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METAL COMPLEXES OF PYRIMIDINE-DERIVED LIGANDS—IV.† SYNTHESIS, CHARACTERISATION AND COORDINATING PROPERTIES OF TWO GUANIDINO PYRIMIDINES: Ni(II) COMPLEXES WITH 2-GUANIDINO-4,6-DIMETHYL PYRIMIDINE AND 2-PHENYL GUANIDINO-4,6-DIMETHYL PYRIMIDINE—POTENTIAL LIGANDS OR BIOLOGICAL INTEREST

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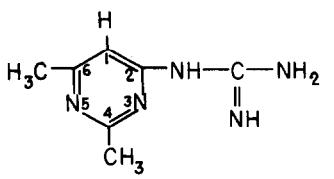
Abstract—Synthesis and spectroscopic characterisation (IR, mass, PMR) of 2-guanidino 4,6-dimethyl pyrimidine (GPym) and 2-phenyl guanidino 4,6-dimethyl pyrimidine (PG-Pym) are reported. Complexation of the title ligands with nickel(II) salts in moisture-free condition furnish complex species of the type: $Ni(GPym)_2X_2$[X = Cl, Br, SCN and NO_3] and $Ni(PGPym)_2X_2$ [X = Cl, Br, I and SCN]. Physico-chemical characterisation of the complex species have been made from molar conductance data, magnetic susceptibility measurements, electronic and vibrational spectra. Magnetic and electronic spectral features suggest a pseudo-octahedral environment of the central Ni(II) ion in all these complexes. IR spectra have furnished positive information regarding the bonding sites of the ligand molecules (namely, the pyrimidyl nitrogen and the imino nitrogen of the guanidine residue) and the mode of the attachment of the counterion(X) to the metal ion.

It is well-documented that pyrimidine derivatives play a significant role in many biological systems, the ring system being a component of nucleic acids, several vitamins, co-enzymes etc. and provide potential binding sites for metal ions. Moreover, pyrimidine analogues have the capacity to impede the bio-synthesis of pyrimidine nucleotides. Certain of the drugs with pyrimidine ring are employed in the treatment of neoplastic diseases and infections caused by fungi and DNA containing viruses. On the other hand, biguanides and guanyl ureas which have attracted much attention because of their well-acclaimed medicinal values (e.g. anti-malarial activity of paludrine) are also well established as coordinated agents. In the living systems, biguanide is known to undergo cyclisation to form triazine which is the active substance to act as anti-malarial drug. It was, therefore, considered necessary to have pyrimidine derivatives containing the guanidine moiety as a side chain, with the hope that the resulting compounds might have biological potency and with a view to study the coordination pattern of such ligands by complexation with metal ions in order to understand more precisely the role of such metal ions in living systems. As a part of our programme [1,2] of investigating the interaction of biologically potent pyrimidine-based ligands with metal ions, the present communication is intended to report the synthesis, characterisation and coordinating behaviour of the title ligands viz. the guanidino pyrimidines, together with preparation and physico-chemical characterisation of a few bis-Ni(II) complexes with the title ligands (**1a** and **1b**).



1a

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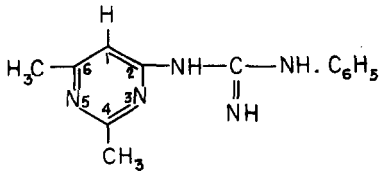
†For Part III: see Ref 2b.



1b

EXPERIMENTAL

The title ligands viz. 2-guanidino 4,6-dimethyl pyrimidine and 2-phenyl guanidino 4,6-dimethyl pyrimidine were prepared by condensation reactions of free biguanide/phenyl biguanide with acetyl acetone according to similar but somewhat modified methods of Poddar *et al.*[3] Normal biguanide sulphate was prepared according to the method of Ray *et al.*[4] On recrystallisation from hot water the product melted at 230°C (lit. m.p 231°C). Free normal biguanide was obtained according to known methods.[5,6]

Preparation of 2-guanidino-4,6-dimethyl pyrimidine. 1.2 g (0.05 mole) clean and dried sodium dissolved in perfectly dry alcohol (50 cm^3) was refluxed with 5 g (0.025 mole) powdered biguanide sulphate for 1 hr with usual precautions. The resulting alcoholic solution of free biguanide was mixed thoroughly with freshly distilled acetyl acetone [3 g, 0.03 mole] and the resulting mixture was refluxed for 2 hr at water-bath temperature. The reaction mixture, upon cooling to room temperature (25°C) deposited fine needle-shaped white crystals; these were filtered off and recrystallised from boiling methanol to remove a little of triazine which might have been formed due to a side reaction. The recrystallised product was dried in a vacuum desiccator over fused $CaCl_2$.

The compound is insoluble in water but soluble in alcohol, DMSO, acetone and dilute mineral acids. It melted with decomposition at 242 ± 2°C. Found: C, 50.83; H, 6.69; N, 42.21. Calc. for $C_7H_{11}N_5$: C, 50.91; H, 6.67; N, 42.42%.

Preparation of 2-phenyl guanidino-4,6-dimethyl pyrimidine. Phenyl biguanide hydrochloride[7] (10 g, 0.045 mole) was converted to free base in the usual manner. An alcoholic solution of the free phenyl biguanide base was refluxed with 4.7 cm^3 [4.7 g, 0.047 mole] distilled acetyl acetone for 2 hr. Upon cooling at room temperature, fine needle-shaped white cyrstals were deposited. These were recrystallised from boiling ethanol to remove any triazine that might have formed. The compound was insoluble in water but soluble in alcohol, acetone and dilute mineral acids. It melted with decomposition at 200 ± 2°C. Found: C, 64.64; H, 6.26; N, 28.92. Calc. for $C_{13}H_{15}N_5$: C, 64.51; H, 6.20; N, 29.05%.

Preparation of Ni(II) complexes. The Ni(II) complexes of the title ligands could not be isolated in the pure state starting with hydrated Ni(II) salts. However, successful synthesis of the desired complexes was made using anhydrous Ni(II) salts as detailed below:

Preparation of anhydrous Ni(II) salts. About 2 gms of $NiX_2.nH_2O$ [X = Cl/Br/I/NO_3, n = 3 to 6] taken in suspension with 5 cm^3 triethyl orthoformate [b.p. 146°C] were refluxed for about 2 hr on a hot plate at regulated temperature in moisture free condition. The resultant mixture was distilled on an oil bath at 80°C at reduced pressure [0.4 mm of Hg]. The left-out residue was kept in a vacuum desiccator over fused $CaCl_2$ for 48 hours. Anhydrous $Ni(NO_3)_2$, $NiCl_2$ and $NiBr_2$ were obtained as golden yellow micro-crystalline solid compounds. Anhydrous NiI_2 was obtained as iron-black solid.

Preparation of Ni(II) chelates. The Ni(II) chelates with GPym and PGPym were prepared by refluxing anhydrous Ni(II) salt [0.001 mole] with the corresponding ligand [0.002 mole] in dry alcohol on a hot plate at 60–80°C for 14–16 hr maintaining anhydrous conditions. The yellowish green solution obtained after the reflux, on cooling to room temperature, deposited micro crystals of the desired complex species in each case.

The product, in each case, was filtered off, washed with ice-cold dry alcohol and finally dried in a desiccator over fused $CaCl_2$.

Nickel(II) thiocyanate complexes of both the ligands GPym and PGPym were obtained by refluxing the corresponding chloro complex with potassium thiocyanate in dry ethanol medium for 15 min and filtering off the precipitated potassium chloride. The bluish green solution on concentration at water-bath temperature followed by cooling to *ca.* 25°C deposited a blue–violet product in each case.

Elemental analyses and physico-chemical measurements like equivalent conductances, magnetic susceptibilities and the electronic [both in solid and in solution] and the vibrational spectra of the complexes were carried out as described earlier.[2] The mass spectra of the ligands were recorded on an AEIMS 12 spectrometer at 70 eV. The PMR spectra of the guanidino pyrimidines (GPym and PGPym) were recorded in DMSO-d_6 solvent in a Varian CFT-I 60 MHz NMR spectrometer using TMS as internal standard reference.

RESULTS AND DISCUSSION

Characterisation of the ligands. The electron impact mass spectra of the ligands showed molecular ion peaks at m/z 165 for GPym and 241 for PGPym confirming the synthesised ligands to have

molecular formulae $C_7H_{11}N_5$ (GPym [**1a**] and $C_{13}H_{15}N_5$ (PGPym) [**1b**] respectively. The important ion peaks for both the ligands with percentage of relative intensity are given in Table 1 showing most plausible formulations of the species. The fragmentation peaks are in well agreement with Structures (**1a**) and (**1b**) proposed for 2-guanidino-4,6-dimethyl pyrimidine and 2-phenyl guanidino-4,6-dimethyl pyrimidine respectively.

The 60 MHz PMR spectra of GPym and PGPym show 6-protons singlet around δ 2.22 which might be ascribed to the methyl groups at C-4 and C-6 positions of pyrimidine ring.[8] The lone pyrimidine proton (at C-1), in both the cases appear as a singlet at δ 6.6. In case of PGPym, the aromatic protons of the phenyl component appear as a complex signal in the region δ 7.2–7.6. The triplet at δ 1.04 could be ignored since the compound has been recrystallised from ethanol which might be retained as alcohol of crystallization. The corresponding methylene signals merged with noise of the base line. However, the protons bonded to the nitrogens of the guanidine moiety of the molecules do not appear in the spectra and they might have undergone exchange with HOD present in the solvent. Thus the mass spectra and the PMR data rightly characterise the synthesised compounds as 2-guanidino-4,6-dimethyl pyrimidine and 2-phenyl guanidino-4,6-dimethyl pyrimidine.

Characterisation of the Ni(II) complexes. The analytical results for the Ni(II) complexes of GPym and PGPym along with other pertinent data are given in Table 2. All the bis-complexes are soluble in low molecular weight alcohols, acetone and in coordinating solvents like DMF, DMSO, etc. All the Ni(II) complexes are magnetically normal 6-coordinate complexes [μ_{eff} = 2.74–2.98]. The molar conductance values of 121.9–142.4 mho cm^2 $mole^{-1}$ in DMF [Table 2] indicate their 1 : 2 electrolytic nature in the said solvent.[9] The following schematic formulation may be represented to express the extensive solvolysis which might be responsible for the observed conductance data.

$$[Ni(N\text{–}N)_2X_2] \xrightarrow{DMF} [Ni(N\text{–}N)_2(DMF)_2]^{2+} + 2X^-$$

where N–N represents one molecule of ligand viz. GPym/PGPym, X = Cl/Br/I/SCN/NO_3.

Electronic spectral data (Table 3) indicate that most of the Ni(II) complexes probably belong to O_h or D_{4h} or a group of lower symmetry.[10] The diffuse reflectance spectra of the complexes were characterised by three main bands appearing in the region 8500–10,400, 14,200–15,800 and 21,200–25,000 cm^{-1} which may be assigned to $[^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)]$, $[^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)]$ and $[^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)]$ transitions respectively in an idealised O_h symmetry. For the complexes $Ni(GPym)_2X_2$ [X = Cl, SCN] and $Ni(PGPym)_2X_2$ [X = Br, I, SCN] and ν_2/ν_1 ratio lying between 1.53 and 1.68 characterise them as essentially pseudo-octahedral in the solid state. However, ν_2/ν_1 values for the rest of the Ni(II) species are found to fall in the range 1.78–1.85 indicating appreciable degree of tetragonal distortion in these octahedral species.[11] Electronic spectral data of most of the complexes recorded in DMF solutions suggest that no gross change occurs in the electronic or geometric structures of the complexes on dissolution in the said solvent and show three principal bands in the range 8900–9400 cm^{-1} (ν_1), 14,000–16,500 cm^{-1} (ν_2) and 23,200–25,000 cm^{-1} (ν_3). The low values of molar extinction coefficients (ϵ = 2.21–6.1) for the observed spectral bands are consistent with a pseudo-octahedral arrangements of the ligands,[12] in these species. In case of electronic spectra of the DMF solutions of $Ni(GPym)_2Br_2$, $Ni(GPym)_2(NO_3)_2$ and $Ni(PGPym)_2Cl_2$, it is observed that the respective ν_2/ν_1 ratios (Table 3) have come down to the pseudo-octahedral range ($\sim$ 1.55–1.58). The data reasonably suggest that there might be an effective change from D_{4h} to O_h summetry due to solvation effects.

Construction of molecular models suggest that the formation of a stable six-membered ring system with the central Ni(II) ion having N–N donor function taking one of the pyrimidyl ring nitrogens and the imino nitrogen (> NH) of the guanidine residue as bonding sites is the most probable proposition; this substantiated through the present IR spectral studies recorded down to 200 cm^{-1}.

In the IR spectra of all the Ni(II) complexes, the bands in the 3μ region arising due to ν_{asy}(N–H) (3300–3390 cm^{-1}) and ν_{sy}(N–H) (3100–3140 cm^{-1}) modes of vibration of the guanyl group[13] are observed almost in the same positions as those in the original ligand molecules with slight decrease in intensities suggesting participation of ligands in complex formation without deprotonation. The ν(C=N) stretching bands of the guanidine part of both the ligand [Schemes 1(a) and 1(b)] appearing around 1650 cm^{-1} [14–16] has been found to experience a negative shift of (10 ± 5) cm^{-1} pointing to the probable participation of the imino nitrogen of the guanidine moiety of the ligands in complex formation with Ni(II). IR bands due to diazine (pyrimidine) system appearing around 1540 (ν C—C) and 1590 cm^{-1} (ν C—N)[17] in the free ligand have been found to experience shifts in the higher energy side ($\Delta\nu \sim 15 \pm 5$ cm^{-1}) in the metal complexes indicat-

Table 1. Field desorption mass spectral data of the ligand molecules

Ligands	Important ion peaks (m/z)	% of Relative intensity	Plausible formulation
	165	65.21	$C_7H_{11}N_5$ (M^+)
GPym(L_1)	148	22.86	$C_7H_8N_4$ [M^+-NH_3 (17 unit)]
	123	100.00	$C_6H_9N_3$ [M^+-$H_2N.C \equiv N$ (42 unit)]
	96	30.00	$C_5H_8N_2$ [m/z 123-HCN (27 unit)]
	241	77.63	$C_{13}H_{15}N_5$ [M^+]
PGPym(L_2)	224	22.37	$C_{13}H_{12}N_4$ [M^+-NH_3 (17 unit)]
	147	100.00	$C_7H_7N_4$ [m/z 224-C_6H_5 (77 unit)]
	117	19.74	$C_5H N_4$ [m/z 147-$2CH_3$ (30 unit)]

Table 2. Physical properties and the analytical data of the complexes

Complex	Colour	% Metal		Found (%)			Calc. (%)			Magnetic moment μ_B at 301°K	Molar conductance conc. 1.0×10^{-3}M in DMF at 30°C (mho cm^2 $mole^{-1}$)
		Found	Calc.	C	N	X	C	N	X		
$Ni(L_1)_2Cl_2$	green	12.75	12.77	36.29	30.84	15.36	36.35	30.96	15.45	2.92	140.7
$Ni(L_1)_2Br_2$	green	10.60	10.68	30.48	25.43	29.12	30.58	25.52	29.17	2.90	132.8
$Ni(L_1)_2(SCN)_2$	blue violet	11.54	11.61	33.24	33.18*	-	33.33	33.27	-	2.88	126.4
$Ni(L_1)_2(NO_3)_2$	blue violet	11.34	11.43	32.62	32.82**	-	32.77	32.77	-	2.96	138.2
$Ni(L_2)_2Cl_2$	green	9.52	9.58	49.92	22.79	11.52	50.01	22.89	11.61	2.74	142.4
$Ni(L_2)_2Br_2$	green	8.29	8.36	44.32	19.92	22.76	44.41	19.98	22.84	2.89	127.7
$Ni(L_2)_2I_2$	blue violet	7.29	7.37	39.19	17.52	32.03	39.26	17.61	31.96	2.98	121.9
$Ni(L_2)_2(SCN)_2$	violet blue	8.86	8.93	47.50	25.43*		47.52	25.54	-	2.84	123.6

L_1 = 2-Guanidino-4,6-dimethyl pyrimidine; L_2 = 2-Phenyl guanidino-4,6-dimethyl pyrimidine.

*Including nitrogen present in thiocyanate; **Including nitrogen present in nitrate.

Table 3. Electronic spectral data of the complexes

Complexes	State	Absorption maxima kK (ϵ_{max})	ν_2/ν_1
$Ni(L_1)_2Cl_2$	Reflectance	9.2, 15.6, 21.2	1.68
	DMF (green)	8.9 (2.21), 14.1(2.46), 23.2(5.71)	
$Ni(L_1)_2Br_2$	Reflectance	8.5, 15.8, 21.3	1.85
	DMF (green)	8.9(2.43), 14.0(2.51), 23.5(5.6)	1.57
$Ni(L_1)_2(SCN)_2$	Reflectance	9.2, 15.1, 25.3	1.64
	DMF (pale blue)	9.3(2.46), 16.5(2.62), 24.6(6.1)	
$Ni(L_1)_2(NO_3)_2$	Reflectance	8.9, 15.6, 25.4	1.74
	DMF (blue violet)	8.9(2.27), 14.1(2.32), 23.6(5.3)	1.58
$Ni(L_2)_2Cl_2$	Reflectance	8.6, 15.3, 25.0	1.78
	DMF (green)	9.0(3.21), 14.0(4.26), 23.6(5.37)	1.55
$Ni(L_2)_2Br_2$	Reflectance	8.5, 14.2, 23.8	1.67
	DMF (green)	8.9(2.26), 14.2(4.29), 23.5(5.33)	
$Ni(L_2)_2I_2$	Reflectance	10.4, 14.6, 24.3	1.55
	DMF (pale blue)	8.9(2.61), 14.08(4.21), 23.5(6.1)	
$Ni(L_2)_2(SCN)_2$	Reflectance	10.0, 15.3, 24.0	1.53
	DMF (blue)	9.0(2.71), 16.4(4.92), 25.0(6.0L)	

L_1 = 2-Guanidino-4,6-dimethyl pyrimidine; L_2 = 2-Phenyl guanidino-4,6-dimethyl pyrimidine.

Table 4. Some characteristic IR bands (550–200 cm^{-1}) of the ligands together with the complexes

Compounds	ν M-N (guanidine)	ν M-N (Pym ring)	ν M-X	Other bands
GPym	-	-	-	550s, 470s, 400ms, 380w, 360w, 300w, 265ms, 240s, 230ms, 205s.
PGPym	-	-	-	555s, 530w, 500s, 481w, 460w, 435w, 410m, 380ms, 350w, 250s, 225ms, 210s, 205m.
$Ni(L_1)_2Cl_2$	540s	248s,240w	290s	570s, 460w, 440s, 400s, 370w, 310s, 245s, 230m, 220s.
$Ni(L_1)_2Br_2$	535s	245ms	265s	560ms, 520w, 480w, 435ms, 380w, 355w, 305m, 245w, 220w, 215w.
$Ni(L_1)_2(SCN)_2$	530s	245s	275ms	540w,510ms,480w,465w,410ms,380ms,260w,230ms,215w.
$Ni(L_1)_2(NO_3)_2$	535s	250ms	-	560ms,500w,440w,390ms,320ms,300w,270w,230ms,210w.
$Ni(L_2)_2Cl_2$	525ms	280ms	285s	590w, 560m, 470w, 420m, 370w, 240m, 210w.
$Ni(L_2)_2Br_2$	528s	275ms	260s	560m, 520w, 450w, 400m, 340ms, 290w, 260m, 210m.
$Ni(L_2)_2(SCN)_2$	540ms	245ms	270ms	550ms, 490w, 410w, 380ms, 310w, 230ms, 205w.

s = strong; m = medium; w = weak

L_1 = 2-Guanidino-4,6-dimethyl pyrimidine; L_2 = 2-Phenyl guanidino-4,6-dimethyl pyrimidine.

ing, thereby, the expected involvement of the pyrimidyl ring nitrogen in complexation.

The above proposition has been further substantiated by far IR spectra of the metal complexes (Table 4) through the appearance of new bands in the range of 280–240 cm^{-1} and 525–540 cm^{-1} which may safely be assigned to ν_{M-N} (Pym)[18] and ν_{M-N} (guanidine).[19-21]

A monodentate nitrate in C_{2v} symmetry is present in $Ni(GPym)_2(NO_3)_2$ as is evidenced by three IR bands at 1415(ms), 1310(s) (components of ν_3) and 827(ms) cm^{-1} (ν_2).

The IR spectra of thiocyanate complexes have three bands at 2100–2110, 790 and 480 cm^{-1} in the regions of $\nu_{C\equiv N}$, ν_{C-S} and δ NCS vibrations respectively indicating the presence of N-bonded[23] thiocyanate group.

The diagnostic band frequencies of the other counterions (X), (X = Cl/Br) ν_{M-Cl} 285–290 cm^{-1} and ν_{M-Br} 260–265 cm^{-1}[24], indicate the coordinated nature of Cl^- and Br^- ions respectively.

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