Metal Complexes of Uracil and Thymine

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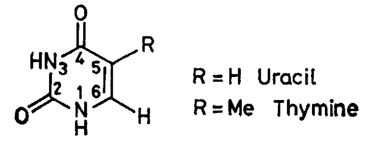
The preparation is described of complexes of uracil and thymine with Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}, Zn^{II}, and Cd^{II}, containing the ligands as neutral molecules. Physical measurements indicate that the ligands are bonded to the metal ions through the carbonyl groups.

IN spite of the recent surge of interest in the interaction of transition-metal ions with components of nucleic acids, there have been relatively few reports of complexes of uracil (ura) and thymine (thy). There is strong evidence that both these molecules exist in the dilactam form (1) both in the solid state and in neutral aqueous solution. The nitrogen atoms can therefore act as donors only under basic conditions, unless there is a considerable shift of the tautomeric equilibrium under the influence of the metal ions. In agreement with this, the only known metal complexes of thy [1,2] contain this ligand in the anionic form, while one complex, dichlorobis(uracil)mercury(II), contains ura as a neutral ligand donating through an oxygen atom.[3]



(1)

TABLE 1

Analytical results (%) for the complexes

Complex	Colour	Found C	Found H	Found N	Found X	Calc. C	Calc. H	Calc. N	Calc. X
$[MnCl_2(ura)]\cdot H_2O$	Pale pink	19.0	2.05	11.05	27.8	18.75	2.35	10.95	27.7
$[MnBr_2(ura)_2]$	Pale pink	21.8	1.85	12.75	36.45	21.9	1.85	12.75	36.4
$[Mn(ClO_4)_2(ura)_2]\cdot H_2O$	Pale pink	19.45	2.40	11.15		19.35	2.05	11.3	
$[CoCl_2(ura)(H_2O)_2]$	Pink	17.65	2.95	10.15	25.55	17.35	2.90	10.1	25.5
$[CoBr_2(ura)_2]$	Blue	19.7	1.90	12.2	35.6	21.7	1.80	12.65	36.1
$[Co(ClO_4)_2(ura)_2]\cdot H_2O$	Pink	19.6	2.45	11.0		19.2	2.00	11.2	
$[NiCl_2(ura)]\cdot 2.5H_2O$	Yellow	16.95	2.60	9.75	24.3	16.75	3.15	9.75	24.75
$[Ni_3Br_6(ura)_4]\cdot 4H_2O$	Yellow	16.4	2.50	9.60	40.7	16.35	2.05	9.55	40.75
$[Ni(NO_3)_2(ura)_4]\cdot 2H_2O$	Pale green	28.7	3.05	20.45		28.8	3.00	21.0	
$[CuCl_2(ura)]\cdot H_2O$	Khaki	18.1	2.85	10.35	26.7	18.15	2.30	10.6	26.8
$[Cu(ClO_4)_2(ura)_2]\cdot 2H_2O$	Pale green-blue	19.35	2.40	10.65		18.4	2.30	10.7	
$[Zn(ClO_4)_2(ura)_2]\cdot 3H_2O$	White	17.8	2.30	10.4		17.7	2.60	10.35	
$[CdCl_2(ura)]$	White	16.0	2.05	9.60	23.85	16.25	1.35	9.50	24.0
$[MnCl_2(thy)]\cdot 2H_2O$	Pale pink	20.6	3.30	9.35	24.0	20.85	3.50	9.75	24.6
$[MnBr_2(thy)]\cdot 2.5H_2O$	Pale pink	15.6	2.60	7.25	41.55	15.55	2.85	7.25	41.4
$[FeCl_2(thy)]\cdot 2H_2O$	Pale yellow	20.8	3.45	9.55	24.7	20.8	3.50	9.70	24.55
$[CoCl_2(thy)(H_2O)_{2.5}]$	Pale lilac	20.1	3.25	9.25	23.35	19.95	3.70	9.30	23.55
$[CoBr_2(thy)_2(H_2O)_{1.5}]$	Pink	24.25	3.15	11.3	31.85	24.1	3.05	11.25	32.1
$[Ni(NO_3)_2(thy)_2]\cdot 4H_2O$	Pale green	23.2	3.45	16.4		23.7	4.00	16.6	
$[CuCl_2(thy)]\cdot 2.5H_2O$	Yellow-green	19.95	2.95	4.00	24.35	19.65	3.65	9.15	23.2
$[Cu(ClO_4)_2(thy)_2]\cdot 4H_2O$	Pale green	20.7	3.20	9.40		20.45	3.45	9.55	
$[CdCl_2(thy)]\cdot 1.5H_2O$	White	17.65	2.60	8.20	21.7	17.85	2.70	8.35	21.1

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

RESULTS AND DISCUSSION

For Mn^{II}, Co^{II}, Ni^{II}, Cu^{II}, Zn^{II}, and Cd^{II}, complex formation was attempted using the chlorides, bromides, iodides, nitrates, and perchlorates. For Fe^{II}, only the chloride and bromide were used. The complexes obtained are listed in Table 1. With copper(II) nitrate some complex formation appeared to take place with both ligands, but no acceptable analyses could be obtained. In the other cases there appeared to be no complex formation. All the complexes exist as microcrystalline powders, insoluble in non-polar solvents and decomposed by polar ones. Their X-ray powder patterns differed from those of the ligands, but in some cases prolonged exposure to X-rays appeared to decompose them, giving free ligand. Many of the complexes are hygroscopic, and the degree of hydration is variable. The analyses and physical measurements were carried out on freshly prepared samples, stored in desiccators.

Stereochemistry of the Complexes.—Electronic spectra show the metal ions to be six-co-ordinate in nearly all cases. The hydrated cobalt complexes show bands near 8 000 and 19 000 cm^{-1} (Table 2) which may be assigned

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[1] L. D. Kosturko, C. Folzer, and R. F. Stewart, *Biochemistry*, 1974, **13**, 3949.

[2] T. J. Kistenmacher, T. Sorrell, and L. G. Marzilli, *Inorg. Chem.*, 1975, **14**, 2479.

[3] J. A. Carrabine and M. Sundaralingam, *Biochemistry*, 1971, **10**, 292.

respectively as due to $^4T_{1g}(F)\rightarrow{}^4T_{2g}$ and $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$ transitions. Weaker bands near 16 000 cm^{-1} arise either from the two-electron jump $^4T_{1g}(F)\rightarrow{}^4A_{2g}$, or from transitions to upper states derived from the ^2G free-ion term. The band near 19 000 cm^{-1} is generally well resolved, and shows clearly the splitting by spin-orbit coupling, the intensity enhancement of the transition to $^2\Gamma_6(^2G)$, and the difference in ligand field between the chloro- and the bromo-complexes.

TABLE 2

Diffuse-reflectance spectra (cm^{-1})

Complex	
$[CoCl_2(ura)(H_2O)_2]$	*ca.* 7 840w,^{a} 16 130w, 18 350(sh), 19 300m ^{b}
$[CoCl_2(ura)]$	6 150m, 12 890(sh), 14 490(sh), 17 100s, 17 610(sh) ^{b}
$[CoBr_2(ura)_2]$	5 990m, 12 120(sh), 14 080(sh), 17 540s ^{b}
$[Co(ClO_4)_2(ura)_2]\cdot H_2O$	8 000w, 20 120s, 21 500(sh)
$[NiCl_2(ura)]\cdot 2.5H_2O$	*ca.* 7 550m,^{a} 12 500m, 13 700(sh), 20 000(sh), 22 990s
$[Ni_3Br_6(ura)_4]\cdot 4H_2O$	6 950m,br, 12 050m, 16 670(sh), 20 620(sh) ^{c}
$[Ni(NO_3)_2(ura)_4]\cdot 2H_2O$	8 700w, 14 490w,br, 23 310m, 25 190m
$[CuCl_2(ura)]\cdot H_2O$	12 820s
$[Cu(ClO_4)_2(ura)_2]\cdot 2H_2O$	12 120s
$[FeCl_2(thy)]\cdot 2H_2O$	9 430w
$[CoCl_2(thy)(H_2O)_{2.5}]$	*ca.* 8 060w,^{a} 16 260w, 18 520(sh), 19 490s ^{b}
$[CoCl_2(thy)]$	6 060m, 8 700(sh), 12 500(sh), 15 150(sh), 16 610s ^{b}
$[CoBr_2(thy)_2(H_2O)_{1.5}]$	*ca.* 7 140w,^{a} 15 380w, 18 020(sh), 18 870s ^{b}
$[CoBr_2(thy)_2]$	5 750s, 14 290vs, 15 380(sh)
$[Ni(NO_3)_2(thy)_2]\cdot 4H_2O$	8 770w,br, 14 490w,br, 23 530m, 25 380m
$[CuCl_2(thy)]\cdot 2.5H_2O$	11 760s
$[Cu(ClO_4)_2(thy)_2]\cdot 4H_2O$	8 000(sh), 12 820m

^{a} Low-energy band obscured by vibrational bands. ^{b} Spin-forbidden bands above 17 000 cm^{-1} are omitted. ^{c} Obscured by charge-transfer band.

On dehydration, the chloro- and bromo-cobalt complexes turn blue, but except for $[CoBr_2(thy)_2]$ their electronic spectra still suggest six-co-ordination. The $^4T_{1g}(F)\rightarrow{}^4T_{2g}$ transition now appears near 6 000 cm^{-1} and $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$ near 17 000 cm^{-1}, with shoulders on the latter due to $^4T_{1g}(F)\rightarrow{}^4A_{2g}$ and to spin-forbidden bands. The intensities are similar to those of the hydrated complexes. For $[CoBr_2(thy)_2]$, however, the intensities are much higher and the band profile in the visible region quite different. The spectrum is in agreement with an essentially tetrahedral structure with a weak ligand field (Δ *ca.* 3 000—3 500 cm^{-1}).

For the nickel complexes the electronic spectra suggest essentially octahedral structures, with $\Delta =$ *ca.* 7 000 (bromides), *ca.* 7 500 (chlorides), and *ca.* 8 750 cm^{-1} (nitrates). In most of the complexes the $^3A_{2g}\rightarrow{}^3T_{1g}(P)$ transition appears to be split, but in each case the lower component is probably a spin-forbidden band, with an excited state arising from the ^1G free-ion term. With thymine, complexes with unusually low ratios of ligand to nickel halide were obtained, and it is not certain that these are true compounds, although they are fairly reproducible and the i.r. spectra indicate co-ordination of the ligand (see below). It is likely that the structures are based on NiX_2 chains, with thymines bonded to some of the metal ions. These compounds are very hygroscopic with the water molecules doubtless filling the empty co-ordination sites.

All the copper complexes show a low-intensity absorption near 12 000 cm^{-1}, consistent with six-co-ordination. The e.s.r. spectra (Table 3) are also in agreement with this, with the spectrum of $[CuCl_2(ura)]\cdot H_2O$ giving a broad spectrum indicative of exchange coupling, and, probably, a polymeric structure.

The manganese halogeno-complexes all give single, rather broad, e.s.r. signals at $g_{\text{eff.}} = 2$, indicative of polymeric octahedral structures. For the perchlorate complex $[Mn(ClO_4)_2(ura)_2]\cdot H_2O$ there is also a signal at $g_{\text{eff.}} = 2$, but with a slight inflection indicating some distortion from regular cubic symmetry. The electronic spectra of the manganese complexes were too weak to be observed with certainty.

Mode of Bonding of the Ligands.—The ligand field in all the complexes appears very weak. This is seen most clearly in the cobalt complexes, most of which have fairly simple stoicheiometries. The anhydrous chloro-complexes have Δ *ca.* 6 000 cm^{-1}, and $[CoBr_2(ura)_2]$ has an even lower figure. There is no observable splitting of the first ligand-field band. Even assuming bridging halide ions, *i.e.* a ligand field of the L_2Cl_4 type, the field generated by the neutral ligands must be quite weak, probably comparable with that of chloride ion. In tetrahedral $[CoBr_2(thy)_2]$, the ligand field is similar to that of $[CoBr_2(PPh_3O)_2]$. It is likely, therefore, that the donor atom in these ligands is a carbonyl oxygen.

TABLE 3

Powder e.s.r. results for some of the complexes

	g_1	g_2	g_3
$[Cu(ClO_4)_2(ura)_2]\cdot 2H_2O$	2.08	2.17	2.35
$[CuCl_2(thy)]\cdot 2.5H_2O$	2.05	2.19	2.25
$[Cu(ClO_4)_2(thy)_2]\cdot 4H_2O$	2.07	2.21	

The i.r. spectra of the ligands in the carbonyl-stretching region show considerable changes on complex formation, but their interpretation is by no means simple. The most complete interpretations of the vibrational spectra of uracil and thymine are those of Susi and Ard,[4,5] who assigned bands in the 1 500—1 800

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[4] H. Susi and J. S. Ard, *Spectrochim. Acta*, 1971, **A27**, 1549.

[5] H. Susi and J. S. Ard, *Spectrochim. Acta*, 1974, **A30**, 1843.

cm^{-1} region to $\nu(C^2{=}O)$, in-phase $\nu(C^4{=}O) + \nu(C{=}C)$, and out-of-phase $\nu(C^4{=}O) + \nu(C{=}C)$; the last appears only weakly, if at all, in the i.r. spectrum.

For some of the uracil complexes, the carbonyl absorption in the i.r. spectrum appears only as a broad band, with its centre of gravity shifted to lower energy compared with the free ligand. In other cases, however, two or three separate bands are resolved (Table 4) and it is clear that $\nu(C^2{=}O)$ is essentially unchanged on co-ordination, while the band at 1 675 cm^{-1} is shifted to lower energy. The third component sometimes observed may be the Raman band activated on co-ordination. The most probable explanation of these changes is that donation to the metal ion occurs through $C^4{=}O$, as in $[HgCl_2(ura)_2]$, which has a similar i.r. spectrum.[3]

TABLE 4

Shifts (cm^{-1}) of i.r. bands on complex formation

Compound	$\nu(C{=}O) + \nu(C{=}C)$	' Amide II ' bands
Uracil	1 716s, 1 675s	
$[MnCl_2(ura)]\cdot 2H_2O$	1 650s,br	
$[MnBr_2(ura)_2]$	1 650s,br	
$[Mn(ClO_4)_2(ura)_2]\cdot H_2O$	1 665s,br	
$[CoCl_2(ura)(H_2O)_2]$	1 716s, 1 660s,br, 1 597s	
$[CoCl_2(ura)]$	1 716s, 1 656s,br, 1 600s	
$[CoBr_2(ura)_2]$	1 711s, 1 651s,br, 1 610(sh)	
$[Co(ClO_4)_2(ura)_2]\cdot 2H_2O$	1 665s,br	
$[NiCl_2(ura)]\cdot 2.5H_2O$	1 716s, 1 640br	
$[Ni_3Br_6(ura)_4]\cdot 4H_2O$	1 716s, 1 660(sh), 1 625s	
$[Ni(NO_3)_2(ura)_4]\cdot 2H_2O$	1 716s, 1 656s,br	
$[CuCl_2(ura)]\cdot H_2O$	1 716s, 1 656s,br, 1 587s	
$[Cu(ClO_4)_2(ura)_2]\cdot 2H_2O$	1 676s,br	
$[Zn(ClO_4)_2(ura)_2]\cdot 3H_2O$	1 716s, 1 675s, 1 648(sh)	
$[CdCl_2(ura)]$	1 716s, 1 657s,br, 1 590m	
Thymine	1 735m, 1 677s	1 495w(sh), 1 406vw
$[MnCl_2(thy)]\cdot 2H_2O$	1 690s, 1 656s, 1 624s	1 497m, 1 412m
$[MnBr_2(thy)]\cdot 2.5H_2O$	1 692s, 1 651s, 1 619s	1 494mw, 1 424m
$[FeCl_2(thy)]\cdot 2H_2O$	1 695s, 1 652ms, 1 621ms	1 492m, 1 422ms
$[CoCl_2(thy)(H_2O)_{2.5}]$	1 742s, 1 676s,br, 1 600s	1 491mw, 1 420m
$[CoCl_2(thy)]$	1 735(sh), 1 690s,br, 1 623ms	1 495mw, 1 426m
$[CoBr_2(thy)_2(H_2O)_{1.5}]$	1 710s, 1 687s, 1 632ms	1 504mw, 1 424m
$[CoBr_2(thy)_2]$	1 650s,br	1 490m, 1 425m
$[Ni(NO_3)_2(thy)_2]\cdot 4H_2O$	1 735m, 1 675s, 1 600(sh)	obscured by NO_3 bands
$[CuCl_2(thy)]\cdot 2.5H_2O$	1 710s, 1 658s, 1 638s	1 495w, 1 413m
$[Cu(ClO_4)_2(thy)_2]\cdot 4H_2O$	1 700s, 1 653s, 1 608s	1 508mw, obscured by $\delta_{asym}(CH_3)$ band
$[CdCl_2(thy)]\cdot 1.5H_2O$	1 709s, 1 676s, 1 647s, 1 631s	1 495mw, 1 417m

For thymine, however, the situation is more complicated. Susi and Ard[5] again assigned the highest band in this region to $\nu(C^2{=}O)$, although they had some reservations concerning this. Their assignment was based on bond lengths reported[6] for thymine hydrate, although the spectrum corresponds with that of our anhydrous form. The anhydrous form, in contrast to the hydrate, has $C^4{=}O$ shorter[7] than $C^2{=}O$. The i.r. spectrum of the hydrate shows two broad bands in this region, with greater separation than in the anhydrous form. It is possible that some decomposition of the hydrate occurred in the beam, and that the true spectrum should be even more different from that of the anhydrous material.

Both the observed bands for thymine undergo shifts to lower energy on co-ordination, in contrast to the situation for uracil, and for thymine hydrate, although complex formation through $C^4{=}O$ might be expected to show similarity to hydration through $C^4{=}O$. One possible explanation would be that $C^2{=}O$ is used for co-ordination in this case, because the steric effect of the methyl group on C^5 makes $C^4{=}O$ a less attractive donor. However, we have no definite evidence for this.

For uracil, the remaining bands above 400 cm^{-1} show no significant shifts on co-ordination, but for thymine some changes are observed, which, although fairly small, are sufficient to indicate the presence of co-ordinated thymine. The band at 984 cm^{-1} (CH_3 rock) is reduced in intensity in the complexes, and that at 1 203 cm^{-1} [ν(ring) + $\nu(C{-}CH_3)$] is shifted to *ca.* 1 220 cm^{-1}. Both the in-plane N–H deformations (or ' amide II ' bands, since there is considerable coupling with the C=O stretches) which appear quite weakly at 1 406 and 1 495 cm^{-1} in the ligand have enhanced intensity in the complexes, and the lower band is shifted to *ca.* 1 420 cm^{-1} (Table 4). A similar, although greater, increase of both frequency and intensity for this band (due to $N^3{-}H$ coupled with both $C^2{=}O$ and, more strongly, $C^4{=}O$) has been observed on helix formation between polyuridylic acid and polyadenylic acid,[8] and was thought to be due to hydrogen bonding of the $N^3{-}H$ group.

Conclusion.—This work shows clearly that pyrimidinone oxygen atoms can act as donors in a variety of complexes. The weakness of the field generated is in

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[6] R. Gerdil, *Acta Cryst.*, 1961, **14**, 333.

[7] K. Ozeki, N. Sakabe, and J. Tanaka, *Acta Cryst.*, 1969, **B25**, 1038.

[8] H. T. Miles, T. P. Lewis, E. D. Becker, and J. Frazier, *J. Biol. Chem.*, 1973, **248**, 1115.

accord with the high π-charge density calculated for both oxygens in uracil and thymine.[9] These atoms would be expected to act as moderately strong π donors, with a ligand field at the low end of the oxygen-donor range. The metal–ligand bond may well be fairly strong, in accord with the stability of the complexes to heat, but the low crystal-field stabilisation energies make the complexes very labile under polar conditions.

EXPERIMENTAL

All the complexes except $[CoBr_2(ura)_2]$ and $[FeCl_2(thy)]\cdot 2H_2O$ were prepared by the following method. Finely powdered samples of the ligand and the hydrated metal salt were mixed together, dry, in 1 : 1 stoicheiometric quantities, and dry ethyl acetate (*ca.* 35 cm³) was added. After boiling under reflux for *ca.* 15—20 min, the metal salts dissolved, followed, more slowly, by dissolution of the ligand, and simultaneous precipitation of the product. Refluxing was continued until all the ligand had reacted, a process which was usually complete within a few hours for uracil, but often required longer (a day or so) in the case of thymine. The dense flocculent precipitates thus obtained were filtered off, washed with ethyl acetate (2 × 5 cm³), and dried over silica gel.

For $[CoBr_2(ura)_2]$ the process was as detailed above, except that anhydrous cobalt(II) bromide was used as starting material, and the reflux was carried out under anhydrous conditions. The blue product was filtered off under dry nitrogen, washed with ethyl acetate, and dried over P_4O_{10}.

The following complexes were also prepared: $[CoCl_2(ura)]$, on heating $[CoCl_2(ura)(H_2O)_2]$ to constant weight *in vacuo* at 110 °C (weight loss found: 13.15%. Calc.: 13.0%); $[CoCl_2(thy)]$, on heating $[CoCl_2(thy)(H_2O)_{2.5}]$ to constant weight *in vacuo* at 110 °C (weight loss found: 13.3. Calc.: 13.65%); and $[CoBr_2(thy)_2]$, on heating $[CoBr_2(thy)_2(H_2O)_{1.5}]$ to constant weight *in vacuo* at 120 °C (weight loss found: 5.50%. Calc.: 5.45%). Analysis results for the blue complexes obtained indicated the presence of small amounts of water. However, these very hygroscopic complexes always gained weight during weighing for analysis; it is considered, therefore, that the blue forms are truly anhydrous.

Dichloro(thymine)iron(II) *Dihydrate.*—A solution of $FeCl_2\cdot 4H_2O$ (0.199 g, 1 mmol) in a deoxygenated mixture of anhydrous ethanol (*ca.* 8 cm³) and 2,2-dimethoxypropane (*ca.* 1 cm³) was added, under nitrogen, to a suspension of thymine (0.126 g, 1 mmol) in deoxygenated, anhydrous, ethyl acetate (*ca.* 30 cm³). The mixture was boiled under reflux in a nitrogen atmosphere for *ca.* 4 h, by which time all the ligand had dissolved and a very dense pale yellow precipitate had formed. The complex was filtered off under nitrogen, washed with ethyl acetate, and dried over silica gel.

Physical Measurements.—Reflectance spectra were obtained using a Beckman DK2A recording spectrometer, i.r. spectra using Perkin-Elmer 257 and 457 spectrophotometers, and e.s.r. spectra using a Varian E12 spectrometer. All measurements were at room temperature.

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[9] I. Kulakowska, M. Geller, B. Lesyng, and K. L. Wierchowski, *Biochim. Biophys. Acta*, 1974, **361**, 119.