Metallation of Ligands with Biological Activity: Synthesis and X-Ray Characterization of Polymeric $[Cd(sulfamethoxazolato)_2(CH_3OH)_2]_n \cdot x(CH_3OH)$

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Sulfamethoxazole (5-methyl-3-isoxazolyl sulfanilamide) reacts with cadmium acetate in methanol in a steel autoclave at 150 °C to give crystalline $[Cd(sulfamethoxazolato)_2(CH_3OH)_2]_n \cdot x(CH_3OH)$ (**1**) the structure of which was characterized by single crystal X-ray diffraction. The triclinic crystals belong to the space group *P*1. In the polymeric assembly the Cd(II) centers are linked through sulfamethoxazolato anions which alternate in their coordination with the isoxazolic N-atoms and the aromatic amino groups. The chains of vicinal rings build tunnels along the crystallographic *c* axis.

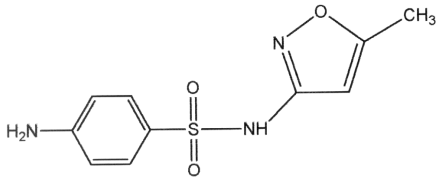
Key words: Sulfamethoxazole Complexes, Bioinorganic Chemistry of Cadmium, Metallation of Biological Ligands

Introduction

It is well known that through exchanges of different functional groups without modification of the structural $-S(O)_2N(H)-$ features, sulfonamide derivatives can exhibit a wide variety of pharmacological activities, such as antidiabetic, antibacterial and antitumor [1 – 4]. It is also known that the pharmacological activity of the sulfanilamides has often been increased by coordination with metal ions [5, 6], and many examples of this class of compounds have been reported, especially concerning the use of sulphadiazine complexes in the medical treatment of skin disorders (burns) [7 – 10].

Recently we have described [11] the synthesis and the characterization of $[(SDAZ)_2Au_2(dppe)]$ {SDAZ = Sulphadiazinide anion; dppe = 1,2-bis(diphenylphosphanyl)ethane}, complementing the large spectrum of gold drugs responsible for the explosive growth of the bioinorganic chemistry of gold(I) in the last decade [12 – 15]. Lately, gold(I) complexes with bidentate phosphanes such as $[Au(dppe)_2]Cl$ [16] have also been found of great chemotherapeutical potential in cancer treatment [17, 18].

Given the ability of sulfanilamide derivatives to coordinate to metal atoms in different manners, considerable interest in the synthesis and structural aspects of new complexes has arisen [19 – 22]. Nevertheless, only a few examples of crystal structures of complexes of the polymorphous [23] sulfanilamide derivative sulfamethoxazole (5-methyl-3-isoxazolyl sulfanilamide) (**A**) have been reported.



A

The first complex described [19] shows a tendency of the ligand to coordinate through the isoxazolic nitrogen atom, even in cases where the sulfonamidic nitrogen atom was deprotonated. Recently we have partially confirmed this trend with the synthesis of $[Cu_2(\mu\text{-}CH_3CO_2)_4(sulfamethoxazole)_2]$ and $[Hg(sulfamethoxazolato)_2] \cdot 2DMSO$ [24]. Although in the copper complex the coordination is attained through isoxazolic nitrogen atoms from neutral sulfamethoxazole ligands and acetato anions, in the Hg compound the sulfamethoxazolato anions behave also as bidentate bridging ligands and are coordinated through the sulfonamidic nitrogen atoms and the *two* oxygen atoms of the $S(O)_2$ groups. This result corroborates that the noteworthy chemical ability of the sul-

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Table 1. Crystal data and structure refinement for $[Cd(sulfamethoxazolato)_2(CH_3OH)_2]_n \cdot x(CH_3OH)$.

Empirical formula	$C_{13}H_{22}Cd_{0.5}N_3O_6S$
Formula weight	404.60
T [K]	293(2)
Radiation, λ [Å]	Mo-K$_\alpha$, 0.71073
Crystal system, space group	triclinic, $P\bar{1}$
Unit cell dimensions a, b, c [Å]	$a = 8.559(5)$
	$b = 9.984(5)$
	$c = 10.807(5)$
α, β, γ (°)	$\alpha = 106.139(5)$
	$\beta = 92.834(5)$
	$\gamma = 91.437(5)$
V [Å^3]	885.3(8)
Z, Calculated density [g·.cm^{-3}]	2, 1.518
Absorption coefficient [mm^{-1}]	0.800
F (000)	418
Crystal size [mm]	$0.12 \times 0.1 \times 0.09$
θ Range [°]	3.18 – 29.29
Index ranges	$-11 \le h \le 11$, $-13 \le k \le 13$, $0 \le l \le 14$
Reflections collected	4766
Reflections unique	4766
Completeness to theta max.	98.4%
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4766 / 3 / 216
Goodness-of-fit on F^2	1.083
Final R indices $[I > 2\sigma(I)]$	$R_1 = 0.0440$, $wR_2 = 0.1229$
R Indices (all data)	$R_1 = 0.0475$, $wR_2 = 0.1247$
Largest diff. peak and hole [e·Å^{-3}]	2.050 and −1.317

fanilamides to act as ligands is based upon the acidity of the $S(O)_2N-H$ function [11], allied with the presence of vicinal nitrogen or oxygen atoms of the substituents, as potential coordination sites. Thus, the deprotonation of the NH group yields an anionic donor ligand, and, in case of sulfamethoxazole, the isoxazole ring affords the stereochemical requisites for the achievement of complexes with a monodentate, chelating or bridging ligand.

With the aim to provide new contributions about the coordination modes of sulfamethoxazole in metal complexes, we report the synthesis and the structural characterization of the polymeric complex $[Cd(sulfamethoxazolato)_2(CH_3OH)_2]_n \cdot x(CH_3OH)$, obtained from the reaction of cadmium acetate and sulfamethoxazole in methanol, in a steel reactor at 150 °C. In the crystalline assembly of the novel compound the Cd(II) centers are linked through two sulfamethoxazolato anions, which alternate in their coordination with the isoxazole and the aniline N-atoms. This architecture leads to the formation of chains of spirocyclic rings with the contour of tunnels or channels.

Table 2. Selected bond lengths [Å] and angles [°] for $[Cd(sulfamethoxazolato)_2(CH_3OH)_2]_n \cdot x(CH_3OH)$.

Bond lengths		N(1)–Cd–O(4)	92.64(10)
N(1)–O(1)	1.417(4)	O(4)–Cd–O(4)”	180
N(1)–Cd	2.308(3)	N(1)”–Cd–N(3)”’	91.43(10)
N(2)–S	1.575(3)	N(1)–Cd–N(3)”’	88.57(10)
O(2)–S	1.455(3)	O(4)–Cd–N(3)”’	84.16(9)
O(3)–S	1.446(3)	O(4)”–Cd–N(3)”’	95.84(9)
O(4)–Cd	2.333(2)	N(1)”–Cd–N(3)’	88.57(10)
Cd–N(3)’	2.382(3)	N(1)–Cd–N(3)’	91.43(10)
Bond angles		O(4)–Cd–N(3)’	95.84(9)
N(1)”–Cd–N(1)	180	O(4)”–Cd–N(3)’	84.16(9)
N(1)”–Cd–O(4)	87.36(10)	N(3)”’–Cd–N(3)’	180

Symmetry transformations used to generate equivalent atoms: (’) $-x+2, -y, -z$; (”) $-x+1, -y, -z$; (”’) $x-1, y, z$.

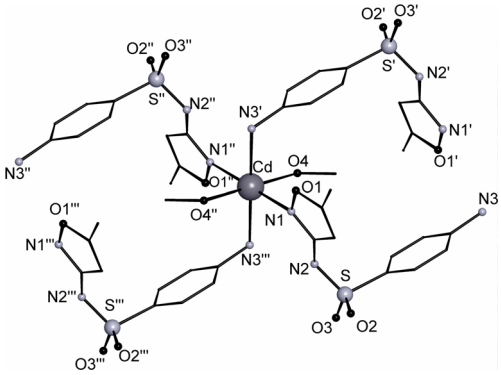

Fig. 1. Octahedral coordination of the Cd centers in the structure of $[Cd(sulfamethoxazolato)_2(CH_3OH)_2]_n \cdot x(CH_3OH)$. Symmetry transformations used to generate equivalent atoms: (′) $-x+2, -y, -z$; (″) $-x+1, -y, -z$; (‴) $x-1, y, z$.

Results and Discussion

The reaction of 2 equivalents of sulfamethoxazole with 1 equivalent of cadmium(II) acetate in methanol leads to the deprotonation of the sulfonamidic nitrogen atom to form $[Cd(sulfamethoxazolato)_2]$ and acetic acid according to

$$Cd(CH_3COO)_2 + 2\ \text{sulfamethoxazole} \rightarrow [Cd(\text{sulfamethoxazolato})_2] + 2\ CH_3COOH.$$

From X-ray diffraction data of the triclinic crystals, the space group $P\bar{1}$ was chosen on the basis of statistics and later justified by the successful refinement. Crystal data and experimental conditions are given in Table 1. Selected bond distances and angles of $[Cd(sulfamethoxazolato)_2(CH_3OH)_2]_n \cdot x(CH_3OH)$ (**1**) are listed in Table 2. Fig. 1 displays the octahedral coordination of the Cd centers. The asymmetric unit $\{Cd_{0.5}(sulfamethoxazolato)(CH_3OH)\}$ is related with

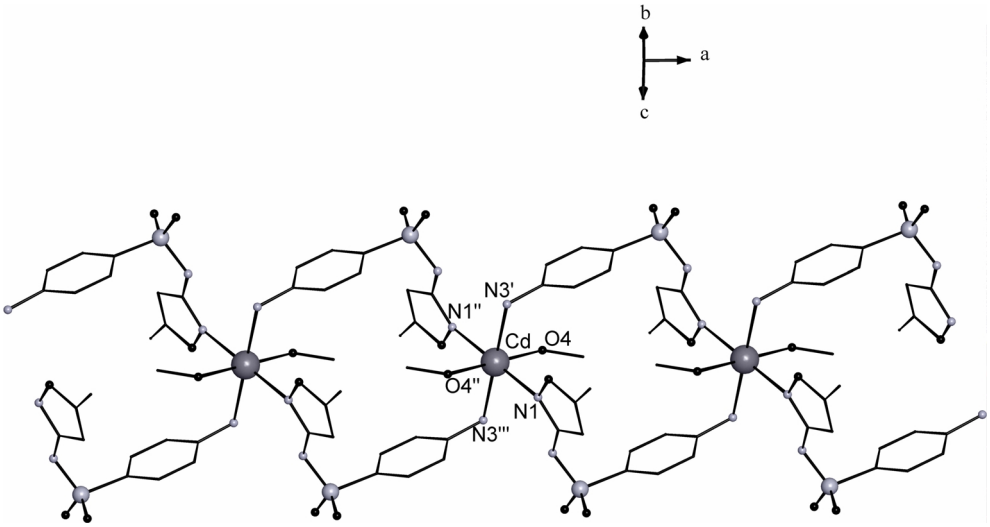

Fig. 2. Symmetrical linkage of the Cd atoms through alternate isoxazole and aniline N sites of the sulfamethoxazolato bridges. Symmetry transformations used to generate equivalent atoms: (′) $-x+2, -y, -z$; (″) $-x+1, -y, -z$; (‴) $x-1, y, z$.

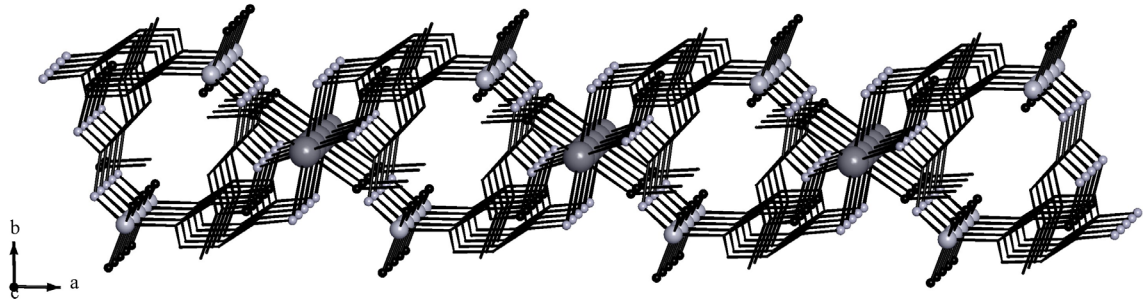

Fig. 3. Channels in the lattice of $[Cd(sulfamethoxazolato)_2(CH_3OH)_2]_n \cdot x(CH_3OH)$ along the *c* axis.

the other half of the cell through a crystallographic inversion center located at the metal atom. The Cd atoms are coordinated by two isoxazole and two aniline N atoms – of four sulfamethoxazolato anions – besides two methanol molecules. In the structure of **1** are also enclosed two molecules of solvate (methanol) pro formula (see Table 1): a well defined methanol molecule (C82, O81), and another one appearing in two crystallographic positions (disorder: C62, O61 and C72, O71); these methanol molecules do not entertain hydrogen bonds. Fig. 2 shows the polymer chain with the Cd atoms symmetrically linked through alternating isoxazole and amino N sites, achieving the octahedral coordination through methanol molecules. The two reciprocal equatorial Cd–N bonds [2.308(3) Å] are shorter than the axial ones [2.382(3) Å], nonetheless the octahedron presents itself with only quite small distortions, since all the *trans* Cd bonds are symmetrically linear (180°). The *cis* Cd bonds, however, present a small deviation from orthogonality (see Table 2).

The polymeric assembly of $[Cd(sulfamethoxazolato)_2(CH_3OH)_2]_n \cdot x(CH_3OH)$, in which the Cd atoms are linked through sulfamethoxazolato bridges along the *a* axis, comprises the formation of rings containing two Cd centers and two sulfamethoxazolato anions. Such a polymeric structure is not usual in metal complexes of sulfanilamide derivatives; most of the compounds of this class present simple architectures, which seem to be a major plus regarding the biological activity. Many biologically active metal complexes of sulfadiazine or dppe, for example, are not highly structured.

In the case of **1**, the chains of spirocycles build up tunnels in the structure along the crystallographic axis *c*, as shown in Fig. 3. Until the present day we are not able to understand how this structural feature could affect the biological activity of the new com-

plex. Although Cd^{2+} might be toxic in higher concentrations, it is a soft trace metal ion naturally present in the human organism. In ATP various metal chelates of the α, β, and γ phosphate groups have been identified by X-ray crystallography and by ^{31}P NMR spectroscopy [25]. Two of the known structures are, for example, $[Cd^{II}(H_2O)_5GMP]$ (GMP = guanosine monophosphate) and $[Co^{III}(NH_3)_4$(triphosphate)].

Experimental Section

Preparation of [Cd(sulfamethoxazolato)$_2$(CH$_3$OH)$_2$]$_n$· x(CH$_3$OH)

0.126 g (0.5 mmol) of sulfamethoxazole was fully dissolved in absolute methanol in a glass tube. Separately, 0.066 g (0.25 mmol) of cadmium acetate was also dissolved in dried methanol, and the two solutions were mixed in the glass tube which was introduced in a steel autoclave and heated to 150 °C. Subsequently the autoclave was allowed to cool to room temperature. The vessel was opened and the solvent was evaporated overnight from the glass tube. After 12 h the product was isolated by filtration and dried: 0.079 g (78% based on cadmium acetate) of air-stable white crystals, m. p. 207 – 210 °C.

IR (KBr): ν = 1156 [s, $\nu_s(SO_2)$], 1366 [m, $\nu_{as}(SO_2)$], 3246 [m, $\delta(NH_2)$], 3297 [m, $\nu_s(NH_2)$], 3466 [m, $\nu_{as}(NH_2)$]. Analysis for $C_{13}H_{22}Cd_{0.5}N_3O_6S$ (404.60): calcd. C 38.60, H 5.48, N 10.38; found C 37.32, H 5.01, N 11.18.

Structure determination

X-ray data were collected on a Bruker SMART CCD diffractometer. The structure of [Cd(sulfamethoxazolato)$_2$(CH$_3$OH)$_2$]$_n$(CH$_3$OH)$_x$ was solved by direct methods (SHELXS-97) [26]. Refinements were carried out with the SHELXL-97 package [27] by full-matrix least-squares on F^2 with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were included in the refinement in calculated positions.

Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC-277443. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int. code +(1223)336-033; e-mail for inquiry: fileserv@ccdc.cam.ac.uk).

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