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Study of the reactions of cisplatin with ranitidine and nizatidine by means of ^{1}H NMR spectroscopy in D_2O

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Abstract The reactions of cisplatin with nizatidine and ranitidine were studied in D_2O at *pD* 7.4 and 298 K by means of ^{1}H NMR spectroscopy. The second order rate constants, k_2, for the reaction of cisplatin with nizatidine is $(2.71 \pm 0.11) \times 10^{-4}\, M^{-1}\, s^{-1}$, and for the reaction with ranitidine $(6.72 \pm 0.17) \times 10^{-4}\, M^{-1}\, s^{-1}$. The reactions of nizatidine and ranitidine were also studied with other Pd(II) and Pt(II) complexes. The set of the complexes was selected because of their difference in reactivity, steric hindrance, and binding properties.

Keywords Cisplatin; Ranitidine; Nizatidine; NMR spectroscopy.

Introduction

Ranitidine, {2-[5-(dimethylaminomethyl)furfurylthio]ethyl}-*N*′-methyl-2-nitro-1,1-ethenediamine, and nizatidine, [2-[[2-[(dimethylaminomethyl)-1,3-thiazol-4-yl]methylsulfanyl]ethyl]-*N*′-methyl-2-nitroethane-1,1-diamine], are widely used in medicine as the most effective antiulcer agents [1, 3]. It is generally accepted that these molecules are effective as an H_2-receptor antagonist in the treatment of gastric and duodenal ulcers. Nizatidine and ranitidine each contain the *N*-ethyl-*N*′-methylnitroethenediamine moiety. This functionality has been shown to undergo rapid tautomerization in solution. The crystal structure of nizatidine and many of its spectroscopic properties have been reported [4].

Cimetidine, ranitidine, and nizatidine could act as effective ligands towards metal ions with very strong coordination ability. Moreover, these molecules could act as bidentate ligands, forming five membered rings through the imidazolic nitrogen and the sulfur atom, or as tridentate ligands by coordination through the imidazolic nitrogen, the sulfur atom, and the nitrile group. The composite structure of these ligands induces an equilibrium between different conformations, that are well characterized by IR, X-ray [4, 5], and NMR spectroscopy [6, 7]. The most extensively studied ligand is cimetidine. Probably this could be ascribed to the fact that cimetidine was the first one introduced on the market. The coordination properties of cimetidine, famotidine, and ranitidine towards Pt(II) ions have been studied by different methods [8]. Also, recently a very nice paper on the interactions of Pd(II) and Pt(II) with cimetidine has been published [8]. The crystal structure of a Pt-cimetidine compound shows two molecules of cimetidine coordinated to the metal trough thioether sulfur and imidazolic nitrogen, whereas spectroscopic studies in solution for Pd-cimetidine reveal that the ratio of the metal to cimetidine

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is 1:1 with identical coordination environments [8]. It has also been published that $PdCl_2$ reacts with famotidine, nizatidine, and ranitidine and form yellow colored water soluble complexes. Moreover, $PdCl_2$ has been proposed as suitable analytical reagent for the determination of nizatidine in pharmaceutical analyses [9, 10].

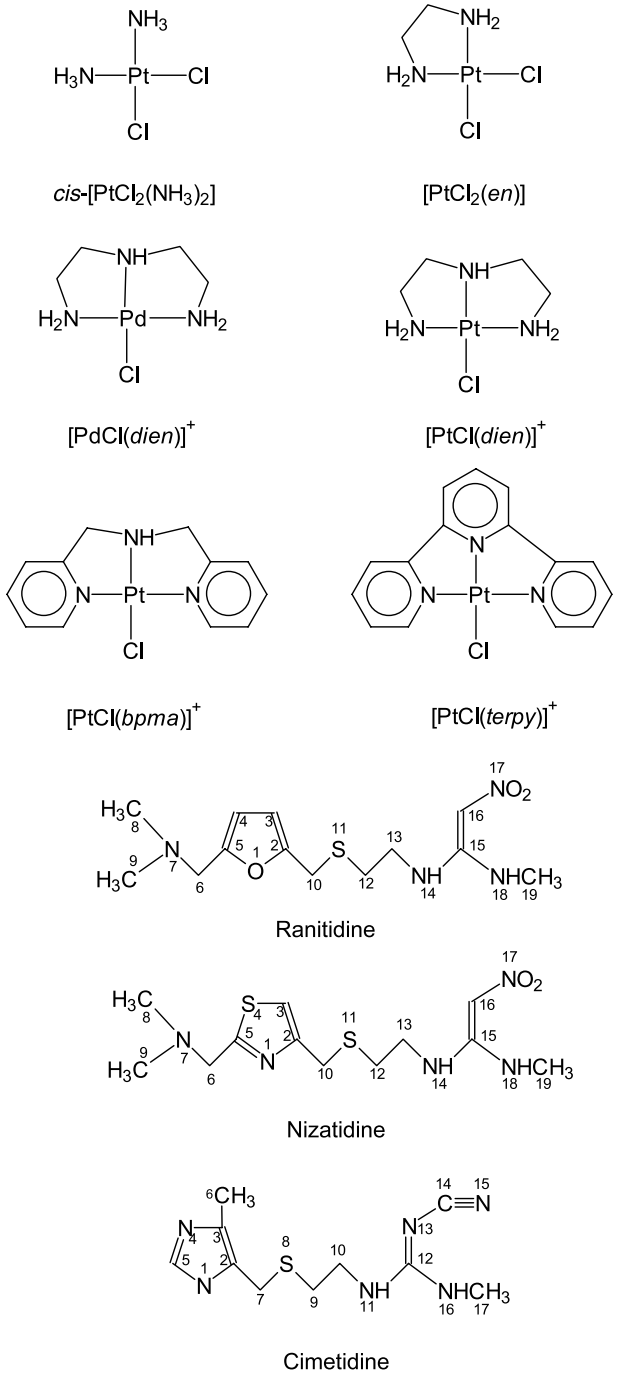

Fig. 1 Structures of the investigated complexes and ligands along with the adopted abbreviations

Our work has been focused on the interactions between Pd(II) and Pt(II) complexes with different sulfur- and nitrogen-bonding ligands including biomolecules. With the objective to extend our earlier work [11–15] and to gain further insight into structure-reactivity relationships, we have now performed and we report here a detailed study on the complex-formation of Pd(II) and Pt(II) with ranitidine and nizatidine. The reactions were studied in aqueous solutions by means of ^{1}H NMR techniques. It was envisaged that this study could throw more light on the interactions of platinum anti-tumor complexes with nitrogen- and sulfur-donor nucleophiles. Figure 1 shows the structures of the investigated complexes and ligands.

Results and discussion

^{1}H NMR spectroscopy was used to investigate the kinetics of the reactions of cisplatin, *cis*-[$PtCl_2$-$(NH_3)_2$], with nizatidine and ranitidine (1:1, molar ratio) in aqueous solution at *pD* 7.4 and 298 K. In both reactions there is only one product and the yield is almost 100%. The ligands are coordinated bidentate *via* the heteroatom in the ring (*O*1 in ranitidine and *N*1 in nizatidine) and *S*11 from the chain. Second-order rate constants, k_2, for the first coordination were obtained from Eq. (1).

$$k_2 t = x/a_0(a_0 - x) \qquad (1)$$

where x is the amount of the product and a_0 the initial concentration of the complex [16]. Calculations were performed by relative integration (estimated error is 5%) of suitable proton signals, H3, H6, and H10 for nizatidine, and H3, H4, H6, and H10 for ranitidine (see Fig. 1) of both reaction products and starting materials during the reaction. A plot of the right hand side of Eq. (1) *versus* reaction time results in a straight line passing through the origin, as shown as an example for the reaction of cisplatin and ranitidine in Fig. 2. The value of k_2 was obtained from the slope of this line. The second order rate constant, k_2, for the reaction of cisplatin with nizatidine, at *pD* 7.4 and 298 K, is $(2.71 \pm 0.11) \times 10^{-4}\, M^{-1}\, s^{-1}$, and k_2 for cisplatin with ranitidine, at *pD* 7.4 and 298 K, is $(6.72 \pm 0.17) \times 10^{-4}\, M^{-1}\, s^{-1}$.

Ranitidine is a better nucleophile than nizatidine. On the other hand, ranitidine and nizatidine cannot be compared with respect to their nucleophilicity

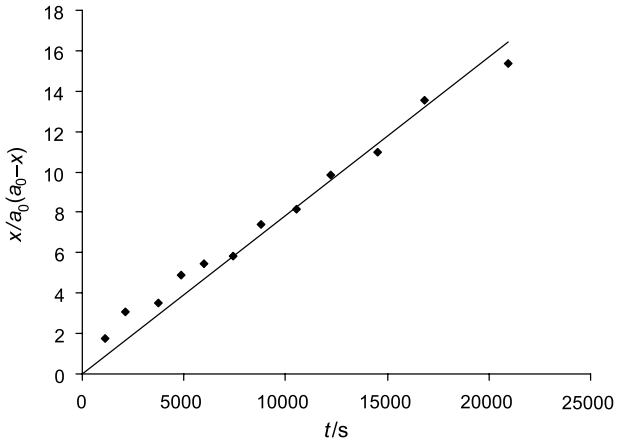

Fig. 2 Determination of second-order rate constants for the reaction of cisplatin (30 m*M*) with ranitidine (30 m*M*) at *pD* 7.4 and 298 K

with the other sulfur containing ligands, such as glutathione, L-methionine, or L-cysteine in the reactions with cisplatin [17, 18]. The steric hindrance cannot be the main reason for the lower nucleophilicity of ranitidine and nizatidine, but could be explained by coordination over oxygen from the heterocyclic ring in the case of ranitidine, and by coordination *via* nitrogen from the heterocyclic ring in the case of nizatidine.

The effect of cimetidine, which is of very similar nucleophilicity as nizatidine and ranitidine on patients treated with cisplatin has been published [17, 18]. However, the results are in disagreement. In one paper [19] it has been concluded that the administration of cisplatin together with cimetidine and verapamil prevents nephrotoxicity. In the other one [20], it has been found that the administration of cisplatin with cimetidine increased nephrotoxicity and decreased antitumor activity in mice.

Figure 3 shows the time course of the reaction between cisplatin and nizatidine. The peak for the free nizatidine H3 is at $\delta = 7.42$ ppm and for the coordinated nizatidine the peak H3* is at $\delta =$ 7.76 ppm. However, during the reaction the peak at $\delta = 7.76$ ppm, which corresponds to the product, increased in intensity, while the peak for the free nizatidine ($\delta = 7.42$ ppm) decreased in intensity.

The ^{1}H NMR spectrum for the reaction of cisplatin and ranitidine is shown in Fig. 4. The peaks for the free ranitidine are H3 at $\delta = 6.69$, H4 at 6.40, H6

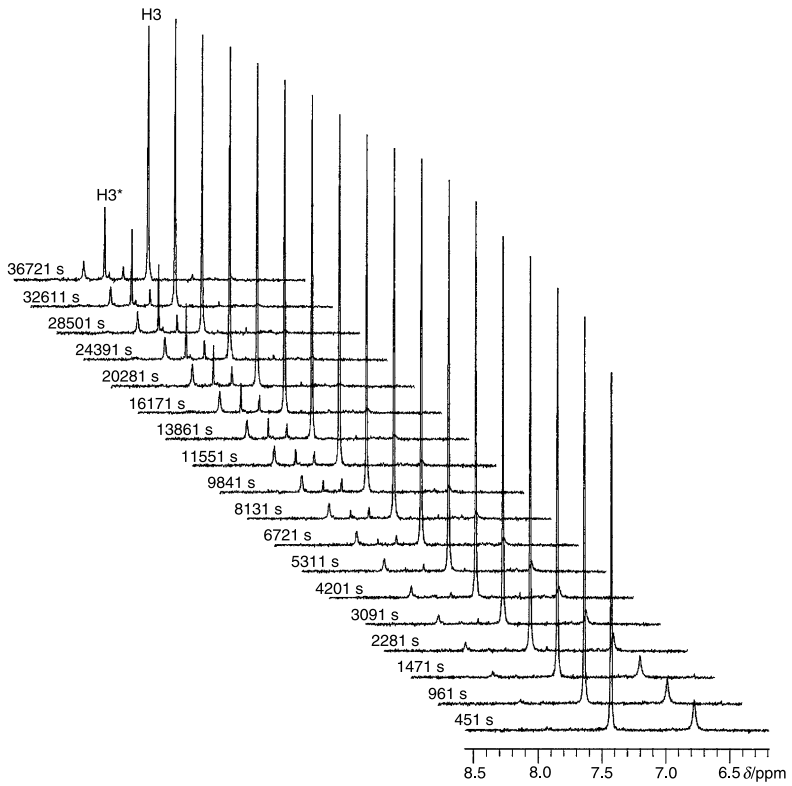

Fig. 3 ^{1}H NMR spectra of the reaction of cisplatin (30 m*M*) with nizatidine (30 m*M*) where H3 is the signal for the free nizatidine and H3* is the signal for the coordinated nizatidine

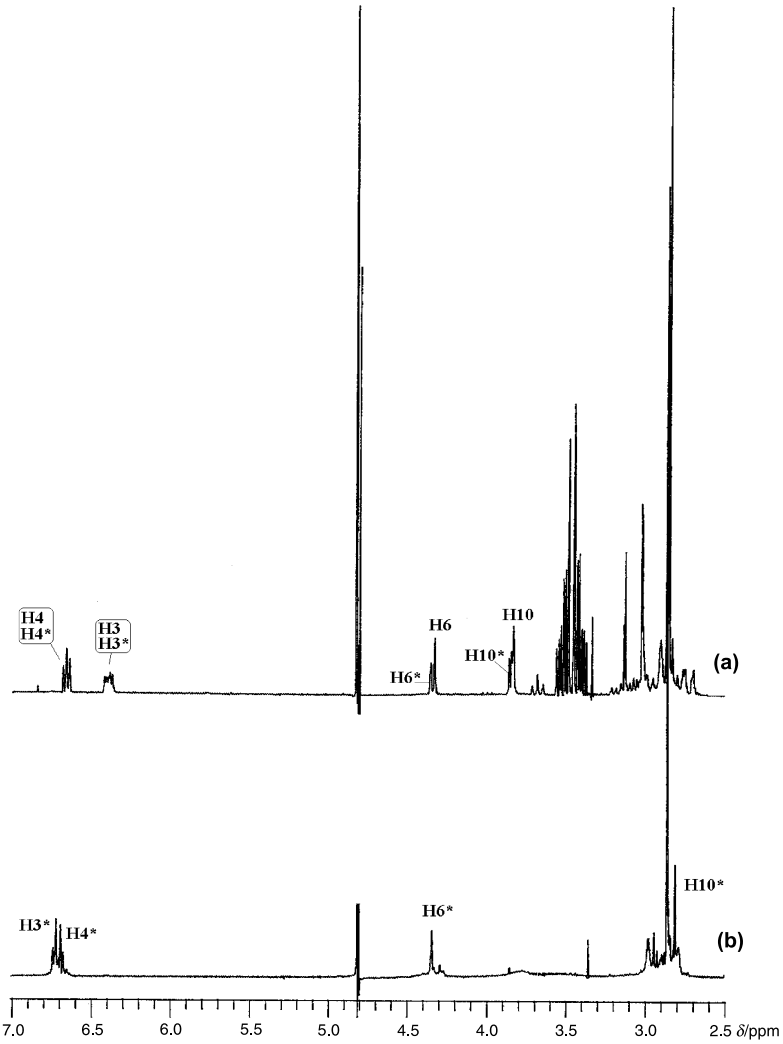

Fig. 4 ^{1}H NMR spectra of the reactions of [PdCl(*dien*)]$^{+}$ (**a**) and cisplatin (**b**) with ranitidine

Table 1 ^{1}H NMR chemical shifts/ppm of coordinated ligands at *pD* 7.4 and 298 K. The peaks for the free nizatidine are H3 at 7.61, H6, and H10 at 3.95, and for ranitidine H3 at 6.66, H4 at 6.38, H6 at 4.34, and H10 at 3.84 ppm

Complex	Nizatidine			Ranitidine			
	H3*	H6*	H10*	H3*	H4*	H6*	H10*
[PdCl(*dien*)]$^{+}$	s 7.64 s 7.76	s 3.97 s 3.98		d 6.68	d 6.40 d 6.42	s 4.36	s 3.85 s 3.88
[PtCl(*dien*)]$^{+}$	s 7.63 s 7.75	s 4.41 s 4.46	s 4.31 s 4.33	d 6.77	d 6.70	s 4.37 s 4.58	s 4.38 s 4.42
[PdCl(*terpy*)]$^{+}$	s 7.68 s 7.80	s 3.95 s 3.98		d 6.69	d 6.40	s 4.38	s 3.86
[PdCl(*bpma*)]$^{+}$	s 7.65	s 4.41 s 4.50	s 3.92	d 6.68	d 6.40 d 6.42	s 4.41 s 4.50	s 3.86
[PdCl$_2$(*en*)]	s 7.76 s 7.93	s 3.97 s 3.99		d 6.76	d 6.70	s 4.59	s 3.86

at 4.34, and H10 at 3.86 ppm, and the new peaks for the coordinated ranitidine are H3* at $\delta = 6.75$, H4* at 6.69, H6* at 4.36, and H10* at 2.81 ppm.

The reactions of nizatidine and ranitidine have been also studied with the other Pd(II) and Pt(II) complexes. The set of the complexes was selected because of their difference in reactivity, steric hindrance, and binding properties (structures are shown in Fig. 1). The ^{1}H NMR spectra of some studied Pd(II) and Pt(II) complexes are shown in Fig. 4.

In the reactions with the other monofunctional Pd(II) and Pt(II) complexes, such as $[PdCl(dien)]^+$, $[PdCl(terpy)]^+$, $[PdCl(Me_4dien)]^+$, $[PdCl(bpma)]^+$, and $[PtCl(dien)]^+$ with ranitidine and nizatidine, there were two reaction paths. In one product the ligands coordinated *via* heteroatom from the ring (*O*1 from ranitidine and *N*1 from nizatidine) and in the other product the ligands coordinated *via* *S*11 from the chain (thioether sulfur). In the reactions of $[PdCl_2(en)]$ with the two nucleophiles the yields were very small and hydrolyses of the ligands were observed. The chemical shifts for the complexes and the coordinated ligands are presented in Table 1.

Only with the $[PdCl(Me_4dien)]^+$ complex there occurred no reactions, which could be explained by steric hindrance of the complex and the nucleophiles as well.

Conclusion

This study demonstrated that ranitidine and nizatidine coordinate to cisplatin. The reactions were slow, but ranitidine is a better nucleophile than nizatidine. The lower nucleophilicity of these ligands could be explained by coordination over oxygen from the heterocyclic ring in the case of ranitidine, and by coordination *via* nitrogen from the heterocyclic ring in the case of nizatidine.

Experimental

The complexes, $[PdCl(dien)]Cl$, $[PdCl(bpma)]Cl \cdot H_2O$, $[PdCl(terpy)]Cl \cdot 3H_2O$, $[PdCl_2(en)]$, and $[PtCl(dien)]Cl$, (where *dien* is diethylenetriamine, *bpma* is bis(2-pyridylmethyl)amine, *terpy* is 2,2′:6′,2″-terpyridine, and *en* is ethylendiamine) were prepared according to a literature method [21–23]. Chemical analysis, UV-Vis, and ^{1}H NMR spectral data were in good agreement with those obtained in previous preparations. Cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, was purchased from Aldrich. The nucleophiles, ranitidine and nizatidine, were obtained from Acros Organics, and 99.9% D_2O (Deutero GmbH) are commercially available and used as received. All other chemicals were of the highest purity commercially available and were used without further purification.

The NMR spectra were acquired on a Varian Gemini-200 spectrometer. The measurements were performed with a commercial 5 mm Bruker broadband probe. All chemical shifts are referenced to *TSP* (trimethylsilylpropionic acid) in D_2O.

^{1}H NMR measurements of the reaction of the complexes with nizatidine or ranitidine were done on a freshly prepared sample of the reactants. A 60 m*M* solution of the complex was prepared in 300 μm^3 D_2O approximately 10 min prior to the start of the kinetic experiment and put in an ultrasonic bath until complete dissolution (2–5 min). 300 μm^3 of a solution of 60 m*M* ranitidine or nizatidine in D_2O was added to the solution of the complex to initiate the reaction. NMR spectra were recorded at 298 K over a period of several weeks until completion of the reaction was reached.

For the kinetic measurements the reactions of *cis*-$[PtCl_2(NH_3)_2]$ (30 m*M*) and nizatidine or ranitidine (in equimolar amount) were followed at 298 K and at *pH* 7.4. Spectra were recorded subsequently every 15 min automatically. The *pH* was measured with an inoLab SenTix® Mic pH Microelectrode. Meter readings were corrected for the deuterium isotope effect by adding 0.4 units to the display readout ($pD = pH + 0.4$). The *pD* was adjusted with 0.01–0.05 *M* solutions of NaOD and DCl. No buffer was used to prevent increased activation of the complexes due to coordination of phosphate [24], or interfering signals in the observed peak area. All *pD* measurements were performed at 298 K. The *pH* meter was calibrated with Fischer-certified buffer solutions of *pH* 4.00, 7.00, and 11.00.

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References

1. Canellin CR, Parson ME (1982) In: Pharmacology of Histamine Receptors. Wright, Bristol, UK
2. Laniz MD, Wozniak TJ (1990) Am J Hosp Pharm 47:2716
3. Carlucci G (1990) J Chromatogr 525:490
4. Stephenson GA, Wozniak TJ, Stowell JG, Byrn SR (1996) J Mol Struct 380:93
5. Hegedus B, Bod P, Harsanyi K, Peter I, Kalman A, Parkaniyi L (1983) J Pharm Biomed Anal 7:563
6. Geraldes CFGC, Gil VMS, Teixeira MHFS, Texiera F (1987) Magn Reson Chem 25:203
7. Gaggelli E, Marchettini N, Sega A, Valensin G (1988) Magn Reson Chem 26:1041
8. Crisponi G, Cristiani F, Nurchi VM, Silvagni R, Ganada ML, Lubinu G, Maldini L, Panzanelli A (1995) Polyhedron 14:1517

9. Onoa GB, Moreno V, Freisinger E, Lippert B (2002) J Inorg Biochem 89:237
10. Minić D, Petković J, Korićanac Y, Jovanović T (1996) J Pharm Biomed Anal 14:1355
11. Soldatović T, Bugarčić ŽD (2005) J Inorg Bioch 99:1472
12. Bugarčić ŽD, Soldatović T, Jelić R, Algueró B, Grandas A (2004) Dalton Trans:3869
13. Bugarčić ŽD, Heinemann F, van Eldik R (2004) Dalton Trans:279
14. Jaganyi D, Tiba F, Munro OQ, Petrović B, Bugarčić ŽD (2006) Dalton Trans:2943
15. Bugarčić ŽD, Nandibewoor ST, Hamza MS, Heinemann F, van Eldik R (2006) Dalton Trans:2984
16. Laidler KJ (1987) Chemical Kinetics, 3rd edn. Harper and Row, New York, p 22
17. Jerremalm E, Wallin I, Yachnin J, Ehresson H (2006) Eu J Pharm Sci 28:278
18. Petrović D, Petrović B, Bugarčić ZM, Bugarčić ŽD (2007) Bioorg Med Chem 15:4203
19. Sleijfer DT, Offerman JJG, Mudler NH, Verweij M, Van der Hem GK, Schrafford H, Meijer S (1987) Cancer 60:2823
20. Dorr RT, Soble MJ (1988) Cancer Res Clin Oncol 114:1
21. Annibale G, Brandolisio M, Pitteri B (1995) Polyhedron 14:451
22. Karkalić R, Bugarčić ŽD (2000) Monatsh Chem 131:819
23. Bugarčić ŽD, Liehr G, van Eldik R (2002) J Chem Soc Dalton Trans:951
24. Frey U, Ranford JD, Sadler PJ (1993) Inorg Chem 32:1333