Asian Journal of Chemistry Vol. 15, No. 1 (2003), 19–24

Novel Cu(II) Complexes with Ranitidine and Nizatidine

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Two new complexes of Cu(II) with drugs ranitidine (N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl] methyl] thio]ethyl]-N′-methyl-2-nitro-1,1-ethene diamine) and nizatidine (N-[2-[[[2-(dimethyl-amino) methyl]-4-thiazolyl] methyl] thio] ethyl]-N′-methyl-2-nitro-1,1-ethenediamine) of the general formula $[Cu(drug)_2](ClO_4)_2$ were prepared. Elemental analysis, conductometric and magnetic measurements, electronic and IR spectroscopy have been employed to characterize them. The molar conductivity values in ethanol show a behaviour of 1 : 2 electrolytes. IR studies clearly indicate that both the drugs are coordinated to copper ion in the same way *via* the nitro group and the methyl-amino nitrogen atom.

Key words: Copper(II) complexes; Ranitidine; Nizatidine.

INTRODUCTION

Ranitidine, N-[2-[[[5-[dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine **(1)** and nizatidine, N-[2-[[[2-(dimethyl-amino)methyl]-4-thiazolyl]-N′-methyl-2-nitro-1,1-ethenediamine **(2)** **(Scheme-1)** are molecules largely used in medicine[1–5] for their safeguarding action on the stomach walls in ulcer disease, due to a histamine H_2 receptor blocking effect. It can be stated that, to date, surprisingly little is known about the complexation in spite of the fact that the complexes could affect the activity of drugs to a remarkable degree[6]. One single study on ranitidine[7], none at all on nizatidine and some search of the literature revealed, just as for their complexes in solution[8,9]. These molecules, however, should act as effective ligands towards metal ions, each being composed of several groups provided with a very strong coordinating ability, linked to their common structure —CH_2—S—CH_2—CH_2—. A key feature of both structures is N,N′-dialkyl-2-nitro-1,1-ethenediamine moiety[10], but they differ in an essential point. Instead of the furan ring which makes the core of ranitidine **(1)**, nizatidine **(2)** contains thiazolyl ring structure **(Scheme-1)**. To make a clear distinction between the effects of the two moieties, we embarked on the present study to synthesize Cu(II) complexes with ranitidine and nizatidine and determineed the mode of the ligand coordination. In view of the great biological interest in these two drugs as well as copper, their coordination should have significant implications.

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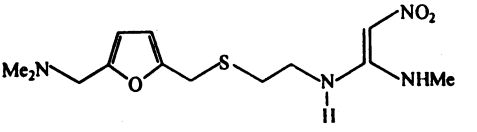
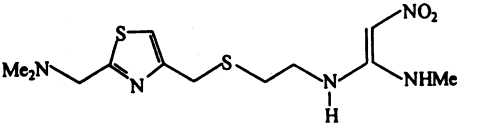


Ranitidine

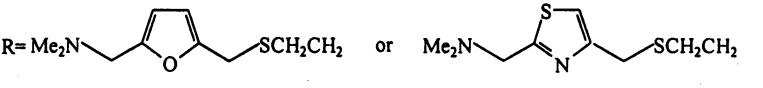


Nizatidine

Enamine

Nitric acid

Imine



SCHEME-I

EXPERIMENTAL

Ranitidine hydrochloride (CAS No. 66 357–59–3) obtained from Zdravlje (Leskovac, Yugoslavia) and nizatidine (CAS No. 76 963–41–2) supplied from ICN Galenika (Belgrade, Yugoslavia) were used without further purification. The other chemicals were of reagent grade quality.

Syntheses of the $[Cu_2(drug)_2](ClO_4)_2$ complexes: Into a solution containing ranitidine hydrochloride (705 mg, 2 mmol) or nizatidine (660 mg, 2 mmol) dissolved in water (20 cm^3), gradually was added aqueous solution (20 cm^3) of $Cu(ClO_4)_2 \cdot 6H_2O$ during 1 h with continuous stirring and heating on a water bath at 50°C. The entire matrix was refluxed for 4 h using air condenser. The filtrate was concentrated in a vacuum evaporator to 10 cm^3. On cooling to room

temperature crude products were precipitated. After recrystallization from water the corresponding complexes separated out which were filtered off and washed well with water and dried over $CaCl_2$. **(I)** $[Cu(ranit)_2](ClO_4)_2$, dark green. Yield: 106 mg (82%). Anal., Calcd. for $CuC_{26}H_{46}N_8O_{14}S_2Cl_3$ (%): C, 35.06; H, 5.17; N, 12.68. Found: C, 35.43; H, 5.05; N, 12.82. **(II)** $[Cu(nizat)_2](ClO_4)_2$, light brown. Yield: 96 mg (87%). Anal., Calcd. for $CuC_{24}H_{42}N_{10}O_{12}S_4Cl_2$ (%): C, 31.14; H, 4.54; N, 15.14. Found: C, 31.51; H, 4.43; N, 15.21.

Elemental analyses (C, H, N) were performed by standard micromethods at the Department of Instrumental Analysis of the Faculty of Chemistry, Belgrade. Electronic spectra of the aqueous solution (1×10^{-3} mol dm^{-3}) were recorded on a GBC UV/VIS 911A spectrophotometer. IR spectra in the 4000–400 cm^{-1} range were measured on a Perkin-Elmer 317 25 X FTIR spectrophotometer, using the KBr discs. Molar conductivity of ethanol solutions (1×10^{-3} mol dm^{-3}) was measured at 20°C by a Jenway-4009 conductometer. Magnetic susceptibility was determined at room temperature (25 ± 2°C) using an MSB-MKI balance. Data were corrected for diamagnetic susceptibilities.

RESULTS AND DISCUSSION

The complexes were obtained by mixing $Cu(ClO_4)_2 \cdot 6H_2O$ and the respective drugs in a 1 : 2 molar ratio. Analytical results confirmed the composition proposed. The compounds are air-stable, coloured and appear to be powdered, soluble in water and in common organic solvents. The molar conductivity values obtained for the 1×10^{-3} mol dm^{-3} solution of **(I)** and **(II)** complexes in ethanol [λ_M = 140 and 160 Ω^{-1} cm^{-1} mol^{-1}, respectively] fall into the range anticipated for 1 : 2 electrolytes[11]. The complexes possess magnetic moments ($\mu_{BM/Cu}$], which are [2.16 for **(I)** and 2.10 for **(II)**] shifted to the higher limit of experimentally observed values (1.73–2.20)[12].

Electronic absorption spectra

The absorbances at 625 (ε = 444) for **(I)** and 643 nm (ε = 331 mol^{-1} dm^3 cm^{-1}) for **(II)** can be related to d–d transitions[13]. The short wavelength maximum at 228 for **(I)** and 259 nm for **(II)** stems mainly from the heterocyclic ring chromophore, with the contribution from the 2-nitroethenediamine chromophore. The other main absorptions at 313 for **(I)** and 318 nm for **(II)** could be assigned as charge transfer bands probably from ligand to metal[12].

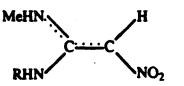
IR spectra

In Table-1 the pertinent IR data of the free and coordinated drugs are presented. A comparison of IR spectra of the complexes obtained with those of free ligands helps to distinguish their coordination mode. In principle, attention has been focused on a limited number of bands, which provide considerable structural significance in order to suggest the most probable manner of coordination.

High sensitivity of (at least) one of the stretching bands of the nitro group in the presence of the copper ion supports that coordination occurs at this group although it is regarded as a weak donor group to the copper atom. It is however well known that it can participate through a chelating effect[14], which seems to be operative also in binding 2-alkylamino-1-nitroethenic moieties. On the other hand, it is interesting

to note that atoms (or groups) such as sulfur, furan and thiazolyl ring, turned out to be less preferred[8]. As it can be seen, marked change occurs for the values of ν_{asym} and ν_{sym}, which are lower than in the corresponding drugs. Such a shifting may occur when NO_2^- group takes part in hydrogen bond formation, or when oxygen atom participates in coordination[15]. Due to steric hindrance, NO_2^- group in complexes is less accessible for hydrogen bonding than in drugs. The complex (I) has a somewhat greater $\Delta\nu$ as well as ν_{asym} in comparison with the complex (II) which means that it has a slightly stronger Cu—O bond and a more asymmetrically bonded nitro group[15]. It also turned out that the marked change occurs for ν(N—CH_3) bonds of ranitidine and nizatidine (at 1415 and 1418 cm^{-1} respectively), which are shifted to lower frequencies (1400 and 1401 cm^{-1} for (1) and (2) respectively) (Table-1), when the methyl-amino nitrogen atom is coordinated. It indicates the formation of a strong highly covalent metal-nitrogen bond [8]. At this point of view, bands assigned to ν(N—C—C) at 1010 cm^{-1} for (I) and 1006 cm^{-1} for (II) reflect the partial double character. These bands in comparison with those of ranitidine and nizatidine (bands of which are at 1000 cm^{-1} and 998 cm^{-1}, respectively) are shifted to higher frequencies. This fact can be attributed to the electron releasing ability of this part of molecules which forces high electron density towards copper ion, *via* the π-system, producing greater double bond character in the N—C—C group. This higher conjugate effect indicates that the methyl-amino nitrogen atom is the second strong binding site for copper atom.

TABLE-1
CHARACTERISTIC IR FREQUENCIES (cm^{-1}) FOR THE DRUGS AND THEIR COPPER(II) COMPLEXES

Compound	NO_2					ν(N–CH_3)	ν(N–C–C)	Metal-drug	
	ν_{as}	ν_{sym}	$\Delta\nu$	ν(N–C)	ν(C–C)			ν(Cu–O)	ν(Cu–N)
Ranitidine	1380	1212	168	1635	1570	1415	1000	—	—
Complex (I)	1368	1155	213	1620	1555	1400	1010	425	477
Nizatidine	1377	1208	169	1630	1572	1418	998	—	—
Complex (II)	1365	1173	192	1624	1567	1401	1006	429	474

The coordination of the drugs is further substantiated in the far IR spectra (480–420 cm^{-1}) by the appearance of the medium-strong additional bands of ν(Cu—N) and ν(Cu—O) frequencies absent in the spectra of the free ligands.

Thus, these important features of the IR spectra provide a consistent picture that both the drugs act as bidentate ligands, as can be seen in Fig. 1. Unfortunately, single crystals of these complexes could not be obtained and IR spectra together with other data confirmed their most probable structures.

Structure

In theory, ranitidine and nizatidine, taking in account their common fragment, could exist in one of the three main tautomeric forms **(Scheme-1)**. In addition,

the enamine could exist as two geometrical isomers and the nitronic acid and imine forms could both exhibit further prototropic tautomerism within the amidine group as well as *syn-anti* isomerism about the C—N bonds[16–20]. NMR data[21] completely excluded imino form and showed that the nitroethene dialkylamine group exists virtually exclusively in the enediamine tautomeric form[16].

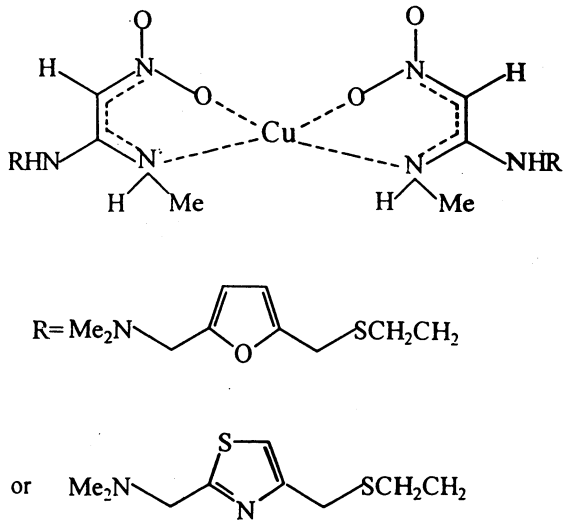


Fig. 1. Suggested Structure of the Complex Cation $[Cu(drug)_2]^{2+}$ [drug = ranitidine (**1**); drug = nizatidine (**2**)]

On the grounds of the results presented in this work, taking into account the aforementioned considerations, a very similar general scheme of complexation has been predicted for both compounds of the general formula $[Cu(drug)_2](ClO_4)_2$. Two strong binding sites in each drug are indicated,, the nitro group and the methyl-amino nitrogen atom, which in the same way contemporaneously bind the copper ion. The two drugs in both the complexes are coordinated forming two 6-membered rings. This is not surprisingm since this unusual structure (Fig. 1) is a consequence of the combination of the electronic and steric effects of the drugs. Namely, these unique stereoelectronic properties with a high degree of conjugation stabilize these two 6-membered rings quite well[8]. Regarding the steric effects, however, the space required to accommodate the metal atom will prune the number of complexation possibilities significantly. It is worthy to note that this structure with the two nitro groups from the two drugs in *cis* position is assumed as more possible, since an intramolecular hydrogen bonding presented in free drugs between the nitro group and the neighbouring hydrogen from Me group[22] would disable the donating ability of the nitro group to copper ion and exclude the structure with the consequent *trans* position of the two nitro groups.

REFERENCES

1. R.M. Brogden, A.A. Carmine, R.C. Hell, T.M. Speight and G.S. Avery, *Drugs*, **24**, 267 (1982).
2. J. Dawson, R. Cockel, G.T. Dixon, D.A. Richards and R. Stables, *Clin. Hosp. Pharm.*, **8**, 1 (1983).
3. M.J. Daly and B.J. Price, *Prog. Med. Chem.*, **20**, 337 (1983).
4. A.H. Price and R.N. Brogden, *Drugs*, **36**, 521 (1988).
5. H. Siegel, Metal Ions in Biological Systems, Marcel-Dekker, Inc., New York (1980).
6. M. Mathur, S. Shrivastava and N.M. Shrivastava, *Asian J. Chem.*, **12**, 371 (2000).
7. A. Sega, F. Moimas, E. Decorte, R. Toso and V. Sunjić, *Gazz. Chim. (Ital.)*, **112**, 421 (1982).
8. G. Crisponi, F. Cristiani, V.M. Nurchi, R. Silvagni, M.L. Ganadu, G. Lubinu, L. Naldini and A. Panzanelli, *Polyhedron*, **14**, 1517 (1995).
9. S. Rajappa, *Tetrahedron*, **37**, 1453 (1981).
10. W.J. Geary, *Coord. Chem. Rev.*, **7**, 81 (1971).
11. F.A. Cotton, G. Wilkinson, C.A. Murillo and M. Bochmann, Advanced Inorganic Chemistry, 6th Edn., John Wiley & Sons, New York (1999).
12. B.N. Figgis, Introduction to Ligand Fields, Interscience, New York (1966).
13. J. Reuben, *J. Am. Chem. Soc.*, **98**, 3726 (1976).
14. K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds, 3rd Edn., John Wiley & Sons, New York (1988).
15. T.J. Cholerton, J.H. Hunt, G. Klinkert and M.M. Smith, *J. Chem. Soc., Perkin Trans. I*, 1761 (1984).
16. P.A. Haywood, M.M. Smith, T.J. Cholerton and M.B. Evans, *J. Chem. Soc., Perkin Trans.*, 951 (1987).
17. C.F.G.C. Geraldes, V.M.S. Gil and M.H.S.F. Teixeira, *Magnet. Reson. Chem.*, **25**, 203 (1987).
18. E. Gaggelli, N. Marchettini, A. Sega and G. Valensin, *Magnet. Reson. Chem.*, **26**, 1041 (1988).
19. G.A. Stephenson, T.J. Wozniak, J.G. Stowell and S.R. Byrn, *J. Mol. Struct.*, **380**, 93 (1996).
20. S. Rajappa, R. Sreenivasan, B.G. Advani, R.H. Summerville and R. Heffmanann, *Indian J. Chem.*, **15B**, 297 (1977).
21. T.J. Cholerton, J.H. Hunt, G. Klinkert and M.M. Smith, *J. Chem. Soc., Perkin Trans.*, 1761 (1984).

(*Received*: 9 March 2002; *Accepted*: 28 June 2002) AJC-2786