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Note

Novel palladium(II) and platinum(II) complexes of biocidal benzisothiazolinone (Bit); X-ray crystal structures of co-crystallised Bit/BitO and *cis*-Pd(en)(Bit_{-1H})$_2$·H_2O

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ABSTRACT

Reaction of benzisothiazolinone (Bit), a well-known biocide, with the Pd(II) and Pt(II) am(m)ine precursors *cis*-[Pd(en)(H_2O)$_2$](NO_3)$_2$ and *cis*-[Pt(NH_3)$_2$(H_2O)$_2$](NO_3)$_2$ yielded *cis*-Pd(en)(Bit_{-1H})$_2$ and *cis*-Pt(NH_3)$_2$(Bit_{-1H})$_2$, respectively. Bit is bound to the metal centres in both cases through the deprotonated isothiazolinone *N*. The crystal structures of a Bit/BitO co-crystal and *cis*-Pd(en)(Bit_{-1H})$_2$·H_2O are also described.

1. Introduction

Platinum group metals are the subject of intense interest owing to their rich and diverse coordination chemistry [1,2], biological activity [3–7] and applications as catalysts [8–12]. We have been interested in the metal binding properties of hydroxamic acids [13], with a particular interest in their reactions with platinum group metals, of which there is little information in the literature [14]. We recently for example reported a series of Pt(II) [15–17] and Ru(III) [18–20] hydroxamato and hydroximato [19] complexes. The complexation behaviour of hydroxamic acids can be enhanced and tailored by the incorporation of ancillary coordinating groups [13,14,21], such as amino or thiol groups, at adjacent sites in the molecule.

With a view to investigating the different metal coordination modes of 2-mercaptobenzohydroxamic acid, an attempted synthesis did not yield the desired hydroxamic acid but benzisothiazolinone (Bit).

Bit, first synthesised in 1923 [22], is a widely used preservative and biocide with potent antimicrobial [23], and antifungicidal [23] properties and is structurally similar to the well-known artificial sweetener Saccharin).

Surprisingly and in direct contrast with Saccharin [24–26] there are no reported metal complexes of Bit in the literature. Bit is potentially a versatile polyfunctional ligand and offers the possibility of coordination to metal centres via a number of chelation modes, including N, O or S monodentate coordination or bidentate chelation.

Herein we report the complexation behaviour of Bit in relation to the soft (HSAB) square planar Pd(II) and Pt(II) centres.

2. Experimental

2.1. Materials

Methylthiosalicylate and hydroxylamine hydrochloride were purchased from Aldrich and used without further purification. *cis*-[Pt(NH_3)I_2] [27] and *cis*-[Pd(en)Cl_2] [28] were synthesised as previously reported.

2.2. Instrumental methods

IR spectra were recorded as KBr discs (4000–400 cm^{-1}) on a Mattson Genesis II CSI FTIR spectrometer and the spectra analysed using WinFirst software. ^1H NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer and the spectra analysed using TopSpin 1 software. The residual undeuterated DMSO signal at 2.505 ppm was used as an internal reference. Liquid chromatography–mass spectrometry experiments were performed on a Quattro Micro quadrupole electrospray mass spectrometer (Micromass, Waters Corp., USA): 10 μL of the samples were injected in 300 μL of acetonitrile:water (60:40, v/v). The mass spectrometry data were acquired both in positive and negative ion modes. Crystal

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analyses were determined on a Bruker Smart Apex CCD diffractometer. Elemental analysis was performed by the RCSI Analytical Service, Department of Pharmaceutical and Medicinal Chemistry, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland.

2.3. Synthesis of Benzisothiazolinone (Bit)

Hydroxylamine hydrochloride (4.16 g, 60 mmol) was added to an aqueous sodium hydroxide (4.80 g, 120 mmol) solution ($25\ cm^3$) and then added dropwise to a methanolic solution ($50\ cm^3$) of methylthiosalicylate (5 g, 30 mmol). The solution was stirred at room temperature for 72 h, after which time the solution was acidified to pH 4.5 using 5% HCl solution. A white solid precipitated, which was filtered and dried. The white solid was recrystallised from hot water:methanol (2:1) to give white crystals of Bit. Yield: 1.5 g, 33%. *Anal.* Calc. for C_7H_5NOS: C, 55.61; H, 3.33; N, 9.26; S, 21.21. Found: C, 55.22; H, 3.30; N, 9.03; S, 21.20%. ν_{max}/cm^{-1} 3039s, 3058s (N–H), 1655vs, 1636vs (C=O); δ_H (400 MHz, d6 DMSO): 11.89 (1H, br s, NH), 7.98 (1H, d, ^3J 8.0 Hz, aromatic H), 7.88 (1H, d, ^3J 7.8 Hz, aromatic H), 7.61 (1H, t, ^3J 7.5 Hz, aromatic), 7.41 (1H, t, ^3J 7.5 Hz, aromatic H); ESI-MS *m/z*: 152 ($[M-H]^+$).

Good-quality crystals of a benzisothiazolinone:benzisothiazolinone-1-oxide, Bit/BitO, co-crystal were obtained from the filtrate after 1 month standing at room temperature.

2.4. Synthesis of cis-Pd(en)(Bit$_{-1H}$)$_2$·H$_2$O

$Pd(en)Cl_2$ (0.19 g, 0.80 mmol) and $AgNO_3$ (0.27 g, 1.56 mmol) in deionised water ($15\ cm^3$) were stirred overnight in the dark. The insoluble AgCl was filtered and Bit (0.25 g, 1.68 mmol) dissolved in an aqueous solution ($5\ cm^3$) of NaOH (0.067 g, 1.68 mmol) was added to the filtrate. A cream/yellow solid precipitated instantly. The reaction was stirred at room temperature for 1 h, filtered, washed with cold H_2O and dried over P_2O_5. Yield: 0.26 g, 68%. *Anal.* Calc. for $C_{16}H_{18}N_4O_3PdS_2$: C, 39.63; H, 3.74; N, 11.55; S, 13.23. Found: C, 39.25; H, 3.55; N, 11.32; S, 13.05%. ν_{max}/cm^{-1} 3224s, 3196s (N–H, NH_2), 1656vs, (C=O); δ_H (400 MHz, d6 DMSO): 7.69 (2H, d, ^3J 7.7 Hz, aromatic H), 7.62 (2H, d, ^3J 8.0 Hz, aromatic H), 7.39 (2H, dt, ^3J 7.8 and ^4J 1.2 Hz, aromatic H), 7.22 (2H, dt, ^3J 7.0 and ^4J 0.8 Hz, aromatic H), 5.47 (4H, br, s, NH_2), 2.59 (4H, br, s, CH_2); ESI-MS *m/z*: 466 ($[M-H]^+$).

Good-quality crystals of *cis*-Pd(en)(Bit$_{-1H}$)$_2$·H$_2$O were obtained from a cooled, saturated aqueous methanol solution.

2.5. Synthesis of cis-Pt(NH$_3$)$_2$(Bit$_{-1H}$)$_2$.DMF

Cis-$Pt(NH_3)I_2$ (0.54 g, 1.12 mmol) and $AgNO_3$ (0.37 g, 2.19 mmol) in deionised water ($15\ cm^3$) were stirred overnight in the dark. The insoluble AgI was filtered and Bit (0.37 g, 2.46 mmol) dissolved in an aqueous solution ($5\ cm^3$) of NaOH (0.098 g, 2.46 mmol) was added to the filtrate. A yellow solid precipitated instantly. The reaction was stirred at room temperature for 1 h, filtered, washed with cold H_2O and dried over P_2O_5. The yellow solid was subsequently recrystallised from a cooled, saturated DMF solution. Yield: 0.34 g, 50%. *Anal.* Calc. for $C_{17}H_{23}N_5O_3PtS_2$: C, 33.77; H, 3.83; N, 11.58; S, 10.61. Found: C, 33.38; H, 3.50; N, 11.26; S, 10.36%. ν_{max}/cm^{-1} 3200s, 3097s (N–H, NH_3), 1663vs (C=O); δ_H (400 MHz, d6 DMSO): 7.69 (2H, d, ^3J 7.8 Hz, aromatic H), 7.61 (2H, d, ^3J 8.3 Hz, aromatic H), 7.39 (2H, t, ^3J 7.5 Hz, aromatic H), 7.22 (2H, t, ^3J 7.3 Hz, aromatic H), 4.67 (6H, br, s, NH_3); ESI-MS *m/z*: 530 ($[M-H]^+$).

Table 1
Crystallographic data collection and experimental conditions for Bit/BitO and *cis*-Pd(en)(Bit$_{-1H}$)$_2$·H$_2$O.

Compound	Bit/BitO	*cis*-[Pden(Bit$_{-1H}$)$_2$]·H$_2$O
Empirical formula	$C_{14}H_{10}N_2O_3S_2$	$C_{16}H_{18}N_4O_3S_2Pd$
Temperature	293(2) K	100(2) K
Crystal system	monoclinic	triclinic
Space group	$P2_1/n$ (#14)	$P\bar{1}$ (#2)
a (Å)	14.1571(12)	5.5189(4)
b (Å)	6.9559(6)	10.0133(8)
c (Å)	15.1323(13)	16.7384(13)
α (°)	90	72.199(2)
β (°)	111.288(1)	85.255(2)
γ (°)	90	85.7870(10)
Z	4	2
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
Goodness-of-fit (GOF) on F^2	1.042	1.058
Reflections collected	21 905	10 711
Independent reflections	3023 [R_{int} = 0.0213]	4901 [R_{int} = 0.0235]

2.6. X-ray data collection and structure determination for Bit/BitO and cis-Pd(en)(Bit$_{-1H}$)$_2$·H$_2$O

Crystal data and experimental details for Bit/BitO and *cis*-Pd(en)(Bit$_{-1H}$)$_2$·H$_2$O are summarised in Table 1. Additional data are available in the Supplementary material. X-ray data were collected with a Bruker Smart Apex CCD diffractometer at 293 and 100 K, respectively using monochromated Mo Kα radiation, (λ = 0.71073 Å) and the ϕ–ω scan method. The structures were solved by direct method (SHELXS-97) [29] and refined by full-matrix least-squares using SHELXL 97-2 package [29].

3. Results and discussion

3.1. Synthesis and spectroscopic characterisation of Bit

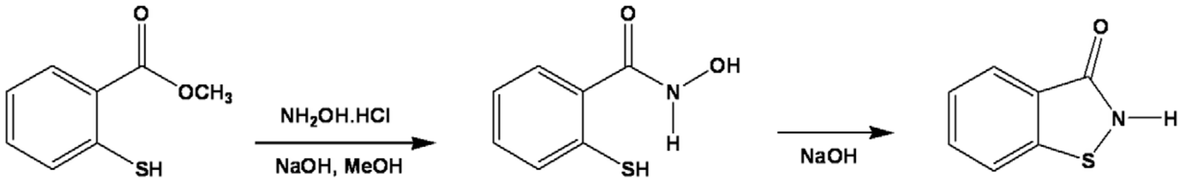
Bit was unexpectedly synthesised by reacting methyl thiosalicylate with hydroxylamine hydrochloride in the presence of NaOH (Scheme 1). Synthesis of Bit has been previously reported and *via* a number of routes; the transamination of sulfonamides [30], the cyclisation of acyl azides [31] and significantly the cyclisation of thiobenzohydroxamic acids [32]. Therefore it is proposed that reaction of methyl thiosalicylate with a twofold excess of hydroxylamine and fourfold excess of base initially gave 2-mercaptobenzohydroxamic acid, which subsequently cyclised in the presence of NaOH to give Bit (Scheme 1).

Bit was obtained in low yield but excellent purity and was characterised by elemental analysis, IR and ^1H NMR spectroscopy and mass spectrometry. The IR spectrum of Bit contains bands at 1655 and 1637 cm^{-1} which may be assigned as the symmetric and asymmetric stretches corresponding to ν(C=O). The ^1H NMR spectrum of Bit in d6 DMSO shows an N–H resonance at 11.89 ppm and exhibits 4 resonances at 7.98, 7.88, 7.61 and 7.41 ppm corresponding to the four aromatic protons. ESI-MS in the positive mode assisted in identifying Bit with a mass peak at 152 amu.

Good-quality crystals of co-crystallised Bit/BitO were obtained from the mother liquor after 1 month standing suggesting that Bit is air oxidised over time to give the corresponding 1-oxide, BitO.

3.2. X-ray structural characterisation of Bit/BitO

The structure of co-crystallised Bit/BitO is shown in Fig. 1; selected bond lengths and angles are given in the Supplementary



Scheme 1. Synthesis of Bit.

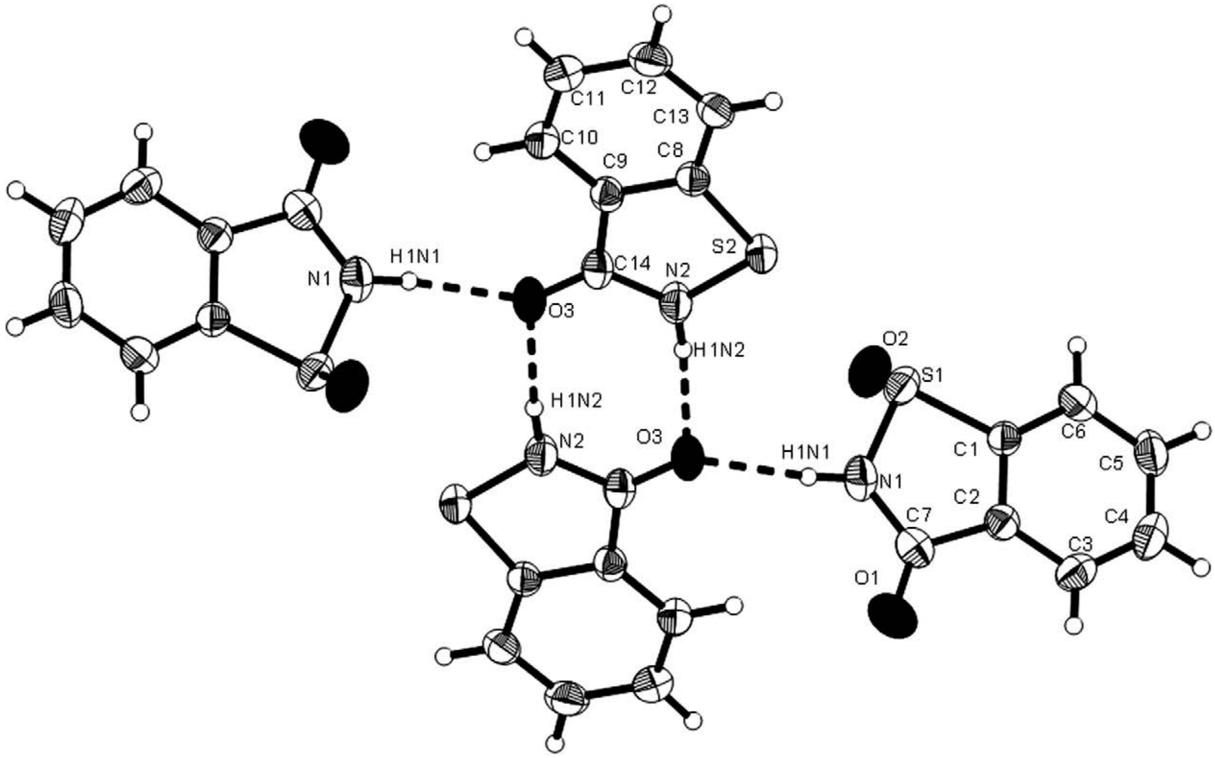


Fig. 1. ORTEP diagram of Bit/BitO. Thermal ellipsoids are drawn at the 40% probability level.

material. The crystal packing of Bit/BitO features H-bonded centrosymmetric dimers of Bit molecules, a motive frequently encountered in crystals of amides and hydroxamic acids. In addition, the O3 atom of the Bit molecule acts as an H-bond acceptor for the NH-group of the BitO molecule. The C=O and N–S bond lengths both in Bit [1.204(2) and 1.6843(2) Å] and BitO molecule [1.2496(19) and 1.6965(14) Å] compare favourably with those observed in saccharin [1.220(2) and 1.663(2) Å, respectively] [33]. The 1-oxide S=O bond length, 1.4694(14) Å, is also close to the lengths of analogous bonds in saccharin [1.427(2) and 1.428(2) Å] [33].

3.3. Synthesis and characterisation of cis-Pd(en)(Bit$_{-1H}$)$_2$ and cis-Pt(NH$_3$)$_2$(Bit$_{-1H}$)$_2$

Cis-Pd(en)Cl$_2$ and *cis*-Pt(NH$_3$)$_2$I$_2$ were selected for the synthesis and characterisation of Pd(II) and Pt(II) Bit complexes. We envisaged that the presence of the diam(m)ine ligands would prevent the possible formation of complex polymeric species. *Cis*-Pd(en)Cl$_2$ and *cis*-Pt(NH$_3$)I$_2$ were initially treated with 1.95 equivalents of AgNO$_3$ to give the intermediates, *cis*-[Pd(en)(H$_2$O)$_2$](NO$_3$)$_2$ and *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$](NO$_3$)$_2$, respectively.

As Bit is relatively insoluble in water, a 2.1 fold excess of the water soluble sodium Bit$_{-1H}$ was added to *cis*-[Pd(en)(H$_2$O)$_2$](NO$_3$)$_2$ and *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$](NO$_3$)$_2$ in water, affording immediately the yellow solids, *cis*-Pd(en)(Bit$_{-1H}$)$_2$ and *cis*-Pt(NH$_3$)$_2$(Bit$_{-1H}$)$_2$ in good yield and high purity.

Micro-analytical data are consistent with the presence of one diam(m)ine Pd(II) or Pt(II) moiety bound to two Bit$_{-1H}$ ligands and the absence of counterions suggesting neutral complexes. The presence of two Bit$_{-1H}$ ligands per Pd(II) or Pt(II) centre suggests that Bit$_{-1H}$ coordinates in a monodentate fashion.

In the ^{1}H NMR spectrum of both the Pd(II) and Pt(II) complexes, the isothiazolinone N–H resonance of the uncoordinated Bit ligand (cf. 11.89 ppm) is clearly absent indicative of Bit$_{-1H}$ coordination through the deprotonated isothiazolinone *N*. Four very similar resonances (7.69, 7.62, 7.39, 7.22 and 7.69, 7.61, 7.39, 7.22 ppm, respectively) are observed for the Pd(II) and Pt(II) complexes, respectively and correspond to the eight protons of the two aromatic rings. The aromatic protons are shifted upfield when compared with those of the uncoordinated ligand (cf. 7.98, 7.88, 7.61 and 7.41 ppm). In the Pd(II) complex the amine proton signals at 5.47 ppm are observed as a broad singlet and the methylene protons as a broad singlet at 2.59 ppm, whereas in the Pt(II) complex the ammine proton signals are observed as a broad singlet at 4.67 ppm.

IR spectra of the Pd(II) and Pt(II) complexes exhibit distinctive ν(C=O) at 1656 and 1663 cm^{-1}, respectively, which is not consistent with complexation via the ν(C=O) of Bit as one would expect a decrease in the ν(C=O) of the free ligand (cf. 1655 cm^{-1}). ESI-MS

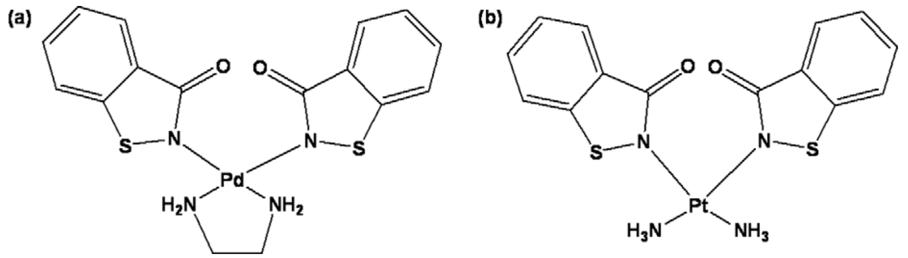


Fig. 2. Structure of (a) *cis*-Pd(en)(Bit_{-1H})$_2$ and (b) *cis*-Pt(NH_3)$_2$(Bit_{-1H})$_2$.

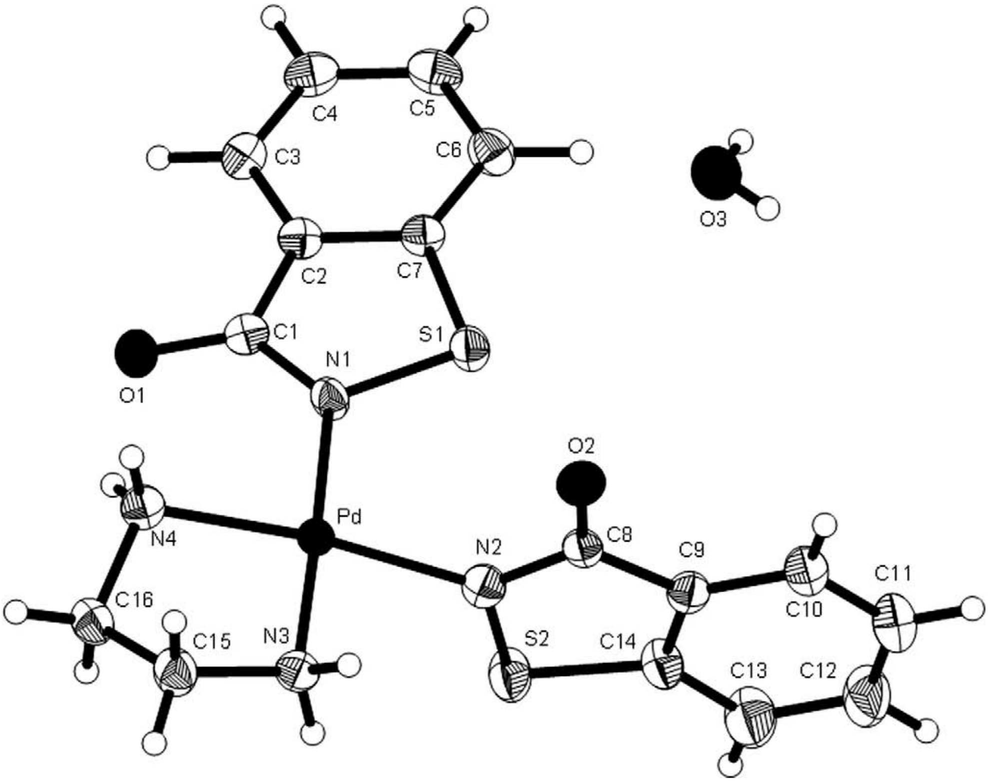


Fig. 3. ORTEP diagram of *cis*-Pd(en)(Bit_{-1H})$_2$·H_2O. Thermal ellipsoids are drawn at the 80% probability level.

in the negative mode was used to unequivocally identify *cis*-Pd(en)(Bit_{-1H})$_2$ and *cis*-Pt(NH_3)$_2$(Bit_{-1H})$_2$ with mass peaks at 466 and 530 amu, respectively and both spectra display the correct isotopic patterns.

Bit coordination through the deprotonated isothiazolinone *N* to give *cis*-Pd(en)(Bit_{-1H})$_2$ and *cis*-Pt(NH_3)$_2$(Bit_{-1H})$_2$ (Fig. 2) is confirmed by the complexes similar IR and ^{1}H NMR spectral data and the X-ray structural characterisation of *cis*-Pd(en)(Bit_{-1H})$_2$.

3.4. X-ray structural characterisation of cis-Pd(en)(Bit_{-1H})$_2$·H_2O

The structure of *cis*-Pd(en)(Bit_{-1H})$_2$·H_2O is shown in Fig. 3; selected bond lengths and angles are given in the Supplementary material. The metal atom has a slightly distorted square planar coordination. Two Bit_{-1H} ligands are in *cis*- positions, and both are bound to Pd via their deprotonated isothiazolinone N atoms. The Pd–N1 and Pd–N2 bonds, 2.0316(18) and 2.0293(17) Å, however show no difference from the purely coordination Pd–N3 and Pd–N4 bonds, 2.0293(17) and 2.0248(19) Å, respectively. The five-membered chelate ring has an envelope conformation with the C16 atom being displaced by 0.651 Å from the Pd, N3, N4, C15 mean plane.

The planes of two Bit_{-1H} ligands show quite different orientations with respect to the coordination plane of the Pd centre. Indeed, the N1, S1, C1–C7 plane forms dihedral angle of 22.64(8) degrees with the Pd coordination plane, whereas the N2, S2, C8–C14 plane is almost orthogonal to the Pd plane (the dihedral angle is 88.22(4)°).

4. Conclusion

The syntheses of Bit, *cis*-Pd(en)(Bit_{-1H})$_2$ and *cis*-Pt(NH_3)$_2$(Bit_{-1H})$_2$ including X-ray crystal structures of co-crystallised Bit/BitO and *cis*-Pd(en)(Bit_{-1H})$_2$·H_2O were presented. Coordination of Bit to Pt(II) and Pd(II) *via* the deprotonated isothiazolinone *N* has been established. Given that Bit is a potent biocide and potentially a versatile polyfunctional ligand, novel metal complexes of Bit, including those of Pd and Pt, may have applications as antimicrobial agents.

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Appendix A. Supplementary material

CCDC 730373 and 730374 contain the supplementary crystallographic data for Bit/BitO and *cis*-[Pden(Bit$_{-1H}$)$_2$]·H_2O. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2010.02.005.

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