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METAL COMPLEXES OF URACILS

MARGARET GOODGAME and DAVID A. JAKUBOVIC

*Chemistry Department, Imperial College of Science and Technology,
London SW7 2AY (Gt. Britain)*

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CONTENTS

ABBREVIATIONS

dien	diethylenetriamine
DMF	dimethylformamide
DMSO	dimethylsulphoxide
en	ethylenediamine
1-MeC	1-methylcytosine
1-MeT	1-methylthymine monoanion
1-MeU	1-methyluracil monoanion
1-MeB	1-methylthymine or 1-methyluracil monoanion
PBu_3	tributylphosphine
T	thymine monoanion

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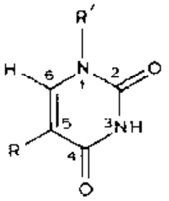
TH	neutral thymine
U	uracil monoanion
u	uracil dianion
UH	neutral uracil

A. INTRODUCTION

In recent years there has been a growing interest in the interaction of metal ions with nucleic acids [1–4]. Such interactions result in physiological effects which can be either detrimental [5,6] or beneficial [7,8]. However, study of such large biological systems, with respect to metal ion binding, is very complex. This is due to the presence of a plethora of potential metal binding sites on the nucleobases, the ribose or deoxyribose sugar, and also on the phosphate backbone. Therefore, to aid in the understanding of these important systems, much work has concentrated upon the study of metal ion interaction with isolated nucleobases [9–12].

This review is concerned with metal complexes of one group of nucleobases, namely, uracils



R = R' = H , Uracil
R = H, R' = Me , 1-Methyluracil
R = Me, R' = H , Thymine
R = R' = Me , 1-Methylthymine

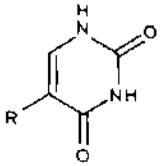
1-Methyluracils are also considered since they are generally agreed to be good models for the uracils when present in nucleic acids since, in nucleic acids, the uracils are bound through N(1) to the sugar. The review also covers binding of "soft" and "hard" metal ions to both neutral and anionic uracils.

B. TAUTOMERISM OF URACILS

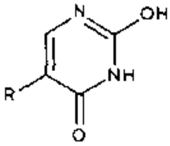
(i) Neutral uracils

Neutral uracils may exist in several different tautomeric forms, and this fact is of major importance when considering the potential binding sites of the nucleobases. The principal tautomeric properties of uracils arise due to the presence of electron donor substituents, namely OH. The labile protons may remain attached at the exocyclic oxygens or migrate to the ring nitrogen atoms. This gives rise to 'lactim–lactam' tautomerism

Uracils can therefore exist in six tautomeric forms



U1



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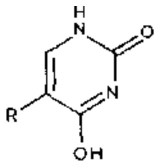

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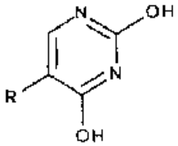

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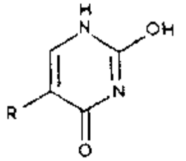

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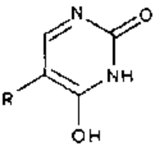


U6

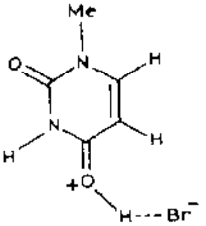
It is worth noting that 1-methyluracils, uridine and thymidine can exist only in forms U1, U3 and U5.

Scanlan and Hillier [13] have recently performed an ab initio study of tautomerism in uracil and thymine, considering the relative stabilities of all six tautomers in both gas phase and solution. Geometry optimization was employed to study the relative energies of the tautomers, the results suggesting molecular geometries in good agreement with currently available experimental data. It was concluded that in the gas phase the diketo tautomer, U1, is the most stable. U2 is the most stable rare tautomer (rather than the more commonly studied U3) with an energy, relative to U1, of 72.1 kJ mol^{-1} for uracil, and 71.0 kJ mol^{-1} for thymine. Upon changing from the gas phase to solution, solvent effects must be considered. These comprise two major components, namely electrostatic solvent–solute interactions and hydrogen bonding. Using the reaction field continuum model Scanlan and Hillier [13] were able to estimate the relative tautomer energies in neutral aqueous solution. The order of stabilities was predicted to be U1 > U3 > U6 > U2 > U5 > U4, with U3 having an energy, relative to U1, of 77.1 kJ mol^{-1} for uracil, and 77.9 kJ mol^{-1} for thymine. These results are in agreement with infra-red and ultra-violet spectral studies [14] which have shown that uracils exist in the diketo form in both the solid state and in neutral aqueous solution.

Crystal structures determined for uracil [15,16], thymine monohydrate [17], 1-methylthymine [18,19], 1-methyluracil monohydrate [20], and the thymine ring within deoxythymidine [21,22] also show that, in the solid state, the bases are present in their diketo form.

The predominance of the diketo tautomer in neutral aqueous solution means that uracils have no unprotonated ring nitrogens and consequently, coordination of metal ions would be expected to occur, if at all, through the exocyclic oxygen atoms. It is known that the carbonyl groups of uracils are strongly polarised and have a concentration of negative charge on the oxygen atoms approximately equal to that on the ring nitrogen atoms [23].

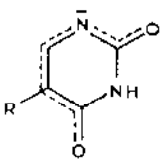
Studies on the protonation of uracil [24] suggest that the monocation derived from protonation of O(4) is considerably more stable than its O(2) protonated isomer. A crystal structure has been determined for the product of protonation of 1-methyluracil by hydrobromic acid [25].



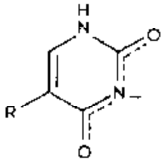
This shows the uracil to be protonated at the O(4) site. However, electron density calculations [23] reveal no great differences in electronegativity between the two oxygen atoms. It is therefore not possible to predict conclusively at which exocyclic oxygen atom metal binding might occur.

(ii) Monoanions of uracils

Uracils behave as weak dibasic acids in aqueous alkaline media, with deprotonation initially occurring at N(3) [24] (pKa = 9.69(uracil), 10.16(thymine)) followed by formation of the dianion, pKa = 14.2(uracil) [24], as a result of deprotonation at N(1). A ^{13}C NMR study on the interaction of Ag(I) with uracil and its monoanion suggests that the N(3) deprotonated monoanion is the more stable form when bound to silver [27]. However the relatively long timescale of NMR experiments means that one cannot expect to observe tautomer interconversion if it is fast. Since the interconversion has in fact been shown to be extremely fast [28,29] the conclusions based upon the ^{13}C NMR spectroscopy are probably irrelevant.



A



B

The crystal structure of potassium thyminate [30] shows the thymine anion to be in the N(1) deprotonated form. It is suspected that the factors of solubility and H-bonding are of importance in deciding which tautomer is present in the potassium salt. Therefore, the presence of the N(1) deprotonated tautomer in this salt gives little indication as to which tautomer, if any, will be favoured in solution.

Lippert [31] has been able to identify, unambiguously, a limited number of twin bands in the Raman spectra of the monoanion which arise from each of the individual tautomers. Changes in the relative intensities of these twin bands upon solvent variation were used to identify the relevant bands. For example, the N(1) deprotonated tautomer, A, with its greater charge delocalization, is increasingly favoured when the dielectric constant (E) of the solvent is decreased. If tautomerism is not possible, as in the anion of 1-methyluracil, then only one band is observed. Although the relative intensities of such twin bands cannot be used quantitatively they do allow approximate estimation of the distribution of monoanions A and B. On changing from pure H_2O to a 1:1 mixture of H_2O:DMF (for H_2O $E(25\,^\circ C) = 78$, for DMF $E(25\,^\circ C) = 36.7$) the distribution changes from roughly 1:1 [32] to 3:1 [31] for the tautomers A:B.

Addition of salts such as LiCl, NaCl and $NaClO_4$ to an aqueous solution of sodium uracilate or thyminate results in a shift toward the N(3) deprotonated tautomer, B, in the $A \rightleftharpoons B$ equilibrium. This arises due to a reduction in the static dielectric constant of the medium upon addition of alkali salts. As well as this cation effect there is an anion effect resulting from an indirect influence of the anions via a change in dielectric constant of the medium which opposes the effect of alkali counter ions. Thus only small changes in the tautomer ratios occur when electrolytes are added to a solution of sodium uracilate or thyminate [31].

With regard to the formation of metal complexes of the individual tautomers it should, in theory, be possible to synthesise complexes of the desired tautomer by using the 'right' solvent, or solvent mixture. When working in a solvent of low dielectric constant the N(1) deprotonated tautomer dominates, but there is no suitable solvent of high enough dielectric constant to produce a solution where the N(3) deprotonated tautomer will dominate.

Under conditions of high pH, uracil and thymine may bind to metal ions in the form of their monoanion via either N(1) or N(3), with the adjacent carbonyl oxygen atoms offering the additional possibility of chelation, or bridging. For 1-methyluracils, uridine, and thymidine, only the N(3) binding site, along with the carbonyl oxygens, is available for metal ion coordination.

C. METAL COMPLEXES OF NEUTRAL URACILS

It must be noted that, so far, the considerations of relative tautomer stabilities have only been for free, i.e. unbound, uracils. When uracils are acting as ligands, the relative stabilities of the bound tautomers will be affected by the difference in the free energy of formation of the complexes with different binding sites, i.e. M–O and M–N bond strengths, and also by the differing possibilities for hydrogen bonding and solvent interaction. However, it is reasonable to assume, due to the large energy difference between the diketo tautomer and the other tautomers, that the relative stabilities can be used as a qualitative guide to likely complex formation when the metal involved does not have a large difference in metal–oxygen and metal–nitrogen bond strengths.

(i) Complexes of "hard" metal ions

An ab initio calculation has been performed upon the interaction of the metal ions Mg(II), Ca(II), Li(I) and Na(I) with thymine [33]. The results show that there are two suitable binding sites, O(2) and O(4), with relative binding energies in the order Mg(II) > Ca(II) > Li(I) > Na(I). Although, for any particular metal ion, the metal–oxygen bond lengths are the same for binding to O(2) or O(4), the bond energies are greater for metal–O(4) binding than for metal–O(2) binding.

Goodgame and Johns [34] have reported complexes of neutral uracil and thymine with coordination at O(4). They prepared many complexes with a general formula $(MX_2L_n)xH_2O$ where:

$X = Cl, Br, ClO_4, NO_3$
L = uracil, thymine
$n = 1, 2$
$x = 0, 1, 2, 3, 4$
M = Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II)

All the complexes exist as microcrystalline powders, are insoluble in non-polar solvents and are decomposed, to yield the appropriate free nucleobase, by polar solvents. Many of the complexes are hygroscopic and the degree of hydration is variable. Electronic spectra show the metal ions to be six coordinate in nearly all cases; for example, all the copper complexes show a low intensity absorption near 12000 cm^{-1}, consistent with six coordination. For the nickel complexes the electronic spectra suggest essentially octahedral structures with $\Delta =$ ca. 7000 (bromides), ca. 7500 (chlorides), ca. 8750 cm^{-1} (nitrates). These low Δ values indicate a very weak ligand field and this is therefore in support of the donor atom being a carbonyl oxygen, which would be expected to act as a moderately strong π

donor with a ligand field at the low end of the oxygen donor range. The ESR spectra of these complexes are also in accord with six coordination [34].

More recently Sarkar and Ghosh [35] reported the interaction of divalent metal ions with uracil. They prepared several complexes with the general formula $[ML_4(H_2O)_2]X_2$ where: M = Mn, Fe, Co, Ni, Cu; X = NO_3, Cl or $1/2(SO_4)$; L = uracil. Again, electronic and infra-red spectra were measured, and from the former they concluded that the Δ values were low (for cobalt complexes ca. 7200, for nickel complexes ca. 7725 cm^{-1}) [35] and that the complexes contained hexacoordinate metal ions.

By comparison of the infra-red spectrum of the complexes with that of the free nucleobase it should, in theory, be possible to determine the binding site of the metal ion. However the infra-red spectrum of uracil in the C=O stretching region is complicated, having two strong bands at 1718 and 1675 cm^{-1}, plus a number of weaker bands. Some uracil complexes show a broad strong absorption in this region, with the centre of gravity shifted to a lower energy compared with that of uracil. Where resolution is good, however, more detailed changes, upon complex formation, can be detected. The higher energy band, at 1718 cm^{-1}, generally agreed to be due to $\nu(C_2{=}O)$ [36,37] is hardly shifted, whereas the band at 1675 cm^{-1}, assigned to $\nu(C_4{=}O) + \nu(C{=}C)$, moves to lower energy upon complex formation, suggestive of metal ion binding at the O(4) site. Frequently, a third strong band is observed near 1600 cm^{-1}.

In the complex $Hg(UH)_2Cl_2$, which has long-range Hg–O interactions [38], there is virtually no change in the uracil spectrum [39].

Assignments for thymine are less certain. In the classic work of Susi and Ard [40] the free ligand bands at 1735 and 1677 cm^{-1} were tentatively assigned as being due to $\nu(C_2{=}O)$ and $\nu(C_4{=}O)$ respectively. A more recent suggestion [41] is that the higher energy band contains both $\nu(C_2{=}O)$ and $\nu(C_4{=}O)$, with $\nu(C{=}C)$ at 1677 cm^{-1}. On complex formation both of these bands are shifted to slightly lower energy, and a third band is normally seen above 1600 cm^{-1} [34]. Therefore, no conclusions could be drawn from this about the site of metal ion binding.

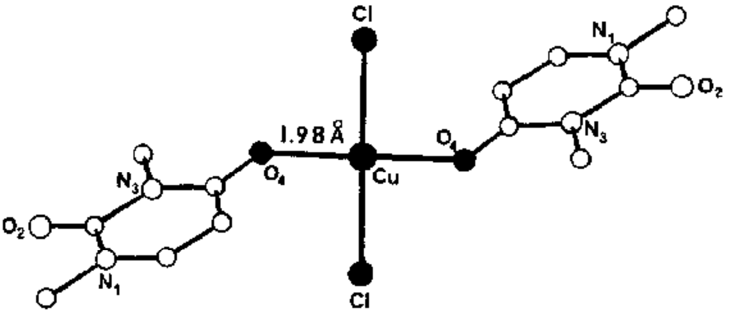


Fig. 1. Cu(1,3-dimethyluracil)Cl_2 [42].

TABLE 1

Infrared data for complexes of neutral uracils

Compound	ν(C=O) and ν(C=C)/cm^{-1}	Ref.
Uracil	1716s 1675s	[36,37]
$[MnCl_2(UH)]2H_2O$	1650s,br	[34]
$[MnCl_2(UH)_2]$	1715s 1635s,br	[35]
$[CoCl_2(UH)]$	1716s, 1660s,br 1597s	[34]
$[Co(UH)_4(H_2O)_2]Cl_2$	1715s 1635s,br	[35]
$[NiCl_2(UH)]2.5H_2O$	1716s 1640,br	[34]
$[NiCl_2(UH)_2]$	1715s, 1640s,br	[35]
$[CuCl_2(UH)]H_2O$	1716s, 1656s,br 1587s	[34]
$[Cu(UH)_4(H_2O)_2]SO_4$	1715s 1640s,br	[35]
$[CdCl_2(UH)]$	1716s 1657s,br 1590m	[34]
Thymine	1735m 1677s	[40]
$[MnCl_2(TH)]2H_2O$	1690s 1656s 1624s	[34]
$[CoCl_2(TH)]$	1735(sh) 1690s,br 1623ms	[34]
$[Ni(NO_3)_2(TH)_2]4H_2O$	1735m 1675s 1600sh	[34]
$[CuCl_2(TH)]2.5H_2O$	1710s 1658s 1608s	[34]
$[CdCl_2(TH)]1.5H_2O$	1709s 1676s 1647s 1631s	[34]

Goodgame and Johns also worked with 1,3-dimethyluracil, which, since it also exists as a dilactam, was considered a reasonable model for neutral uracil, and have reported the crystal structure of a Cu(II) : 1,3-dimethyluracil complex [42] (Fig. 1).

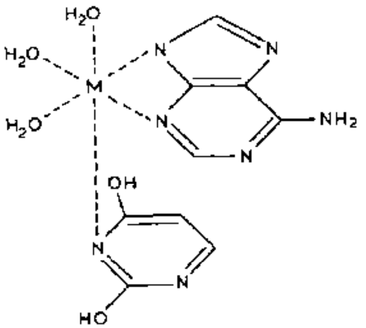
The infra-red spectra of 1,3-dimethyluracil showed changes similar to those produced by uracil upon metal ion binding. Therefore it was suggested that the short (1.985 Å) metal–O(4) bond present in this complex [42] is likely to be present in other transition metal–uracil complexes [43]. This indicates fairly strong metal–O(4) binding in metal–uracil complexes (in accord with the stability of such complexes to heat [34,35]) and shows that the weakness of the ligand field is not due to weak bonding.

Under similar conditions no complexes were obtained for 1,3-dimethylthymine. This is possibly due to the blocking of the O(4) position by the two adjacent methyl groups [44].

The interactions of uridine and thymidine with metal ions have also been studied. Solid complexes of the nucleosides with Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Cd(II), in which the nucleoside ligands were present as neutral molecules, have been prepared [45]. As with the analogous uracil and thymine complexes the ligand field appeared to be weak, which, together with infra-red data, indicates binding of the nucleoside ligands through O(4). However, there is also the possibility of involvement of the ribose oxygens and the extent of their involvement appears to be very dependent upon the nature of the metal ion. For instance, ^{13}C NMR studies [46] have shown that Mn(II) interacts with the carbonyl groups of uridine while proton NMR studies in DMSO [47] show Cu(II) interacting with both the carbonyl groups on the base and the sugar hydroxy groups of uridine. For the compound Fe(uridine)Cl_2 the Mössbauer spectrum and the low temperature magnetic susceptibility [48] indicate an octahedral $FeCl_4O_2$ chromophore, with halide-bridged chains crosslinked by bridging uridine molecules. The uridine is thought to bridge via O(4) and one of the ribose hydroxy groups.

Although no metal binding to the O(2) site has been reported for neutral uracil or thymine it has been reported that 2-thiouracil binds to Cu(I) through S(2) [49,50]. However, this is undoubtedly due to Cu(I) having a higher affinity for sulphur than for oxygen.

Khan and Satyanarayana [51] have reported the stability constants for metal complexes of uracil and mixed-ligand–metal complexes with uracil as a primary ligand and adenine as a secondary ligand. They concluded that the binding of uracil in both the 1 : 1 metal–uracil and 1 : 1 : 1 metal–uracil–adenine complexes was via N(3) with the uracil ligand present in its dihydroxy form. The extra stability of the 1 : 1 : 1 complexes compared with the 1 : 1 was considered to be due to favourable stacking interactions between the uracil and adenine ligands. A possible structure was proposed [51]



This structure appears unlikely since having the uracilate ring perpendicular to the metal–N(3) bond produces a very strained structure. Consequently, stacking interaction between the two ligand rings is unlikely. Also at the pH used for the preparations, namely 'alkaline conditions', the uracil would not be present in the form shown when free in solution, and since the metal ions used were all relatively "hard", namely Cu(II), Zn(II), Ni(II), Co(II) and Mn(II), metal–N(3) binding, which creates the unstable dihydroxy structure of the uracilate, seems improbable.

(ii) Complexes of "soft" metal ions

An ab initio calculation has been performed for the interaction of $Pt(NH_3)_3^{2+}$ with neutral thymine [52]. Again the calculations show O(2) and O(4) to be the two possible binding sites with Pt–O bond energies of 70 and 73 kcal mol^{-1} respectively. The corresponding bond energy for H_2O was calculated to be 56.5 kcal mol^{-1} and since H_2O is a smaller ligand, solvation is likely to increase the effective binding of H_2O relative to thymine. This may explain why Pt(II)–O single-site binding to neutral thymine is not observed.

However, there has been one Hg(II)–uracil complex, containing metal–oxygen binding, reported. Carrabine and Sundaralingam [38] prepared the 2 : 1 complex of uracil–mercuric chloride, $(UH)_2HgCl_2$, and determined its crystal structure (Fig. 2).

The mercury atom is bound directly to the O(4) atoms of inversion-related uracil rings, with an Hg–O bond length of 2.71 Å which suggests only a weak bond. The bases in turn are hydrogen bonded to one another through pairs of N(3)–H · · · O(2) hydrogen bonds forming a zig-zag chain, (the mercury bound O(4) does not participate in any hydrogen bonding). The octahedral coordination of the mercury is completed by chlorine bridges.

Study of the interaction of mercury(II) with uridine has shown that as well as binding at the O(4) site, electrophilic attack on the ring with displacement of a proton and formation of a carbon–mercury bond may

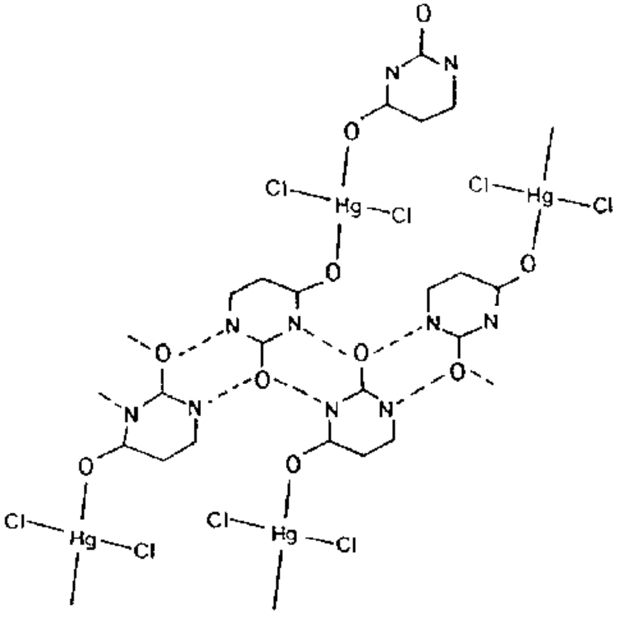
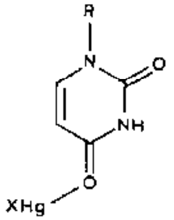


Fig. 2. $(UH)_2HgCl_2$ [38].

occur [39]. Thirdly, electrophilic attack with displacement of a proton and formation of a mercury–nitrogen bond has been observed [39].



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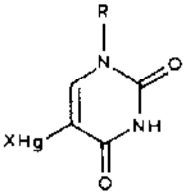

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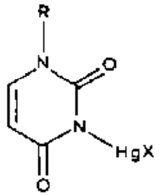
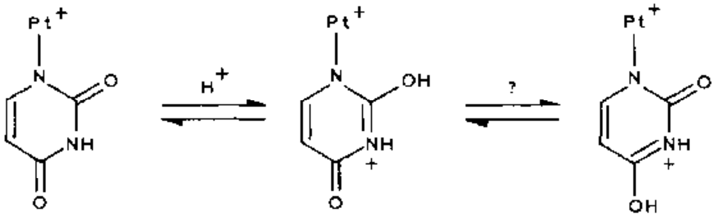
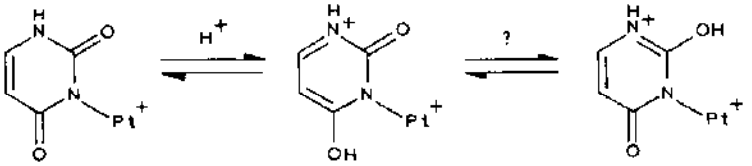


III

Structure II involves metal–carbon bonding, and structure III involves the uridine monoanion (which will be considered in section E).

Pt(II)–uracil complexes containing metal–nitrogen binding, and therefore rare tautomeric forms of neutral uracils, have been reported. $[Pt(NH_3)_3(UH)]^{2+}$ has been isolated and characterised, using proton NMR and Raman spectroscopy, in both the N(3) and N(1) bound forms [53]. They were prepared by protonation of the analogous complexes containing the correspondingly bound uracilate ligands.





The N(1) complex requires a pH < 0 for protonation of the uracilate ligand whereas the N(3) complex will protonate at a pH < 1. It has not been determined whether the protonation occurs at O(2) or O(4) but proton NMR studies [53] indicate that O(4) is not favoured over O(2), as might have been expected from the protonation of free uracil occurring predominantly at O(4) [24,25].

Similarly, for thymine, *cis*-$Pt(NH_3)_2(1\text{-}MeT)_2$ is readily protonated at an exocyclic oxygen to give *cis*-$[Pt(NH_3)_2(1\text{-}MeT)(1\text{-}MeTH)]^+$, pK = 2.05 [54]. This has the neutral 1-methylthymine bound via N(3), and therefore present in its rare iminol tautomeric form. The neutral 1-methylthymine is only weakly bound, being readily displaced.

D. COMPLEXES OF THE MONOANION OF URACILS WITH "HARD" METAL IONS

Under alkaline conditions there is less competition, from protons, for the N(1) or N(3) binding sites. Thus binding of "hard" metal ions can occur at these sites (as opposed to the exocyclic oxygens as described in the previous section).

Potentiometric studies have been carried out on several uracilate and thyminate complexes, with the thermodynamic functions of formation of these complexes being determined from these studies [14,26,55–57]. Srivastava and Srivastava [14] determined values of ΔG, ΔH and ΔS for the formation of 1 : 1 complexes of Be(II) and Hg(II) with uracilate and thyminate. They found that ΔH was negative and ΔS was positive, which implies that both entropy and enthalpy contribute favourably to the formation of these complexes.

Comparison with the values determined by Khan and Satyanarayana [26] for uracilate and thyminate complexes of Cu(II), Zn(II), Ni(II), Co(II), Mn(II) and Mg(II) indicates that both Hg(II) and Be(II) form more stable complexes with uracil under alkaline conditions. (However, since the chemical equations related to these thermodynamic functions were not quoted [14,26], the equations used may have been different, making such a comparison invalid. It is also not clear as to whether the possible formation of hydroxy complexes was considered.)

Khan and Satyanarayana also found that the 1 : 1 metal : uracilate/thyminate complexes were more stable than the corresponding 1 : 2 complexes [26], as would be expected from statistical considerations.

Potentiometric studies on the interaction of uracil with Ni(II), Cu(II) and Ag(I) have shown the 1 : 1 salt to be formed in all three cases with stabilities in the order Ag > Cu > Ni [57]. Since complex formation is accomplished by release of a proton, binding probably occurs at one of the ring nitrogens.

TABLE 2

Thermodynamic functions for 1:1 complexes of Be(II) and Hg(II) with uracilate and thyminate [14]

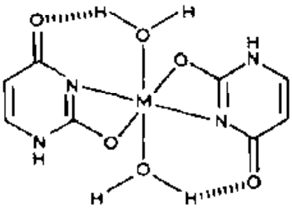
	ΔH (kcal^{-1} mol^{-1})	ΔS (kcal^{-1} mol^{-1} °C^{-1})	ΔG (kcal^{-1} mol^{-1})
Uracil			
Be(II)	-7.8 ± 0.4	4 ± 1.2	-9.0 ± 0.05
Hg(II)	-6.5 ± 0.8	12 ± 2.3	-10.1 ± 0.04
Thymine			
Be(II)	-4.6 ± 0.8	17 ± 2.4	-9.6 ± 0.05
Hg(II)	-8.5 ± 0.4	5 ± 1.2	-10.1 ± 0.04

TABLE 3

Thermodynamic functions for 1 : 1 complexes of various "hard" metal ions with uracilate and thyminate [26]

	ΔH_f^0 (kcal^{-1} mol^{-1})		ΔS_f^0 (kcal^{-1} mol^{-1} C^{-1})		ΔG_f^0 (kcal^{-1} mol^{-1})	
	U	T	U	T	U	T
Cu(II)	−3.7	−5.13	15.5	13.52	−8.3	−9.16
Zn(II)	−5.3	−3.50	5.5	12.80	−7.0	−7.30
Ni(II)	−1.8	−4.80	11.6	4.0	−5.3	−6.0
Co(II)	−2.7	−4.80	8.1	3.60	−5.1	−5.86
Mn(II)	−7.0	−4.80	8.1	0.03	−4.5	−4.80

Electronic and infra-red spectroscopic studies have been carried out on the complexes of Mn(II), Co(II), Ni(II) and Cu(II) with uracil, under alkaline conditions [58]. The synthesis of the complexes was carried out in alkaline methanol (pH ~ 10) by combination of uracil with the appropriate metal chloride. All the complexes were coloured, non-electrolytes with the general formula $[MU_2(H_2O)_2]$ [58]. From the electronic spectra, it was concluded that the complexes had a distorted octahedral structure with a degree of metal–oxygen interaction, with the chelating uracilate ligands, being present. Typical ligand field values were Co, $\Delta = 6725$, Ni, $\Delta = 6950$ cm^{-1}, i.e. a weak ligand field. From infra-red spectroscopy it was concluded that the binding sites, for the uracilate ligand, were N(3) and O(2). The ν(NH(1)) absorption band remains almost unchanged upon complex formation, changing from 3160 cm^{-1} for free, neutral, uracil to 3200 cm^{-1} in the Mn(II) and Cu(II) complexes, whereas the δ(NH(3)), present at 1417 cm^{-1} in free neutral uracil, disappears completely [58]. ν(C(2) = O) changes from 1718 to 1700 cm^{-1} whereas ν(C(4)=O + C=C) remains relatively unaltered, (the small change observed for ν(C(4)=O) is probably due to hydrogen bonding between C(4)=O and the coordinated water molecules). From these facts the following structure, with the uracil monoanion acting as a η^2-bidentate ligand, has been proposed [58]



From infra-red and electronic spectroscopic studies of mixed-ligand (glycine/uracil) Cu^{II}, Ni^{II}, Co^{II} and Zn^{II} complexes, in alkaline conditions, conclusions as to the mode of uracilate binding have been drawn [59]. Only in the case of the copper(II) complex, $Na_2[Cu(glycinate)(U)(OH)_2].H_2O$, was the uracilate shown to be acting as a η^2-bidentate ligand, binding via a ring nitrogen and an exocyclic oxygen. In all the other cases the uracilate was acting as a monodentate ligand binding via a deprotonated ring nitrogen. The carbonyl binding present in the copper complex was deduced from the significant drop in energy of the absorption band due to ν(C=O) upon complex formation, from 1712 cm^{-1}, measured for free neutral uracil, to 1670 cm^{-1} in the complex.

Infra-red spectroscopic studies on the mixed ligand copper(II) complex Cu(II)glycylglycine(uracil)HBr.3/2H_2O indicate binding at the N(1) site of the uracilate ligand. Upon complex formation the N(1)–H bending vibration disappears whereas the N(3)–H bending mode absorption band is still present at 1415 cm^{-1} [60].

Molecular orbital calculations have been made for the interaction of copper(II) with uracilate [61]. Using the Extended Hückel Theory, which gives a good indication of relative parameter variation, it was shown that the presence of Cu(II) alters the charge distribution pattern of practically all of the atoms in uracil. The main effect is to withdraw electron density from the negatively charged nitrogens and positively charged carbons, with the exocyclic oxygens remaining relatively unaltered. An energy minimum lies with the Cu(II) in the plane of the uracilate ring, adjacent to the N(3) atom; non-planar energy minima, with only a small energy difference, also exist. However, as has been shown we see N(1) and N(3) binding, depending upon the method of preparation, in copper(II) complexes of the uracil monoanion. Although this appears to disagree with the molecular orbital calculations it is not surprising since other energetic considerations, such as hydrogen bonding, could well be sufficient to change the preferred structure.

X-ray crystallography has shown that the uracil monoanion is bound via N(1) in diammine-diaqua-bis-(uracilato)-nickel(II) [62]

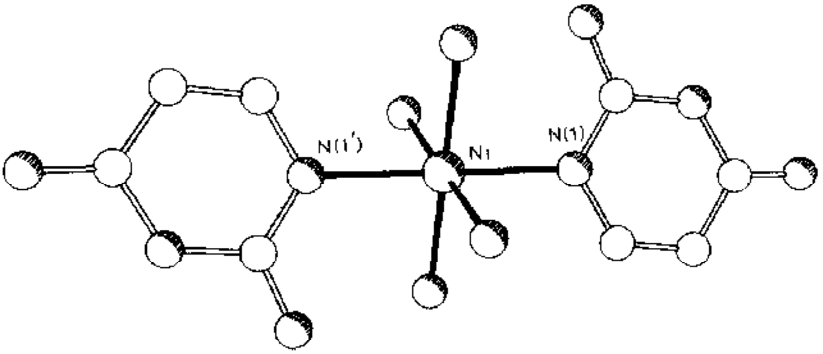


Fig. 3. $(U{-}N(1))_2Ni(NH_3)_2(H_2O)_2$ [62].

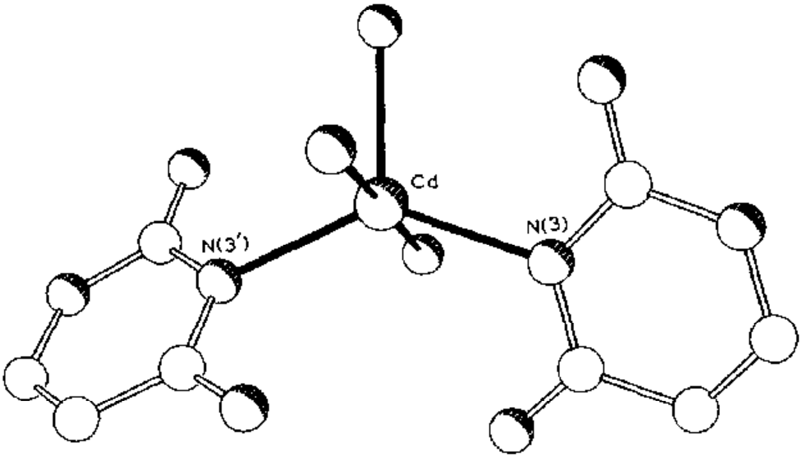


Fig. 4. $Cd(U{-}N(3))_2(H_2O)_3$ [64].

The nickel has an octahedral coordination sphere with the two uracilate ligands *trans* to each other. There exists intermolecular hydrogen bonding, with N(3) and O(4) involved, which holds the solid structure together. Intramolecular hydrogen bonding also exists between O(2) and the ammonia nitrogen N(4).

N(1)–metal-ion binding has also been crystallographically demonstrated for the copper(II) : thyminato complex $(H_2O)Cu^{II}(dien)(T)Br.2H_2O$ [63].

In the complex triaquabis(uracilato)cadmium(II) the uracilate ligand is bound to the cadmium ion via N(3) [64].

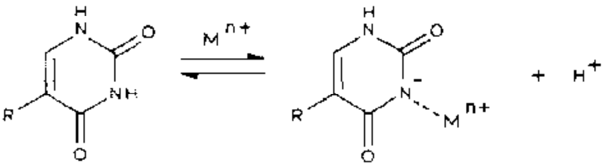
The cadmium ion is five coordinate with the two N(3) atoms being equatorial. Again the solid has a hydrogen bonding network with the three water ligands and N(1), of the uracilate ligand, acting as donors and the exocyclic oxygens acting as acceptors.

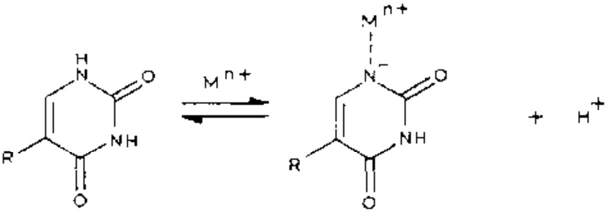
Lanthanide complexes of the uracil monoanion and dianion have been reported with LnUu and Ln_2u_3 stoichiometries, where $Ln = La^{III}$, Pr^{III}, Nd^{III} and u represents the uracil dianion. Infra-red studies upon these complexes show that upon complex formation the absorption bands ν(C(2)=O) (at 1718 cm^{-1}) and ν(C(4)=O + C=C) (at 1675 cm^{-1}) disappear, and a new band appears at 1630 cm^{-1} for Ln_2u_3 and at 1640 cm^{-1} for LnUu. (For the Ln_2u_3 case the δN(1)H, at 1500 cm^{-1}, and the δN(3)H, at 1440 cm^{-1}, of uracil also disappear upon complex formation.) This information was used to conclude that the uracil anions are present in their O-bonded lactim form in these complexes [65].

E. COMPLEXES OF THE MONOANION OF URACILS WITH "SOFT" METAL IONS

(i) Monodentate complexes

In neutral aqueous solution the monoanions of uracils do not exist to any appreciable degree (pKa; uracil = 9.69, thymine = 10.16) [26]. However, relatively "soft" metal ions such as Ag(I), Pt(II), Pd(II) and Hg(II), which have a high affinity for N over O, are able to replace a proton at N(3) or N(1) in neutral or even low pH solutions.





(For 1-methyluracils, uridine and thymidine this can occur only at N(3), since N(1) is bonded to an alkyl group rather than a proton.)

For example, uridine and thymidine undergo proton loss at N(3) and displace all the H_2O ligands from dienM$(H_2O)^{2+}$ and enM$(H_2O)_2^{2+}$, where M = Pt(II) or Pd(II), at values of pH well below the pKa ~ 10 [66].

Solution Raman spectroscopy has shown that the reaction at 25°C between uridine and Hg(II) in aqueous perchlorate solution at pH = 7–9, involves displacement of the proton from N(3) and coordination of mercury [39] (for structure see page 107, structure III).

Addition of HgO to aqueous 1-methylthymine produces a 2 : 1 complex of 1-MeT : Hg(II), the crystal structure of which has been determined [67]. It shows the mercury ion to be bound to the N(3) of both of the 1-methylthymine ligands, forming a linear N–Hg–N unit with N–Hg bond lengths of 2.04 Å.

The crystal structure of a 1 : 1 Hg(II) : 1-MeT complex, $CH_3Hg(1\text{-}MeT).1/2H_2O$, also shows Hg(II) bound to the N(3) site of 1-methylthymine, with a Hg : 1-MeT bond length of 2.08 Å [68].

The complexes *trans*-$L_2M(PBu_3)_2$, where M = Pt(II) or Pd(II) and L = uracilate or thyminate, have been prepared by treatment of *trans*-$Cl_2M(PBu_3)_2$ with the appropriate nucleobase anion [69]. However it has not been shown at which ring nitrogen, N(1) or N(3), the metal ion is bound.

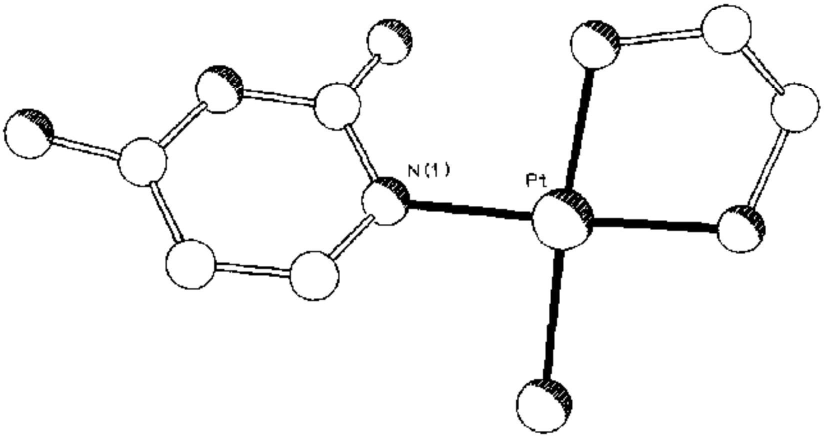


Fig. 5. $(H_5O_2)[PtCl(en)(U{-}N(1))]Cl$ [70].

However, a crystal structure study of the major product of the reaction between $[enPt(H_2O)_2](NO_3)_2$ and uracil in 1.0 M HCl solution at 70 ° C, has shown the product to be pentahydrodioxoniumchloro-(uracilato-N(1))-(ethylenediamine)-platinum(II)-chloride, $(H_5O_2)[PtCl(en)(U)]Cl$ [70], i.e. the Pt(II) is bound to the N(1) site of the uracilate ligand.

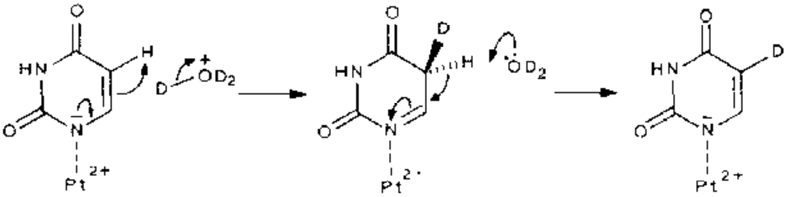
The platinum atom is surrounded by four donor atoms in an approximately square planar arrangement. The uracilate group is twisted so as to bring the O(2) atom close to a nitrogen of the ethylenediamine group, presumably to form weak hydrogen bonds. That the major product is the N(1) bound complex is consistent with the fact that N(3) bound complexes of the uracil monoanion with Pt(II) are less stable to acid treatment than the corresponding N(1) complexes. For example triammine(uracilato)platinum(II) decomposes at pH < 1 when heated to 70 ° C, to yield free uracil [53].

Metal ion binding to the N(1) site of thyminate has also been demonstrated for the complex $[Pt(NH_3)_2(\text{1-methylcytosine})(T)]$ [71].

Differentiation of N(1) and N(3) binding in a monodentate complex is possible using proton NMR. For instance in the uracilate complexes of $Pt(NH_3)_3$, *cis*-$(NH_3)_2Pt$ and enPt, N(1) binding leads to a value of $J_4(^{195}Pt{-}^1H(5)) = 4$Hz whereas N(3) binding leads to a value of $J_4(^{195}Pt{-}^1H(5)) = 15$Hz [53] (N.B. H(5) is the proton on carbon 5 of the uracil).

Another proton NMR method of differentiation is to treat the complex with acid in D_2O. For the N(1)-bound Pt(II) species a collapse of the H(5) signal is observed. Also the H(6) sextet is reduced to a triplet, 1 : 4 : 1, which corresponds to the expected distribution according to the natural abundance of ^{195}Pt (33.8%). No such observations have been made for the N(3)-bound species [53]. This phenomenon is due to a fast D/H exchange at C(5) with complexes containing N(1)-bound platinum, with no such exchange occurring in N(3)-bound complexes under comparable conditions. No exchange at C(6) is observed for either N(1)- or N(3)-bound uracilate.

Although no mechanism for this exchange has been reported a possible mechanism might be



No similar mechanism can be drawn for an N(3)-bound uracilate, or for exchange at C(6) with either N(1)- or N(3)-bound uracilate. Clearly this method of differentiation is unsuitable for thyminate complexes since they do not contain a proton at C(5).

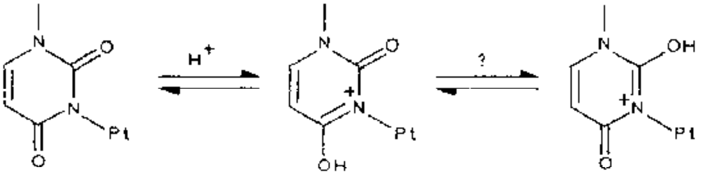
Both of these proton NMR methods are limited to kinetically inert species. With kinetically labile species (interconversion between N(1)- and N(3)-bound species is rapid on an NMR timescale) the methods are of very limited use.

It has, in fact, been demonstrated that some uracilate complexes, under certain conditions, are labile with respect to N(1) : N(3) binding-site interconversion. Platinum(II) uracilate complexes containing an aquo ligand in the first coordination sphere i.e. coordinatively unsaturated with respect to the platinum, for example enPt(U-N(1))H_2O^+ and *cis*-Pt$(NH_3)_2$(U-N(1))H_2O^+ [53], form bridged species, as do the analogous 1-methyluracilate complexes. These bridged species provide a route for N(1) ⇌ N(3) binding-site interconversion

Although "saturated" platinum(II) uracilate complexes are stable in this respect when in isolation, in the presence of "unsaturated" platinum(II) complexes they also interconvert. An example of this is the $(NH_3)_3$Pt(II) complex of the uracil monoanion in the presence of $(NH_3)_3Pt(H_2O)^+$. Proton NMR spectroscopy has been used to demonstrate the N(1) : N(3) interconversion [53].

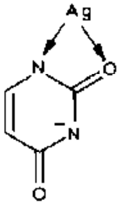
$$(NH_3)_3Pt(U\text{-}N(1)) \rightleftharpoons (NH_3)_3Pt(U\text{-}N(3))$$

The pH of the solution falls and it is thought that the intermediate between mono N(1) and mono N(3) bound uracilate is an N(1),N(3) bridged dimer.

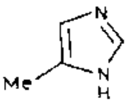


The formation of this species, which has not been isolated, is believed to proceed via a less stable N- and O- complexed intermediate [53]. However the mechanism has not been demonstrated, nor this route to interconversion unambiguously verified.

Studies of the interaction of silver(I) with uracil in aqueous alkaline media may lend some support to the idea of an N-,O- bound uracilate intermediate. Association of uracil to Ag(I) in aqueous solution at pH = 14 leads to substantial deshielding of C(2) and C(6) in the ^{13}C NMR [27]. This suggests complexing of the silver(I) to an $^{2}\eta$ bidentate uracil dianion, with N-,O- binding.



It has been shown that Raman spectroscopy is a useful technique for differentiation of the two possible ring nitrogen binding-sites of 4-methylimidazole [72,73].

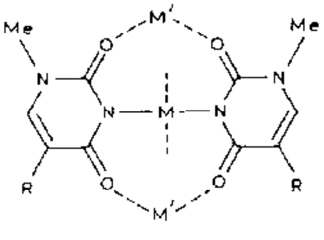


However, Lippert has concluded that for a platinum–uracil system containing more than one distinct species, Raman spectroscopy as a method for N(1),N(3) binding-site differentiation is very restricted [53]. This is due to the occasional strong overlap of corresponding modes in different species and the dark colour of many of the solutions.

(ii) Multidentate complexes

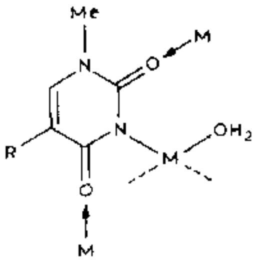
The relatively few examples of complexes with "soft" metal ions and monodentate monoanions of uracils is due to the high tendency of such complexes to bind additional metal ions to form di-, tri- and tetranuclear complexes, and probably even larger aggregates. This is believed to be due to two effects that arise upon coordination of the first metal ion. Firstly, there is an electronic effect: a "soft" transition metal ion binding to the deprotonated N(3) position of the nucleobase ligand increases electron density upon the exocyclic oxygens, probably through π-donation onto the ring (in contrast to the situation for "hard" metal ions—see section D). Secondly, there is the favourable geometry of these oxygens for further metal coordination [74].

For the monoanions of 1-methyluracils, formation of such aggregates can occur in any of three ways. A complex which has the metal coordinatively saturated, such as *cis*-Pt$(NH_3)_2$(1-MeB$)_2$, requires the presence of other metal ions to form aggregates (if one does not consider the possibility of aggregation through oxidation and metal–metal bond formation).



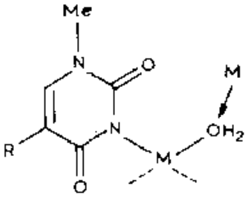
Scheme I

In contrast, complexes where the metal is coordinatively unsaturated (i.e. has an incomplete inner coordination sphere or has a labile ligand, e.g. H_2O), such as *cis*-[Pt$(NH_3)_2$(1-MeB)$H_2O]^+$, have the capacity to form di- or oligomeric structures without the need for the presence of other metal ions. These complexes can self-associate in two principal ways: through N,O-bridging of the uracil



Scheme II

or through OH bridge formation.



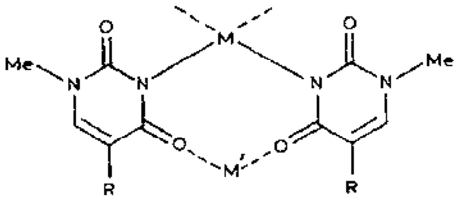
Scheme III

The first possibility is a consequence of the increased electron density upon the exocyclic oxygens, whereas the second is a consequence of the acidity of the coordinated aquo ligand (pK_a typically between 5 and 7) [74]. The ratio of *cis*-[Pt$(NH_3)_2$(1-MeU)$(H_2O)]^+$: *cis*-[Pt$(NH_3)_2$(1-MeU)$]_2^{2+}$: *cis*-[$(NH_3)_2$(1-MeU)Pt(OH)Pt(1-MeU)$(NH_3)_2]^+$, (i.e.

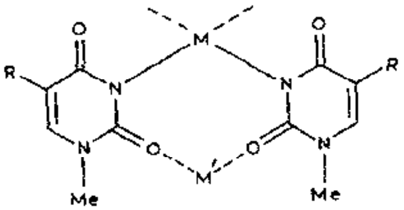
monomer : dimer : hydroxo bridged species), in the pH range 4–5 has been shown to be 35 : 60 : 5 [75]. Thus, under these acidic conditions the hydroxo bridged species does not play an important role. (However as the pH is increased the species increases in abundance.) A more detailed study of the hydroxo bridging case (i.e. scheme III), although of biological interest, lies outside the scope of this review.

A possible rationale for the probable structures formed upon aggregation is as follows:

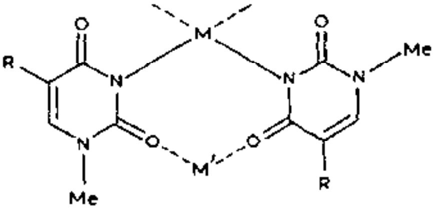
When aggregation occurs via scheme I the bidentate bridging 1-MeB ligands must be arranged in a head–head fashion, assuming that the metal–N(3) bond is inert, i.e. the initial metal–N(3) bond is not broken and reformed elsewhere. (It has in fact been shown that such Pt(II) complexes are kinetically inert with respect to CN$^-$ attack [76], so this assumption seems to be valid for Pt(II))



A

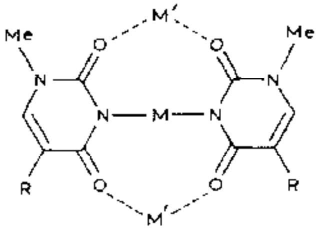


B

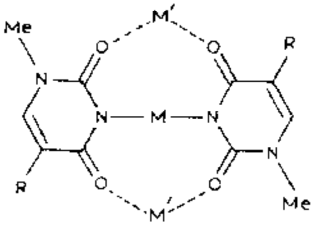


C

For the formation of a trinuclear complex, containing tridentate 1-MeB ligands, scheme I can lead to either head–head or head–tail structures since both involve retention of the original metal–N(3) bonding.

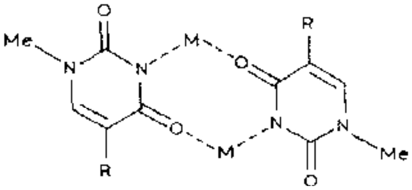


D

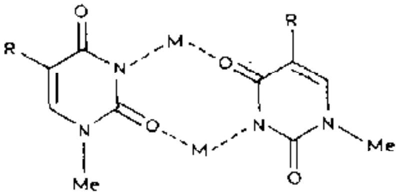


E

However, when aggregation occurs via scheme II only head–tail aggregates with bridging bidentate 1-MeB ligands can result if the original metal–N(3) bond is to be retained.



F



G

(a) Bidentate complexes

There have been no reported dimer complexes of platinum(II) with one of the 1-MeB ligands bridging via N(3), O(4) and the other via N(3), O(2) (i.e. any complexes corresponding to structures C or G). Moreover there are no reported bidentate Pt(II) : 1-MeB complexes with N(3), O(2) bridging (i.e. structure B). This is due to the coordination of second and third metal ions occurring in a stepwise manner, with occupation of the exocyclic oxygens taking place in matched pairs, O(4),O(4) and O(2),O(2). For instance, formation of the N(3),O(4) bridged Pt(II),Cu(II) complex $[(NH_3)_2Pt(1\text{-}MeU)_2Cu(H_2O)_2].SO_4.9/2H_2O$ requires rotation of one of the two 1-methyluracilate ligands about the Pt–N(3) bond [77]. Despite the possibility of coordination through one O(2) and one O(4), which would not involve rotation, twofold N(3),O(4) bridging appears to be more favourable than the mixed N(3),O(4) and N(3),O(2). As well as illustrating the stepwise process for further metal ion coordination this also supports the idea that O(4) is more basic than O(2).

With this information we would thus expect to find bidentate Pt(II) : 1-MeB complexes corresponding only to structures A and F. Looking at the only well authenticated example, *cis*-$[Pt(NH_3)_2(1\text{-}MeB)]_2(NO_3)_2$, this is in fact the case.

The head–head dimer, with the nucleobase being 1-methyluracil, has been prepared by the reaction of *cis*-$Pt(NH_3)_2(1\text{-}MeU)_2$ with *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ (this preparation leads to aggregation via scheme I) and its formation monitored by proton NMR [74]. If no base is added (pH = 3–4) the dimer is almost quantitatively formed within 20 h. at 22° C. The crystal structure has been determined [74].

It consists of two *cis*-$Pt(NH_3)_2$ moieties bridged by two 1-methyluracilate ligands, through N(3) and O(4). The Pt–Pt distance is 2.937 Å.

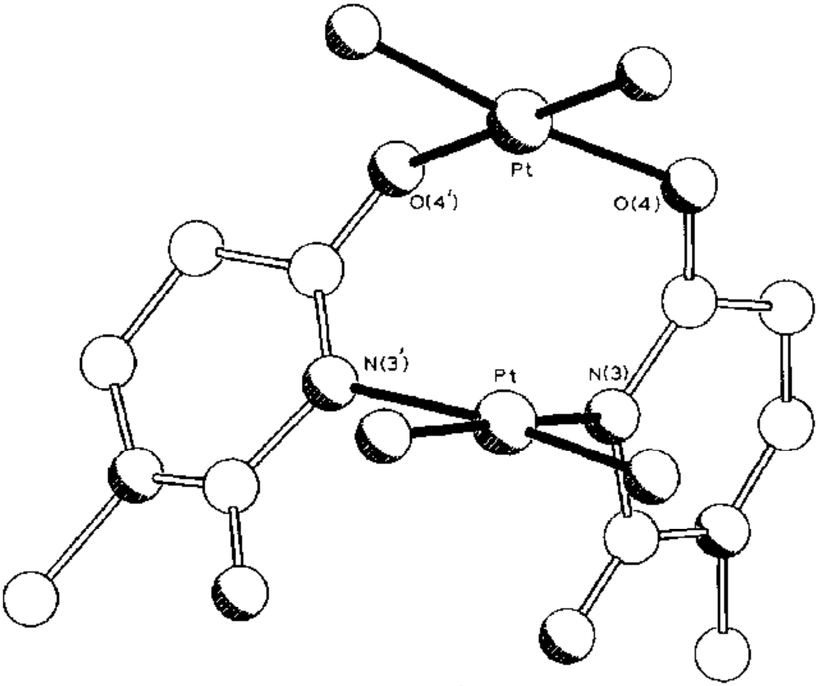


Fig. 6. Head–head $[Pt(NH_3)_2(1\text{-}MeU)]_2^{2+}$ [74].

The analogous 1-methylthymine complex has also been prepared, using essentially the same preparative route, and the structure has been shown to be the same as that of the 1-MeU analogue, but with a Pt–Pt separation of 2.909 Å [78].

The 1-methyluracil head–tail dimer has been prepared by combination of 1-methyluracilate and $(NH_3)_2Pt(OH)_2Pt(NH_3)_2$ at $pH = 7$ (this preparation leads to aggregation via scheme II). The complex has also been crystallographically studied [79].

As with the head–head dimer the 1-methyluracilate ligands are bridging via N(3) and O(4), with the Pt–Pt distance a little longer at 2.954 Å. (It is interesting to note that this preparation might have been expected to yield a mixture of head–head and head–tail isomers, since there were initially no Pt : 1-methyluracilate bonds. The fact that this is not the case supports the stepwise formation of the product via a Pt : 1-methyluracilate monomer bound at N(3).)

Again, the analogous 1-methylthymine complex has been isolated, using the same preparative method, and the crystal structure shown to be similar, but with a Pt–Pt separation of 2.974 Å [80].

A useful method of differentiation of head–head and head–tail dimers has been developed by Lippert and Neugebauer [81], proton NMR and IR spectroscopy having proved to be of little direct use. Treatment of the dimer in solution with excess sodium chloride results in different products for the different dimers. The head–head dimer yields *cis*-$Pt(NH_3)_2(1\text{-}MeB)_2$ and *cis*-$Pt(NH_3)_2Cl_2$ whereas the head–tail dimer yields only *cis*-$Pt(NH_3)_2$(1-

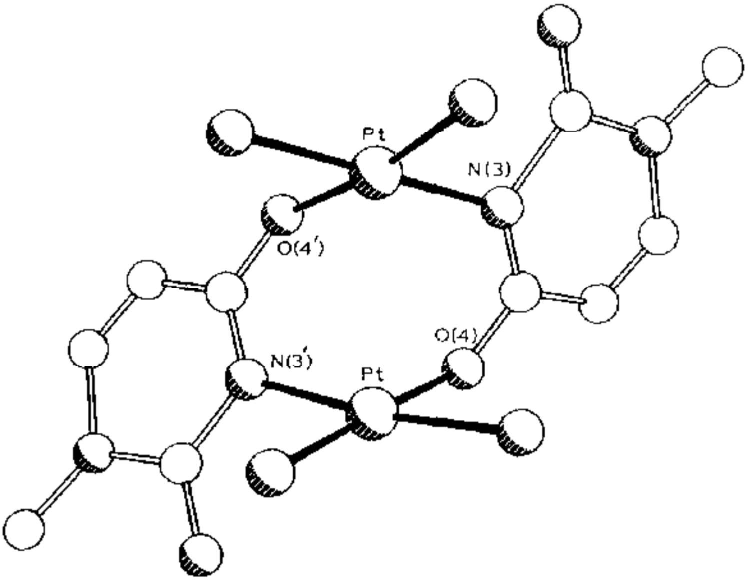


Fig. 7. Head–tail $[Pt(NH_3)_2(1\text{-}MeU)]_2^{2+}$ [79].

MeB)Cl. These products can easily be distinguished using spectroscopic techniques.

This fact also supports the earlier proposed rationale for the formation of the dimers since it follows the reverse of the dimer formation from the appropriate monomer, via scheme I or scheme II.

Another example of oligomer formation occurs with the Pt(II) mixed-nucleobase complex, $[Pt(NH_3)_2(1\text{-}MeU)(1\text{-}MeC)]NO_3.2H_2O$. In the presence of copper(II) it forms a trinuclear complex, $[Pt(NH_3)_2(1\text{-}MeU)(1\text{-}MeC)\text{-}Cu(1\text{-}MeC)(1\text{-}MeU)(NH_3)_2Pt](NO_3)_4.6H_2O$. The crystal structure of this complex has been determined [82].

Both platinum atoms are bound to N(3) of 1-methyluracilate and N(3) of 1-methylcytosine, respectively, while the copper binds to O(4) of 1-methyluracilate and O(2) of 1-methylcytosine in pairs: thus each nucleobase acts as a bridging bidentate ligand. All three metal ions have square planar coordination spheres, with the copper at the inversion centre of the Pt_2Cu unit. The O(2) of the 1-methyluracilate ligands deviates from the plane of the ligand ring, probably due to its involvement in intra- and intermolecular hydrogen bonding. EPR spectral studies, at *X*- and *Q*-band frequencies, are

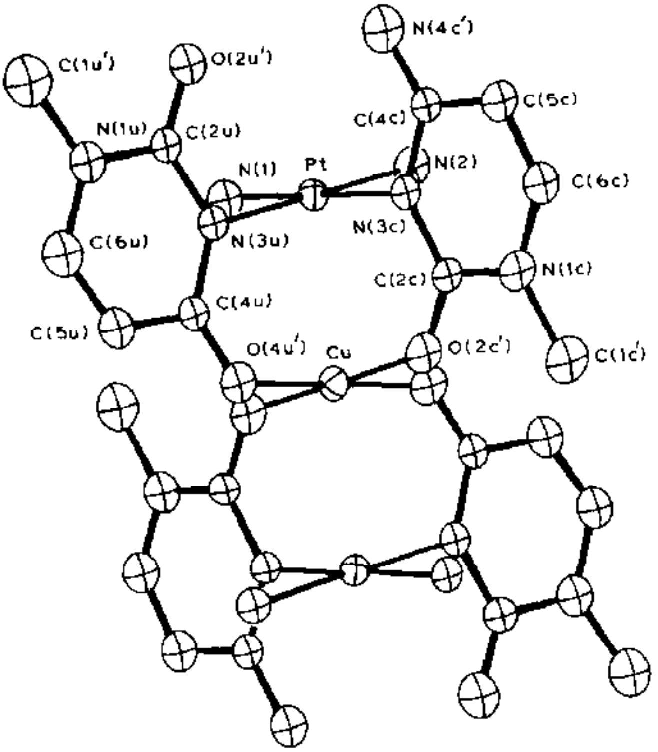


Fig. 8. $[Pt(NH_3)_2(1\text{-}MeU)(1\text{-}MeC)]Cu^{4+}$. Reprinted with permission from Inorg. Chem., 23 (1984) 2807. Copyright (1984) American Chemical Society.

consistent with a tetragonally elongated ligand field about the Cu(II) ion (X-band: $g_{\parallel} = 2.384$, $g_{\perp} = 2.070$, $A_{\parallel} = 10.85$ mT). These values suggest that there is no significant Pt–Cu bonding, in spite of the rather short metal–metal distance (2.681 Å) [82].

Several complexes analogous to this trinuclear Pt_2Cu complex have been reported, with the methods of preparation and crystal structures essentially the same, but with metal ions other than Cu(II) and involving only 1-methyluracils (i.e. not involving 1-methylcytosine).

The complex $Mn[Pt(NH_3)_2(1\text{-}MeT)_2]_2Cl_2.10H_2O$ has been prepared and the crystal structure shows the Mn(II) ion to be at the inversion centre of the Pt_2Mn unit with square planar coordination [83]. The EPR spectra at X- and Q-band showed an extremely large tetragonal distortion of the ligand field round the Mn(II) ion [84].

Goodgame et al. [85] have reported heteronuclear complexes of the general type $cis\text{-}[(NH_3)_2PtL_2ML_2Pt(NH_2)_2]X_n.mH_2O$ where L = 1-MeT or 1-MeU and M = Fe(II), Fe(III), Co(II), Ni(II), Cu(II). In this case no crystal structures were obtained, but the electronic spectra of the complexes where L = 1-MeU, X = NO_3, $n = 2$ and M = Fe, Co or Ni are reported. These show that the $trans\text{-}MO_4Pt_2$ geometry again results in a very severely *trans*-elongated ligand field about the central metal ion, M. This conclusion is supported by the Mossbauer spectrum in the case of the iron(II) complex [48], and the EPR spectrum of the copper(II) complex [82].

A crystal structure of the trinuclear complex $Ag[cis\text{-}Pt(NH_3)_2(1\text{-}MeT)_2]_2NO_3.5H_2O$ has been reported [86] and shows the coordination around the silver(I) ion to be distorted tetrahedral.

For the reaction of zinc sulphate with $cis\text{-}(NH_3)_2Pt(1\text{-}MeU)_2$ the product is a dinuclear complex of composition $[(NH_3)_2Pt(1\text{-}MeU)_2Zn(H_2O)_3]SO_4.2H_2O$ [87] rather than a trinuclear complex as is the case in the previous examples.

In all of these cases the 1-MeB ligands are bidentate, bridging through N(3) and O(4).

(b) Tridentate complexes

Bidentate 1-methyluracilate complexes can undergo further complexation to give tridentate 1-methyluracilate. This occurs via occupation of the O(2) coordination site.

Co-crystallisation of $AgNO_3$ with either the head–head [30] or the head–tail [75] isomer of $cis\text{-}[Pt(NH_3)_2(1\text{-}MeU)]_2(NO_3)_2$ produces a mixed Pt(II)/Ag(I) complex containing tridentate 1-methyluracilate. The crystal structures of both products have been determined and show that the binding of the additional metal ion, Ag(I), does in fact occur at the exocyclic oxygen, O(2), of the 1-methyluracilate.

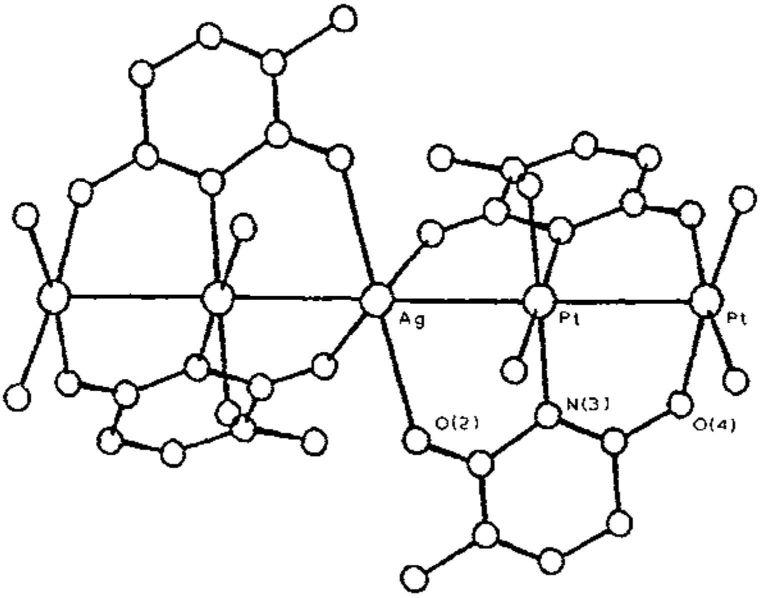


Fig. 9. Head–head $[Pt(NH_3)_2(1\text{-}MeU)]_4Ag(NO_3)_5.4H_2O$. Reprinted with permission from Inorg. Chem., 21 (1982) 451. Copyright (1982) American Chemical Society.

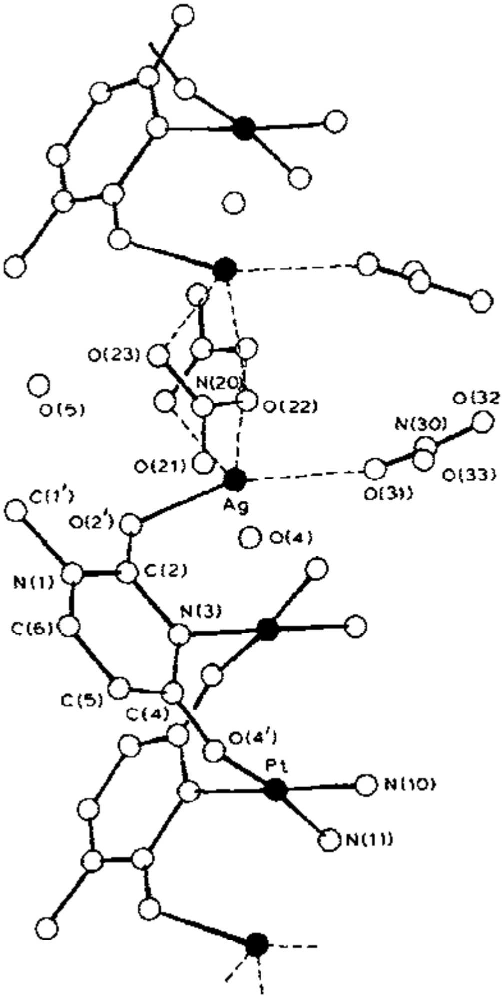


Fig. 10. Head–tail $[(NH_3)_2Pt(1\text{-}MeU)Ag]_2(NO_3)_4.2H_2O$. Reprinted with permission from Inorg. Chem., 23 (1984) 1713. Copyright (1984) American Chemical Society.

As can be seen from these crystal structures, the head–head arrangement of the 1-methyluracilate ligands allows the formation of a "closed" trinuclear unit. The Ag(I) is at the inversion centre of the cation, and has a square planar coordination with four O(2) oxygens from the 1-methyluracilate ligands.

On the other hand the head–tail complex has a more open structure. The Ag(I) ion does not exhibit a distinct coordination geometry, forming reasonably strong bonds with only two of the six surrounding oxygens: the exocyclic O(2) of the 1-methyluracilate (2.386 Å) and O(22) of the nitrate (2.421 Å). Formally, O(22) can be considered as a bridge between two symmetry-related Ag(I) ions. The packing of the crystals is such as to produce infinite chains of $Pt_2Ag_2L_2$ cations with Ag(I)–Ag(I) separations of 3.954 Å.

As with related complexes of *cis*-$(NH_3)_2$Pt(II) [74,77,79], the platinum coordination planes in both of these Pt(II)/Ag(I) structures are tilted towards each other. For the head–head complex the angle is 31.5° [88] and it is 29.8° [75] for the head–tail; this compares to 35.6° [79] in the head–head dimer and 34.1° [74] in the head–tail dimer.

Proton NMR spectroscopy has been used to confirm the bonding suggested by the crystal structures of the two species. Ag(I) binding to the exocyclic oxygens is evident from the downfield shifts of the 1-methyluracilate resonances upon addition of Ag(I) to the parent $Pt_2(NH_3)_4(1\text{-MeU})_2$ dimers [75]. Fast exchange between free and unbound Ag(I) is shown by the absence of distinct signals of heteronuclear Pt,Ag complexes [75]. This indicates that the Ag–O bonding is fairly labile. These proton NMR studies also indicate that the Pt–O bonds are fairly labile, since some monomer is produced due to competition from Ag(I) for the O(4) site of the 1-methyluracilate ligand.

From the studies carried out upon these mixed Pt(II)/Ag(I) complexes [75,88] we can conclude that: firstly, the metal oxygen binding in the complexes is fairly labile for both Pt(II)–O and Ag(I)–O and, secondly, that the increased electron density upon the exocyclic oxygens, resulting from platinum coordination to N(3), is the primary reason for the binding of additional metal ions at these sites. This can be concluded from the fact that both the head–head complex, where the O(2) oxygens are favourably positioned (sterically) for binding of the Ag(I), and the head–tail complex, where the O(2) oxygens are not favourably positioned, exist.

(c) Tetradentate complexes

In the heteronuclear complex *trans*-$(NH_3)_2Pt(1\text{-MeU})_2Ag_2(NO_3)_2(H_2O).H_2O$, trinuclear $PtAg_2L_2$ units, containing Pt coordinated to N(3) of 1-MeU and Ag bound through mixed O(4),O(2) coordination, are linked

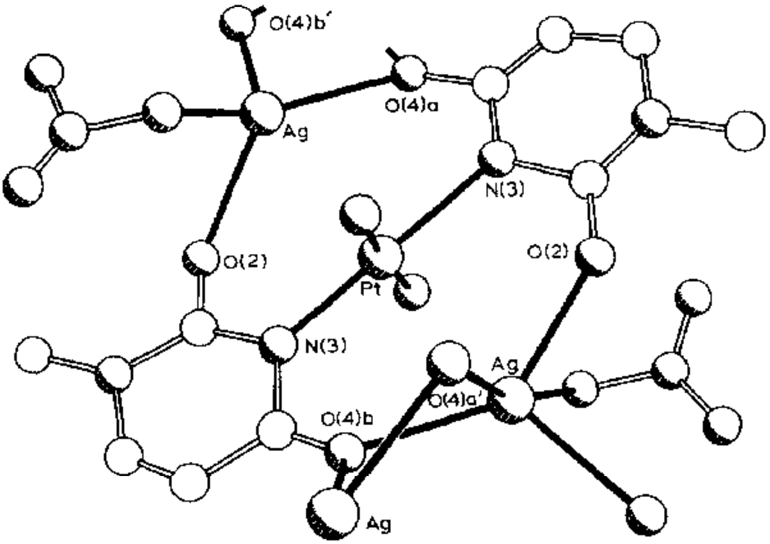


Fig. 11. $[(NH_3)_2Pt(1\text{-}MeU)_2Ag_2(NO_3)_2(H_2O)].H_2O$ [89].

through additional binding between O(4) of 1-MeU and Ag of the adjacent molecule, thus creating a polymeric arrangement of $PtAg_2L_2$ with tetradentate 1-methyluracil ligands [89].

The most interesting aspect of this structure is the role of the exocyclic oxygens O(4a) and O(4b) of the two 1-MeU rings in linking the Ag(I) ions of adjacent molecules, thus creating an infinite array of $PtAg_2L_2$ units. While the intermolecular interaction between Ag and O(4a) is rather weak, 2.838 Å, it is strong in the case of O(4b), giving an intermolecular Ag–O distance of 2.368 Å, shorter than some of the intramolecular Ag–O separations.

This is the only reported complex containing a tetradentate uracil and the observed feature of O(4) acting as a bridge between two metal ions provides additional evidence for the increased basicity of this site as a consequence of Pt(II) substituting the proton at N(3) of the neutral ligand.

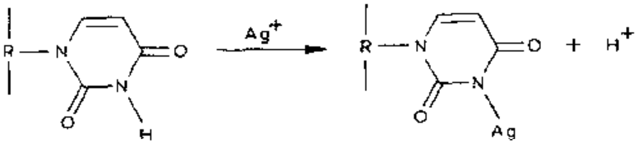
(iii) Silver(I) complexes

Although the majority of work published involving the interaction of uracils with "soft" metal ions has been in regard to platinum(II) compounds, a fair amount has also been published on silver(I) complexes.

It has been shown, by potentiometric titration, ultra-violet spectroscopy and binding studies, that silver binds especially strongly to polyuridylic acid [90]. This produces highly ordered, multistranded, helices under conditions which would otherwise lead to random coils. The nature of the interaction is dependent upon the pH, the Ag(I) : uracil ratio and the ionic strength of the medium. For instance at low values of pH (< 6.0) the stable structure has an Ag(I) : uracil ratio of 1 : 1 and is formed by displacement of the N(3) proton of the base [90]

$UH + Ag^+ \rightarrow UAg + H^+$

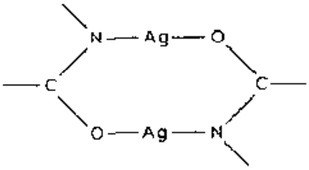
or structurally



The strong tendency of Ag(I) to have a coordination number of two, with linear bonds, leads to polymerization.

$2UAg \rightarrow U_2Ag_2$

The extent of this polymerization has not been determined, nor the nature of the binding but is thought to be

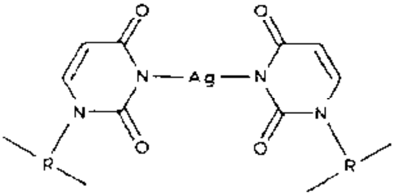


(i.e. bidentate uracilate ligands bridging two Ag(I) ions with N(3) and O(4)/O(2))

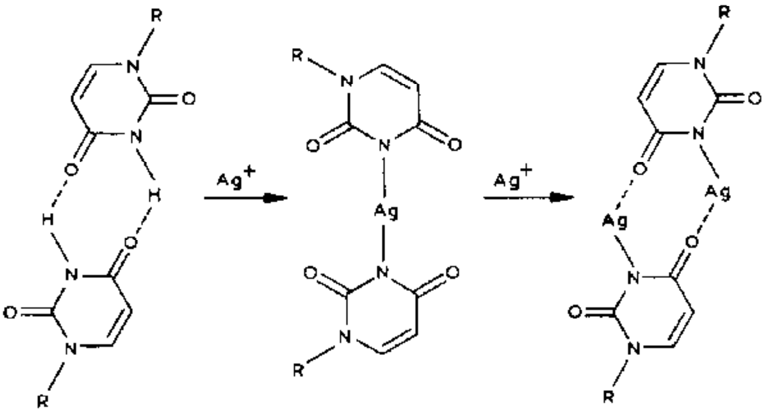
At higher pH values (> 8.0) and with an increased uracil : Ag(I) ratio a 2 : 1 complex exists [90].

$2UH + Ag^+ \rightarrow U_2Ag + 2H^+$

or structurally



A high ionic strength favours this 2 : 1 complex over the 1:1 dimer since it has a lower positive charge between the strands. An overall scheme has been proposed [90].



This final structure has been drawn with N(3), O(4) bridging uracilate. Although this has not been proved conclusively (no crystal structure has been determined) the trinuclear structures of $[Ag(1\text{-}MeU)]_3$ [91] and $[Ag(1\text{-}MeT)]_3$ [92] support the involvement of O(4) rather than O(2).

In this structure the 1-methyluracilate ligands coordinate to three silver(I) ions through the ring nitrogen, N(3), and the exocyclic carbonyl oxygen atoms O(2) and O(4). Comparison of the Ag–O bond lengths reveals that the Ag–O(4) bond is the shorter (Ag–O(2) = 2.51 Å, Ag–O(4) = 2.40 Å) [91]. (The trinuclear structure of $[Ag(1\text{-}MeT)]_3$ has essentially the same structure with bond lengths of Ag–O(2) = 2.51 Å and Ag–O(4) = 2.33 Å

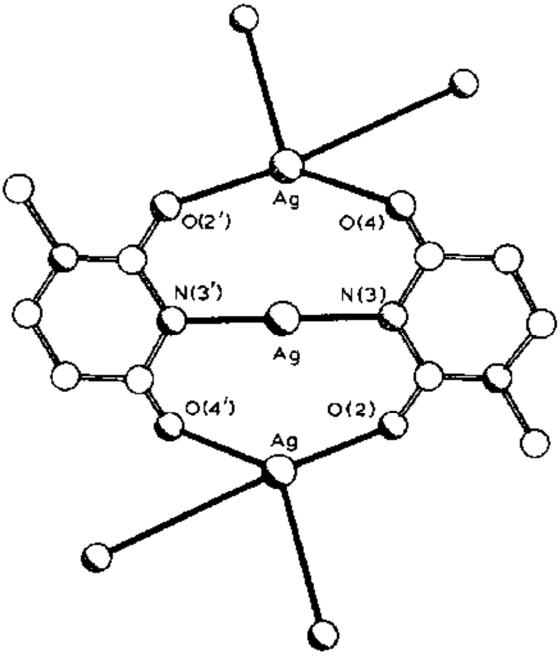
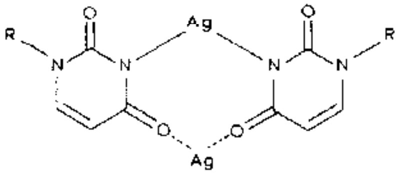


Fig. 12. $[Ag(1\text{-}MeU)]_3$ [91].

[92].) This agrees with previous suggestions that O(4) is more basic than O(2) and thus forms a stronger metal–oxygen bond. However, although this is supportive of the involvement of O(4) rather than O(2) in an Ag_2U_2 dimer there is also the possibility of the structure being a head–head dimer rather than a head–tail dimer (as shown on page 127).



In fact since the dimer is prepared by addition of extra Ag(I) to the 2 : 1 U : Ag complex then, from experience of the corresponding platinum(II) system, one might expect this head–head structure to be correct. However, the lability of the silver–nitrogen bonds removes the restriction that the original metal–N(3) bond must be retained.

F. COMPLEXES OF URACILS WITH HIGHER OXIDATION STATES OF PLATINUM

Platinum : uracil blues have been reported [88,93–96] and the presence of ambidentate-bridged, oligomeric species with partial metal–metal bonding and mixed oxidation states has been inferred [88] by analogy with the well characterised, related compound, *cis*-diammineplatinum α-pyridone blue [97–102].

Work has also been published on the interaction of *cis*-diammineplatinum with uridine which has been shown to form a "platinum blue" complex under certain conditions [93,94]. These complexes have been shown, by X-ray absorption fine structure spectroscopy [94], to have "partial" but distinct Pt–Pt bonding (2.9 Å compared to 2.77 Å in metallic platinum).

In 1984 Lippard reported the (highly reproducible) synthesis, X-ray crystal structure determination and magnetic and spectroscopic properties of *cis*-diammineplatinum 1-methyluracil blue, $[Pt_4(NH_3)_8(1\text{-}MeU)_4]^{5+}$ [103].

The structure consists of a tetranuclear unit of overall charge +5, corresponding to an average oxidation state of +2.25 per platinum atom. Two *cis*-diammineplatinum units are bridged in a head–head fashion by two 1-methyluracilate ligands via deprotonated N(3) and O(4). Two of these binuclear units are further associated through partial metal–metal bonding and NH--O hydrogen bonding across the central pair of platinum atoms in the Pt cation. The magnetic susceptibility of a solid sample of the nitrate salt gave a $\mu(\text{eff}) = 1.89$ per tetrameric unit [103]. This value confirms the presence of one unpaired electron per tetrameric unit. The EPR spectra of a frozen (77 K) aqueous solution of the cation revealed Pt hyperfine-coupling

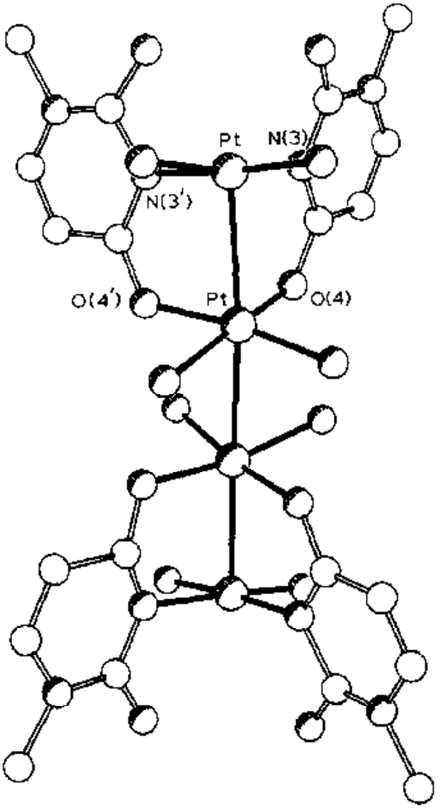


Fig. 13. $[Pt_4(NH_3)_8(1\text{-}MeU)_4]^{5+}$ [103].

interactions consistent with delocalization of the unpaired electron spin over all four platinum atoms in the chain [103].

This characterization of *cis*-diammineplatinum 1-methyluracil blue is the first such characterization of a platinum pyrimidine blue and will perhaps facilitate further evaluation of this class of compounds as antitumour drugs.

Further discussion of platinum blues lies outside the scope of this review but has been covered in the recent review, of platinum(III) chemistry, by Woollins and Kelly [104].

Platinum–platinum bonding has also been demonstrated in the diplatinum(III) complex with 1-methyluracil, $[(H_2O)(NH_3)_2Pt(1\text{-}MeU)_2Pt(NH_3)_2(NO_2)]^{3+}$. This complex has been prepared, by the oxidation of the head–tail dimer *cis*-$[(NH_3)_2Pt(1\text{-}MeU)]_2(NO_3)_2$ with a mixture of nitrous and nitric acid, and crystallographically studied [105].

The Pt–Pt distance within the dinuclear cation is 2.574 Å and corresponds to a single Pt–Pt bond.

Two analogous head–head diplatinum(III) complexes have been reported: $[Cl(NH_3)_2Pt(1\text{-}MeU)_2Pt(NH_3)_2Cl]Cl_2.7/2H_2O$ (in which the Pt–Pt separation is 2.573 Å), and $Cl(NH_3)_2Pt(1\text{-}MeU)_2PtCl_3.2H_2O$ (Pt–Pt = 2.543

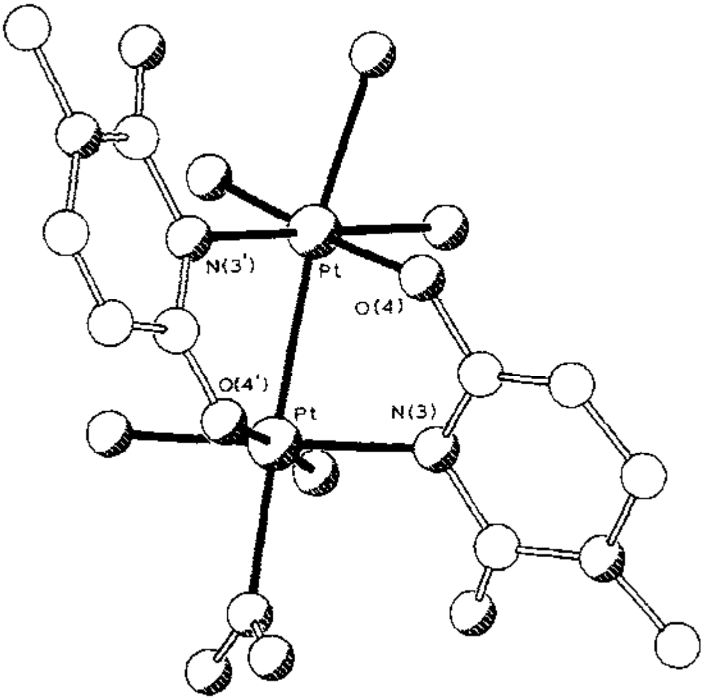


Fig. 14. $[(H_2O)(NH_3)_2Pt(1\text{-}MeU)_2Pt(NH_3)_2(NO_2)]^{2-}$ [105].

Å) [106]. These two complexes have structures similar to that for the previous diplatinum(III) complex but with the 1-methyluracil ligands arranged in a head–head, rather than a head–tail, fashion. Both of these complexes were prepared via another head–head diplatinum(III) compound, *cis*-$[(NO_2)(NH_3)_2Pt(1\text{-}MeU)_2Pt(NH_3)_2](NO_3)_3.H_2O$ [106]. This complex is the first structurally characterised diplatinum compound with unequal coordination numbers (5 and 6) of the two Pt(III) ions, the Pt–Pt separation being 2.607 Å [107].

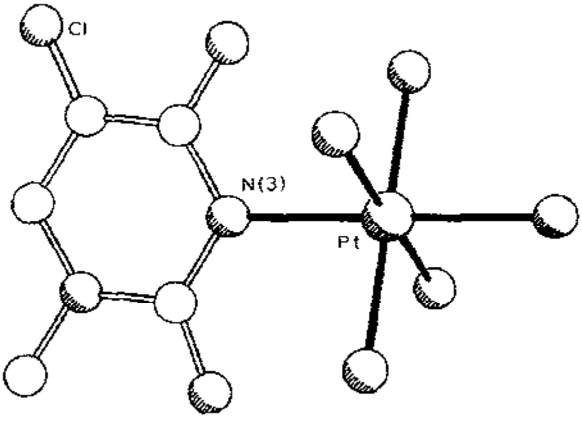


Fig. 15. $(NH_3)_2PtCl_3(1\text{-}MeUCl)$ [108].

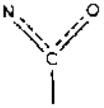
A platinum(IV) : 1-methyluracilate complex has also been recently reported and is the first example of a 1-methyluracil derivative containing an octahedrally coordinated metal bound to N(3) of the 1-methyluracilate [108]. An aqueous solution of Cl_2 was used to oxidise Pt(II) in *cis*-$(NH_3)_2$Pt(1-MeU)Cl to the corresponding hexacoordinated Pt(IV) complex, *mer*-$(NH_3)_2PtCl_3$(1-MeU). At the same time substitution of H(5) of the 1-methyluracilate ligand by Cl resulted, yielding some *mer*-$(NH_3)_2PtCl_3$(1-MeUCl). Although a crystal structure study of the unsubstituted 1-methyluracilate complex was not possible the structure of the chloro substituted derivative has been determined, and it is thought that this has the same structure as the unsubstituted analogue.

G. SUMMARY

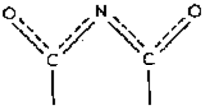
Uracil and thymine do not compete well with water for coordination sites unless they are deprotonated, but in less polar solvents they form strong bonds to metal ions. Neutral uracils usually bind through O(4), probably with some π-donor involvement in the bonding: the protons remain attached to nitrogen. A few cases do occur of N-bonded neutral uracils with protonated oxygen, but only in inert systems. Metal binding to O(2) may be more favoured for thymine because of the steric hindrance close to O(4).

Anionic uracils bind more strongly and, in the presence of metal ions, proton loss may occur even at low pH. This is particularly true for "soft" metal ions which prefer N-bonding; even deprotonation of C(5) is possible. Such metal ions may therefore be expected to bind to uracils at physiological pH values.

Binding of the anion is usually through one of the ring nitrogens, with no particular preference for either N(1) or N(3). Almost certainly some π-back-bonding to the ring is involved, since the oxygens then become good donors, and bridging, through



and even



is common.

Uracil dianions are rarely formed but are known in complexes with lanthanoids: they appear to be bonded through oxygen.

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