Pergamon

Polyhedron Vol. 14, No. 11, pp. 1517–1530, 1995

0277–5387/95 $9.50+0.00

0277–5387(94)00379–3

A POTENTIOMETRIC, SPECTROPHOTOMETRIC AND ^{1}H NMR STUDY ON THE INTERACTION OF CIMETIDINE, FAMOTIDINE AND RANITIDINE WITH PLATINUM(II) AND PALLADIUM(II) METAL IONS

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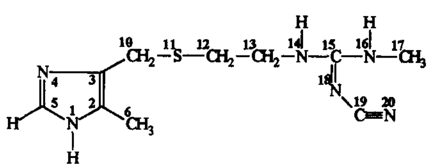
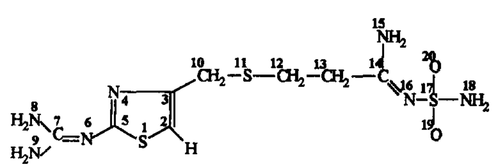
(*Received* 28 *March* 1994; *accepted* 16 *September* 1994)

Abstract—Spectrophotometric, potentiometric and ^{1}H NMR results on the M–L systems [M = Pd^{II} or Pt^{II} and L = cimetidine, famotidine or ranitidine] are clearly indicative of the strong chelating ability of these antiulcerative drugs towards metal ions. In view of the great biological interest in these two metals, their coordination to such drugs should have significant implications.

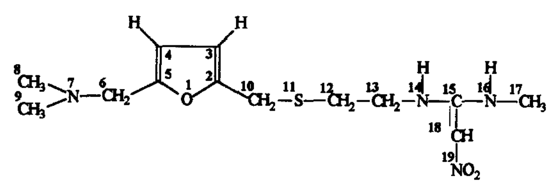
Cimetidine [N-cyano-N′-methyl-N″-[2-[[(5-methyl-1H-imidazol-4-yl)methyl]thio]ethyl]guanidine],



famotidine [3-[[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]thio] - N - (aminosulfonyl)propanimidamide]



and ranitidine [N-[2-[[[-5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl] - N′ - methyl - 2 - nitro-1, 1-ethene-diamine]



are molecules largely used in medicine[1–3] for their safeguarding action on the stomach walls in ulcer disease, due to a histamine H_2 receptor blocking effect. The numbering scheme in the above formulae is used for convenience and differs from that in IUPAC names. The interest towards metal ion complexation in order to understand pharmacological action has led to extensive literature on cimetidine interaction[4–13] as compared to one single study on famotidine[14] and none at all on ranitidine. Presumably this is to be ascribed to the fact that they were introduced on the market at different times.

All these molecules should act as effective ligands towards metal ions, each being composed of several

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groups provided with a very strong coordinating ability, linked to their common structure —CH_2—S—CH_2—CH_2—. Furthermore, the composite structure of famotidine and ranitidine induces equilibria between different conformations, that are well characterized by infrared and X-ray data[15] and by NMR spectroscopy.[16,17] These conformations can play an important role not only in their biological action but also in their behaviour as coordinating agents.

EXPERIMENTAL

Reagents

Cimetidine was purchased from Sigma; famotidine and ranitidine were kindly furnished by Therapicon. The purity of the three ligands, used without any further purification, was checked by ^{1}H NMR and potentiometric measurements. K_2PtCl_4, K_2PdCl_4, NaCl, NaOH, HCl, KNO_3, D_2O, NaOD and DCl were reagent grade Aldrich products.

Potentiometric measurements

Titrations were performed on a Diosimat 655 Metrohm automatic titrator equipped with a pH-M-84 Radiometer pH meter, using a Metrohm combined pH electrode for highly alkaline solutions, at an ionic strength of 0.1 M NaCl for palladium and 0.1 M KNO_3 for platinum studies. In all titrations the ligand was 2×10^{-3} M (with HCl added at the same concentration) and the metal ranged from 0.5×10^{-3} to 2×10^{-3} M. The solutions (25 cm^3) were titrated under a nitrogen atmosphere with NaOH (0.1 M) at 25°C.

Spectrophotometric measurements

The spectrophotometric measurements were carried out on a Hewlett–Packard 8452 diode array spectrophotometer at 25°C. The six M–L systems were studied according to a Job[18] scheme, obtained by mixing in the ratios 9 : 1, 8 : 2, . . , 1 : 9 equimolar solutions of ligand and metal whose concentrations were:

	[Metal]	[Ligand]
Pd–Cim[a]	1.252×10^{-4}	1.248×10^{-4}
Pt–Cim[b]	0.833×10^{-4}	0.832×10^{-4}
Pd–Fam[a]	1.218×10^{-4}	1.217×10^{-4}
Pt–Fam[b]	0.833×10^{-4}	0.835×10^{-4}
Pd–Ran[a]	1.252×10^{-4}	1.248×10^{-4}
Pt–Ran[b]	1.280×10^{-4}	1.248×10^{-4}

[a]NaCl 0.1 M; [b]KNO_3 0.1 M.

A further spectrophotometric analysis was accomplished in order to obtain reliable spectra of 1 : 1 and 1 : 2 M–L complexes. For the 1 : 1 case, we examined a set of solutions, in which metal concentration was constant and that of the ligand increased up to that of metal. For the 1 : 2 case the ligand concentration was constant and the metal concentration increased up to half that of the ligand.

	1 : 1		1 : 2	
	[Metal]	[Ligand]	[Metal]	[Ligand]
Pd–Cim	1.252×10^{-4}	$0–0.624 \times 10^{-4}$[a]	$0–0.626 \times 10^{-4}$	1.248×10^{-4}
Pt–Cim	1.104×10^{-4}	$0–1.104 \times 10^{-4}$	$0–0.530 \times 10^{-4}$	1.077×10^{-4}
Pd–Fam	1.214×10^{-4}	$0–1.241 \times 10^{-4}$	$0–0.306 \times 10^{-4}$[a]	1.217×10^{-4}
Pt–Fam	0.848×10^{-4}	$0–0.842 \times 10^{-4}$	$0–0.424 \times 10^{-4}$	0.842×10^{-4}
Pd–Ran	1.043×10^{-4}	$0–1.040 \times 10^{-4}$	$0–0.522 \times 10^{-4}$	1.040×10^{-4}
Pt–Ran	1.104×10^{-4}	$0–1.104 \times 10^{-4}$	$0–0.529 \times 10^{-4}$	1.077×10^{-4}

[a]For higher ligand or metal concentrations turbid solutions were obtained.

The solutions with platinum were studied at an ionic strength 0.1 M of KNO_3; NaCl prevented any association between platinum and the three ligands and was therefore substituted with KNO_3; literature Cl^- formation constants at 25°C for Pt^{II}[19] (log $K_1 = 5.0$, log $\beta_2 = 9.0$, log $\beta_3 = 11.8$ and log $\beta_4 = 13.8$) are in fact almost two orders of magnitude greater than those for Pd^{II}[20] (log $K_1 = 4.47$, log $\beta_2 = 7.76$, log $\beta_3 = 10.2$ and log $\beta_4 = 11.5$).

NMR measurements

^{1}H NMR spectra were obtained in solution with a Varian VXR-300 spectrometer at a probe temperature of 25°C. The chemical shifts are reported as δ (ppm), downfield from TMS. Typical Fourier Transform conditions, under which the ^1H results were obtained, were the following: sweep width 3000 Hz and 19 μs pulses. A ligand in excess of the 2:1 [ligand]/[metal] ratio was mainly used for two reasons: (a) to force the equilibrium to the formation of a pure ML_2 complex and (b) to have a sufficient amount of free ligand, in excess of that implied in the ML_2 complex, to observe its signal separately from that of ML_2 under the same pH conditions.

The following solution concentrations were used:

	[Metal]	[Ligand]	[Ligand]/[Metal]
Pd–Cim	2.818×10^{-3}	9.127×10^{-3}	3.2
Pt–Cim	2.529×10^{-3}	7.936×10^{-3}	3.1
Pd–Fam	1.315×10^{-3}	3.853×10^{-3}	2.9
Pt–Fam	1.265×10^{-3}	4.051×10^{-3}	3.2
Pd–Ran	2.818×10^{-3}	7.888×10^{-3}	2.8
Pt–Ran	2.529×10^{-3}	8.164×10^{-3}	3.2

The spectra of the above solutions were measured at various pH values properly adjusted by NaOD.

Calculation

Potentiometric data for electrode standardization were analysed with the Gran method[21] using our program GRANPLOT. The ionization constant of the pure ligand and the formation constants of its complexes with platinum and palladium were calculated by a slightly modified version of the program[22] PSEQUAD.

The analysis of spectral data was performed with our program SPECPEAK;[23] this program allows the decomposition of spectra into the component Gaussian bands by a non-linear least-squares calculation of the maximum wavelengths (F) and half-bandwidths (W) of each peak and a linear least-squares calculation of heights (H). These distinctive features allow the estimation of non-linear F and W parameters based on the simultaneous analysis of various spectra and the estimation of peak heights in each single spectrum. In this way it is possible to separate the contribution of each species to the spectra and therefore to have a trend of concentration of each single absorbing component as a function of the reagent concentrations without resort by to any model assumption.

RESULTS AND DISCUSSION

Spectrophotometric results

The Job method[18] for analysing spectrophotometric equilibrium data has been extensively criticized[24] when applied to systems where multiple equilibria coexist. In our opinion reliable information on complexation models can be achieved when heights of Gaussian peaks are reported vs the molar fraction X after the decomposition of spectra obtained by a Job scheme. A thorough study on such a procedure will be reported elsewhere.

The results of Job analysis for the systems Pt–Cim, Pd–Cim, Pt–Ran, Pt–Fam and Pd–Fam show the existence of both 1:1 and 1:2 complexes, as can be argued by the plots reported as an example in Fig. 1. For the Pd–Ran system only evidence of a 1:1 complex was obtained.

In order to acquire reliable absorptivity spectra of pure complexes, spectra of different solutions were collected according to the schemes reported in the experimental section and analysed with the program SPECPEAK. The spectra of seven solutions with constant cimetidine and variable palladium, acquired to estimate the spectrum of $PtCim_2$ complex, are reported in Fig. 2 as an example.

In all the examined cases peak heights vs variable reagent show a linear trend, and through their extrapolation to values corresponding to 1:1 and 1:2 complexes the spectra reported in Fig. 3(A–F) can be obtained. It is to be observed that reagents were mixed without adjusting the pH and this could cause some uncertainty in the absorptivity spectra.

Although made up of bands similar to those of the two components, the spectra of the complexes clearly show the formation of a new band at about 250 nm for 1:1 palladium complexes with cimetidine and famotidine ($\varepsilon \cong 7000$) and 270 nm for the 1:2 complexes ($\varepsilon \cong 10{,}000$). Both corresponding platinum complexes present the same band at about 240 nm. Ranitidine, on the other hand, shows the formation of a strong band at 240 nm for the 1:1 palladium complex and for both platinum complexes, with a very strong ε.

NMR results

The interpretation of NMR findings can give detailed information concerning the structure of complexes. It is to be pointed out that the spectrum reported in a previous paper[13] and interpreted on the grounds of distribution curves based on potentiometric equilibrium results refer to the isolated solid compound $PtCim_2$ dissolved in D_2O.

In the present work, completely different ^1H NMR spectra were acquired from solutions in which cimetidine and Pt^{II} were mixed in a 3:1 ratio. This indicates that the solid $PdCim_2$ is different

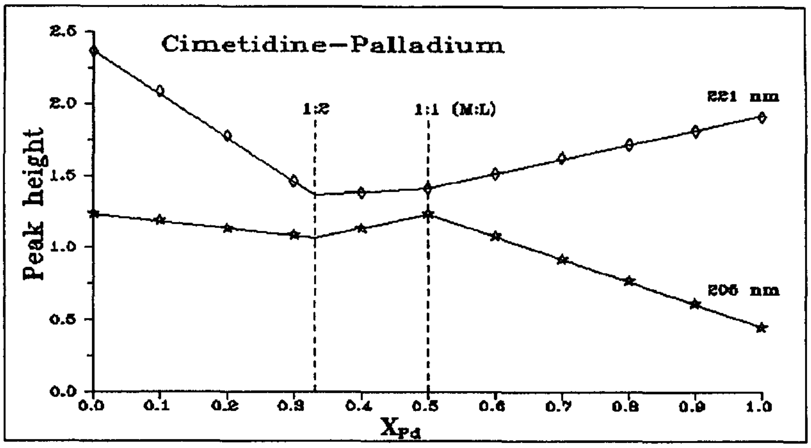


Fig. 1. The heights of the peaks centred at 205 and 221 nm (calculated with SPECPEAK program) for 11 solutions (see Experimental section) are reported vs the palladium molar fraction.

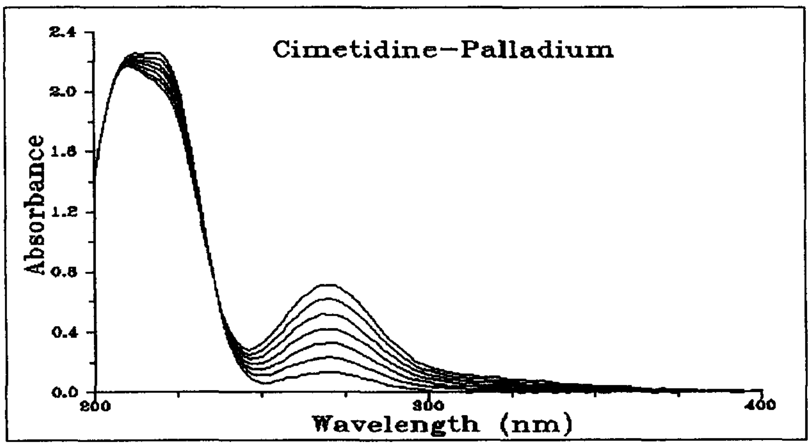


Fig. 2. Spectra of seven solutions with constant cimetidine 1.25×10^{-4} M and palladium systematically increasing up to 0.6×10^{-4} M.

from the equilibrium adduct with the same stoichiometry. The spectra for the six systems at variable pD, reported in Figs 5, 7 and 9 will be discussed later.

Potentiometric results

The titration curves of the solutions with metal–ligand 1 : 1, 1 : 2, 1 : 3 and 1 : 4 ratios confirm the models obtained by the spectrophotometric analysis and are fitted agreeably using the ionization and formation constants reported in Table 1.

In Fig. 4 some distribution curves which can be useful in the next discussion will be reported.

Discussion

The objective of this work is to provide evidence of the species at equilibrium and by the concurrent use of the three reported techniques to acquire some insight into the structural features of the complexes. In the subsequent discussion in Fig. 4 some distribution plots will be presented (a) for solutions having an excess of metal ion and concentrations of the order 10^{-4} M, as those used in the evaluation of the UV spectra of 1 : 1 complexes [A]; (b) in the conditions used for potentiometric measurements with equimolar metal–ligand concentrations [B] and (c) which refer to NMR measurements with an excess of ligand [C]. A variety of situations arise depending on the concentration ranges used and on the reagent ratios. The behaviour of the three ligands will be analysed taking into account all available experimental information.

Cimetidine. Metal ligand complexes (1 : 1 and 1 : 2) are formed with platinum : in the case of metal excess, Fig. 4(A), a $|PtCim|^{2+}$ complex is already formed at pH 3 which coexists with $|PtCim_2|^{2+}$

up to pH ≅ 7, where the 1 : 1 complex deprotonates and the 1 : 2 complex disappears giving $|PtCimOH|^+$ and at pH > 11 the neutral complex $|PtCim(OH)_2|$. The evaluated UV spectra were therefore perturbed by 25% of the 1 : 2 complex, roughly constant along the spectrophotometric titration.

On the contrary, when a large excess of free cimetidine is used, as for NMR measurements, $|PtCim_2|^{2+}$ is stable up to pH ≅ 8, where it loses two

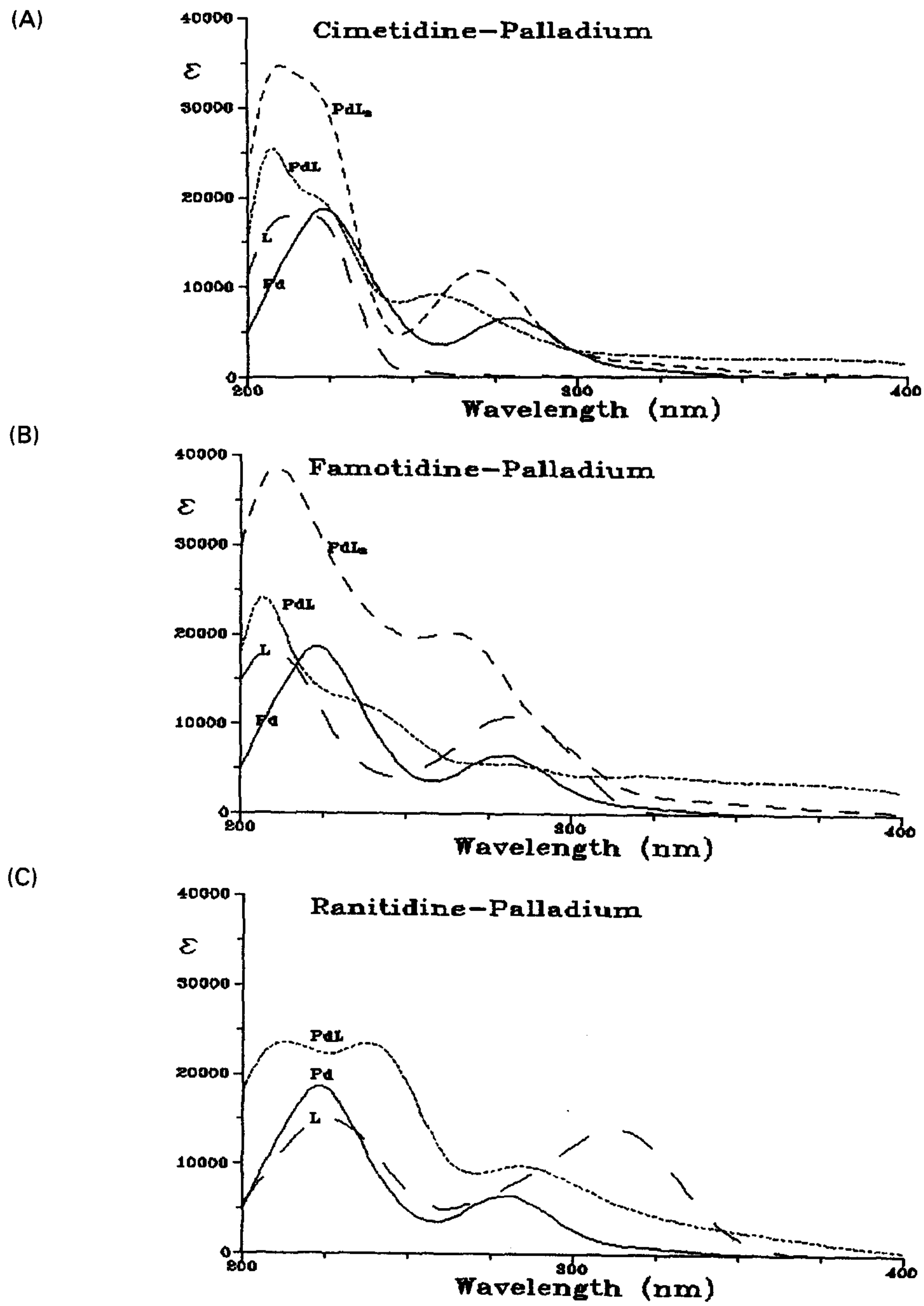
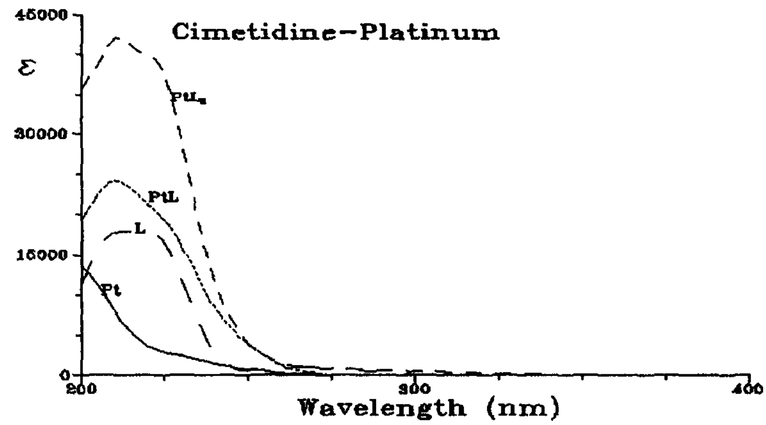
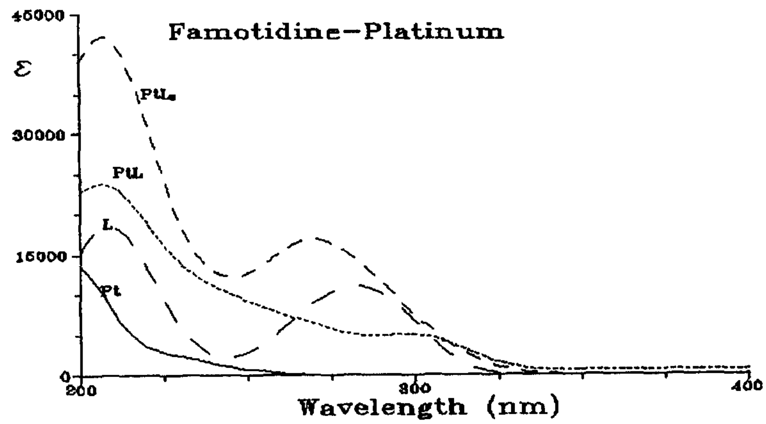


Fig. 3. (A) Absorptivity spectra of pure cimetidine (L), pure K_2PdCl_4 (Pd), 1 : 1 PdCim complex (PdL) and 1 : 2 $PdCim_2$ complex (PdL_2). (B) Absorptivity spectra of pure famotidine (L), pure K_2PdCl_4 (Pd), 1 : 1 PdFam complex (PdL) and 1 : 2 $PdFam_2$ complex (PdL_2). (C) Absorptivity spectra of pure Ranitidine (L), pure K_2PdCl_4 (Pd), 1 : 1 PdRan complex (PdL). (D) Absorptivity spectra of pure cimetidine (L), pure K_2PtCl_4 (Pt), 1 : 1 PtCim complex (PtL) and 1 : 2 $PtCim_2$ complex (PtL_2). (E) Absorptivity spectra of pure famotidine (L), pure K_2PtCl_4 (Pt), 1 : 1 PtFam complex (PtL) and 1 : 2 $PtFam_2$ complex (PtL_2). (F) Absorptivity spectra of pure ranitidine (L), pure K_2PtCl_4 (Pt), 1 : 1 PtRan complex (PtL) and 1 : 2 $PtRan_2$ complex (PtL_2).

(D)



(E)



(F)

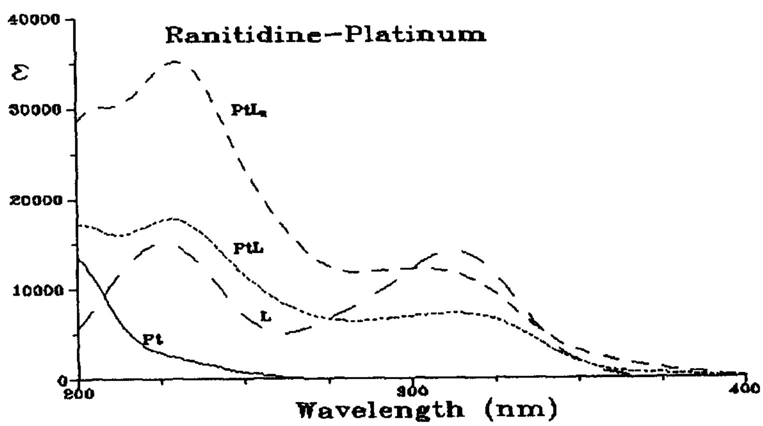


Fig. 3—*continued.*

protons giving the $|PtCim_2(OH)_2|$ neutral complex, in rapid succession. The deprotonations take place at pK 7.42 and 11.36 for the 1 : 1 complex and at pK 8.32 and 9.08 for the 1 : 2 complex. The behaviour of palladium complexes is very similar to that of platinum but formation constants lower by about one order of magnitude are to be pointed out.

* The pH meter readings in D_2O solutions (pD) can be transformed into pH values by adding 0.4 units.[25]

The ^1H NMR spectra shown in Fig. 5(A) and (B) for cimetidine with Pt^{II} and Pd^{II} respectively allow the following remarks:

(i) separate signals are present for complexed and free cimetidine. This is indicative for a slow exchange between the two forms;
(ii) the trend of free cimetidine shifts as a function of pD* (Fig. 6), follows the trend reported previously;[13]
(iii) the signals of the complexed form exhibit a downfield shift with respect to pure cime-

Table 1. Logarithms of the formation constants β_{hlm}

H	Cim	Pt	log β	pK	H	Cim	Pd	log β	pK
1	1	0	7.01±0.01		1	1	0	7.01±0.01	
0	1	1	8.82±0.01		0	1	1	7.63±0.01	
−1	1	1	1.41±0.01	7.41	−1	1	1	0.52±0.01	7.11
−2	1	1	−9.96±0.01	11.37	−2	1	1	−10.95±0.01	11.47
0	2	1	16.90±0.01		0	2	1	15.13±0.01	
−1	2	1	8.60±0.01	8.30	−1	2	1	7.87±0.01	7.26
−2	2	1	−0.48±0.01	9.08	−2	2	1	−1.18±0.02	9.05
H	**Fam**	**Pt**	**log β**	**pK**	**H**	**Fam**	**Pd**	**log β**	**pK**
1	1	0	6.87±0.01		1	1	0	6.87±0.01	
0	3	3	25.21±0.01		0	1	1	6.20±0.01	
−1	3	3	21.12±0.01	4.09	−1	1	1	1.20±0.01	5.00
−2	3	3	15.71±0.01	5.41					
1	2	1	15.74±0.01		1	2	1	18.40±0.01	
0	2	1	10.31±0.01	5.43	0	2	1	12.69±0.01	5.71
−1	2	1	3.89±0.02	6.42	−1	2	1	6.23±0.01	6.46
H	**Ram**	**Pt**	**log β**	**pK**	**H**	**Ram**	**Pd**	**log β**	**pK**
1	1	0	8.35±0.01		1	1	0	8.35±0.01	
0	1	1	6.15±0.01		0	1	1	9.97±0.01	
−1	1	1	−1.26±0.01	7.41	−1	1	1	2.41±0.01	7.56
−2	1	1	−10.01±0.01	8.75	−2	1	1	−6.88±0.02	9.29
0	2	1	10.55±0.01						
−1	2	1	2.76±0.01	7.79					
−2	2	1	−5.72±0.01	8.48					

tidine at basic pD, except for those of $CH_3(17)$ which are shifted highfield;

(iv) the multiplicity of all CH_2 signals is varied, due to a non-equivalence of the two protons as a consequence of the embedded rotation;

(v) the signals of the complexed form do not show any shift with pD. At pD = 10.4 for platinum and pD = 11.0 for palladium only the signals of free cimetidine appear, due to the precipitation of the neutral complex.

On the grounds of these considerations we can therefore assume 1 : 2 Pt^{II} and Pd^{II} complexes of a similar structure, bound by N(4) and S(11) as can be argued both from the pronounced chemical shifts of $CH_2(10)$, $CH_2(12)$, $CH_2(13)$ and CH(5) and from the change in multiplicity of the CH_2 signals. Moreover the formation of hydroxy complexes appear linked only to precipitation phenomena not bound to any conformational change of the molecule whose signals do not vary with pD.

Famotidine. As a first instance the variability of the shifts of pure famotidine with pD gives evidence of protonation on the N(4) ring atom: in fact the chemical shifts of CH(2) experience a strong highfield shift with pD, to a lesser extent those of $CH_2(10)$, while the $CH_2(12)$ and $CH_2(13)$ shifts are practically unaffected. A completely different behaviour is presented by famotidine complexes with both metal ions: with platinum the 1 : 1 complex is in fact a 0, 3, 3 complex which loses two protons with pK 4.1 and 5.4. This can be thought of as a polymeric complex with platinum atoms bonded by μ-water, which stabilizes at acidic pH giving hydroxo-complexes. An analogous complex is likely to be formed by palladium. As far as regards 1 : 2 complexes they should be quite different from those formed by cimetidine. The first to form is in fact $MeFam_2H$, which deprotonates at pK 5.4 and 6.4 for Pt^{II} and pK 5.7 and 6.5 for Pd^{II} giving $MeFam_2$ and $MeFam_2H_{-1}$. Different coordination sites are therefore involved. According to the findings by Kozlowski,[14] N(15) and N(18) should be involved at acidic pH, while a change of bonding should take place at higher pH with an involvement of thiazole nitrogen, which deprotonates easily (p$K \cong 5$), in contrast with the higher values for cimetidine. The ^1H NMR spectra reported in Fig. 7 for acidic pD are not easily attributable. Nevertheless on the basis of the previous cimetidine study a downfield shift of all the CH_2 signals is visible as well as a change of their multiplicity. A second situation is to be remarked: the signals of $CH_2(10)$ clearly decompose in two AB spectra, and the signal of CH(2) gives at least two distinct signals in the complexed form. These facts can be due both to the different kind of complexes in slow exchange at this pD value, and to a lack of symmetry in the two bonded molecules in each 1 : 2 complex.

Ranitidine. Ranitidine behaviour as a function of pD is well illustrated in the work by Geraldes *et*

(A)

(B)

(C)

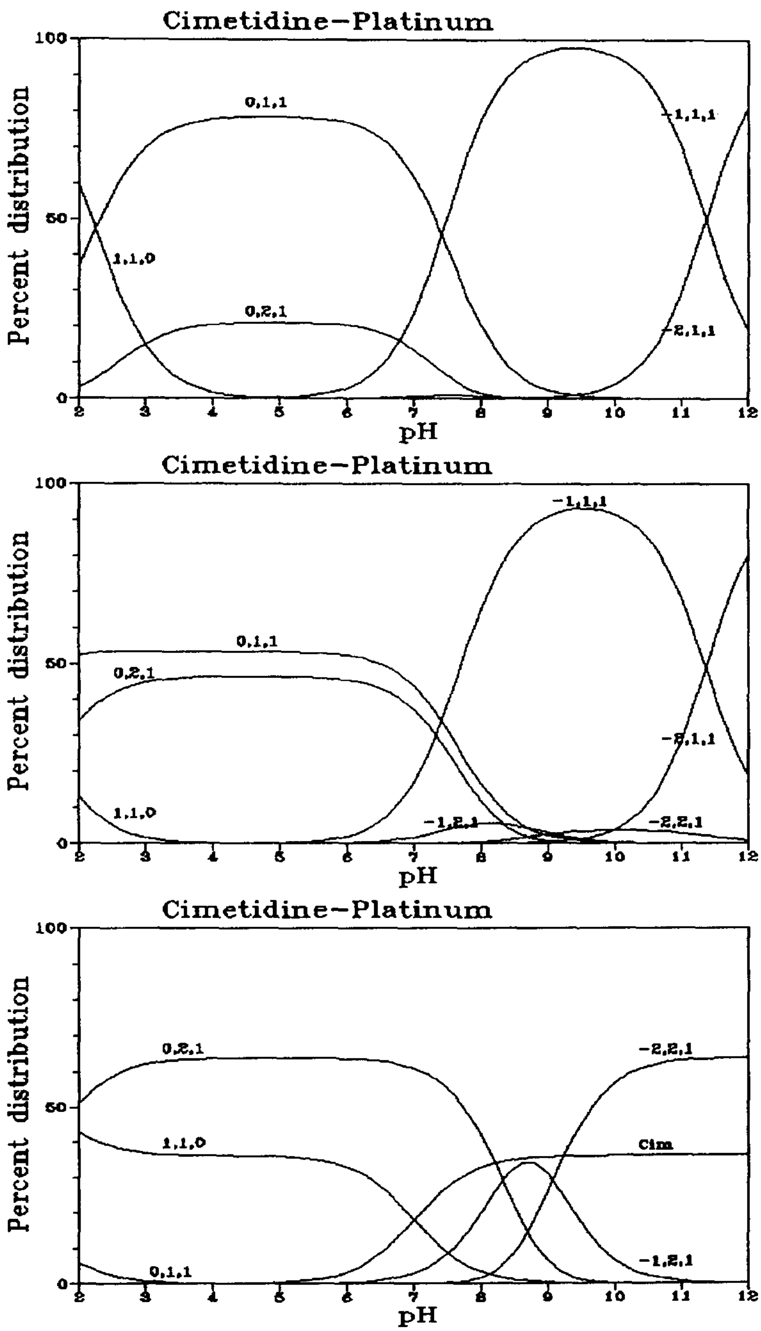


Fig. 4. Distribution curves of cimetidine–platinum species as a function of pH for (A) [Cim] = 0.55×10^{-4} M–[Pt^{II}] = 1.1×10^{-4} M, (B) [Cim] = 2.0×10^{-3} M–[Pt^{II}] = 2.0×10^{-3} M and (C) [Cim] = 7.9×10^{-3} M–[Pt^{II}] = 2.5×10^{-3} M and distribution curves of cimetidine–palladium species as a function of pH for (D) [Cim] = 9.1×10^{-3} M and [Pd^{II}] = 2.8×10^{-3} M.

(D)

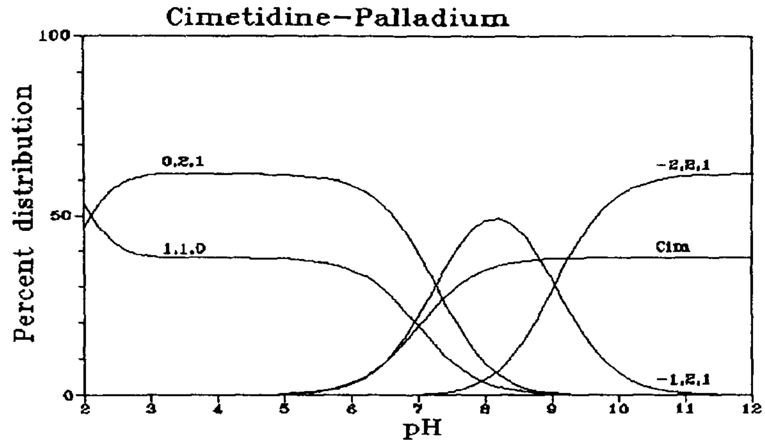


Fig. 4—*continued*.

(A)

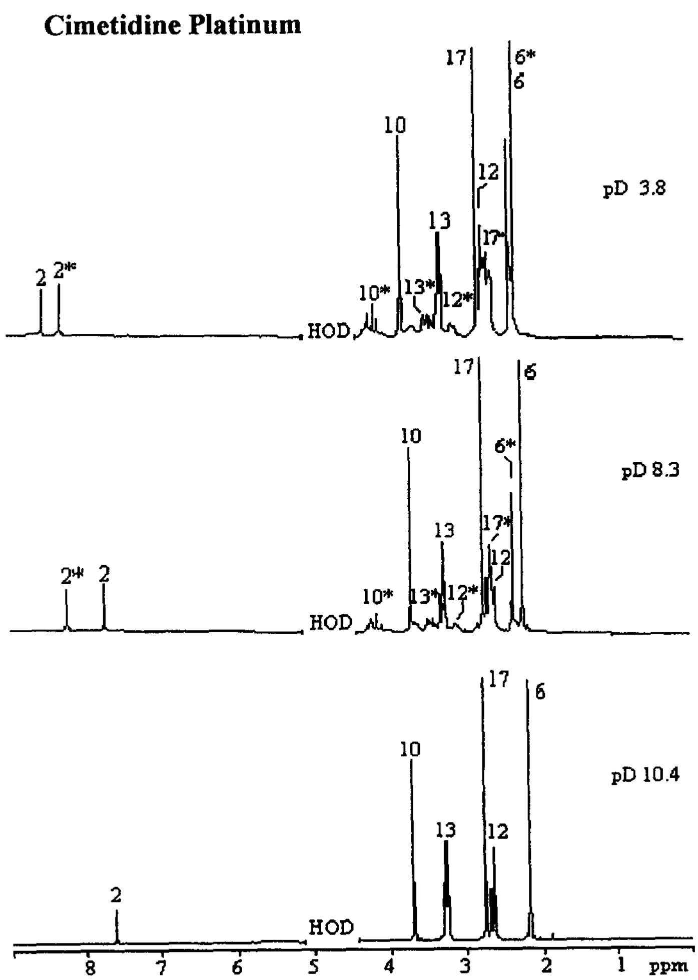


Fig. 5. ^1H NMR spectra of (A) [Cim] = 7.9×10^{-3} M in presence of [Pt^{II}] = 2.5×10^{-3} M at different pD values, (B) [Cim] = 9.1×10^{-3} M in presence of [Pd^{II}] = 2.8×10^{-3} M at different pD values. The assignments with * refers to complexed cimetidine.

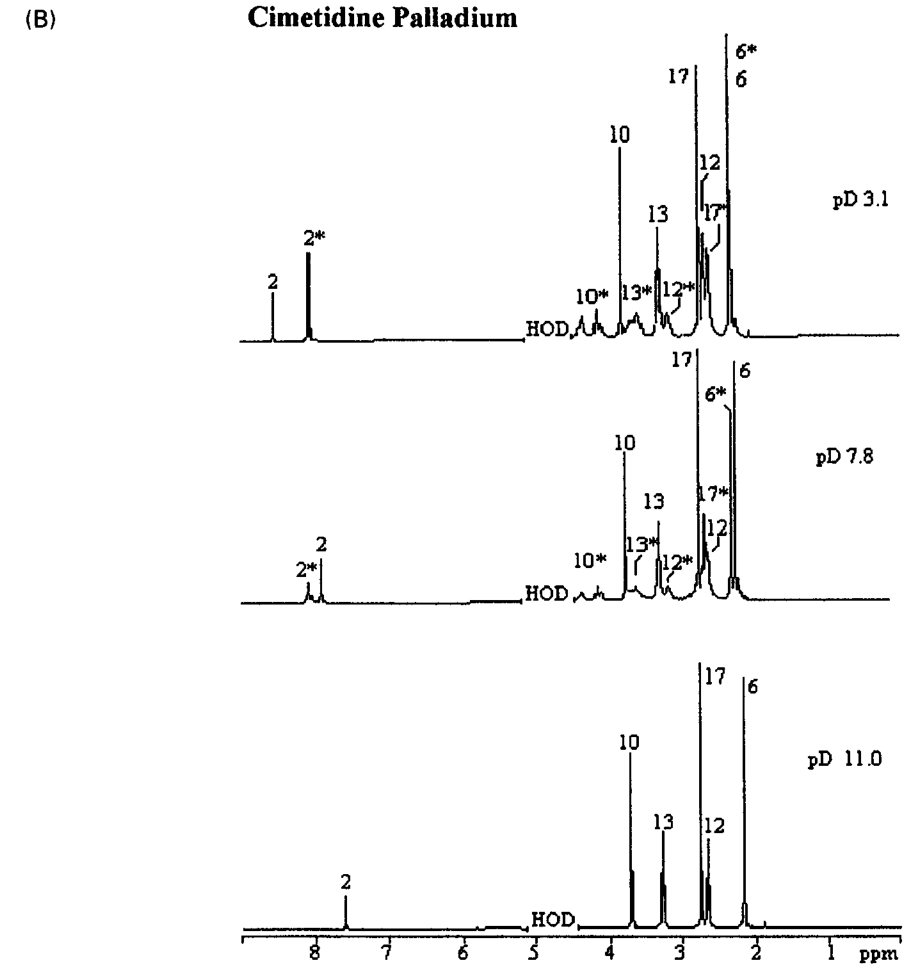


Fig. 5—*continued.*

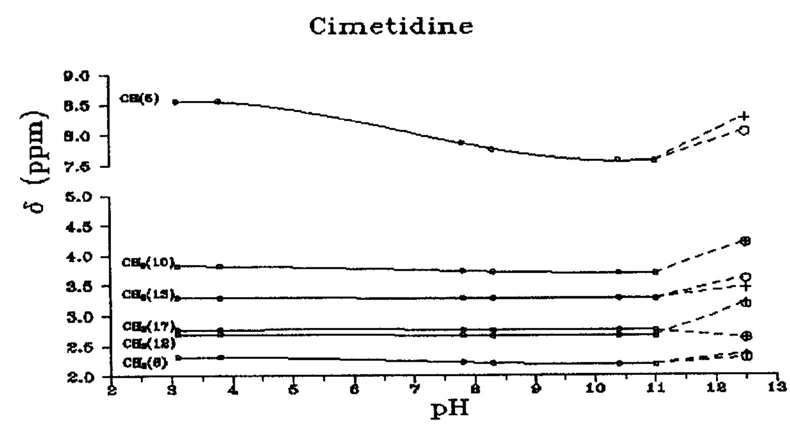


Fig. 6. The ^{1}H NMR chemical shifts of pure cimetidine are reported as a function of pD. The right side of figure shows the chemical shifts of the 1 : 2 complexed forms with [o] Pd^{2+} and [+] Pt^{2+}.

al.;[16] the spectra in Fig. 8 gives evidence of the following:

(i) the remarkable shift of $CH_3(8)$ and $CH_3(9)$ as well as $CH_2(6)$, CH(4) and $CH_2(10)$ observed from pD = 9 to pD = 5 is ascribed to the protonation of N(7) at pK = 8.2.[26] These signals are considered as a mean between the signals of E and Z isomers in fast exchange on an NMR time scale.

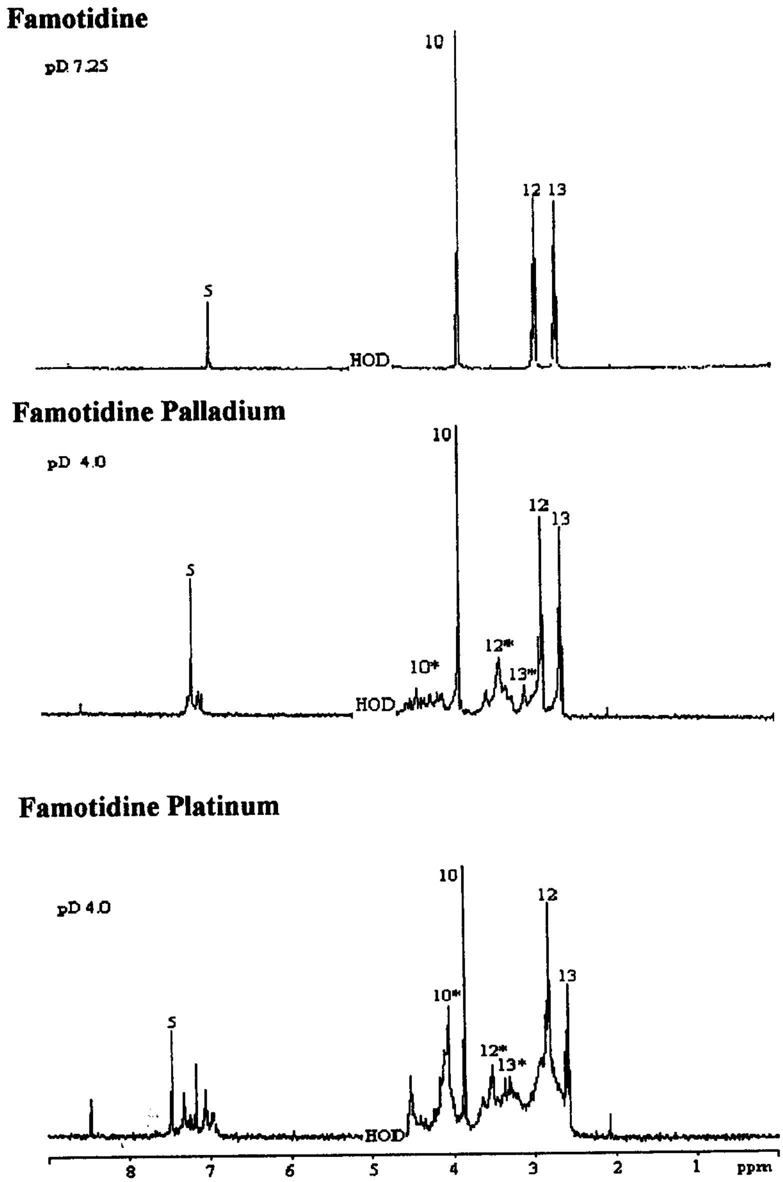
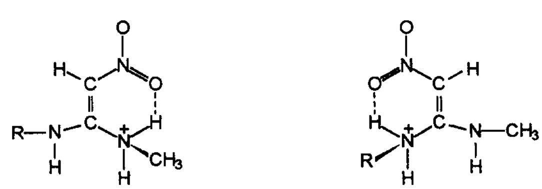


Fig. 7. ^1H NMR spectra of (upper) [Fam] = 3.9×10^{-3} M, (medium) [Fam] = 3.8×10^{-3} M in presence of [Pd^{II}] = 1.3×10^{-3} M and (lower) [Fam] = 4.1×10^{-3} M in presence of [Pt^{II}] = 1.3×10^{-3} M. The assignments with * refers to complexed famotidine.

E Z

(ii) at pD < 3 two sets of signals appear other than those observed at higher pD values, ascribed to three different species in slow exchange, due to the diprotonated A and B isomers (protonated on N(7) and also on N(16) or N(14) respectively) in slow exchange between themselves and with the monoprotonated form.



A B

(iii) at pD = 1.2 only the A and B species are present. Intramolecular hydrogen bonding

Ranitidine

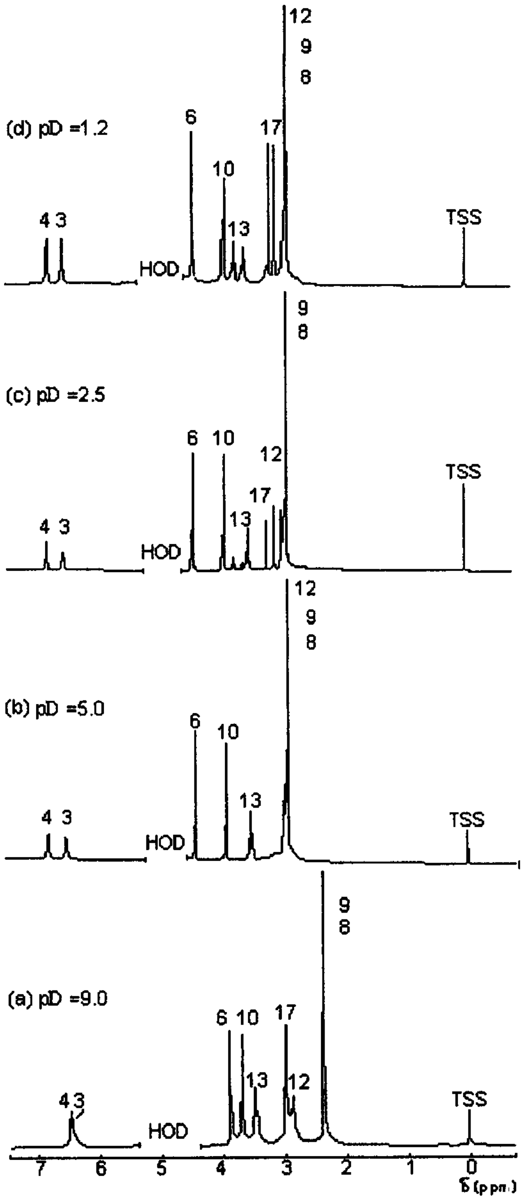


Fig. 8. The ^{1}H NMR spectra of pure ranitidine at various pD taken from Ref. 16.

in both configurations explains the slow rotation around the C(15)—C(18) bond.

From the spectra of ranitidine, observed in the presence of Pt^{II} in a 1 : 3 metal–ligand ratio at various pD values, and reported in Fig. 9(A), some considerations can be made:

(i) as with previous ligands new signals appear indicative of a slow exchange between free and bonded ranitidine at all pD values;

(ii) from a contemporaneous observation of ranitidine spectra with added Pt^{II} from pD 2.1 to 9.7 (Fig. 9(A)), and the results by Geraldes[16] (Fig. 8), it is clear that the signals CH(3), $CH_2(10)$, $CH_2(12)$, $CH_2(13)$ do not vary with pD while the protonation on N(7) affects $CH_2(6)$, CH(4) and the equivalent $CH_3(8)$ and $CH_3(9)$ signals. In our opinion the assignments by Geraldes at pD = 9.0 are to be reversed as far as regards CH(3)—CH(4) and $CH_2(10)$—$CH_2(6)$. Therefore N(7) protonation does not affect the opposite lateral chain;

(iii) platinum complexation at pD = 2.1 affects the CH(4) and CH(3) chemical shifts which, together with $CH_2(10)$ and $CH_2(6)$ are downfield shifted. As pD increases these signals as well as those of $CH_3(8)$ and $CH_3(9)$ show a sensible shift to higher fields;

(iv) a dramatic highfield shift is observed at pD = 9.7, associated with the shifts due to the N(7) protonation in free ranitidine.

As regards platinum complexation with ranitidine we suggest a bonding at very acidic pD only by the oxygen atom in the heterocyclic ring. This bonding transmits an inductive effect on the vicinal $CH_2(6)$ and $CH_2(10)$ which produces the observed downfield shift. As pD is raised a deprotonation takes place on water molecules bound to Pt^{II} forming hydroxo-complexes. This is why the highfield shift of $CH_2(6)$, $CH_2(10)$, CH(4) and CH(3) with pD occurs. Complex formation does not greatly influence the deprotonation on N(7), which begins at pD = 6.6 [see $CH_3(8)$ and $CH_3(9)$ signals]. At any rate this deprotonation produces a highfield shift of the same amount in complexed and free ranitidine. Two separate signals for $CH_3(8)$ and $CH_3(9)$ in complexed ranitidine at pD = 9.7 are to be pointed out. Presumably steric requirements make these two groups distinct on complexation. On the other hand $CH_2(6)$ appears as a single line. We are, therefore, inclined to rule out complexation by N(7), also on the basis of the poor p*K* lowering of N(7) deprotonation on complexation.

Ranitidine behaves analogously with palladium: two spectra at pD = 1.75 and 8.15 are reported in Fig. 9(B). These remarks are in line with the potentiometric findings. While the general scheme of complexation is very similar to that of cimetidine, and also the first deprotonation takes place at similar values, the second is at p*K* 8.75 and 8.48 respectively for 1 : 1 and 1 : 2 platinum complexes and 9.29 for the 1 : 1 palladium complex. Therefore the mechanism proposed on the basis of NMR evidence

(A)

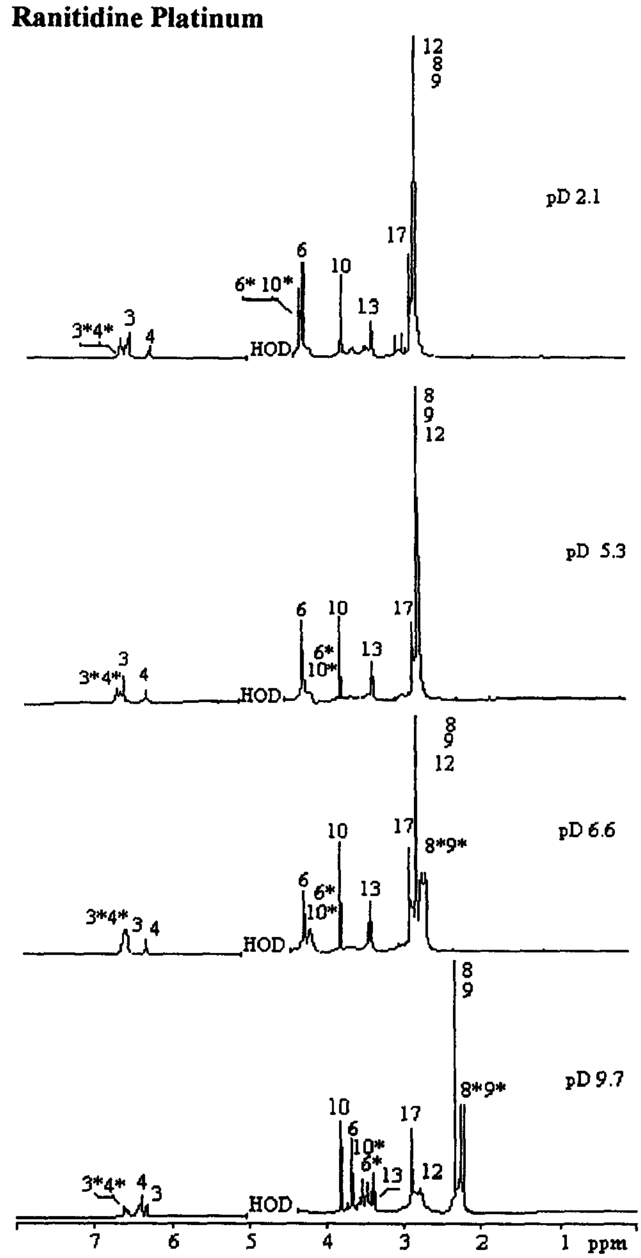


Fig. 9. (A) ^{1}H NMR spectra of [Ran] = 8.2×10^{-3} M in presence of [Pt^{II}] = 2.5×10^{-3} M at different pD values. (B) ^{1}H NMR spectra of [Ran] = 7.9×10^{-3} M in presence of [Pd^{II}] = 2.8×10^{-3} M at different pD values. The assignments with * refers to complexed ranitidine.

is supported. In contrast with cimetidine the second deprotonation is to be attributed to the N(7) atom and not to hydroxo-complex formation.

The very different behaviour of ranitidine with respect to cimetidine and famotidine can be attributed to the oxygen ring atom instead of a nitrogen atom, and is supported also by the preferred conformation of ranitidine in DMSO reported by Valensin *et al.*[17] in which oxygen and sulphur atoms in opposition cannot chelate metal ions.

To sum up, by using these different techniques it has been possible to establish the solution equilibria of the six systems in quantitative terms, and observe behaviours peculiar to each ligand.

(B) **Ranitidine Palladium**

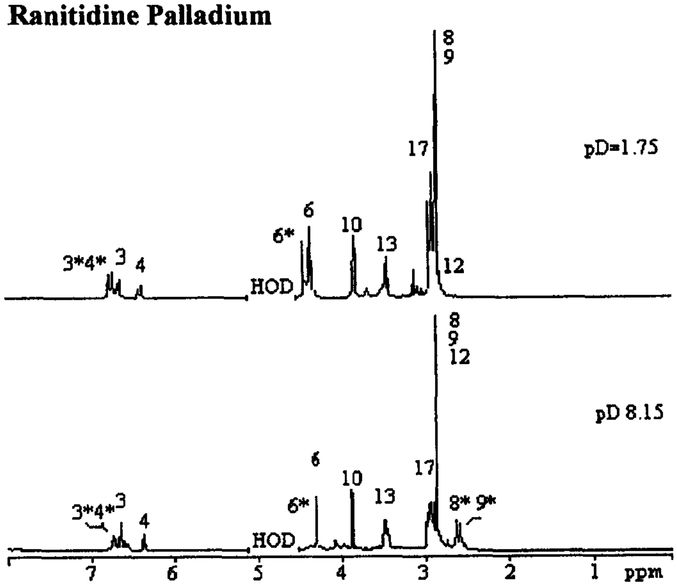


Fig. 9—*continued*.

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