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PLATINUM METAL COMPLEXES WITH SOME NEW BIFUNCTIONAL LIGANDS—I. PYRAZOLE AMIDE COMPLEXES WITH Pd^{II} AND Pt^{II}

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Abstract—The pyrazolyl group has been used in conjuction with the amido group for the design and synthesis of a new series of bifunctional ligands, $PzCH_2C(O)NHR$, where Pz = 1-pyrazolyl/3,5-dimethyl-1-pyrazolyl; R = H(APz/ADMPz), Me(MAPz/MADMPz), Ph(PAPz/PADMPz). These ligands have been characterized based on their mass, IR, ^1H and $^{13}C\{H\}$ NMR spectra and their complexes with Pd^{II} and Pt^{II} reported. Simple mixing of aqueous solutions of $K_2[MCl_4]$ (M = Pd, Pt) and the pyrazole amide in a 1 : 2 ratio gave neutral complexes of the type *cis*-MCl_2L_2. Alternatively, an aqueous solution of $K_2[MCl_4]$ added to an aqueous solution of ligand at pH ~ 8.0 afforded neutral bis-chelates of the type ML_2. A neutral monodentate coordination (LH) has been assigned for the ligand in the former complexes, whereas uninegative bidentate coordination through deprotonated amide nitrogen has been assigned in the latter complexes.

Although the field of nitrogen-ligated metal complexes has expanded greatly in recent protein model studies and drug design, further research is required. Obviously imidazole and imidazole-like ligands, such as their isomeric pyrazoles, are prime candidates in this regard. Therefore, we have directed our efforts towards exploring polyfunctional ligands containing pyrazole moieties so that the structural, electronic and mechanistic factors that control catalytic or drug functions can be evaluated.[1] The coordination chemistry of pyrazole and its derivatives has been the subject of many other types of studies.[2,3] The use of pyrazole ligands has thus become increasingly popular in synthetic inorganic, bio-inorganic and organometallic chemistry.[4,5] Pyrazole-derived ligands have been used as mimics for its isomeric imidazole coordination in models for the active sites of metalloenzymes.[6] The coordination chemistry of pyrazoles with functional substituents at the 1-position such as carboxylates[7] and amides[8] was of considerable interest recently.[4] This is due to the fact that the appended functions confer some special electronic and steric properties. In this regard, functionalized pyrazoles containing weakly coordinating amide groups are of interest, since they confer sufficient lability by generating a vacant site on the metal ion for substrate binding.

Many pyrazole ligands with additional coordinating sites are known.[4,9-15] These ligands are highly functionalized with coordination occuring through N(2) of pyrazole and the appended coordination sites may be any of the hetero atoms such as O, N, S, P or an olefin double bond. Pyrazoles functionalized with allyl or vinyl substitutes are potentially bidentate and these ligands sometimes form only simple monodentate, nitrogen-bonded complexes.[9-11] Some of these complexes have shown anti-tumour activity.[12]

In view of the present upsurge in their coordination chemistry and as part of our wide studies on metal–amide interactions,[16-19] we have undertaken a study of the reaction chemistry and synthesis of group VIII metal amido complexes. The present work deals with the preparation and characterization of Pd^{II} and Pt^{II} complexes of some new pyrazole amide ligands represented by the general structure shown in Fig. 1.

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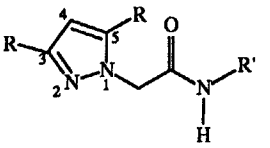


R = H; R' = H(APz), CH_3(MAPz), C_6H_5(PAPz)

R = CH_3; R' = H(ADMPz), CH_3(MADMPz), C_6H_5(PADMPz)

Fig. 1. Structure and abbreviated for the bifunctional ligands.

EXPERIMENTAL

A sample of $PdCl_2$ of commercial grade was obtained from Johnson Matthey (U.K.). 2-(Chloro) acetamide was purchased from Fluka chemical company (Switzerland) and chloroacetylchloride was obtained from Merck (Germany). Triethylamine stored over dry KOH pellets was employed wherever necessary. K_2MCl_4[20,21] (M = Pd and Pt) and *cis*-$PtCl_2(NH_3)_2$,[22,23] used for the preparation of metal complexes, were synthesized by reported procedures.

C, H and N analyses were carried out at the University of Hyderabad, India, on a Perkin–Elmer 240C elemental analyser. IR spectra were recorded in KBr discs on a Shimadzu IR 435 spectrometer. ^1H NMR spectra in deuterated solvents were run on a Varian XL-200 spectrometer at 200 MHz. ^{13}C NMR spectra of ligands were recorded on a Bruker 300 spectrometer at 75.5 MHz. Mass spectra of the ligands were obtained on a Perkin–Elmer Hitachi RMU-6L spectrometer. Melting points were recorded with a Toshniwal Hot-stage melting point apparatus and are uncorrected. Digisun digital conductivity bridge DI 909 was used to determine the conductivity. Magnetic susceptibility measurements were made at room temperature on a Faraday Balance Model 7550. All complexes were found to be diamagnetic. The physical and analytical data are presented in Table 1.

Synthesis of pyrazole amides

1-(*Acetamido*)*pyrazole* (*APz*). Chloroacetamide (4.67 g, 0.05 mol) in benzene (25 cm^3) was added slowly to a refluxing solution of pyrazole (3.4 g 0.05 mol) and triethylamine (6.06 g, 0.06 mol) in benzene (30 cm^3). Refluxing was continued for 3 h when a white sticky solid separated out. Excess benzene was removed by vacuum distillation and the resulting solid was recrystallized from hot ethanol as a white crystalline compound. Yield: 4.0 g (64%) m.pt 137°C.

1-(*N-Methylacetamido*)*pyrazole* (*MAPz*). A mixture of pyrazole (3.4 g, 0.05 mol) and sodamide (2.0 g, 0.06 mol) in dry benzene (50 cm^3) was heated under reflux for 30 min. N-methylchloroacetamide was prepared from aqueous methylamine and ethylchloroacetamide, as reported earlier,[24] dissolved in dry benzene (10 cm^3) and was added dropwise to the above mixture. Refluxing was continued for another 2 h and the contents were allowed to cool to room temperature and filtered. The solid was slurried with hot chloroform, filtered and the filterate evaporated to dryness. The resulting residue was recrystallized from ethanol to obtain a white crystalline product. Yield: 4.8 g (69%), m.pt 73°C.

1-(*N-Phenylacetamido*)*pyrazole* (*PAPz*). A solution of pyrazole (3.4 g, 0.05 mol) with a slight excess of triethylamine (6.06 g, 0.06 mol) and N-phenylchloroacetamide (8.5 g, 0.05 mol) (prepared from aniline and chloroacetylchloride) in benzene (60 cm^3) was allowed to reflux for 6 h. In the process an off-white solid started appearing. The excess solvent was removed under reduced pressure and the resulting residue was placed in ice-cold water overnight. A white crystalline solid was filtered the next day, washed repeatedly with ether and finally recrystallized from hot water to give white needles. Yield: 8.6 g (86%), m.pt 121°C.

1-(*Acetamido*)-3,5-*dimethylpyrazole* (*ADMPz*). To 3,5-dimethylpyrazole (4.8 g, 0.05 mol) in benzene (30 cm^3) in the presence of a slight excess of triethylamine (6.06 g, 0.06 mol) was added chloroacetamide (4.67 g, 0.05 mol). The contents were refluxed on a water bath for 3 h. An off-white solid was obtained after the excess benzene was distilled off under reduced pressure. The residue was recrystallized from ethanol to white needles. Yield: 5.43 g (71%), m.pt 183°C (lit. 192°C).[25]

1-(*N-Methylacetamido*)-3,5-*dimethylpyrazole* (*MADMPz*). A suspension of sodamide (2 g, 0.06 mol) in dry benzene was introduced into a flask containing 3,5-dimethylpyrazole (4.08 g, 0.05 mol) in dry benzene (50 cm^3) while under reflux. After 30 min, N-methylchloroacetamide (0.05 mol), prepared as described previously, was added dropwise to the above mixture and the contents refluxed for 3 h. The crude residue, obtained on cooling to room temperature, was treated with hot chloroform in several portions and filtered. An off-white solid obtained on evaporating these filtrates was recrystallized in ethanol to white needles. Yield: 6.2 g (74%), m.pt 79°C.

1-(*N-Phenylacetamido*)-3,5-*dimethylpyrazole* (*PADMPz*). A benzene (80 cm^3) solution of 3,5-dimethylpyrazole (4.8 g, 0.05 mol) with tri-

Table 1. Physical and analytical data of the complexes

Sl. No.	Complex	Colour	M.pt[a] (°C)	Analysis[b] C	H	N	λ_z (S cm^2 mol^{-1})[c]
1	*cis*-$PdCl_2(APz)_2$	Light yellow	198–200	27.8 (28.1)	3.2 (3.3)	19.4 (19.7)	14
2	*cis*-$PdCl_2(ADMPz)_2$	Light yellow	208	34.0 (34.8)	4.5 (4.5)	17.1 (17.4)	12
3	*cis*-$PdCl_2(MAPz)_2$	Pale yellow	187–188	30.9 (31.6)	3.7 (3.9)	17.9 (18.5)	14
4	*cis*-$PdCl_2(MADMPz)_2$	Pale yellow	206–208	37.5 (37.6)	5.0 (5.1)	16.3 (16.4)	16
5	*cis*-$PdCl_2(PAPz)_2$	Light yellow	192	45.5 (45.6)	3.7 (3.8)	14.4 (14.5)	12
6	*cis*-$PdCl_2(PADMPz)_2$	Light yellow	211–212	48.9 (49.1)	4.8 (4.7)	13.4 (13.2)	18
7	$[Pd(MADMPz)_2]\cdot 2H_2O$	Light yellow	197–200	41.1 (40.3)	5.8 (5.5)	17.9 (17.6)	16
8	$[Pd(PADMPz)_2]\cdot 2H_2O$	Light yellow	201–202	52.7 (52.7)	5.3 (5.1)	15.0 (14.2)	18
9	*cis*-$PtCl_2(APz)_2\cdot 2H_2O$	Off white	183–185	22.1 (21.7)	3.4 (3.3)	15.1 (15.2)	—
10	*cis*-$PtCl_2(ADMPz)_2\cdot H_2O$	Pale yellow	198–200	27.9 (28.5)	4.2 (4.1)	14.4 (14.2)	12 (30)
11	*cis*-$PtCl_2(MAPz)_2\cdot 2H_2O$	Pale yellow	189–190	25.0 (24.8)	3.9 (3.8)	14.3 (14.5)	—
12	*cis*-$PtCl_2(MADMPz)_2\cdot H_2O$	Light yellow	202	29.9 (31.1)	4.3 (4.5)	13.6 (13.6)	12 (32) 282[d]
13	*cis*-$PtCl_2(PAPz)_2\cdot 2H_2O$	Light yellow	192–193	37.7 (37.5)	3.7 (3.7)	12.1 (11.9)	16 180[d]
14	*cis*-$PtCl_2(PADMPz)_2\cdot H_2O$	Light yellow	204–205	42.0 (42.0)	4.4 (4.3)	11.6 (11.3)	18 (32)
15	$[Pt(MADMPz)_2]\cdot 2H_2O$	Off white	212–214	34.1 (34.0)	5.3 (5.3)	7.1 (7.4)	14 (19) 272[d]
16	$[Pt(PADMPz)_2]H_2O$	Off white	206–208	46.9 (47.0)	4.9 (4.8)	6.3 (6.3)	12 (36)
17	$[Pt(ADMPz)_2]\cdot 2H_2O$	Light yellow	188–190	32.0 (31.1)	4.9 (4.8)	7.6 (7.8)	14 195[d]

[a] Decomposition temperatures.
[b] Calculated values in parentheses.
[c] Measured on DMSO solutions and the values given in parentheses refer measurements in dry MeOH.
[d] Measured in aqueous solutions.

ethylamine (0.06 mol) was refluxed with N-phenylchloroacetamide (8.5 g, 0.05 mol) for 4 h. The residue obtained after removing the excess solvent was poured in cold water to give a white solid, which was filtered, washed with ether and recrystallized from EtOH–H_2O (1 : 1). Yield : 8.2 g (71%), m.pt 162°C.

Syntheses of metal complexes

Palladium(II) *complexes*: *cis*-$PdCl_2L_2$(*L* = *APz*, **1**; *ADMPz*, **2**; *MAPz*, **3**; *MADMPz*, **4**; *PAPz*, **5**; *PADMPz*, **6**). K_2PdCl_4 (0.10 g, 0.3 mmol), dissolved in water (20 cm^3), was added to 2 equiv. of ethanolic solutions of APz, ADMPz, MAPz,

MADMPz, PAPz or PADMPz at room temperature and stirred for 4 h, when a pale yellow solid separated. Light yellow complexes crystallized out from hot methanolic solutions of the crude products. Yields: 0.16 g (62%, **1**), 0.18 g (68%, **2**), 0.17 g (67%, **3**), 0.20 g (69%, **4**), 0.13 g (74%, **5**), 0.15 g (76%, **6**).

$Pd(N\text{-}N)_2$(N-N = MADMPz, **7**; PADMPz, **8**). To a suspension of *cis*-$[PdCl_2(MADMPz)_2]$ (0.10 g, 0.195 mmol, **4**) or *cis*-$[PdCl_2(PADMPz)_2]$ (0.10 g, 0.159 mmol, **6**) in water (20 cm^3), 2 equiv. of aqueous 0.5 M NaOH was slowly added at room temperature, with stirring. The suspension cleared as soon as the addition of the base was complete and the product complex gradually appeared over a period of 3–4 h of stirring. Light yellow products were filtered, washed with cold water and dried over P_2O_5 *in vacuo*. Yields: 0.07 (83%, **7**) and 0.07 g (79%, **8**).

Platinum(II) *complexes*: *cis*-$PtCl_2L_2$ (*L* = *Apz*, **9**; *ADMPz*, **10**; *MAPz*, **11**; *MADMPz*, **12**; *PAPz*, **13**; *PADMPz*, **14**). Aqueous ethanolic (1 : 1) solutions of the ligands APz, ADMPz, MAPz, MADMPz, PAPz or PADMPz were added to K_2PtCl_4 (0.10 g, 0.24 mmol) dissolved in water, with stirring at room temperature. The resulting solutions were stirred for 3 h. The solvent was evaporated completely and the residue taken in CH_2Cl_2 was filtered to remove KCl. The filtrate was concentrated and the complexes precipitated by the addition of n-hexane to give off-white (**9**) and light yellow (**10**–**14**) products. Complexes **13** and **14** were isolated in di- and monohydrate forms, respectively. Yields: 0.09 (68%, **9**), 0.09 (67%, **10**), 0.10 (75%, **11**), 0.11 (78%, **12**), 0.13 (78%, **13**) and 0.09 g (74%, **14**)

$Pt(N\text{-}N)_2$ (N-N = *MADMPz*, **15**; *PADMPz*, **16**). $PtCl_2(MADMPz)_2$ (0.10 g, 0.16 mmol, **12**) or $PtCl_2(PADMPz)_2$ (0.10 g, 0.13 mmol, **14**) was suspended in water (20 cm^3) and stirred at room temperature. A few drops of ethanol was introduced to ensure partial solubility. At this stage 2 equiv. of aqueous 0.05 M NaOH was added dropwise to the stirring suspension at the end of which the suspension became almost clear and gradually turned to white turbid mixture. After stirring for 3 h the product was filtered, washed with cold water, followed by ether and then dried *in vacuo* over P_2O_5. Yields: 0.07 (80%, **15**) and 0.08 g (88%, **16**).

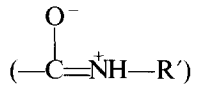
$Pt(ADMPz)_2$(**17**). To a solution of K_2PtI_4 (0.10 g, 0.12 mmol), prepared *in situ*,[26] was added 2 equiv. of ADMPz (0.04 g) with constant stirring. Immediately after the addition of the ligand the colour changed from dark brown to light yellow. After stirring for 3 h, silver sulphate (0.041 g, 0.13 mM) dissolved in water (20 cm^3) was added to the above solution. The mixture was then heated with stirring on a sand bath (70–80°C) for 10–15 min. The solution was filtered and the filtrate was evaporated to dryness. The residue redissolved in CH_2Cl_2 yielded a light yellow solid on precipitation with n-hexane. Yield: 0.052 g (78%, **17**).

RESULTS AND DISCUSSION

Pyrazole amide ligands

Some new bifunctional pyrazole amides whose analogues have proved to be biologically very useful were prepared and characterized in the present investigation. The ligands are soluble in common organic solvents and water, except when R′ = Ph. All the compounds were shown to be pure by thin layer chromatography and were unambiguously characterized based on their IR, ^1H, $^{13}C\{H\}$ NMR and mass spectral data (Table 2, 3 and 4).

The IR spectra of ligands in the solid state contain characteristic bands due to >C=O, $—NH_2$ and —NH— and the frequencies are assigned according to Bellamy.[27] The absorption bands in the 1630–1690 cm^{-1} region, which is generally assigned as amide I band due to ν(CO), are found to depend on the nature of the substituent (R′) on the amide nitrogen. Table 2 reveals an increase in the ν(CO) absorption frequencies with respect to R′: H > Ph > Me. This may be explained due to the variance in amide resonance. When the amide hydrogen is replaced either by Ph or Me group, C=O polarization is more favoured



by mesomeric and inductive effects, respectively. Amide II and III bands have been assigned tentatively and are subject to uncertainties owing to the presence of skeletal vibrations due to the phenyl ring and the bending vibrations due to methyl groups absorbing strongly in the same region. The bands at *ca* 1555(s), 1440(m) and 1035(m) may be assigned to ν(C=C), ν(C=N) and ν(N—N), respectively, of the pyrazole ring. There are also other medium sharp bands appearing in the range 690–840 cm^{-1} due to out-of-plane ring deformation (breathing) vibrations.[28]

The ^1H NMR spectra of the ligands are well resolved and the data presented in Table 3. The chemical shifts found were to be in the upfield order: H(4) > H(3) > H(5) for APz, MAPz and PAPz, and a similar trend was reported for some of the related compounds such as 1-carboxamide pyrazoles[29] and $Pz—(CH_2)_n—CO—X$ (X = Me, Et,

Table 2. Important bands in the infra red spectra of some ligand/metal complexes[a]

Ligand[b]/ complex	ν(N—H)[c]	Amide bands I	II	III	ν(M—Cl)
APz(125)	3370m, 3150m	1680s	1635s	1250sh	
MAPz(139)	3285m	1665m	1645m	1250m	
PAPz(201)	3260s	1675m	1645m	1255m	
ADMPz(153)	3360s, 3180s	1690m	1635s	1265s	
MADMPz(167)	3280s	1650s	1635sh	1250m	
PADMPz(229)	3260s	1670s	1600s	1260m	
1	3400s, 3300m	1675s	1655sh	1300w	305m, 270s
2	3380s, 3180s	1680s	1650m	1280sh	320m, 275m
3	3380s	1670s	1645sh	1250sh	310m, 280s
4	3300s	1660s	1620sh	1250m	325m, 265m
5	3300m	1695s	1645sh	1250m	310m, 270s
6	3290s	1680s	1650sh	1250sh	325m, 270s
7	3400br	1585s			—
8	—	1580s	1588m		—
9	3380m, 3110m	1670s	1645sh	1250sh	340m, 300m
10	3350m, 3150m	1680m	1620m	1240w	—
11	3100m	1685m	1610m	1230w	335m, 300s
12	3290s	1660m	1630sh	1250m	—
13	3280m	1680s	1650sh	1255w	—
14	3270m	1680s	1650sh	1255w	—
17	3250m	1570s			—

[a] Identified and assigned according to ref. 27; spectra recorded in KBr discs; s = strong, m = medium, w = weak and sh = shoulder.

[b] Values in parentheses correspond to *m/z* (parent peak).

[c] Primary amides show two bands: high energy band corresponding to as (asymmetric) and the lower one to s (symmetric) stretching vibrations.

Ph, MeO, EtO or NHR; $n = 0$ or 1; Pz = 1-pyrazolyl).[30] Also, the relative chemical shifts of the $-CH_3$ groups are found to be in the upfield order: Me(3) > Me(5). A low-field resonance for Me(5) is expected because of the anisotropy of the adjacent >C=O bond.[29] When N(1) of pyrazole is substituted with an electron-withdrawing group, the chemical shift difference in R(3) and R(5) is larger than when N(1) is substituted with electron-donating group. However, there is an appreciable difference in the fields of absorption of R(3) and R(5), although small (~0.1 ppm) in the case of methyl groups, when the $-CH_2CONHR$ group is substituted at the 1-position in all the ligands (Table 3). The data on some of the known compounds have also been included in Table 3 for comparison. The chemical shift due to $-CH_2-$ protons has been found to be sensitive with respect to substituents on amide nitrogen and varies in the order: $-NH_2$ > —NHMe > —NHPh. A range of values is observed for the solvent and concentration-dependent amidic protons and have been assigned based on deuterium exchange studies.

The $^{13}C\{H\}$ NMR spectral data with probable assignments for all the carbon atoms present in the pyrazole amide ligands APz, PAPz, ADMPz and PADMPz are given in Table 4. The signals due to C(3), C(4) and C(5) have been assigned easily.[31] The resonances due to C(3) and C(5) of pyrazole appear to be sensitive to the nature of the substituents at the 3 and 5 positions. The singlet resonances due to methylene carbons in the ligands also appear to be dependent on the nature of the ring substituents at the 3 and 5 positions. Thus, the corresponding singlets of ADMPz (50.97 ppm) and PADMPz (51.74 ppm) with methyl substituents occur in the upfield region compared with the singlets of APz (53.78 ppm) and PAPz (54.49 ppm) with no substituents at C(3) and C(5). Besides, there is hardly any effect on the methylene resonance as the substituents on the amide nitrogen are viewed (Table 4). However, the effect of substitution on the amide nitrogen can be clearly seen in the carbonyl carbon resonances (Table 4). The other singlet resonances in the range 119–139 ppm correspond to phenyl carbons (PAPz and PADMPz) and in the range 10–14 ppm to methyl carbons (ADMPz and PADMPz).

Table 3 ^{1}H NMR spectral data of the pyrazole amide ligands[a]

Ligand	—CH_2—	H(4)	H(3)/Me(3)	H(5)/Me(5)	—NH_2/—NH—[b]	N—Me/Ph	Solvent
APz	4.74(s)	6.22(m)	7.35(d) (J = 1.68Hz)	7.64(d) (J = 2.05 Hz)	7.11(br, s)	—	DMSO-d
MAPz	4.83(s)	6.38(m)	7.50(d) (J = 1.7 Hz)	7.68(d) (J = 2.1 Hz)	6.22(br)	2.80(d) (J = 4.12 Hz)	$CDCl_3$
PAPz	5.01(s)	6.22(dd) (J = 1.8 Hz)	7.46(d) (J = 1.69 Hz)	7.77(d) (J = 2.12 Hz)	10.30(br, s)	7.06(m) 7.31(m) 7.56(m)	DMSO-d
ADMPz	4.55(s)	5.78(s)	2.05(s)	2.12(s)	7.17(br, s) 7.36(br, s)	—	DMSO-d
MADMPz	4.60(s)	5.84(s)	2.19(s)	2.20(s)	6.17(br)	2.75(d) (J = 4.9 Hz)	$CDCl_3$
PADMPz	4.82(s)	5.82(s)	2.06(s)	2.19(s)	10.26(s)	7.06(m) 7.31(m) 7.56(m)	DMSO-d
CADMPz[c]	—	5.91	2.20	2.54	—	—	$CDCl_3$
MCADMPz[c]	—	5.88	2.18	2.55	7.30	—	$CDCl_3$
EAPz[c]	4.90	6.31	7.47	7.54	—	—	$CDCl_3$

[a] δ, ppm; chemical shifts are relative to TMS; s = siglet; d = doublet; dd = doublet of doublet; br = broad and m = multiplet.

[b] Spectra were recorded in each case after the addition of 2–3 drops of D_2O to identify —NH—/—NH_2 protons and a new peak at ~4.80 δ was always observed due to HOD.

[c] Taken from refs 29 and 30; and the peak multiplicities were not reported for the compounds with the following abbreviations: CADMPz = 1-(carboxamido)3,5-dimethylpyrazole; MCADMPz = 1-(N-methyl)carbaxamido 3,5-dimethylpyrazole; EAPz = 1-(ethylacetato)pyrazole.

Table 4. $^{13}C\{H\}$ NMR spectral data for pyrazole amide ligands in DMSO-d_6[a]

			δ(C)[b]				
Ligand	—CH_2—	3-CH_3 (5-CH_3)	>C=O	C(3)[c]	C(4)	C(5)[c]	Phenyl
APz	53.78	—	169.02	139.04	105.36	131.53	—
PAPz	54.49	—	165.54	139.07	105.33	131.64	119.10, 119.21 123.62, 128.87 138.66
ADMPz	50.97	13.27 (10.62)	169.01	145.88	104.77	139.75	—
PADMPz	51.74	13.29 (10.72)	165.82	146.17	104.80	140.12	119.08, 119.17 123.56, 128.86 138.71

[a] δ, ppm; all are singlet resonances.

[b] Chemical shifts are relative to the internal standard $(CH_3)_4Si$, positive shifts representing deshielding; spectra recorded on a Bruker 300 MHz spectrometer.

[c] Assigned and identified based on ref 31.

Pyrazole amide complexes

Pyrazole-containing systems have assumed importance in view of their hypoglycemic (anti-diabetic),[25] anti-tuberculosis[32] and anti-tumour[12] properties. These properties were found when administered as pure organic compounds. There were no reports on the nature of their activity against the above disorders when they are administered as metal complexes, with altered steric, electronic and other properties. There have been a good number of reports on the coordinating tendencies

of a number of monodentate pyrazole derivatives in the literature.[4] However, examples of polyfunctional pyrazole derivatives and their metal complexes appear to be scarcely reported. Saha *et al.*[7,8] have investigated the coordinating ability of certain functionalized pyrazolyl ligands with 3*d* and platinum group metal ions.

Interesting possibilities arise in structures of metal complexes with bifunctional ligands containing an ambidentate amide group. Despite the presence of two potential donor sites (N and O), the amide group by itself is a weakly coordinating ligand and often needs a chelate anchor to form stable complexes.[33] For example, formamide derivatives (HCONHR; R = H, Me, Ph) are very poor ligands and have no known metal complexes. A good account of their ligational tendencies has been revealed when substitutions are made for H atoms on the formamide carbonyl group. Thus, the substitution of H by $—CH_2NH_2$ yields glycinamides which have been widely studied for their varying coordination tendencies by Taube and coworkers[34] and Appleton *et al.*[35,36] Substitution of H by 1-pyrazolyl methyl group yielded the ligands reported in the present investigation. Both glycinamides and pyrazole amides can be simply viewed as formamide derivatives with tremendous potential for the development of new coordination chemistry. The resemblance between glycinamides and pyrazole amides is of interest. Both the systems have chelate anchors in amine (glycinamide) or pyrazole (pyrazole amide) nitrogen, although the latter is a poor σ-donor. It has been established that pyrazolyl ligands coordinate to the metal ions through the unsubstituted N(2) (pyridine-nitrogen) from X-ray crystal studies on some related metal complexes.[37,38]

Palladium(II) *complexes*

The complexes of palladium have been prepared by two general procedures. In (i), simple mixing of K_2PdCl_4 with the ligand in a 1:2 ratio in water precipitated neutral monomeric light-yellow complexes of the type *cis*-$PdCl_2L_2$. In (ii), addition of aqueous solution of K_2PdCl_4 to a solution of ligand, which was pre-adjusted to pH ~8 with 0.5 M aqueous NaOH, or reaction of $PdCl_2L_2$ suspended in water with 2 equiv. of 0.5 M aqueous NaOH solution yielded neutral bis-chelates of the type Pd(N-N)$_2$ (N-N = deprotonated pyrazole amide).

cis-$PdCl_2L_2$ (*L* = *Apz*, **1**; *ADMPz*, **2**; *MAPz*, **3**; *MADMPz*, **4**; *PAPz*, **5**; *PADMPz*, **6**. A 1:2 complex (metal:ligand) was always obtained irrespective of the metal–ligand ratio employed. Lesser yields were obtained, however, when the ratio was 1:1. The complexes behave as non-electrolytes in DMSO, suggesting their neutral configuration (Table 1). The far-IR spectra of these metal complexes can be used with the advantage of assessing the *cis*- or *trans*-isomeric nature of the $PdCl_2$ unit. The *cis*-isomer (C_{2v} local symmetry) exhibits two ν(Pd—Cl) bands (A_1 and B_2), whereas the *trans*-isomer (D_{2h} local symmetry) exhibits only one strong ν(Pd—Cl) band (B_{3u}).[39] Also, in planar Pd^{II} or Pt^{II} complexes, ν(M—X) (X = halogen) is sensitive to the ligand *trans* to the M—X bond. The far-IR spectra of complexes **1–6** exhibit bands corresponding to the *cis*-$PdCl_2$ unit in the ranges 310–330 and 265–280 cm^{-1} (Table 2). However, it was not possible to attribute any of the bands due to Pd—N (R′ = Ph), since the ligand spectrum is rich with bands in the region 300–330 cm^{-1} and one of the ν(Pd—Cl) bands is also expected to occur in this range.

For the pyrazole amides (L) in $PdCl_2L_2$, a monodentate coordination has been assigned through N(2) of pyrazole based on their IR spectra. The IR spectra of the solid ligands are compared with the IR. spectra of their corresponding palladium complexes in order to identify the diagnostic bands. Three bands corresponding to the amide group (amide I, II and III bands) and ν(C=N) and ν(N—N) bands of the pyrazolyl ring have been monitored in order to ascertain the mode of coordination of these bifunctional ligands. When the amide group coordinates to the metal through the carbonyl oxygen, a negative shift is normally expected but may not necessarily be observed. Instead, the amide I band either remains unmodified or shifts only a little towards higher or lower frequency regions. The absence of any such recognizable shift of the amide I band in the spectra of the complexes may be explained in terms of hydrogen bonding.[7,27] The ligands contain, in the solid state, hydrogen-bonded >C=O groups which absorb in the ranges cited in Table 2.[27] Also, the appearance of these amide I bands in the IR spectra of the ligands in solutions at comparatively higher frequencies confirm the presence of hydrogen bonding in the ligands. A positive shift is expected for the amide groups remaining non-coordinated. Based on these considerations, the bonding of pyrazole amide ligands with a free or coordinated amide function was ascertained. The IR spectral data presented in Table 2 for complexes **1–6** are indicative of monodentate coordination of pyrazole amides via the N(2) atom only. Appreciable positive shifts of the ν(C=N) (*ca* 15–40 cm^{-1}) and the ν(N—N) (~20–30 cm^{-1}) modes of the pyrazole ring in the IR spectra of the palladium (II) complexes **1–6** compared with their corresponding free ligand band positions also support the above proposition that N(2) of pyrazole is the bonding site.[7,40]

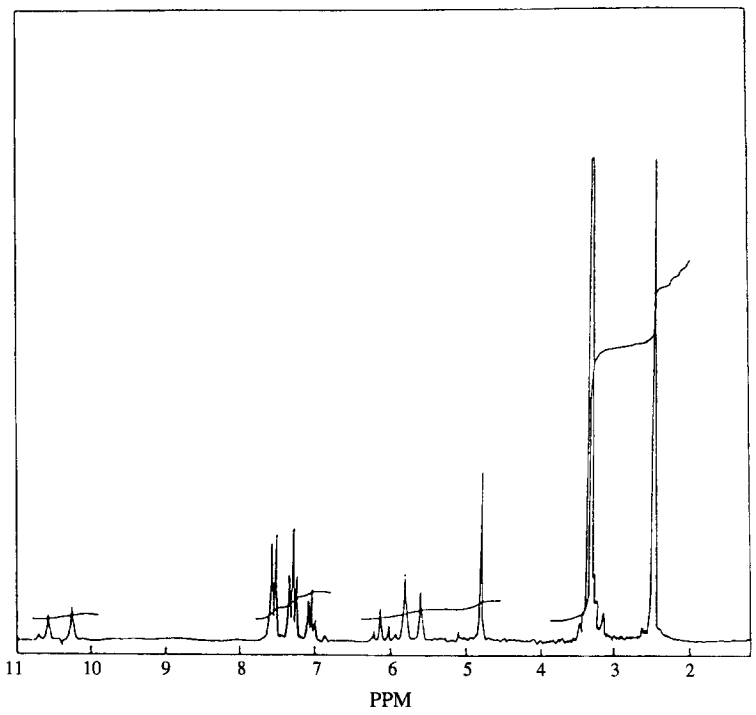
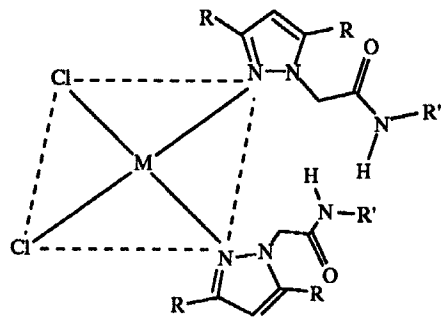


Fig. 2. ^{1}H NMR spectrum of $PdCl_2(PAPz)_2$.

The ^{1}H NMR spectra of complexes **1–6** also support the monodentate coordination for pyrazole amides (Table 6). The spectra exhibit bands due to H(3), H(4) and H(5) of the pyrazole ring with a consistent upfield coordination shift. This is expected as the pyrazole ring suffers some loss in its aromaticity due to the withdrawal of electron density from N(2) to Pd^{II} and as a result of this the ring protons experience a higher shielding effect. The ^{1}H NMR spectrum of complex **5** is more interesting in that the bands due to H(3) and H(5) have undergone unusually large upfield shifts ($\sim$1.9 δ) and occur at 5.6 and 5.81 δ, respectively. However, the resonance due to H(4) occurs as a multiplet at 6.15 δ with a marginal upfield shift (Fig. 2). The resonances due to —CH_2— protons are found in a slightly upfield region and this can be explained on the basis of the reasons related to the loss of aromaticity discussed above for ring protons.

Similar features are observed in the ^{1}H NMR spectra for complexes **2**, **4** and **6** except for the appearance of a multiplet at $\sim$5.5 δ, the origin of which is not known at present. Further, the spectra also contain resonances due to the N—ph, N—Me_3, Me(3), Me(5) and —NH—/—NH_2 protons in the appropriate ranges as complex multiplets with slight shifts (Table 5). An assimilation of all these data coupled with analytical and magnetic evidence point to the fact that complexes **1–6** are square planar with *cis*-$PdCl_2$ units and the pyrazole amide ligands coordinating as neutral monodentate (Fig. 3).

$Pd(N\text{-}N)_2$ (N-N = *MADMPz*, **7**; *PADMPz*, **8**). These bis-chelate compounds always crystallized with at least two molecules of water, as evidenced from the analytical data and the presence of a strong and broad band around 3400 cm^{-1}. TGA profile on the complexes is in conformity with this. A typical IR spectrum for one of the complexes, $Pd(MADMPz)_2 \cdot 2H_2O$ (**7**), is reproduced in Fig. 4. A single intense band due to ν(C=O) (amide I) at 1585 cm^{-1}, shifted downfield by 65 cm^{-1} from that in the free ligand, is typical of an amide group



M = Pd(II), Pt(II)

Fig. 3. A possible stereochemistry for complexes of the type $MCl_2(L)_2$.

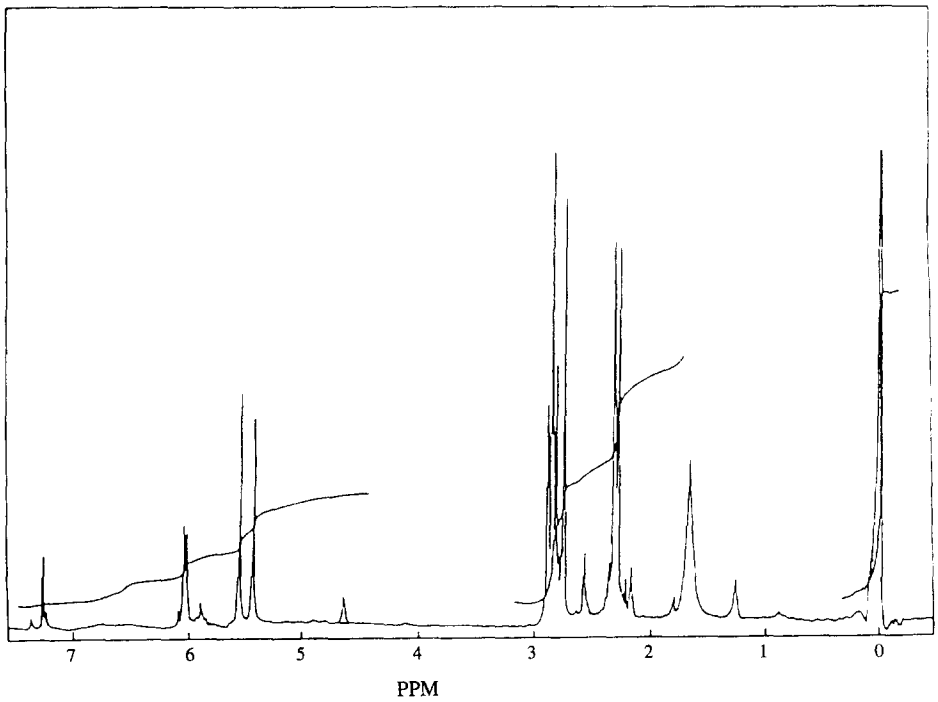


Fig. 4. ^{1}H NMR spectrum of $Pd(MADMPz)_2 \cdot H_2O$.

coordinated through deprotonated nitrogen.[41] A similar band at 1580 cm^{-1} is present in the IR spectrum of complex **8** due to the amide I mode, suggesting the deprotonated amide structure for PADMPz ligands. The presence of many other bands corresponding to the amide function and pyrazolyl moiety also support the bifunctional nature of these ligands (Table 2).

From the ^{1}H NMR spectra of complexes **7** and **8** (Table 5) and the resonances due to —CH_2— protons can be assigned as diagnostic to the structures proposed in Fig. 5 and a bidentate mode of coordination (N-N$^-$) is suggested for each of the ligands MADMPz or PADMPz in their complexes. In the spectrum of complex **7** the —CH_2— protons resonated as an AB quartet centred at 5.49 ppm, 0.9 ppm downfield compared with —CH_2— in MADMPz (4.60 ppm). —CH_2CONHR'— is part of a stable chelate ring. The —CH_2— protons lie in the molecular plane of the hetero-aromatic pyrazole ring and are deshielded due to the "ring-current effect". The multiplicity of the methylene protons signal can be explained due to the anisotropy induced by the adjoining carbonyl group. As shown in Fig. 5, it can be inferred that the pyrazolyl ring is almost co-planar with the six-membered chelate ring, involving NNCCN$^-$ ring closure occurring through N(2) of pyrazole and N$^-$ of the amide to Pd^{II}. The resonances corresponding to Me(3), Me(5) and N—Me of chelated MADMPz occur slightly downfield than in the free ligand (Table 6), thus the singlets at 2.30 and 2.35 δ correspond to Me(3) and Me(5) and a large multiplet centred at 2.90 δ to N—Me groups.

The ^{1}H NMR spectrum of complex **8** shows the same pattern of resonance, which conforms to the structure shown in Fig. 5 (Table 5). However, an interesting observation can be made from the ^{1}H NMR spectrum of $Pd(PADMPz)_2$ (**8**) with reference to Me(3) and Me(5) resonances. A multiplet at 2.35 δ and two well-separated singlets at 2.80 and 2.95 δ can be assigned due to Me(3) and Me(5) groups, respectively, on the coordinated pyrazolyl ring (see the ^{1}H NMR spectrum of complex **8** presented in Fig. 6). Similar spectral bands were probably present in the complex $Pd(MADMPz)_2$ (**7**), but owing to the presence of N—Me groups it was not possible to locate and analyse the largely downfield shifted overlapping resonances due to Me(5) groups. This large separation of singlets due to Me(5) and Me(3) in both complexes **7** and **8** can be attributed to the presence of the steric/spatial interaction of the Me(3) groups on two *cis*-disposed pyrazolyl rings of either MADMPz or PADMPz (Fig. 5). This is suggested as one of the reasons to account for the above resonances while there being several other unknown possibilities.

Platinum(II) *complexes*

cis-$PtCl_2L_2$ (**9–14**). The use of $PtCl_4^{2-}$ as a reactant, rather than $Pt(H_2O)_4^{2+}$[42] or even the diaquo

Table 6. ^{1}H NMR spectral data for some metal complexes in DMSO-d_6[a]

Entry No.	—CH_2—	H(4)	H(3)/Me(3)	H(5)/Me(5)	—NH_2/—NH—[b]	N—Me/—Ph
1.	4.77(s)	6.25(s)	7.40(s)	7.68(s)	7.23(br,s)	—
2.	4.59(s)	6.12(d)	2.13(d)	2.16(d)	7.20–7.50(br,m)	—
3.	4.76(s)	6.24(s)	7.42(s)	7.68(s)	7.9–8.1(br,m)	2.65(d)
4.	4.56(s) 5.50(m)	6.08(d)	2.10(d)	2.25(d)	7.85–8.2(br,m)	2.65(m)
5.	4.81(s)	6.15(m)	5.60(s)	5.81(s)	10.25(s)	7.0–7.70(br,m)
6.	4.81(s)	5.6–5.8(br,m)	2.10(d)	2.25(d)	10.25(s)	7.05–7.55(br,m)
7.[c]	5.42(s) 5.56(s)	6.02(m)	2.30(s)	2.35(s)	—	2.90(m)
8.[c]	5.65(s) 5.85(s)	6.08(s)	2.35(m)	2.80(s) 2.95(s)	—	7.0–7.75(br,m)
9.	4.73(s)	6.24(m)	7.45(s)	7.71(m)	7.5–8.3(br,m)	—
11.	4.76(s)	6.24(m)	7.43(m)	7.71(m)	8.0–8.2(br,m)	2.64(m)
16.	4.77(s)	5.83(m)	2.03(s)	2.17(s)	10.23(s)	7.0–7.6(br,m)

[a] δ ppm, against internal standard Me_4Si; s = singlet, d = doublet, m = multiplet and br = broad.
[b] Spectra were recorded in each case after the addition of 2–3 drops of D_2O to identify —NH—/—NH_2 protons.
[c] Spectra recorded in $CDCl_3$. The resonances correspond to peaks 2 and 3 of AB quartet. Peaks 1 and 4 are not discernible.

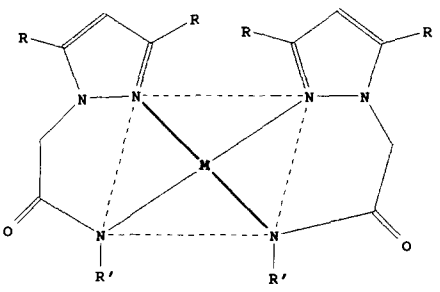


Fig. 5. Possible structure for complexes of the type M(N–N)$_2$. (N–N = uninegative bidentate ligand.)

species $[Pt(NH_3)_2(H_2O)_2]^{2+}$,[35] is advantageous because chloride bound to platinum(II) prevents the precipitation of a platinum hydroxide complex even when the reactions are conducted at higher pH. The stepwise equilibrium dissociation constants[43] determined for the loss of Cl from $PtCl_4^{2-}$ indicate that the chloride appears to suppress the successive chelation as well as unwanted initial hydrolysis of Pt^{II}.

Although the Pt^{II}–pyrazole amide solutions obtained by mixing $PtCl_4^{2-}$ with the appropriate pyrazole amide ligands in a 1 : 2 ratio, were kept for more than 24 h to ensure complete reaction, hydrolysis of the pyrazole amide was not observed. This either suggests the presence of mono-coordinated pyrazole amide bound to platinum(II) through N(2) of the pyrazole with a dangling amide function or the existence of a chelated pyrazole amide to Pt^{II} through amidic carbonyl oxygen with Pt^{II} not being very effective in making the carbonyl group susceptible to any nucleophilic attack. The conductivity data on the DMSO or MeOH solutions of complexes **9–14** are consistent with a neutral configuration (Fig. 3). However, the aqueous solutions of these complexes are highly conducting[44] (Table 1), which certainly suggests that the aquation reactions are occurring with the formation of the species of the type presented in Fig. 7.

The presence of amide I bands with slight positive or zero shifts are observed in the IR spectra of the complexes and are assigned to the free amide end of the pyrazole amides. The amide II and III (secondary amides) bands are found to remain stationary and the entire free-ligand spectrum is repeated except for some perceptible changes in the bands, due to ν(C=N) and ν(N—N) of pyrazole in the appropriate ranges (Table 2). The far-IR spectrum for *cis*-$PtCl_2(APz)_2$(**9**) shows two medium intense bands at ~340 and ~300 cm^{-1} due to ν(Pt—Cl) suggesting unequivocally the *cis* orientation of the chloride ligands.[39] It was not possible, however, to ascertain and identify the bands due to ν(Pt—N).

As discussed earlier for the Pd^{II} complexes, the resonances due to the —CH_2— protons are observed at slightly downfield and occur at 4.73, 4.76 and 4.77 δ in complexes **9**, **11** and **12**, respec-

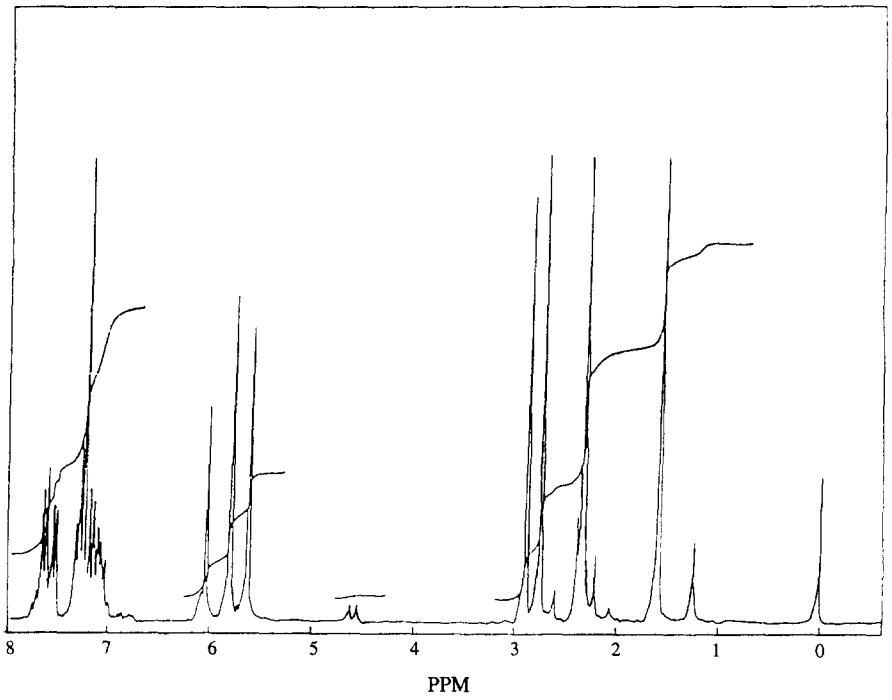


Fig. 6. ^{1}H NMR spectrum of $Pd(PADMPz)_2 \cdot H_2O$.

tively. The multiplets at 6.24, 7.43 and 7.71 δ are shifted slightly to upfield and correspond to H(4), H(3) and H(5), respectively, of the coordinated MAPz ligands in complex **11**. An upfield doublet centred at 2.64 δ due to N—Me protons is also present. A structure similar to the palladium complexes (**1–6**) is assigned for all these complexes (Fig. 3).

Chemical resemblance of cis-$PtCl_2L_2$ *with* cis-$PtCl_2(NH_3)_2$

When *cis*-platin is used as a drug for treating certain oncological disorders, the initial and most likely reaction appears to be the hydrolysis or aquation (or even base hydrolysis) in the surrounding medium with varying concentrations of Cl^- and

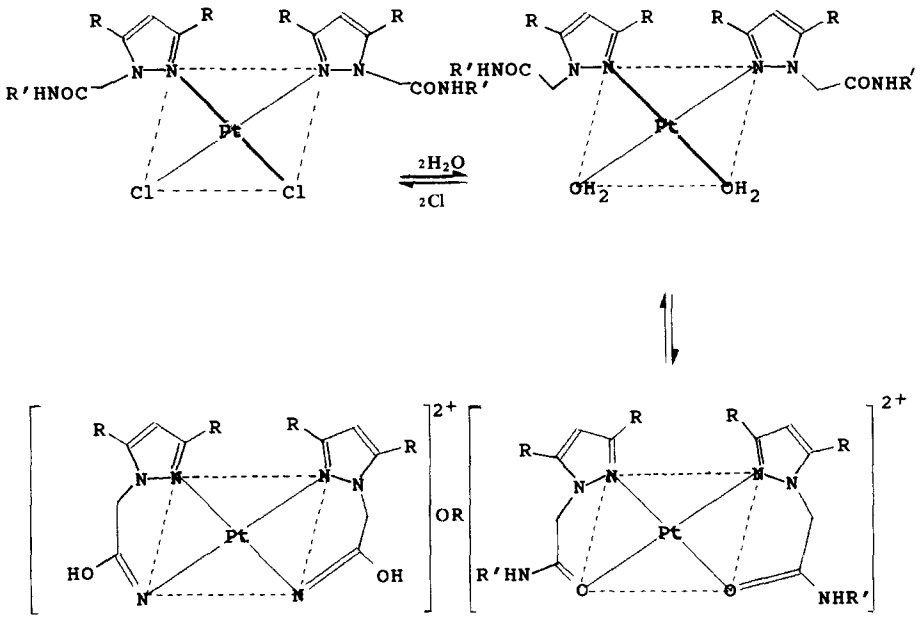


Fig. 7. Aquation or hydrolysis of the complex *cis*-$PtCl_2(L)_2$ in water and the possible species in solution.

pH. When *cis*-$PtCl_2(NH_3)_2$ is dissolved in water, it loses Cl^- ions and forms aqua or/and hydroxo complexes. Hydrolysis occurs inside the cells where the Cl^- concentration is 4 mM and outside the cells it is largely prevented since Cl^- concentration is rather high ($\sim$100 mM).[3]

The complexes *cis*-$PtCl_2L_2 \cdot nH_2O$ (**9**–**14**) are all water soluble and are totally non-conducting when dissolved in non-aqueous solvents like DMSO and DMA. However, their water solutions are highly conducting (at pH $\sim$5.0) and their ionicity corresponds to 1 : 2 electrolytes[44] (Table 1). This could be certainly explained based on the assumption that the complexes are hydrolysing rapidly when dissolved in water and an aquated species of the type, $[Pt(H_2O)_2L_2]Cl_2$ may exist in solution. The complexes resemble *cis*-platin in this regard. Further, on treating the aqueous solution of these complexes for pH variations, the following results have been obtained. (i) Upon treatment of these solutions with 6N HCl solution up to pH $\sim$2 (excess Cl^-), a sample identical to the starting complex $PtCl_2L_2$ was isolated. However, there was no hydrolysis of the coordinated ligands under these acidic conditions. (ii) Upon standing in water and reprecipitating the product afforded a diaquo species, $[Pt(H_2O)_2L_2]Cl_2 \cdot nH_2O$. (iii) On gradually changing the pH to $\sim$8.0, a less well-characterized species, which corresponded to the deprotonated amido complex (amide I band at 1570 cm^{-1}),[41] was obtained. A competing reaction between deprotonation at the amide nitrogen and hydrolysis of a metal-bound water molecule is suggested and one or both of these may be taking place.

The fact that the water bound to the metal ion hydrolyses simultaneously with the deprotonation of the amide group, has been demonstrated in a potentiometric titration experiment using a 1 : 1 (metal–ligand) ratio in the presence of the appropriate amount of acid with Cu^{II} and Ni^{II} and ADMPz. The results are in accordance with those reported for some of the dipeptides,[45] where it was shown that the dipeptide ligand complexed with Cu^{II} at higher pH and bound in a bidentate manner undergoing deprotonation of the amide group. It may be mentioned here that ionization of an amide hydrogen cannot be distinguished unambiguously from the hydrolysis of the coordinated water, since both will have the same apparent stoichiometry.[45]

While there have been several efforts to improve the water solubility of such compounds as *cis*-dichloro-(1,2-diaminocyclohexane)platinum(II), which possesses excellent anti-tumour activity and no nephrotoxicity (Khokhar *et al.*[46,47]) by the substitution of two chloride ions with mono- or bis-carboxylates, complexes **9** and **14** need no further modifications in this regard. Thus, these complexes promise high optimism for anti-tumour activity and stand as unique complexes with configurational and chemical similarities to *cis*-platin and like drugs with exceptional water solubility, although their activity against any cancerous tumours is yet to be tested.

$Pt(N\text{-}N)_2$ (n = 1, N-N = *PADMPz*; n = 2, N-N = *ADMPz*, *MADMPz*) (**15**–**17**). Complexes of the type $PtCl_2L_2$ (**10**, **12** and **16**) when dissolved in water and treated with 2 equiv. of 0.5 M aqueous NaOH at room temperature, $Pt(N\text{-}N)_2 \cdot nH_2O$-type products were briskly precipitated as off-white crystalline materials. These products with satisfactory elemental analysis are briefly characterized as bis-chelated complexes on the basis of conductivity and IR spectral data alone (Tables 1 and 2). The IR spectrum of the complex $Pt(ADMPz)_2$ (**17**) exhibits a strong band at 1570 cm^{-1}.[41] The absence of typical primary amide bands corresponding to $\nu(NH_2)$ of ADMPz at 3360 and 3170 cm^{-1} and the appearance of a new band at 3250 cm^{-1} suggests the coordination of a deprotonated amide group. Similarly, in complexes **15** and **16** the presence of a band at $\sim$1590 cm^{-1} suggests deprotonated amido nitrogen coordination.[41] The downfield shift of the amide I band in these complexes has been attributed earlier to the participation of the nitrogen atom of the peptide group in complex formation.[48]

CONCLUSIONS

The ligands used in this work ($PzCH_2CONHR$) are in fact higher homologues of some of the known systems[4] with PzCONHR structure. The incorporation of a —CH_2— unit between Pz and CONHR not only alters the electronic effect on the Pz ring, as evidenced from the free-ligand chemical shifts due to the —CH_2— group in both ^1H and $^{13}C\{H\}$ NMR, but also offers a greater ligand "bite" in the present ligand systems. The larger ligand bite is suitably exploited to form stable complexes of platinum group metal ions with larger ionic sizes. The six-membered chelates thus formed are expected to be more stable.

In view of the toxicities[49] and other aspects mentioned for *cis*-platin,[50,51] a number of new platinum complexes as possible second or third generation drugs were reported.[52] One such compound, *cis*-dichloro-(1,2-diaminocyclohexane)platinum(II), with excellent anti-tumour activity and no nephrotoxicity was reported,[46] but it is insoluble in water. In order to enhance its water solubility while maintaining most of its biological attributes, both its chloride ligands were substituted by mono- or bis-carboxylates.[47]

The complexes, *cis*-$PtCl_2L_2$ (L = APz, MAPz, ADMPz MADMPz), reported in the present work have advantages in that they are highly water soluble, lose two chlorides easily in aqueous solutions and contain simple amide groups appended to a biologically relevant pyrazolyl moiety, unlike the earlier complexes where "$Pt(am)_2^{2+}$" was treated with various expensive amide functionalized steroidal hormones which give only suspensions in water.[53] Also, the pyrazole amide ligands in these complexes do not hydrolyse, thus avoiding the danger of hydrolysis before that parent complex could reach the target cell.

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