Synthesis and Characterization of the Acetazolamide Complexes of Co(II) and Zn(II)

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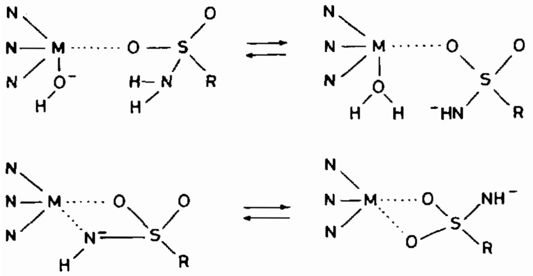
Abstract

The preparation and characterization of the complexes of Acetazolamide** (Acm) with Co(II) and Zn(II) are described. The complexes are of the type $M(Acm)_2(NH_3)_2$. Monodentate or bidentate behaviour of Acm from the electronic properties and the IR spectral data is discussed. The probable structures of the complexes are proposed.

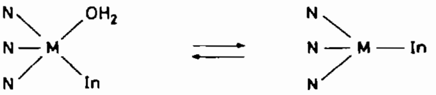
Introduction

The sulfonamides are substances usually employed as drugs. Acm is one of the diuretic sulfonamides and is used in the treatment of glaucoma and as an anticonvulsant [1, 2]. The Ag(I) complexes of sulfonamides are used for the treatment of burns [3]. Acm is an anhydrase carbonic inhibitor [4]. It has been proved that the inhibition occurs through binding at the metal ion of the enzyme [5, 6]. Acm binds in the sulfonamidato anionic form. There are several mechanisms proposed to explain the role of Acm in the anhydrase carbonic inhibition. Bauer [7] indicated the following mechanism for the human isoenzyme where Acm acts as a monodentate or bidentate ligand (Scheme 1).



Scheme 1.

Bertini *et al.* [8–10] studied the behaviour of the sulfonamides with respect to cobalt substituted Bovine Carbonic Anhydrase II. They concluded that the inhibitor acts as a monodentate ligand in the following equilibrium (Scheme 2).



Scheme 2.

Vedani and Dunitz [11] analyzed the intermolecular environments of the sulfonamide group (RSO_2NH_2) from Cambridge Crystallographic Data File and they concluded that the sulfonamide N atom occupies the fourth coordination site in the carbonic anhydrase replacing the Zn-bound water molecule in the native enzyme. One oxygen atom of the sulfonamide group binds weakly with the metal to give a distorted (4 + 1) 'tetrahedron'.

Sudmeier [12] has shown through ^{113}Cd NMR spectroscopy that the nitrogen of the sulfonamides binds the metal ion.

In view of the above results, it seemed of interest to prepare Zn complexes with Acm. In this paper the preparation and characterization of Co(II) and Zn(II) complexes are reported.

Experimental

Acm was supplied as powder material by Lederle Laboratories. It was purified by recrystallization from methanol. All reagents used were of analytical grade.

Synthesis of $Co(Acm)_2(NH_3)_2$

To an ethanolic solution (200 cm^3) of $CoCl_2$ 10^{-2} M were added 2.20 g of Acm (molar ratio Acm/Co = 5:1). After warming and stirring a solution was obtained. Then, 9 cm^3 of concentrated NH_3 (11 M) was added. Immediately the solution became violet and a precipitate of the same colour was obtained. The product was filtrated, washed with EtOH and dried at 40 °C. The obtained product is a crystalline violet solid.

Synthesis of $Zn(Acm)_2(NH_3)_2$

To a methanolic solution of Acm (1.87 g in 500 cm^3 of MeOH) 5 cm^3 of conc. NH_3 were added. Then

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**5-acetamido-1,3,4-thiadiazol-2-sulfonamide.

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125 cm^3 of $ZnCl_2$ (1.51 g in 500 cm^3 of MeOH) were added with stirring. The molar ratio Acm/Zn was 3:1. Slowly, a white precipitate appeared. The mixture was allowed to stand at room temperature for about 3 h. The voluminous substance was collected by filtration, throughly washed with water and dried at 60 °C. The final form of the complex was a white powder.

Physical Measurements and Analyses

The content of Co and Zn was determined by atomic absorption spectroscopy after previous decomposition of the complex with boiling hydrochloric or nitric acid. Carbon, hydrogen and nitrogen analyses were carried out by Elemental Analysis.

The IR spectra were recorded on a Perkin-Elmer Model 1330 infrared spectrophotometer in the region 4000–200 cm^{-1}. The spectra were obtained as KBr or CsI pellets.

The UV spectra of the DMSO solutions were obtained at room temperature on a Shimadzu UV Model 240.

The visible reflectance spectrum of the Co(II) complex was obtained in a Perkin-Elmer spectrophotometer Model Hitachi 200 with a diffuse reflectance sphere.

The magnetic measurements of finely powdered complexes were carried out at room temperature by the Gouy method. Mercury(II) tetrathiocyanate cobaltate(II) was used as the magnetic susceptibility standard.

The ^1H NMR and ^{13}C NMR of the ligand and saturated Zn complex solutions in DMSO-d_6 were registered on a Brucker NP 80SY spectrophotometer.

The thermal analyses by means of TG and DTA were carried out on a Rigacku Thermobalance in an air dynamic atmosphere. Experiments were carried out on samples of *ca.* 10 mg at a heating rate of 4 °C/min using ignited Al_2O_3 as reference.

The X-ray powder diffraction patterns were obtained through a Kristalloflex 810 Siemens diffractometer using Cu Kα diffraction.

Results and Discussion

The analytical data for the complexes are summarized in Table I. Elemental analyses showed that the materials obtained correspond well to the formula $M(Acm)_2(NH_3)_2$. Analyses for chloride proved negative. This suggest that the sulfonamide group is deprotonated yielding a neutral complex.

The conductance data (Table I) indicate that the complexes behave as non-electrolytes in DMSO.

IR spectra of $M(Acm)_2(NH_3)_2$, the sodium salt and of the free sulfonamide were registered. A tentative assignment of the bands of the groups that may interact to the metal ion has been given in Table II. The assignment has been made by comparison with the related sulfonamides spectra [13] and with the literature values [14, 15].

It can be seen from Table II that the $NH_{Acetamide}$ stretching vibration does not vary in the IR spectra of the sodium salt and the complexes. However, the bands due to the $NH_{Sulfonamide}$ stretching vibration are shifted in the salt and in the complexes with respect to the Acm presumably because of Acm deprotonation. On the other hand, in the Co and

TABLE I. Analytical Data and Properties of the Complexes

Compound	Analysis (found (calc.)) (%)				Colour	μ_{eff} [a] (BM)	Λ_M [b] (ohm^{-1} mol^{-1} cm^2)	Yield (%)
	C	H	N	M^{2+}				
$Co(Acm)_2(NH_3)_2$	18.1 (17.9)	3.0 (3.0)	26.5 (26.3)	10.8 (11.0)	violet	4.13	26	98
$Zn(Acm)_2(NH_3)_2$	18.0 (17.9)	2.9 (2.9)	25.5 (25.8)	11.8 (12.1)	white		17	96

[a] Gouy measurement ±0.05 BM, at room temperature. [b] 10^{-3} M solution in DMSO, 298 K.

TABLE II. IR Spectral Bands

Compound	$\nu(NH)_{Acetamide}$	$\nu(NH)_{Sulfonamide}$	$\nu(NH)_{(Ammonia)}$	$\nu(C{=}O)$	$\nu(SO_2)_{asym}$	$\nu(SO_2)_{sym}$	$\nu(M{-}N)$	$\nu(M{-}O)$
$Co(Acm)_2(NH_3)_2$	3300	3170, 3030	3350	1705	1290	1145	399	341
$Zn(Acm)_2(NH_3)_2$	3293	3165, 3025	3346	1699	1285	1145	400	350
NaAcm	3291	3159, 3019		1704	1310	1174		
Acm	3299	3182, 3089		1672	1318	1170		

Zn complexes there is a new band attributed to the ammonia group.

The band assigned to $\nu(C{=}O)_{Acetamide}$ is shifted to higher frequencies in the Acm derivatives. This increase may be interpreted by the dissociation of some hydrogen bonds which appear in the Acm crystal structure [16].

The bands attributed to the SO_2 group are shifted to lower frequencies in the Co and Zn complexes but not in the sodium salt. This is the result of the sulfonamido group interacting with the metal ion.

A tentative proposition is that the bands at 400, 399, 350 and 341 cm^{-1} correspond to the metal donor stretching vibrations where the donor atoms can be either nitrogen or oxygen [17, 18].

The visible reflectance spectrum of $Co(Acm)_2(NH_3)_2$ shows two broad bands at *ca.* 8000 and 18180 cm^{-1} due to the transitions $^4A \rightarrow {}^4T_1$ and $^4A \rightarrow {}^4T1(P)$, respectively; this seems to indicate that the Co(II) ion environment is tetrahedral [19]. The spectral parameters deduced by the electronic spectrum are $Dq = 5200$ and $B = 830$ cm^{-1}. Bult [3, 20] indicates that the products formed in the reaction of sulfanilamides with Co(II) in methanol have the composition CoL_2Y_2 and are tetrahedral (violet) or octahedral (pink–red) depending of the nature of the substituent.

The magnetic moment value for Co(II) ion (4.1 BM) is somewhat lower than the values usually found for tetrahedral compounds which display a lower magnetic moment than five or six coordinated complexes. Thus the magnetic susceptibility measurements are consistent with the reflectance spectra [21].

Acm in DMSO solution shows a maximum at 267 nm ($\epsilon = 9600$ cm^{-1} mol) and a shoulder at 316 nm ($\epsilon = 300$ cm^{-1} mol). The sodium acetazolamide shows two maximums at 260 nm ($\epsilon = 5200$ cm^{-1} mol) and at 314 nm ($\epsilon = 7600$ cm^{-1} mol); the former is attributed by Abdine *et al.* [22] to a conjugation of the three chromophores (thiadiazol ring, sulfonamide and acetamide groups) and the latter corresponds to an ionized sulfonamide group conjugated with the thiadiazol ring. The bathochromic shift of the 260 nm and 314 nm peaks is consistent with the fact that the π-electrons associated with each double bond are able to move with increased freedom throughout the ionized structure of Acm. The UV spectra of the Co and Zn complexes are similar to the sodium salt but with higher absorptions according with the existence of two Acm per mole (see Fig. 1). This supports the presence of ionized sulfonamide in DMSO solutions.

The ^1H NMR spectra of Acm, the sodium salt and Zn complex show no shift of the methyl group, which indicates no interaction between the acetamide group and the metal ion. The ^{13}C NMR spectra of the compounds do not indicate direct interaction between the atoms linked to carbon atoms and the metal ion.

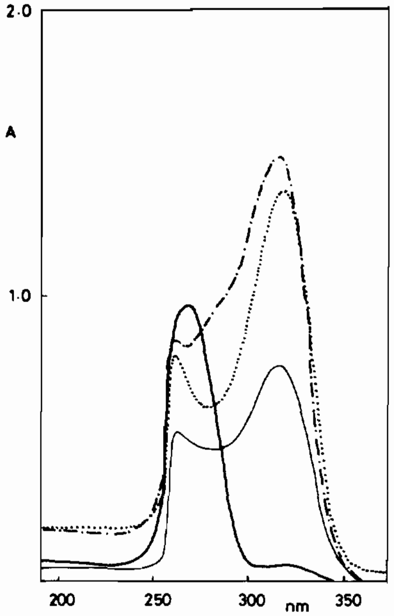

Fig. 1. UV spectra of Acm (——), NaAcm (——), $Zn(Acm)_2(NH_3)_2$ (–·–) and $Co(Acm)_2(NH_3)_2$ (······).

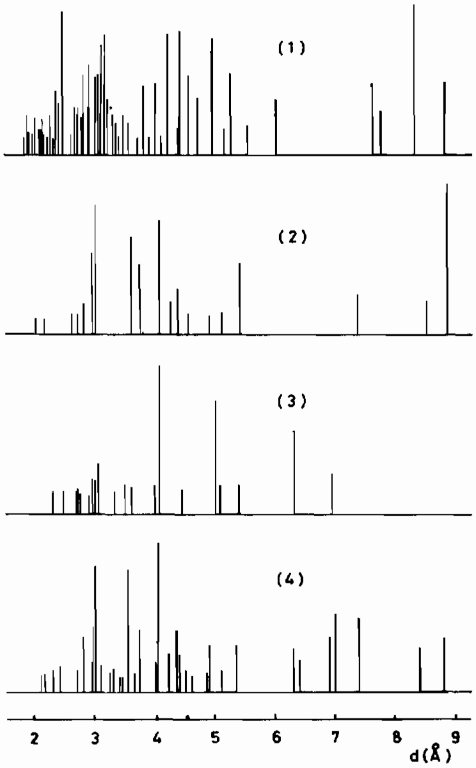

Fig. 2. X-ray powder diffraction patterns of NaAcm (1), Acm (2), $Co(Acm)_2(NH_3)_2$ (3) and $Zn(Acm)_2(NH_3)_2$ (4).

The X-ray powder patterns of the Co and Zn complexes, sodium salt and Acm have been recorded

(Fig. 2). It can be inferred that the Zn and Co complexes are not isostructural.

The thermal decomposition of the complexes shows that they are stable up to 200 °C, then deammination and pyrolytic decomposition take place. The end products are a mixture of metal sulphates and oxides.

Conclusions

All the data support the hypothesis that $M(Acm)_2(NH_3)_2$ contains an acetazolamidato anion. Since the complexes are pseudotetrahedral, if the two ammonia molecules are bound, then Acm should behave as a monodentate. However, bidentate ligands with a small bite like nitrate and carboxylates give rise to electronic spectra and magnetic moments which resemble those of the monodentate ligands [23]. On the other hand, the IR spectra indicate oxygen binding and the proton release indicates binding through nitrogen.

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