**) [117], N4 (**29**) [118–121], C5 (**30**) [60], or in a π-fashion through C5 and C6 (**31**) [122a]. With isolated cytosine bases, binding to either N3 or O2 is favored, depending on the softness/hardness of the metal ion and possibly steric aspects. In B-DNA, O2 of C in the minor groove is a site of alkali metal (Scheme 3) ion binding [96a]. Of all endocyclic N atoms of the four common nucleobases, N3 of C is the most basic one, hence has the highest pK_a value and the highest affinity for H^+. Nevertheless it is not the preferred binding site for Pt^{II} or Pd^{II} ions [56]. N4 metal binding requires, as in the case of N6 binding with adenine (c.f. Section 4.4.2), initial deprotonation of this position (**29a**), but reprotonation of N3 is facile (**29b**) and leads to a metalated form of the rare imino-oxo tautomer of cytosine. Formation of (**29b**) has been studied in detail [119,121,123] (see also below).

Neutral cytosine ligands can also bind metal ions simultaneously through N3 and O2, either in a chelating (or semichelating) fashion (**32**) [124] or in a bridging fashion (**33**) [125]. Once the cytosine ligand becomes anionic, additional possibilites arise: N3,N4 chelation (**34**) has been verified with Pt^{IV} [123] and $(Cp)_2Mo^{IV}$ [110] and N3,N4 bridge formation (**35**) in a series of complexes containing two identical metal ions (CH_3Hg^{II}; Pt^{II}; Pt^{III}; Pd^{II}) [126–131] or two different metal ions (e.g. Pt^{II}; Pd^{II}; Pt^{II},Cu^{II}; Pt^{II},Hg^{II}) [132–136]. Chelate **34** has been found to represent an intermediate between **27** and **29b** in the case of *trans*,*trans*-$(NH_3)_2(OH)_2Pt^{IV}$ [119,123], hence between the kinetic and the thermodynamic product. The process **27** → **29b** has been followed by ^{1}H-NMR spectroscopy and X-ray crystallography. In addition to intermediate **32** a second one, displaying both coordination mode **27** and **34**, has likewise been isolated and identified by X-ray analysis, making it a textbook example for metal migration process [119,120,123].

There are numerous interesting aspects in the chemistry of compounds of type **35** which include relative orientations of the two metals (*syn* to each other or *anti*) [121], inversion of the two metal ions (e.g. Pt^{II} at N3, Hg^{II} at N4 or vice versa



Scheme 3.

[121,133]), and metal–metal bond formation. Metal–metal distances (M ... M′) depend both on the electronic configuration of the two metals (d^8, d^9 or d^{10} [135]) and, surprisingly, on their geometry. Thus, if d_z^2 orbitals of d^8 metal ions (e.g. $enPd^{II}$ [129]; *cis*-$(NH_3)_2Pt^{II}$ [128], $trpyPd^{II}$ or $trpyPt^{II}$ [131]) are facing each other (M = M′) the bond order is $\cong 0$ and the metal-metal separation is relatively large (2.9–3.04 Å), but in favorable cases (e.g. with *cis*-$(NH_3)_2Pt^{II}$) there exists the possibility of removal of electrons from the d_z^2 orbitals and oxidation to $[Pt^{III}]_2$, leading to short metal–metal bonds of ca. 2.5 Å [128,130]. On the other hand, if two d^8 metal ions (*trans*-$(NH_3)_2Pt^{II}$, P^{II}) have their square-planar coordination planes perpendicular to each other, short dative metal–metal bonds of also ca. 2.5 Å are formed [132,135,136], but the formal + II oxidation states of both metal ions are retained.

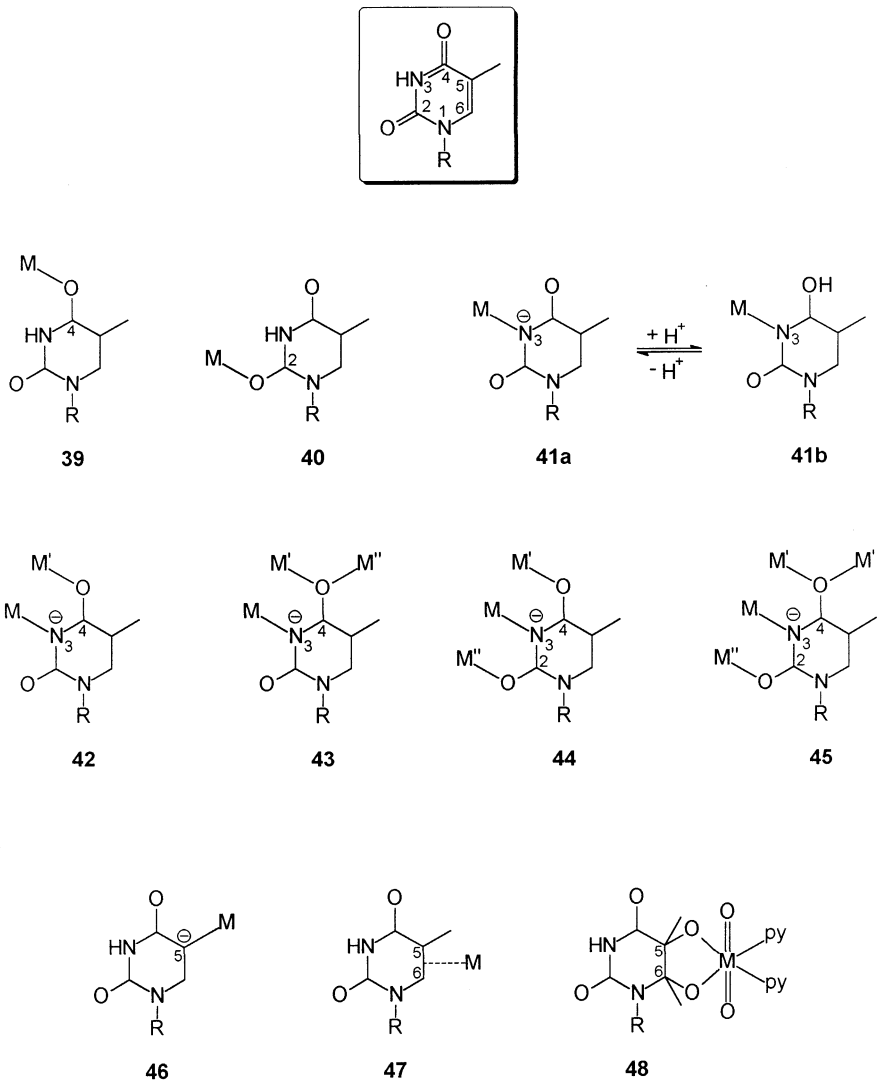
Binding pattern **36** is to be considered an extension of **35** with a third metal binding to O2. Several examples with $M = Pt^{II}$ and $M' = Ag^+$ [137], Pd^{II} [138], Cu^{II} [139], and Co^{III}, Na^+ [139] have been structurally characterized. Among these, the $Cu^{II}Pt^{II}Cu^{II}$ combination [139], derived from the tetrakis (1-methylcytosine-N3) Pt^{II} cation is particularly interesting in that the central Pt^{II} ion functions as a mediator of strong antiferromagnetic coupling between two Cu^{II} ions which are 5 Å apart.

Three metal ions, in the combination N1,N4,N4, and with cytosine acting as a dianion, are also present in the trinuclear CH_3Hg^{II} complex **37** [57b]. Finally, in **38** again a dianion of the cytosine nucleobase is present, yet metal binding is through N3(Pt^{II}), N4(Hg^{II}) and C5(Hg^{II}) [140].

4.4.4. Thymine and uracil

Metal binding to the O4 position of a neutral pyrimidine-2,4-dione nucleobase **(39)** was first unambiguously demonstrated in two adducts of $HgCl_2$ with (unsubstituted) uracil and (unsubstituted) 5,6-dihydrouracil [141]. This binding pattern was later also (Scheme 4) proven to be relevant for a series of main group and transition metal compounds of N1 blocked model nucleobases [88,142–144]. Binding of alkali metal ions to O2 (**40**) can occur in the minor groove of B-DNA [96] and has been observed with model compounds as well [88,144,145]. The thermodynamic stabilities of these complexes are generally low, unlike in metal complexes, where binding takes place through the deprotonated N3 site (**41a**). X-ray crystal structures for this form of coordination exist for Hg^{II} [146], Pt^{II} [50,147,148], Pt^{IV} [149], Rh^{I} [150], Au^{I} [151], and Au^{III} [152]. Protonation of the anionic nucleobase ligand in **41a** is possible, either at O4 or O2, to give metalated forms of the rare hydroxo-oxo tautomers **41b** of these bases [153]. Although unstable in solution, and converting to the preferred dioxo tautomer form with cleavage of the metal N3 bond, compounds of composition **41b** have crystallized with kinetically inert Pt^{II} residues [153].

Binding motif **41a** is also responsible for binding patterns **42–45**: Metal coordination to the deprotonated N3 position leaves residual basicity at the exocyclic oxygen atoms, notably O4, as established by vibrational spectroscopy [154,155] and potentiometry (pK_a values of **41a** [153b]). As a consequence, the exocyclic oxygen atoms become generally better donors than in the unmetalated, neutral base (for an



Scheme 4.

exception, see [152]) and metal binding to O4 or O4/O2 is facilitated. Favorable interactions between other ligands of the metal ions (e.g. stacking of heteroaromatic chelate ligands) and/or metal–metal interactions can further assist realization of motifs **42–45.** It appears that as far as numbers of X-ray crystal structure determinations of Pt^{II} containing nucleobase complexes are concerned, these motifs exceed all others (for a comprehensive list of compounds see, for example, [156,157]). In brief, compounds of type **42** consist of dinuclear Pt^{II} compounds ($M = M' = Pt^{II}$) of different stoichiometries (e.g. Pt_2L_2 [50], Pt_2L [158] with L =

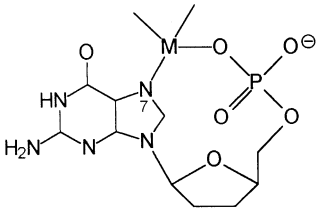
uracil or thymine nucleobase), different arrangements of the bases in Pt_2L_2 (head–head or head–tail), or heteronuclear complexes ($M = Pt^{II}$, $M' =$ other transition metal ion or main group metal ion) of different stoichiometries (e.g. PtL_2M' or $PtL_2M'L_2Pt$). Diplatinum(III) or mixed-valence Pt compounds are also of type **42** [159], as are heteronuclear compounds containing CH_3Hg^{II} and Na^+ [160]. Three different metal ions ($M = Pt^{II}$, $M' = Ag^+$, $M'' = Na^+$) are bound in a compound **43** derived from *trans*-$(NH_3)_2PtL_2$ (L = 1-methyluracilate) [161]. Motif **44** is observed in polymeric complexes of Ag^+ ($M = M' = M'' = Ag^+$) [162] and mixed Pt^{II}, Ag^+ compounds ($M = M' = Pt^{II}$; $M'' = Ag$) [163] containing 1-methyluracil or 1-methylthymine nucleobases, whereas **45** is seen in a polymeric complex ($M = Pt^{II}$, $M' = M'' = Ag^+$), again derived from *trans*-$(NH_3)_2PtL_2$ (L = 1-methyluracilate) [164].

There are three metal binding modes **(46–48)** which involve reactions at C atoms of pyrimidine-2,4-dione ligands. Among these, C5 metal binding to uracil nucleobases appears to be most common. **46** originally had been observed upon reaction of uracil containing nucleobases, including polynucleotides, with $Hg(CH_3COO)_2$ [60]. It was later verified in model nucleobases also for a diplatinum(III) complex [165], for Pt^{II} [61], and Au^{III} [166]. Interestingly, Au^{III} binding to C5 can precede oxidative dimerization of uracil nucleobases [167]. The η^2 coordination mode of a complex Ru^{II} anion, $[Ru(hedta)]^-$ (hedta = *N*-(hydroxyethyl)ethylenediaminetriacetato), to C5,C6 (**47**) still represents a curiosity of metal-nucleobase chemistry [122a–c], although it is now established for many other related heterocycles [122d,e]. Finally, attack of an OsO_4 moiety to the C5,C6 double bond, frequently applied in molecular biology to identify un- or mispaired thymine residues in DNA, again is unique in that it gives a cis osmate ester **48**, as verified by X-ray crystallography for 1-methylthymine [168] and unsubstituted thymine [169]. MnO_4 appears to act in a similar fashion, but the ester is unstable, giving rise to differently oxygenated species [170].

4.5. Combinations

The combination of different metal binding moieties, e.g. heterocycle and phosphate group ('macrochelate formation') or phosphate group and ribose have also been studied. The latter possibility has been discussed, on the basis of EPR spectroscopy, for vanadyl(IV) species [171]. 'Macrochelate formation', on the other hand, appears to be more widespread and includes both purine and pyrimidine nucleobases. Originally proposed by Szent-Györgyi [172] for the interaction of Mg^{2+} with adenosine triphosphate, this motif has subsequently been shown, in particular by Sigel and his group [173], to be common for many metal ion complexes of purine nucleoside 5′-monophosphates, including *cis*-$(NH_3)_2Pt^{II}$ [174–176] and $(Cp)_2Mo^{IV}$ [110,177,178]. In these cases the N7 positions of guanine and adenine are metal binding sites (**49**, **50**). As to 'macrochelates' involving pyrimidine bases, they have also been established for $(Cp)_2Mo^{IV}$ [110,177,178] and *cis*-$(NH_3)_2Pt^{II}$ [179]. Metal coordination is via N3 of the thymine or cytosine base (**51**, **52**) possibly also the deprotonated N4 position of cytosine (**53**) (Scheme 5).

Convincing evidence for the existence of these 'macrochelates' stems from a range of spectroscopic and physico-chemical investigations in solution, but confirmation by a solid state X-ray structure determination is not available as yet. In fact, X-ray analysis of a $[(Cp)_2Mo(5'\text{-dGMP})]_2$ complex [110] reveals a dinuclear composition with inter- rather than intracomplex N7,O(phosphate) bridging (**54**), and for $(en)Pt^{II}$ and 5′-CMP likewise a structure with discrete dimers (N3,O(phosphate) bridging) was established many years ago [180]. It thus appears that the monomeric 'macrochelate' exists in equilibrium with its head–tail dimer, depending on conditions.



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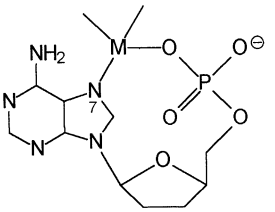

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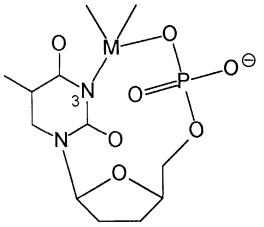

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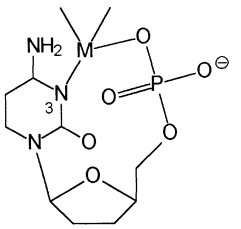

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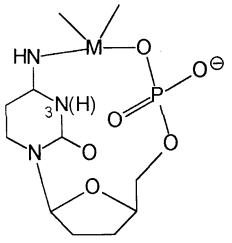

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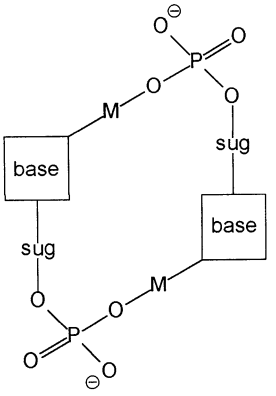

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Scheme 5.

5. Summary and outlook

This review lists and categorizes binding motifs of metal ions to nucleobases. With very few exceptions, the binding patterns have been established by X-ray crystallography with pyrimidine bases blocked at N1 and purine bases blocked at N9 to make them biologically relevant. A comprehensive knowledge of metal binding modes is crucial for an understanding of the effects of metal ions on the nucleobase or the nucleic acid and for its translation into biology. At this point, approximately 50 years after the initiation of systematic metal-nucleobase studies, and some 30 years after the onset of X-ray crystallography of metal–nucleobase complexes, the following conclusions can be drawn:

(i) Metal binding motifs. More than 50 metal binding patterns to nuclesides and nucleotides (as well as their model compounds) of the common bases guanine, adenine, cytosine, thymine and uracil are now established, which involve direct binding of the metal ion to the base (as opposed to 'indirect' binding modes between ligands of the metal ion and nucleobases and binding to the phosphate and sugar entities). This number does not include binding patterns to rare nucleobases or nucleobase derivatives, which in many cases have been studied by X-ray crystallography as well (for selected examples, see [181]). It is unlikely that the number of principal binding motifs will increase substantially in the future, simply because almost every feasible binding pattern has been already realized. It is likely that only a limited number of all established binding modes is relevant to the 'natural' cations present inside cells. However with metal–nucleic acid interactions becoming increasingly significant in applications of molecular biology and medicine, many of the established motifs will be of relevance to the chemistry of exogenous or 'artificial' metal species. It is also clear now that metal ions or metal moieties can utilize different binding sites, depending on nucleic sequence and other conditions, and that metal migration or linkage isomerization processes occur even with metal ions generally considered to form kinetically inert products [54a, 119, 123, 182].

(ii) Accomplishments and challenges. Research in the field of metal–nucleic acid chemistry started out with a phenomenological description of effects of metal ions on particular physicochemical properties such as DNA melting or nucleic acid viscosity, to name these only. Much remains to be done to fully correlate cause and effect. For example, even for metal ions studied the longest, Hg^{2+}, Ag^{+} and Zn^{2+}, no conclusive picture exists as to how these metal ions realize their preference for specific sequences (A,T preference of Hg^{2+}; G,C preference of Ag^{+}) or what is so unique about Zn^{2+} in reversibly unzippering double-stranded DNA. In model studies frequently only a single type of nucleobase has been applied rather than (at least) two, thereby limiting the relevance. X-ray crystallography of suitably metalated DNA fragments [183], systematic metal staining experiments with pregrown nucleic acid crystals, as well as sophisticated NMR spectroscopy with carefully chosen DNA sequences [184] are highly desirable and will eventually provide answers to many of the questions raised.

Of all metal ions, Pt^{II} has been studied most intensively and much has been learned about its interactions with nucleic acids. This applies in particular to the antitumor agent Cisplatin and its major cross-link with DNA, the intrastrand G,G adduct. A detailed picture of stereochemical changes of DNA structure [47,185] as a consequence of G,G crosslinking exists now, even though the biochemical cascade triggered by the event of DNA binding remains to be understood [186,187]. Very little is known about the types and potential significance of minor adducts of Cisplatin with DNA. Not even the second major adduct, the A,G intrastrand cross-link is well studied [49], despite its significance as a mutagenic hotspot [188]. However, the question of minor DNA adducts of Cisplatin is now beginning to be addressed [48, 54a, 189].

A reasonably good understanding of spectroscopic changes brought about by Pt^{II} coordination to nucleobases and DNA fragments has been reached. For example, characteristic ^{1}H-NMR chemical shifts of individual resonances in dependence of the environment of the adduct and conformational changes of nucleic acid components, as expressed by changes in coupling constants, pseudorotational equilibria of sugar entities and ^{31}P chemical shifts can frequently be rationalized on the basis of a combination of NMR techniques [54,190] and computational methods [191].

As to more subtle effects of metal binding to nucleic acid properties, the influence of metal coordination on acid-base properties of nucleobases has been quantified in a number of cases [51,192–194]. In general, metal ion binding increases the acidity of NH and NH_2 groups while decreasing the basicity of exocyclic O or endocyclic N sides. As might be expected, the site of metal binding strongly modulates these effects (see, e.g. ref. [99]). For $(NH_3)_5Ru^{III}$ Clarke and coworkers [194] have established a linear relationship between ΔpK_a and r^{-2} (r = distance between the metal ion and the site of ionization) within a range of $4.2 < r < 5.6$ Å for a series of heterocyclic ligands. If metal binding is accompanied with base deprotonation, the basicity of the heterocycle as a whole frequently increases. As we have recently demonstrated [195], P^{II} binding to N7 of guanine reinforces H bonding with the complementary cytosine, hence stabilizes the Watson–Crick pair, in agreement with theoretical calculations [196]. Electronic changes of the nucleobase brought about by metal coordination could have effects on other properties such as base stacking or nucleobase tautomerism and are probably also responsible for the differential effects of metal ions on nucleobase triplet stabilities [197]. The question of the existence of deprotonated nucleobases in DNA [198], which could be relevant to metalated nucleobases, is still in discussion. Finally, by applying kinetically inert metal species it is now well established that 'metal-stablized' rare tautomers can be generated for all four common nucleobases, a feature still occasionally met with scepticism by organic chemists who ignore X-ray crystallographic evidence!

Although not the focus of this review, reactivity as a consequence of initial metal coordination to a heterocyclic ring atom should be briefly mentioned. Among such reactions, hydrolytic cleavage of the glycosidic bond following metal coordination to N7 of a purine bond, hence depurination, is to be mentioned. This process is, for example, accelarated by dienM(II) (M = Pd, Pt) in a pH range (>4) where protonation has no effect [199]. For *trans*-L(py)$(NH_3)_4Ru^{IV}$ (L = guanosine or

deoxyguanosine, py = pyridine), formed in a disproportionation reaction of the corresponding Ru^{II}, species, likewise *N*-glycosidic hydrolysis has been reported [199d]. Interestingly, in the presence of O2, $(NH_3)_5Ru^{III}$ bound to N7 of a purine catalyzes formation of 8-oxopurines [200]. Various oxidative alterations of nucleobases carrying $AuCl_3$ entities have also been reported, e.g. oxidative dimerization of uracil ligands [201] or degradation of guanine bases [202].

(iii) Outlook. Despite much progress accomplished in the area of metal-nucleic acid interactions and a reasonably good understanding of some of the effects of metal ion binding, much remains to be learned (c.f. ii). Research on basic chemistry aspects of this chemistry will continue, but it will increasingly shift from model systems [203] to 'real' oligonucleotides and nucleic acid fragments. In parallel, applications which employ metal ions and nucleic acids in molecular biology [204], medicine [205], nucleic acid diagnosis [206] as well as material sciences [207] will become increasingly important.

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