

Synthesis and characterisation of the first transition metal complex of zoxazolamine (2-amino-5-chlorobenzoxazole): the X-ray crystal structure determination of $[\text{ZnCl}_2(\eta^1\text{-N}^{\text{benzoxazole}}\text{-2-amino-5-chlorobenzoxazole})_2]$ [☆]

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Abstract

The synthesis and characterisation (NMR, X-ray, elemental analysis) of the first transition metal complex of Zoxazolamine (**1**: 2-amino-5-chlorobenzoxazole), viz. $[\text{ZnCl}_2(\mathbf{1})_2]$ (**2**) is described; complex **2** is obtained in 77% yield from the treatment of **1** with ZnCl_2 in acetone solution. The Zn compound is a mononuclear species (X-ray) with a distorted tetrahedral array of ligands around the metal centre with the title ligand bound to Zn via the benzoxazole ring N-atom. The structural properties of **2** are discussed in relation to other mononuclear Zn halide complexes.

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Zoxazolamine (**1**: i.e., 2-amino-5-chlorobenzoxazole or 5-chloro-2-benzoxazolamine: Fig. 1 [1]) is a member of the large class of biologically active 2-amino-2-oxazoles [2]. The compound was first synthesised [1] and clinically investigated in the 1950s ¹ and it soon became a useful pharmaceutical in applications requiring a potent skeletal muscle relaxant [3–8]. Later investigations also clearly indicated that **1** has noteworthy uricosuric prop-

erties as well [9,10]. Despite the initial promising applications of **1** in medicine, the use of the drug in humans was discontinued in 1963 due to the identification of a number of toxic side effects [11–13] in some patients. There were at least three deaths that were later linked to the use of the drug [14–16] in humans. Despite this however, **1** is still used extensively in pre-clinical biological modelling studies [17–19]. Specifically, the known (quantified) muscle relaxant (paralytic) potency of **1** (the so-called “Zoxazolamine Effect”) is employed as a benchmark standard when new compounds are tested as inhibitors of muscle relaxants. Compound **1** is also a very common model substrate for enzyme-catalysed oxidation, often involving Cytochrome P-450 [20–23]. Although **1** has been used in biology and medicine for almost fifty years, there is no report detailing the compound’s metal-coordinating ability, neither with

[☆] Oxazoline and related chemistry: Part VII. For part VI, see [30].

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¹ Compound **1** is or has been sold under a number of trade names that include Deflexol, Flexilon, Flexin, Zoxamin and Zoxine.

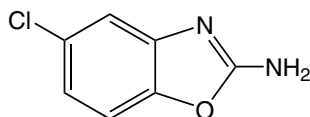
Zoxazolamine: **1**

Fig. 1. The structure of Zoxazolamine.

the biological metals nor any of the other transition and main group elements. Oxazoles and their oxazoline analogues are well known to coordinate to transition metal fragments [24–29] and a large number of such compounds have been isolated from marine organisms that can potentially ligate transition metals [24,25]. Our research endeavours lie in the area of medicinal inorganic chemistry and ligand design [29–34], notably involving substituted oxazoles. Of particular relevance to the work reported herein are the recent investigations of the enzyme inhibiting ability of substituted 4,5-dihydro-2-oxazoles [35–38]. Such compounds are potent inhibitors of Lipid A biosynthesis in Gram negative bacteria (e.g., *Pseudomonas aeruginosa*, *Escherichia coli*). The biological activity is thought to be due to selective coordination of the inhibitor to a specific zinc atom of the enzyme [35,38]. In this communication, we detail the synthesis and characterisation (NMR, X-ray, elemental analysis) of the first transition metal compound of **1** which involves the stable formation of a zinc–zoxazolamine complex.

The treatment of an acetone (~5 mL) solution of **1** (0.50 g: 3.0 mmol) with an acetone (4 mL) solution of ZnCl_2 (0.20 g: 1.5 mmol) and stirring of the resulting mixture gave a light amber coloured solution. The mixture was set aside for 14 h in an attempt to induce crystallisation but no crystals formed and hence the mixture was subsequently stirred at room temperature (RT) for 2 h. Filtration, followed by evaporation of the solvent, yielded an off-white powder. Recovery of this solid was preceded by washing with Et_2O (2×5 mL), a process that leads to the isolation of the white solid *product* (yield 0.54 g: 77%)². Elemental analysis of this material is consistent with the formula $[\text{ZnCl}_2(\mathbf{1})_2]_n$ (i.e., **2**). Complex **2** has a fairly poor solubility in chlorinated solvents and Et_2O and slowly decomposes when placed in water; it is readily soluble in acetone. The ^1H NMR spectrum of **2**² reveals the expected chemical shift differences relative to free zoxazolamine **1**,³ most notably in the signal

² Analytical data for complex **2**: NMR (RT: 200 MHz, acetone- d_6): $\delta_H = 8.25$ (s, br, 2H, NH_2), 7.65 (s, 1H, ArH), 7.42 (d, 1H, $J = 8.6$ Hz, ArH), 7.14 (d, 1H, ArH); elemental analysis: Calc. C, 35.52; H, 2.13; N, 11.83. Found: C, 35.68; H, 2.28; N, 11.77.

³ NMR data for **1** (RT: 200 MHz, acetone- d_6): $\delta_H = 7.22$ (m, 2H, ArH), 6.99 (m, 1H, ArH), 6.92 (s, br, 2H, NH_2).

assigned to the $-\text{NH}_2$ protons. The aromatic protons (Fig. 1) are also slightly shifted and are distinct signals. These results, in combination with the elemental analysis data, suggest the presence of two (symmetry related) and coordinated equivalents of **1** per zinc nucleus but no further overall structural information can be obtained from this data. Zinc halide complexes containing N-donor atom ligands can possess coordination numbers of four, five or six and are known to adopt a wide variety of structural motifs. These can range from a (pseudo) tetrahedral arrangement of ligands around zinc, to square pyramidal and trigonal by pyramidal through to distorted octahedral; multi-metallic species are also not uncommon. As metal complexes of **1** are completely unknown, we carried out a single crystal X-ray diffraction study of complex **2** to elucidate the binding mode of coordinated **1** and the overall solid-state structural aspects of this zinc material. Suitable crystals of **2** were obtained by the gradual mixing of a dichloromethane solution of **2** that had been layered with Et_2O . A diagram of the molecular structure of solid-state **2** is shown in Fig. 2. Complex **2** contains a mononuclear (formally) Zn^{2+} metal atom at the centre of a distorted tetrahedral array of four monodentate ligands. Two equivalents of zoxazolamine are bound to the zinc atom via the benzoxazole ring N-atom, both in an η^1 fashion. The amino groups are not coordinated to the metal but are in relatively close contact with inter- ($\text{N} \cdots \text{Cl} = 3.250$ Å) and intramolecular ($\text{N} \cdots \text{Cl} = 3.323$ Å) chlorine atoms. The rest of the ligand set consists of the two bound (formal) chloride anions. The relevant crystallographic data can

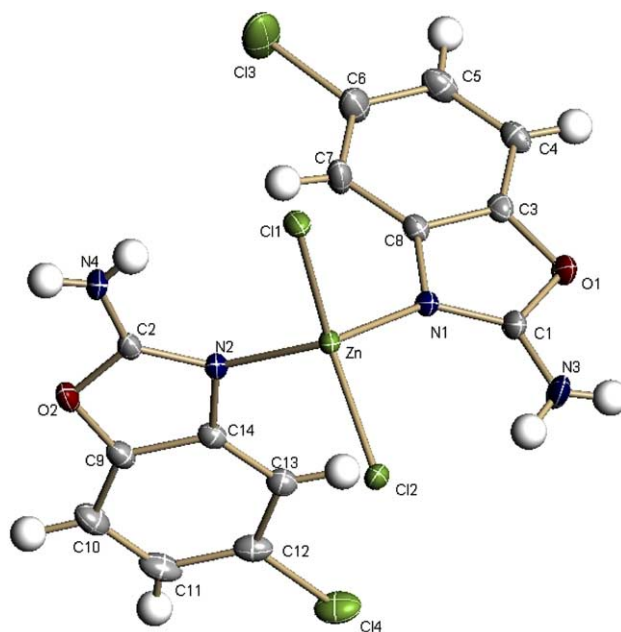


Fig. 2. A diagram of complex **2** showing the atomic numbering scheme (thermal ellipsoids at the 50% level).

Table 1
Pertinent bond lengths (Å) and angles (°) for complex **2**^a

Bonded atoms	Distance	Bonded atoms	Angle
Zn–Cl(1)	2.2273(8)	Cl(1)–Zn–Cl(2)	121.12(3)
Zn–Cl(2)	2.2420(7)	Cl(1)–Zn–N(1)	109.37(7)
Zn–N(1)	2.028(2)	Cl(1)–Zn–N(2)	106.96(7)
Zn–N(2)	2.016(2)	N(1)–Zn–N(2)	104.62(10)
C(1)–N(1)	1.310(4)	N(1)–Zn–Cl(2)	105.91(7)
C(2)–N(2)	1.321(4)	N(2)–Zn–Cl(2)	107.71(7)
C(6)–Cl(3)	1.743(3)	N(2)–C(2)–N(4)	128.0(3)
C(12)–Cl(4)	1.739(4)	N(1)–C(1)–N(3)	128.1(3)

^a Standard deviations for the bond lengths and angles are in parentheses.

be found in the Supplementary Materials. ⁴ A list of pertinent bond lengths and angles is displayed in Table 1. The Cl–Zn–Cl and N–Zn–N angles (121.12(3)° and 104.62(10)°, respectively) are in the range typical for a tetrahedral Zn²⁺ nucleus [29,39–46] and can be compared with the corresponding angles of [ZnCl₂(η¹-N^{thiazole}-2-amino-2-thiazole)₂] (113.47(3)° and 109.61(9)°: **3**) [39], [ZnCl₂(η¹-N-2-phenyl-2-oxazoline)₂] (111.97(3)° and 103.70(7)°: **4**) [29] and in the bis-oxazoline complex: [(2,2'-thiobis[(4*S*)-4-isopropyl-1,3-oxazolinyl-phenyl]) zinc dichloride] (116.70(3)° and 99.70(7)°) [41]. It should be noted that in all three of these cases, the acute angle between similar donor atoms is between the two *N*-donors and the zinc metal centre, as is the case with **2**; hence, the Cl–Zn–Cl bond angle is the larger of the two. This trend is reversed in the related oxazole species [ZnCl₂(η¹-N-{5-β-methylallyl-2-phenyl-1,3-oxazole})₂] (109.6(1)° and 114.6(2)°) [40]. The Zn–N (2.016(2) and 2.028(2) Å) and Zn–Cl bond lengths (2.2273(8) and 2.2420(7) Å) of **2** are unsurprising and can be compared to the related values in **3** (Zn–N_{av}, 2.019(2); Zn–Cl_{av}, 2.255(8) Å) and **4** (Zn–N_{av}, 2.067(4); Zn–Cl_{av}, 2.239(2) Å) [29,39]. The crystal structure of “free” Zoxazolamine has not been disclosed [47]. However, X-ray data of

acid–base adducts of [**1** + H]⁺ with the anion 2-(3,4-dichlorophenyl)oxy)acetate [48] and other acetates [49,50] has appeared. In addition, the benzoxazole ring structure of **1** is similar to that found in the crystallographically characterised natural product (+)-iforrestine [51]. The overall structure of zinc-bound **1** is not significantly different from that of **1** in the above co-crystals and adducts [48–50].

In conclusion, the first transition metal complex of Zoxazolamine (**1**), viz. [bis-(η¹-*N*-zoxazolamine)zinc(II) chloride] (**2**) has been synthesised and fully characterised (NMR, X-ray, elemental analysis). Complex **2** exists as a neutral mononuclear species with a distorted tetrahedral array of two chloride and two zoxazolamine ligands; the latter fragment is bound to Zn through the benzoxazole ring N-atom lone electron pair. Future work will entail the investigation of related bio-inorganic complexes of **1** and a study of their biological properties.

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⁴ Supplementary materials:

X-ray data of complex **2**: FW = 473.43; Formula: C₁₄H₁₀N₄O₂Cl₄Zn; Temp.: 198(1) K; λ = 0.71073 Å; Crystal system: triclinic; Space group: P $\bar{1}$; Unit cell dimensions: *a* = 7.1958(5) Å; *a* = 105.291(1)°; *b* = 9.4253(6) Å; β = 92.834(1)°; *c* = 13.7528(1) Å; γ = 94.660(1)°; Vol. = 894.32(10) Å³; *Z* = 2; Density (calc.): 1.758 mg/m³; Absorption coefficient: 1.986 mm⁻¹; *F*(000): 472; Crystal size: 0.05 × 0.15 × 0.175 mm³; colour/habit: colourless/parallelepiped; θ range for data collection: 1.54–27.50°; Index ranges: −9 ≤ *h* ≤ 9, −12 ≤ *k* ≤ 12, −17 ≤ *l* ≤ 17; Independent reflections: 3290 [*R*(int) = 0.0220]; Completeness to θ = 27.50°: 95.3%; Absorption correction: SADABS; Refinement method: Full-matrix least-squares on *F*²; Data/restraints/parameters: 3920/0/266; Goodness-of-fit on *F*²: 1.080; Final *R* indices [*I* > 2σ(*I*): *R*₁ = 0.0379, *wR*₂ = 0.0963; *R* indices (all data): *R*₁ = 0.0464, *wR*₂ = 0.1004; Largest diff. peak and hole: 2.152 and −1.452 e Å⁻³. Data tables and experimental procedures are available from the authors on request; full details can also be found from CCDC 245372 and is available free on request at request@ccdc.ac.uk.

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