Metal Complexes of Uridine and Thymidine

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The preparation is described of solid complexes of the nucleosides uridine and thymidine with Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}, and Cd^{II}, in which the ligands are present as neutral molecules. Physical measurements indicate that uridine binds to the metal ions primarily through the carbonyl group at C$_4$ of the base, with chelation by the ribose residue in some cases, whereas thymidine is probably bonded predominantly through the deoxyribose unit.

RECENT interest in the interaction of RNA and DNA with metal ions has led to numerous researches into complexes of nucleotides and nucleotide bases. Studies of nucleosides, however, have been less common, and, in particular, the nature of the binding between metal ions and uridine (urd) or thymidine (dthd) appears not to be well understood.

Some investigations, mainly in neutral aqueous or dimethyl sulphoxide (dmso) solution, have revealed no detectable interaction of urd or dthd with Cu^{II},[1,2] Zn^{II},[3,4] Cd^{II},[5] Hg^{II},[4-6] or Pt.[7,8] Other studies, however, show that mercury binds to urd [9-11] and to dthd [12-14] in aqueous solution, and the interaction of Cu^{II} [15,16] and platinum [17] with urd or dthd has also been reported. The metal bonding site in these cases is believed to be deprotonated

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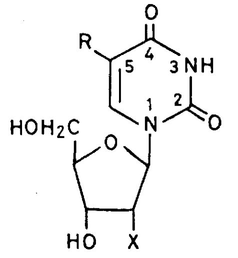
N^3. A ^{13}C n.m.r. study [18] suggested the interaction of Mn^{II} with the carbonyl groups of urd, while ^1H n.m.r. in dmso solution showed binding of Cu^{II} to both the carbonyl and the sugar hydroxyl groups.[19] Attachment to the ribose oxygens only in alkaline solution [20] and in dmso [21] has also been suggested. There have been no reports of the isolation of solid metal complexes of urd or dthd.



(1); R = H, X = OH uridine
R = Me, X = H thymidine

By using as solvent ethyl acetate, whose polarity may well simulate the conditions in parts of the natural systems, we have been able to synthesise a number of complexes of urd and dthd, containing these molecules as neutral ligands.

RESULTS

Preparations were attempted using metal chlorides, bromides, iodides, nitrates, and perchlorates, but only with the chlorides and bromides were pure reproducible complexes obtained. In other cases there was, however, some evidence of complex formation. In nearly all cases only 1 mol of ligand was attached per metal ion. All the complexes exist as microcrystalline powders, insoluble in non-polar solvents, and decomposed by polar ones. Many of them are hygroscopic, and the degree of hydration is variable. The analyses and physical measurements were carried out on freshly prepared samples, stored in desiccators.

Mode of Bonding of the Ligands.—The ligand field in all the complexes appears to be very weak, consistent with donation through an oxygen atom of the ligand. This implies that there is no shift of the tautomeric equilibrium of the uracil nucleus, and that the nitrogen donation postulated in solution applies only under conditions of deprotonation.

The i.r. spectrum of urd in the carbonyl region shows considerable changes on complexation, but its interpretation is by no means simple. Lord and Thomas [22] have assigned bands at 1 672 and 1 698 cm^{-1} to the $\nu(C^4{=}O)$ and $\nu(C^2{=}O)$ vibrations respectively, although other modes undoubtedly also contribute to these absorptions. On complex formation the carbonyl-stretching region sometimes shows only a broad band with its centre of gravity shifted to lower energy compared with the free ligand. In other cases, however, two or three components are resolved, the highest of which, probably essentially $\nu(C^2{=}O)$, generally shows a small increase in energy, while the lowest shows a decrease (Table 1). This is very similar to the behaviour found on complexation of uracil,[23] which was interpreted as due to donation through $C^4{=}O$.

TABLE 1

Bands (cm^{-1}) in the carbonyl-stretching region

Uridine (urd)	1 698s, 1 672vs
$[Mn(urd)Cl_2]\cdot 2H_2O$	1 671vs,br, 1 606 (sh)
$[Fe(urd)Cl_2]$	1 708vs, 1 658vs,br
$[Co(urd)Cl_2]\cdot 5H_2O$	1 670vs,br
$[Co(urd)Br_2]\cdot H_2O$	1 720vs, 1 707vs, 1 651vs
$[Ni(urd)Cl_2]\cdot 4H_2O$	1 670s,vbr
$[Ni(urd)Br_2]\cdot 7.5H_2O$	1 717 (sh), 1 651s,vbr
$[Cu(urd)Cl_2]\cdot 1.5H_2O$	1 668s,vbr
$[Cd(urd)Cl_2]\cdot 5H_2O$	1 697 (sh), 1 665vs,br
Thymidine (dthd)	1 700vs, 1 655vs
$[Mn(dthd)Cl_2]\cdot 4H_2O$	1 700vs, 1 654vs, 1 601s
$[Co(dthd)Cl_2]\cdot 4H_2O$	1 701vs, 1 656vs, 1 600s
$[Cu(dthd)Cl_2]\cdot 3.5H_2O$	1 698vs, 1 656vs, 1 598m
$[Cd(dthd)Cl_2]\cdot 3.5H_2O$	1 703vs, 1 661vs, 1 590w

There are no published assignments for the fundamental modes of dthd. The carbonyl-stretching region shows two strong bands, at 1 700 and 1 655 cm^{-1}, which by analogy with urd, and with thymine itself,[24] may probably be assigned as due essentially to $\nu(C^2{=}O)$ and $\nu(C^4{=}O)$ respectively. In the complexes these two bands remain virtually unchanged, but a third band appears, near 1 600 cm^{-1}. A third band in this region was also found on complexation of uracil and thymine.

In the range 250—400 cm^{-1} both nucleosides show three bands which are not present in the parent bases, and which are assumed to be due to the sugar moieties. In the urd complexes of manganese, cobalt, nickel, and cadmium chlorides there is little change in these bands, but in the other complexes at least one, and usually two, of them disappear. Perturbation of these bands is particularly strong in the anhydrous complexes, and it seems probable that it indicates interaction of the metal ion with one or more of the ribose hydroxyl groups.

The i.r. evidence therefore suggests that for urd co-ordination occurs through $C^4{=}O$ of the uracil, and also, in some cases, through the ribose, and, for dthd through the sugar residue, although involvement of the base cannot be ruled out.

Complexes of Manganese(II) *and Iron*(II).—Only chloro-complexes could be obtained for both metals, and, in the case of Fe^{II}, with urd only. The manganese(II) complexes all give simple e.s.r. spectra, with single, rather broad, signals at $g_{eff.} = 2$, indicative of chloride-bridged polymeric structures. The electronic spectrum of $[Fe(urd)Cl_2]$ (Table 3) indicates octahedral stereochemistry and a weak, somewhat distorted, ligand field. A chloride-bridged polymeric structure seems likely.

Complexes of Cobalt(II).—All the hydrated complexes give electronic spectra indicative of octahedral stereochemistry with Δ values of *ca.* 8 500 (chlorides) and 8 000 cm^{-1} (bromide). The bands at 14 000—15 000 cm^{-1} are due to transitions to the ^2G excited state, and the transition to the ^4P level shows clearly the splitting due to spin–orbit coupling which is characteristic of this range of Δ values.

The anhydrous chloro-complexes also have octahedral stereochemistry, with Δ values of *ca.* 6 500 cm^{-1}. This very low value is similar to that found for uracil and thymine complexes,[23] and the structure is believed, in these cases

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also, to involve chloride bridges. The reflectance spectra of the two complexes are very similar, except that the dthd complex shows a shoulder at 12 500 cm^{-1}, presumably due to the two-electron $^4T_{1g}(F) \rightarrow {}^4A_{2g}$ transition which is predicted [25] at this energy. The anhydrous bromo-complexes, however, give intense reflectance spectra with a band profile quite different from those of the chlorides. They may be interpreted on the basis of tetrahedral geometry with Δ of 3 000—3 500 cm^{-1}, emphasising again the weakness of the ligand field produced by the nucleosides.

TABLE 2

Low-energy i.r. spectra (cm^{-1}) of the compounds

	Ligand bands									ν(M–X)	ν(M–L)	Un-assigned
Uracil	435vs	407 (sh)							195m			
Uridine (urd)		414s,br		360m		312s	293ms	269 (sh)	195m			
[Mn(urd)Cl_2]·$2H_2O$		412s		356s		312s	289ms		*a*	190s	230m,br	161m, 121m
[Fe(urd)Cl_2]				362m		304w		259 (sh)	192 (sh)	216s	244s	166m
[Co(urd)Cl_2]·$5H_2O$		426s,br		361m		312m	283m			210 (sh)	229s	154m
[Co(urd)Br_2]·H_2O		423m,br		363m,br				261ms	187 (sh)	207s,br,[b] 177s	231m	
[Co(urd)Br_2]		450s,vbr		340 (sh)						228s,br [b]		
[Ni(urd)Cl_2]·$4H_2O$		411s		354m		306m	286w	264 (sh)		222s	240m	
[Ni(urd)Br_2]·$7.5H_2O$		411s		342ms			291w		*a*	190s, 164s	225m	143w
[Cu(urd)Cl_2]·$1.5H_2O$		388s		344 (sh)			*a*			300s,br		
[Cd(urd)Cl_2]·$5H_2O$		423s,br		359w		310ms	292m	257 (sh)	*a*	193s, 175s	225 (sh)	
Thymine		425vs				320w	287w		210w			
Thymidine (dthd)	444vs	427vs	394m	374ms	341w	310ms	297m	277m	200s			
[Mn(dthd)Cl_2]·$4H_2O$	443m	427s		370 (sh)		311w	297w	277w	198s [c]	190s	234ms	162ms
[Co(dthd)Cl_2]·$4H_2O$	444ms	427s		366m		310w	297w	277w	200s [c]	185s	240ms	
[Co(dthd)Cl_2]					342m	315w	300w	278w	206s [c]	183 (sh)	238 (sh)	
[Co(dthd)$_2Br_2$]				363m				*d*		228s,br	276s,br	
[Ni(dthd)Br_2]·H_2O	443s	424s	396 (sh)		341w		296w	276w	198s [c]	190s, 162s	210 (sh)	138m
[Cu(dthd)Cl_2]·$3.5H_2O$				366m	330 (sh)		*a*	*a*		288s,br	243mw	
[Cd(dthd)Cl_2]·$3.5H_2O$	444m	427ms	396 (sh)		341w	310mw	296mw	276mw	200s [c]	166s,br	220 (sh)	

[a] May be obscured by ν(M–X). [b] Probably contains contribution from ν(M–L). [c] May contain component of ν(M–X). [d] May be obscured by ν(M–L).

TABLE 3

Electronic spectra of the complexes

Complex	Band maxima (cm^{-1})
[Fe(urd)Cl_2]	6 800 (sh), 9 090w
[Co(urd)Cl_2]·$5H_2O$	8 330w, 14 810 (sh), 18 350m, 20 000 (sh), 21 640 (sh)
[Co(urd)Cl_2]	6 330m, 14 810 (sh), 16 530s, 18 800 (sh)
[Co(urd)Br_2]·H_2O	7 690m, 14 290 (sh), 18 180s, 19 880 (sh), 21 050 (sh)
[Co(urd)Br_2]	5 850s, 14 490vs
[Ni(urd)Cl_2]·$4H_2O$	7 410m, 12 820m,br, 19 800 (sh), 22 830s
[Ni(urd)Br_2]·$7.5H_2O$	7 090br, 12 500m,br, 19 230 (sh), 22 220s
[Cu(urd)Cl_2]·$1.5H_2O$	12 500s,br
[Co(dthd)Cl_2]·$4H_2O$	8 160w, 16 260w, 18 350 (sh), 19 380s, 22 120 (sh)
[Co(dthd)Cl_2]	6 290w, 12 500 (sh), 16 750m, 18 760 (sh), 20 370 (sh)
[Co(dthd)$_2Br_2$]	5 710vs, 14 180vs, 14 920 (sh), 18 620 (sh)
[Ni(dthd)Br_2]·H_2O	7 050m,br, 12 500m, 1 9420 (sh), 22 220s
[Cu(dthd)Cl_2]·$3.5H_2O$	12 500s

Complexes of Nickel(II) and *Copper*(II).—The electronic spectra of the nickel complexes show them to be similar to those of uracil, and, like the latter, they are very hygroscopic, no anhydrous complexes being obtainable. Both the copper complexes show fairly low-intensity absorption at 12 500 cm^{-1}. The e.s.r. spectra are of the 'reversed' type, with $g_{\parallel} = 2.05$ and $g_{\perp} = 2.21$(urd) and *ca.* 2.20 and 2.25 (dthd). The co-ordination is probably distorted octahedral in type, although five-co-ordination, or at least an 'octahedron' with one extra-long bond, cannot be ruled out.

Metal–Ligand Stretching Vibrations.—The chloro-complexes of Mn, Fe, Co, and Ni all show one or, more commonly, two strong bands near 200 cm^{-1} (Table 2). This is strongly suggestive of chloride-bridged polymeric structures. For the copper complexes these bands are replaced by a single strong band at 290—300 cm^{-1}, consistent with terminal, or at least only weakly bridging, Cu–Cl. For cadmium a pair of bands is again present, but at somewhat lower energy than for the lighter metals. It seems probable that the cadmium complexes also have chloride-bridged polymeric structures.

The bromo-complexes of nickel, and also [Co(urd)Br_2]·H_2O, likewise have a pair of bands at 160—190 cm^{-1}, which may be assigned as essentially M–Br stretching vibrations of a halide-bridged polymer. This is consistent with the electronic spectra described above. In the anhydrous bromo-complexes of cobalt, shown by electronic spectroscopy to have tetrahedral structures, these bands are absent, and there is, instead, a strong broad band at 228 cm^{-1}, presumably due largely to the Co–Br stretching vibration.

In most of the octahedral complexes there is a medium to strong band in the range 225—245 cm^{-1}, which seems most reasonably assigned to a metal–oxygen stretching mode. In tetrahedral [Co(dthd)$_2Br_2$] this is replaced by a broad band at 276 cm^{-1}, but it is absent in [Co(urd)Br_2]. However, the stoicheiometry suggests that in the latter complexes the urd molecule may be bridging two metal ions, and a different spectrum is expected.

DISCUSSION

This work shows clearly that uridine and thymidine can act as donors in a variety of complexes. For urd the

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prime co-ordination site is probably C^4=O, but for dthd the approach of the metal ion to this site is hindered by the methyl group on C^5 of the base. Since C^2=O is also hindered by the large sugar residue on N^1, it may well be that in this case co-ordination occurs mainly through the sugar hydroxyl groups.

There is also an indication that, with urd at least, the extent of involvement of the ribose oxygens may be very dependent on the nature of the metal ion. N.m.r. studies have shown that manganese(II) ions bind to C^4=O of urd,[18] while copper(II) ions bond preferentially to the ribose hydroxyl groups,[19] and, as these become saturated, also 'in the vicinity of H^3 and H^5', *i.e.* presumably through C^4=O. The low-energy i.r. bands due to the ribose groups are strongly perturbed in our copper complexes, but not in $[Mn(urd)Cl_2]\cdot 2H_2O$. This suggests that these bands may perhaps be used as an indication of the extent of involvement of the ribose, although, clearly, many more studies on complexes of known structure are desirable.

TABLE 4

Analytical results (%)

Complex	Colour	Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
$[Mn(urd)Cl_2]\cdot 2H_2O$	Pale pink	26.0	3.7	7.0	26.6	3.95	6.90
$[Fe(urd)Cl_2]$	Yellow	29.9	4.2	6.7	29.15	3.25	7.55
$[Co(urd)Cl_2]\cdot 5H_2O$	Pink	23.4	3.7	6.1	23.3	4.80	6.05
$[Co(urd)Br_2]\cdot H_2O$	Pink	22.8	3.1	5.9	22.45	2.95	5.80
$[Ni(urd)Cl_2]\cdot 4H_2O$	Yellow	24.5	4.6	6.3	24.25	4.50	6.30
$[Ni(urd)Br_2]\cdot 7.5H_2O$	Yellow	18.1	3.5	4.6	18.1	4.55	4.70
$[Cu(urd)Cl_2]\cdot 1.5H_2O$	Khaki	26.5	2.9	7.0	26.65	3.75	6.90
$[Cd(urd)Cl_2]\cdot 5H_2O$	White	20.8	2.8	5.3	20.9	4.30	5.40
$[Mn(dthd)Cl_2]\cdot 4H_2O$	Pale pink	27.3	4.4	6.5	27.3	5.05	6.35
$[Co(dthd)Cl_2]\cdot 4H_2O$	Pink	26.3	4.1	6.1	27.0	4.95	6.30
$[Co(dthd)_2Br_2]$	Blue	34.0	4.4	7.9	34.15	4.00	7.95
$[Ni(dthd)Br_2]\cdot H_2O$	Yellow	25.8	4.2	5.7	25.1	3.35	5.85
$[Cu(dthd)Cl_2]\cdot 3.5H_2O$	Pale green	26.9	4.4	6.4	27.3	4.80	6.35
$[Cd(dthd)Cl_2]\cdot 3.5H_2O$	White	24.3	3.0	5.8	24.6	4.35	5.75

EXPERIMENTAL

All the complexes were prepared by the following general method. Finely powdered dry samples of the ligand (10^{-3} mol) and hydrated metal salt (10^{-3} mol) were mixed, and dry ethyl acetate (*ca.* 35 cm^3) was added. After boiling under reflux for 15—20 min, the metal salts dissolved followed, more slowly, by dissolution of the ligand and precipitation of the product. Refluxing was continued until all the ligand had reacted (usually several hours). The dense flocculent precipitates were filtered off, washed with ethyl acetate (2 × 5 cm^3), and dried over silica gel. Analyses are given in Table 4.

The iron(II) complex was prepared under nitrogen. Some anhydrous complexes were made by heating the hydrates to constant weight *in vacuo* {Found: weight loss at 100 °C, 18.9. Calc. for $[Co(urd)Cl_2]\cdot 5H_2O - 5H_2O$, 19.4. Found: weight loss at 120 °C, 4.2. Calc. for $[Co(urd)Br_2]\cdot H_2O - H_2O$, 3.75. Found: weight loss at 120 °C, 15.5. Calc. for $[Co(dthd)Cl_2]\cdot 4H_2O - 4H_2O$, = 16.2%}.

These anhydrous complexes are very hygroscopic, and no reliable analyses could be obtained. Replicate analytical figures suggested the above stoicheiometries plus small but variable amounts of water.

Reflectance spectra were obtained using a Beckman DK2A recording spectrometer, i.r. spectra using Perkin-Elmer 257 and 457 spectrophotometers and a Beckman interferometer, and e.s.r. spectra using a Varian E12 spectrometer.

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