DALTON COMMUNICATION

Crystal structure of zinc(II) 2-sulfanilamidopyrimidine: a widely used topical burn drug

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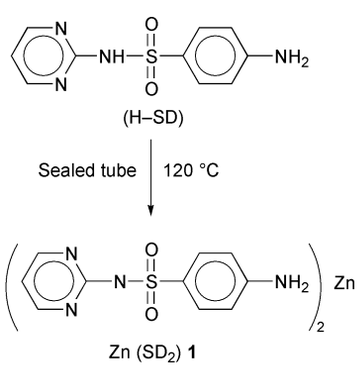
The reaction of H-SD (sulfadiazine) with $Zn(OAc)_2{\cdot}2H_2O$ in water–ethanol under solvothermal reaction conditions yields crystals of $Zn(SD)_2$ (1) suitable for X-ray analysis and its 1-D polymeric nature is biologically relevant to the slow release of Zn^{2+} when applied in topical burn therapy.

The topical application of metal complexes of 2-sulfanilamidopyrimidine (sulfadiazine, H-SD), see Scheme 1, has revived the usefulness of sulfanilamides in medicine.[1] Silver (commercial names Flammazine or Silvederma in Spain)[2a] and zinc salts (commercial name HuangAnXin in China)[2b] of sulfadiazine are widely used to prevent bacterial infection for both humans and animals during burn treatments.[2] These metal complexes are largely insoluble, working through the slow release of the metal ions Ag^+ and Zn^{2+} from polymeric materials. Because the slow release of the metal ions from these drugs is strongly dependent on their binding nature, it is important to understand the coordination environment around the metal which is, in turn, highly relevant to the biological activity of these polymeric drugs. However, due to the difficulty in obtaining suitable crystals for X-ray analysis for zinc sulfadiazine $Zn(SD)_2$ (**1**) prepared by the experimental or industrial reaction of $ZnSO_4$ and NaOH with H-SD in aqueous solution,[3a] only the polymeric silver sulfadiazine (AgSD) is known.[3b,c] Reported structures for zinc sulfadiazine are monomers, crystallized in organic solvents,[4] and are therefore irrelevant to the administered drug $Zn(SD)_2$ in which $Zn(SD)_2$ can be applied in the form of ointment, cream, powder, *etc*. for the promotion of wound healing.[3a] To our surprise, the reaction of $Zn(OAc)_2{\cdot}2H_2O$ with H-SD in water–ethanol under solvothermal reaction conditions yielded crystals of $Zn(SD)_2$ suitable for X-ray analysis. Here we report the first structural evidence for polymeric $Zn(SD)_2$, which is important for the understanding of the mechanism of action of the drug (Scheme 1).

The elemental analysis and IR indicated that the reaction of $Zn(OAc)_2{\cdot}2H_2O$ with sulfadiazine gave **1**.† In the IR spectrum



Scheme 1

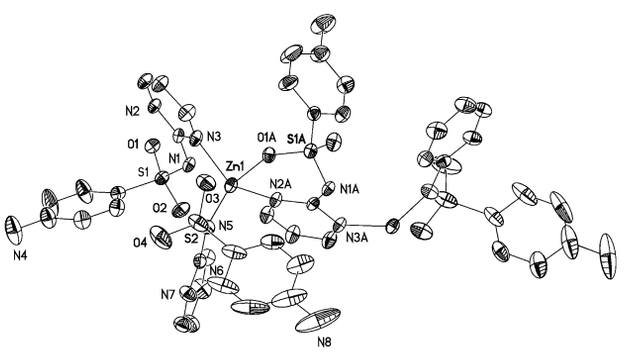


Fig. 1 A representation of the asymmetric unit of $Zn(SD)_2$, H atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Zn(1)–N(5) 1.967(3), Zn(1)–N(3) 2.017(13), Zn(1)–N(2A) 2.060(2), Zn(1)–O(1A) 2.072(2); N(3)–Zn(1)–N(5) 111.81(12), N(2A)–Zn(1)–N(5) 118.44(12), N(3)–Zn(1)–N(2A) 125.95(11), N(5)–Zn(1)–O(1A) 91.44(10), N(2A)–Zn(1)–O(1A) 91.15(9).

of **1**, the diagnostic absorption bands at 3450 and 3350 cm^{-1}, assigned to ν_a and ν_s(N–H) vibrations of the NH_2 group, are significantly shifted compared to those of the free ligand H-SD (3425 and 3360 cm^{-1}).[5,6] Furthermore, the strong bands related to ν_a and ν_s of the (SO_2–N) moiety at 1325 and 1155 cm^{-1} in H-SD show important changes upon complexation. That is the first splits into two peaks at 1295 and 1264 cm^{-1} and the latter appears at 1130 cm^{-1} in **1**. Similarly, the band at 945 cm^{-1}, corresponding to ν(S–N), is shifted to higher wavelength and splits into two peaks (1020 and 990 cm^{-1}) upon complexation. In addition, the band positions for the deprotonated sulfonamide group are very close to the values observed in the corresponding cobalt sulfadiazine complex where the deprotonated sulfonamide nitrogen is an active binding site.[7]

Fig. 1 shows an ORTEP[8] representation of the asymmetric unit cell of **1** in which the local zinc atom lies on the two-fold axis and is coordinated to three nitrogen atoms; one from the pyrimidine ring of SD and two from the sulfonamide nitrogen atoms of two different SD ligands. One oxygen atom of a sulfonyl group completes the tetrahedral geometry around the Zn atom.‡ Overall, the Zn atom binds three SD ligands in which one SD acts as a monodentate ligand (imido nitrogen as the donor atom) and the other two act as tridentate bridging ligands. By contrast, in Ag(SD) all the SD ligands adopt a tetradentate bridging mode, leading to the formation of a 1-D double-chain coordination polymer.[3] Thus, the sulfadiazine moiety in **1** acts as a tridentate bridging ligand through the nitrogen atom of the pyrimidine ring, the imido nitrogen and the oxygen of the sulfonyl group to connect two Zn atoms, resulting in the formation of a one-dimensional polymeric $Zn(SD)_2$ chain, as shown in Fig. 2. In addition, one oxygen atom of the sulfonyl group and the other nitrogen atom of the

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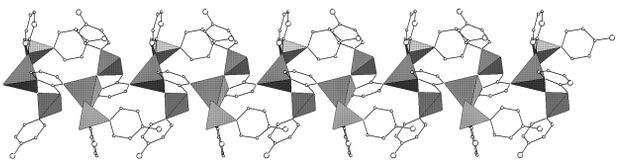

Fig. 2 A 1-D polymeric chain representation of $Zn(SD)_2$, viewed along the *c*-axis. Each tetrahedron shares a corner, the larger tetrahedra are for zinc, the smaller for sulfur.

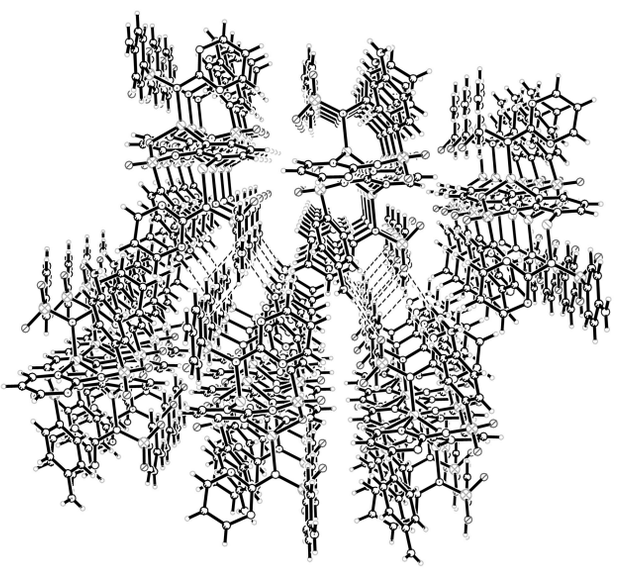

Fig. 3 A 3-D diagram of $Zn(SD)_2$ showing the involvement of arylamino H atoms in hydrogen-bonding (dashed lines).

pyrimidine ring in the same ligand are chelated to the same zinc atom to form a stable six-membered ring. This structural feature may be related to the selectivity of the metal atom toward active binding sites of the ligand. To the best of our knowledge, this is the first structure reported for polymeric zinc sulfadiazine. To balance the charge on Zn^{2+}, each amido group of H-SD is deprotonated. The amine group on the benzene ring does not take part in coordination to the Zn atom, but one of the H atoms from this group is involved in the H-bonding system such as those found between amine N and O atom of sulfonate (3.272 Å), and amine N and the N atom of the uncoordinated pyrimidine ring (3.556 Å). Thus, overall **1** is a three-dimensional H-bonding coordination polymer, as depicted in Fig. 3.

The bond length $Zn–N_{sulfonamido}$ [1.967(3) Å] is slightly shorter than $Zn–N_{pyrimidine}$ [2.017(3) or 2.060(2) Å], probably due to the deprotonated amido N atom being negatively charged and able to bind the Zn^{2+} ions much closer together compared to the N atom of the pyrimidine ring. It is worth noting that the bond distance S(1)–N(1) of the tridentate SD ligand [1.579(3) Å] is slightly shorter than S(2)–N(5) of the monodentate SD ligand [1.620(3) Å], probably owing to the former forming a stable six-membered ring and increasing the delocalization, leading to the S(1)–N(1) bond showing partial π bond character. Moreover, the zinc atom is connected to three nitrogen atoms from three different SD ligands, and the sum of the three bond angles [111.81(12), 118.44(12), 125,95(11)°] around the Zn center is about 356.2°. The plane of N(2A)N(3)N(5)Zn(1) has a mean planar deviation of 0.0852 Å, making the Zn atom center appear like a trigonal pyramid in which 3N atoms (N2A, N3 and N5) occupy the trigonal plane while the pyramidal peak is occupied by O (O1A).

The N(4)–C(8) bond distance [1.368(5) Å] is similar to that for N(8)–C(18) [1.402(9) Å], which is in good agreement with the corresponding bond in sulfadiazine [1.43(3) or 1.41(2) Å][9] and in other metal sulfadiazinato complexes,[3,4a] and appreciably shorter than the 1.470(5) Å proposed by Camerman for the length of a $C(sp^2)–N(sp^2)$ single bond,[10] suggesting considerable double bond character in that bond. The S–C bond length [1.746(4) or 1.768(5) Å] is a normal single bond, so there does not appear to be any extension of the phenyl ring electron delocalisation to include S(1) or S(2). The value is similar to those found in other metal sulfadiazinato complexes.[3,4b,11] The S–O bond lengths are very similar [1.438(2), 1.465(2) and 1.427(3), 1.435(3) Å], and comparable to those found in the other metal sulfadiazinato complexes, but slightly longer than that in free sulfadiazine.[9] The bond lengths and angles in pyrimidine and phenyl rings are in good agreement with the values observed for such rings in free sulfadiazine and metal sulfadiazinato complexes studied. The bonding around the sulfur atoms is distorted from the ideal tetrahedral geometry. The maximum and minimum values of angles around the different sulfur atoms from different ligands are 112.78(14)° [O(2)–S(1)–O(1), 106.36(15)° [O(1)–S(1)–C(5)] and 116.60(19)° [O(4)–S(2)–O(3)], respectively.

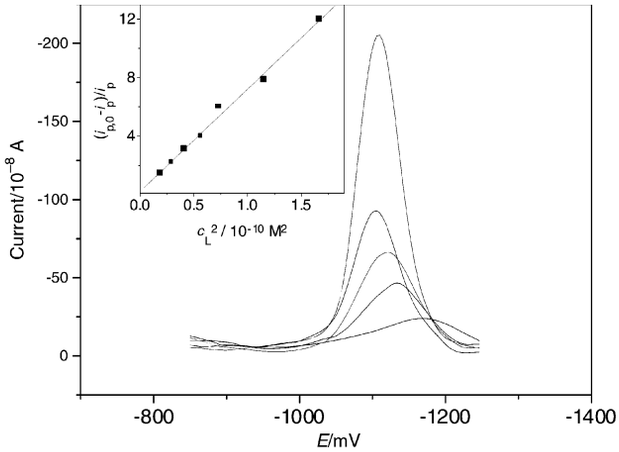

Fig. 4 Differential pulse voltammograms of 1.74×10^{-5} M Zn^{2+} in 0.01 M KNO_3 (pH 3.7) in the presence of 0, 3.2, 5.4, 6.5, 7.5, 8.6, 10.7 and 12.9 μM of ligand. Inset, plot of $(i_{p,0} - i_p)/i_p$ *vs.* c_L^2.

To evaluate the solubility of $Zn(SD)_2$ in water and the slow release of Zn^{2+}, we have measured the equilibrium concentration of Zn^{2+} in water at room temperature and the associated equilibrium constants.§ The ICP results show that the concentration of Zn^{2+} reaches a steady state at *ca.* 13 μg ml^{-1}. Thus, the solubility of $Zn(SD)_2$ in water is estimated to be about 112 μg ml^{-1}. Furthermore, Fig. 4 shows the differential pulse voltammograms of 1.74×10^{-5} M Zn^{2+} in 0.01 M KNO_3 (pH 3.7) with the successive addition of ligand.§ A *K* value of $(7.0 \pm 0.3) \times 10^{10}$ M^{-2} is obtained from the slope of the inset figure.

In conclusion, the crystal structure determination of zinc sulfadiazine reveals that the drug forms a 1-D polymeric chain in which the Zn atom is tightly held by the three SD ligands. The polymeric nature of the drug is biologically relevant to the slow release of Zn^{2+} when applied in topical burn therapy.

Acknowledgements

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Notes and references

† Synthesis of **1**. A mixture of $Zn(OAc)_2 \cdot 2H_2O$ (0.02 g, 0.1 mmol) and sulfadiazine (0.05 g, 0.2 mmol) was thoroughly mixed with ethanol (3 ml) and H_2O (0.25 ml) in a thick walled Pyrex tube. The Pyrex tube was sealed under vacuum and heated in an oven at 120 °C. Colorless rod crystals were harvested after 12 h of heating. Yield: 0.040 g (71%). Anal. calc. for $C_{20}H_{18}N_8O_4S_2Zn$: C, 42.60; H, 3.19; N, 19.88. Found: C, 42.59; H, 3.08; N, 19.96%. IR (cm^{-1}, KBr): 3450(w), 3350(m), 1620(w), 1590(s), 1550(m), 1500(m), 1450(m), 1295(w), 1264(s), 1130(s), 1080(m), 1020(w), 990(w), 800(m), 680(s), 580(s) and 560(m).

‡ Crystal data for **1**: $C_{20}H_{18}N_8O_4S_2Zn$, $M_r = 563.91$, space group $P2_1/n$, $a = 13.9463(3)$, $b = 10.2008(2)$, $c = 17.5299(4)$ Å, $\beta = 113.252(1)°$, $V = 2291.30(8)$ Å^3, $Z = 4$, μ(Mo-Kα) = 1.031 mm^{-1}, $\rho_{calc} = 1.635$ g cm^{-3},

$T = 298$ K, $R1 = 0.0488$, $wR2 = 0.1128$. CCDC reference number 158391. See http://www.rsc.org/suppdata/dt/b1/b100901j/ for crystallographic data in CIF or other electronic format.

§ $Zn(NO_3)_2 \cdot 6H_2O$, KNO_3, KOH and HNO_3 were of analytical reagent grade. All solutions were prepared with double distilled water. A solution of ligand (1.08×10^{-3} M) was prepared with 1 : 1 ethanol–water and was adjusted to pH 3.70 with 0.1 M KOH and HNO_3 solutions. Electrochemical measurements were performed with a BAS 100 B electrochemical analyzer (Bioanalytical Systems Inc., USA) using a standard three-electrode system. A Ag–AgCl–3 M KCl reference electrode was used, with a platinum wire counter electrode and a hanging mercury working electrode. Electrochemical measurements were carried out in 1.74×10^{-5} M $Zn(NO_3)_2$ with 0.01 M KNO_3 as the supporting electrolyte. The solution was maintained at pH 3.70 and deaerated by purging with pure nitrogen and kept under a nitrogen atmosphere at 15 ± 1 °C. The instrumental parameters of differential pulse voltammetry were as follows: pulse amplitude = 50 mV, scan rate = 20 mV s^{-1}, initial potential = −850 mV, sample width = 17 ms, pulse width = 60 ms and pulse period = 200 ms. After the voltammogram was recorded, to obtain the peak current $i_{p,0}$ of 1.74×10^{-5} M Zn^{2+}, ligand was successively added to the solution in order to measure peak current in the presence of ligand.

Theoretical aspects: The model considers reversible reduction of free Zn^{2+} in 0.01 M KNO_3 on the mercury electrode and assumes the absence of electrode adsorption and kinetic effects.[12] The equilibrium established in the presence of ligand L is:

$$Zn^{2+} + 2\,L \longleftrightarrow ZnL_2 \quad (1)$$

The equilibrium constant K is given as:

$$K = \frac{[ZnL_2]}{[Zn^{2+}][L]^2} \quad (2)$$

Electrical charges have been omitted for the sake of simplicity. The peak current, i_p, of the differential pulse voltammogram is proportional to the concentration of free Zn^{2+}, $[Zn^{2+}]$. If the total concentrations of ligand and Zn^{2+} are c_L and c_{zn}, respectively, then:

$$[Zn^{2+}] = \frac{[ZnL_2]}{K[L]^2} = \frac{c_{Zn} - [Zn^{2+}]}{K[L]^2} \quad (3)$$

or

$$\frac{i_{p,0} - i_p}{i_p} = K[L]^2 \quad (4)$$

When the ligand is present in excess, [L] can be considered as c_L, thus the K value can be obtained from the slope of a plot of $\frac{i_{p,0} - i_p}{i_p}$ *vs.* c_L^2.

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