New Dinuclear Palladium Phosphane Complexes Stabilised by 8-Thiotheophylline

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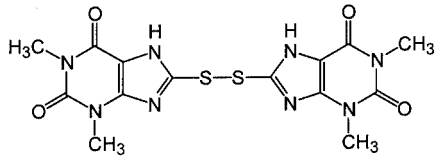
The new purine derivatives SS-bis-8-(thio)-theophylline (8-$BTTH_2$) and 8-phenylthiotheophylline (8-PhTTH), have been synthesised and characterised by elemental analysis, mass spectrometry and standard spectroscopic measurements. Reaction of 8-$BTTH_2$ with *cis*-$[PdCl_2(PPh_3)_2]$ leads to the formation of the binuclear palladium complex $[Pd(PPh_3)(\mu\text{-}Cl)(8\text{-}TT)]_2$ (8-TTH_2 = 8-thiotheophylline) in which PPh_3-induced cleavage of the S–S bridge takes place. This complex reacts with pyridine to give a different dimeric palladium complex, $[Pd(\mu\text{-}S,N\text{-}8\text{-}TT)(PPh_3)Py]_2$, in which each of the two 8-thio-(theophylline) anions binds two metals through the N7 and S atoms. The process leading to the palladium complex has also been elucidated.

Introduction

The interaction between metal ions and purine bases has been an important area of research in recent years. This is mainly a consequence of the biological relevance of purines, which are one of the principal constituents of nucleic acid derivatives.[1,2] Purines possess a variety of potential donor groups in their molecular skeleton and consequently behave as effective ligands towards a wide range of metal ions. Coordination to a metal ion often alters the main chemical properties of the purine molecules.[3,4] As a consequence, some metal complexes are active drugs for medical purposes.[5] The most well-known and best studied metal-based drugs are the anticancer compounds of platinum.[6]

A deep knowledge of the action mechanism of the drugs is indispensable in designing improved drugs with increased potency and reduced side effects. Ligand exchange plays an important role in determining the biological activity, as very few metal-based drugs reach the biological target without being modified. Most of them interact with different macromolecules, such as S-donor compounds, and/or water. Therefore, understanding how a drug is transformed upon interacting with biological ligands has become of paramount importance. Usually, the biomolecules that interact with and alter the metal-based drug, provoking a specialised therapeutic effect, are structurally complicated. As a consequence, it is useful to mimic their reactivity towards the metal centre through simplified model molecules. Aiming at obtaining a new simple model for addressing the interaction of purines with transition metal ions, we have synthesised the new ligand *S*,*S*-bis(8-thiotheophylline) (**1**,8-$BTTH_2$) (Scheme 1) in which two purines are linked by a disulfide group bonded through the C8 atom. This ligand can indeed interact with a metal ion through either the imidazolic N7 atom or the exocyclic O atoms, but the possibility of the sulfur atoms of the disulfide group coordinating to the metal also exists. Accomplishing the latter S-coordination is also important to mimic the coordination abilities of disulfide groups in biomolecules.



8-$BTTH_2$ (**1**)

Scheme 1

The evaluation of the chemical properties of the interaction of **1** with *cis*-$[PdCl_2(PPh_3)_2]$ shows that it is of interest as a biological model. Palladium is a biologically active metal, somewhat similar to platinum, although more reactive, and widely used to promote homogeneous catalytic processes and highly efficient organic syntheses.[7] In the case at hand, the presence of two PPh_3 ancillary ligands, not only makes the palladium complexes soluble in common organic solvents but also provides an NMR-active label, the P-nucleus of the phosphane, which allows us to study its reaction with **1** by $^{31}P\{^1H\}$ NMR spectroscopy.

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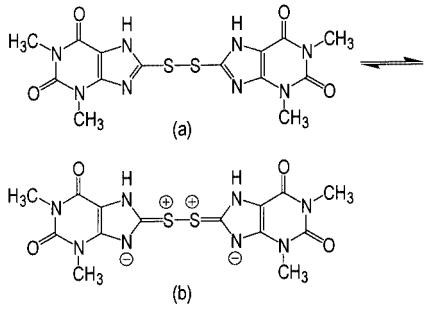
Results and Discussion

Synthesis and Characterisation of *S*,*S*-bis(8-thitheophylline) (1)

The oxidation of the 8-thiotheophillinate potassium salt by the smooth oxidant I_2, which was prepared in situ by reaction of 8-thiotheophylline (8-TTH_2) with KOH, affords the new purine derivative *S*,*S*-bis(8-thiotheophylline) in which two theophylline molecules are held together, through their C8 atoms, by a disulfide bridge.

The IR spectrum of **1** shows a simplification and an intensity reduction of the absorption bands between 2500 and 3700 cm^{-1} compared to that of the parent 8-TTH_2 molecule, which is in agreement with the formation of the disulfide bridge. Key points of the ^1H NMR spectroscopic analysis are the absence of the 8-TTH_2 N−H resonances[8] (δ = 12.95 and 13.36 ppm) and the observation of a unique broad signal at δ = 4.67 ppm that can only be assigned to the imidazolic N−H resonance. The chemical shift of the N7−H proton in **1** appears in the range expected for aliphatic amines, in agreement with their basic character. This fact is better understood by assuming the existence of a partial negative charge on the purine imidazolic ring (Scheme 2). The charge separation may simply be accomplished by moving a lone pair from each of the two S atoms to each of the C8 purine imidazolic carbon atoms. In the resonance structure (b), the S atoms bear a positive charge and, therefore, are well suited to be attacked by nucleophiles. The low acidity of the N7 proton indeed suggests a large contribution of the structure (b) and points to the tendency of this new purine derivative to react with electron rich species through the disulfide group.



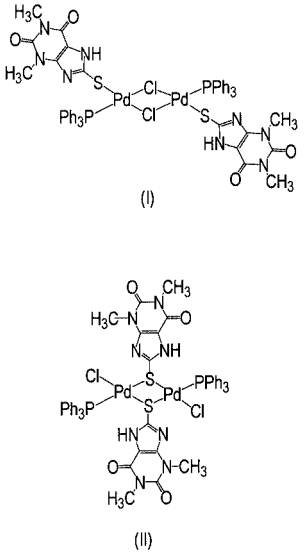
Scheme 2

The $^{13}C\{^1H\}$ NMR spectrum provides the conclusive evidence that confirms the proposed structure for **1**. Particularly, and in keeping with the presence of a substituted S atom, the C-8 resonance appears much closer (δ = 148 ppm) to that in 8-methylthiotheophylline (δ = 153.0 ppm)[12] than in 8-TTH_2 (δ = 163.8 ppm).[13]

Characterisation and Mechanistic Studies of the Formation of the Palladium Complexes 6 and 7

Different synthetic strategies may be used to prepare **6**: (i) the reaction of **1** with *cis*-$[PdCl_2(PPh_3)_2]$ and KOH in refluxing EtOH, (ii) the reaction of **1** with KOH and $Na_2[PdCl_4]$ and PPh_3 in EtOH/H_2O, and (iii) the reaction of **2**, (**3** or **4**) with *cis*-$[PdCl_2(PPh_3)_2]$ (or $Na_2[PdCl_4]$ and PPh_3) in EtOH under reflux. It is also important to point out that **6** was obtained from the above reactions with high yields irrespective of the molar ratio used. However, a higher yield was obtained from method (ii) using a 1:2:2:4 molar ratio between **1**, KOH, Pd^{2+}, and PPh_3.

Unfortunately, **6** was not soluble enough in the non-coordinating solvent to obtain its ^1H, $^{31}P\{^1H\}$ and $^{13}C\{^1H\}$ NMR spectra.[9] We could conclude that the palladium complex **6** contains a PPh_3 group, a chloride ligand and an 8-TTH^- ligand, the latter coordinated through the S donor atom [ν(N7-H) = 3059−2790 cm^{-1}] on the basis of the synthetic procedures, the elemental analysis and IR spectrum. In order to complete the square-planar geometry around the palladium atom, one can hypothesise that a dimeric structure exists in which the bridging tethering ligand is either the chloride (I) or the sulfur atom of the purine group (II) (Scheme 3). Both structures are realistic and have several precedents in the relevant literature.[10−13]



Scheme 3

Although a definitive comparison between the two proposed structures was not possible on the basis of the data collected, an important element in distinguishing between them comes from the observation that dimeric palladium(II) complexes with halide bridges are readily cleaved by unidentate ligands such as pyridine or PPh_3, while the corresponding palladium(II) thiolato bridges are not.[14−16] Since **6** readily reacts with pyridine to give **7**, we may reasonably assume that structure (I) is much more probable than (II).

In order to understand better the metal-purine interaction in the present palladium complexes, we have decided to study the mechanism responsible for the surprising formation of complex **7**, carrying out a variety of experiments that are discussed below. The first aim of our study was to elucidate the process responsible for the S−S bond

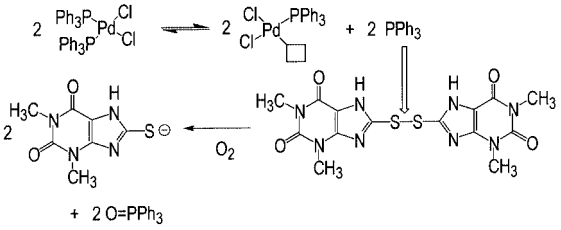
breakage, a result which is quite surprising. The rupture of the S−S bond during the reaction leading to **6** and **7** needs a reducing agent that provides the necessary electrons to accomplish the reduction. Therefore, it is conceivable that the disulfide bond of **1** breaks during the synthetic process leading to **6** and, therefore, it is plausible that one or more compounds implicated in the reaction should take the role of the reducing agent.

Of the several experiments carried out in order to understand the nature of the compounds responsible for the in situ reduction of the disulfide it is worth mentioning the stability tests of **1** in different solvents and pH, and the reactivity tests of 8-TTH_2, **1**, **2**, **3**, and **4** with *cis*-$[PdCl_2(PPh_3)_2]$ (or $[PdCl_4]^{2-}$ and PPh_3) carried out using different stoichiometries and pH conditions. From a perusal of these experiments we may conclude that: a) EtOH and MeOH, in both basic (KOH, pyridine) or acidic (HCl) conditions, do not reduce **1** even after prolonged reflux (up to two days); b) compound **6** was obtained irrespective of the molar proportion of the reagents; c) there are many pathways to access **6** in refluxing EtOH; d) to obtain **6** from 8-TTH_2 a basic medium (KOH or NaOH) is mandatory.

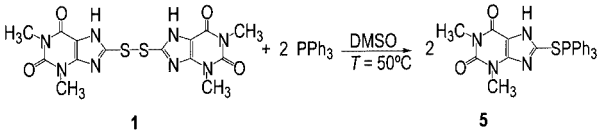
Monitoring the reaction between **1** and *cis*-$[PdCl_2(PPh_3)_2]$ by $^{31}P\{^1H\}$ and ^1H NMR spectroscopy provided additional pieces of information to clarify the reduction step of the S−S bond. This study was carried out as follows: ligand **1** and *cis*-$[PdCl_2(PPh_3)_2]$ (1:2 molar ratio) were placed into an NMR tube and CD_3OD was added from a syringe at 20 °C. At this temperature a $^{31}P\{^1H\}$ NMR spectrum was immediately acquired, showing only the *cis*-$[PdCl_2(PPh_3)_2]$ resonance. A reaction only took place after heating the solution to 50 °C. After 6 hours of heating at this temperature, the *cis*-$[PdCl_2(PPh_3)_2]$ resonance was no longer observed while the $^{31}P\{^1H\}$ resonance of $O{=}PPh_3$ appeared (δ = 29.58 ppm, confirmed also by GC-MS analysis) and a red orange precipitate was formed. This precipitate was filtered out from the solution, washed with ethanol and dried. On the basis of IR data the red solid was assigned as **6**.

An interpretation of the above results suggests that the reducing agent responsible for the S−S bond cleavage should be the PPh_3. In effect, the phosphane may be readily produced from *cis*-$[PdCl_2(PPh_3)_2]$ (Scheme 4) through a dissociation equilibrium[17,18] and its capacity to efficiently reduce disulfide groups in proteins and other disulfide derivatives has been documented.[19] In order to confirm whether PPh_3 is the only reducing agent or whether the palladium metal also plays a role in this process, the reactivity of **1** with PPh_3 in MeOH and DMSO as well as of **3** with PPh_3 in MeOH were studied in situ, carrying out bulk experiments.

From these experiments, we may conclude that PPh_3 alone is responsible for the cleavage of the S−S bond in **1** while the metal plays no role in the process. In this regard, it is important to stress that during the in situ reaction between **1** and PPh_3 in CD_3OD, $O{=}PPh_3$ is produced in quantitative yield. On carrying out the same reaction in DMSO (Scheme 5) the phenylthiotheophylline (**5**, 8-PhTTH), a new thiopurine containing an S-PPh_3 group, was formed. Compound **5** was fully characterised (see Exp. Sect.), but for the present discussion it is important to stress that in the $^{13}C\{^1H\}$ NMR spectrum, C8 resonates at δ = 170.3 ppm ([D_6]DMSO), very deshielded with respect to the corresponding signal for the *S*-alkyl-substituted 8-TTH_2 derivatives[11] ($\delta \approx 150$ ppm).



Scheme 4

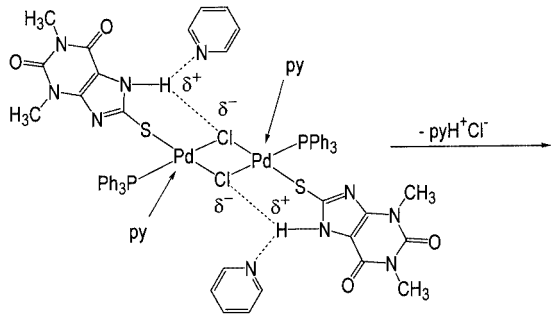


Scheme 5

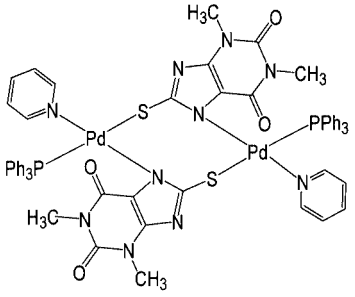
Finally, the orange compound **6** reacts simply with pyridine to give **7** which likely forms via cleavage of the bridging structure followed by nucleophilic substitution of the bridging chloride ligand by pyridine (Scheme 6).[21,22] In this basic medium, deprotonation of the N7 imidazolic nitrogen easily takes place to yield the corresponding anion which may coordinate to the palladium metal. Moreover, and in keeping with this overall mechanism, formation of PPh_3 is not observed by NMR spectroscopic methods when **6** is dissolved in [D_5]pyridine.

Crystal Structure of $[Pd(\mu\text{-S},N\text{-8-TT})(PPh_3)Py]_2{\cdot}9H_2O$ (7)

Orange prismatic crystals of the dimeric palladium complex $[Pd(\mu\text{-S},N\text{-8-TT})(PPh_3)Py]_2{\cdot}9H_2O$ (**7**) suitable for an X-ray study were obtained from a pyridine/acetonitrile solution of complex **6**. Although both IR and $^{31}P\{^1H\}$ NMR ($CDCl_3$) spectra are in good agreement with the solid-state structure of **7**, the ^1H NMR spectrum recorded in $CDCl_3$ does not match up with it. The most significant discrepancy is the appearance of four different singlets in the range typical of the $N{-}CH_3$ groups of the purines (δ = 3.14, 3.22, 3.40 and 3.52 ppm). Such behaviour points to the magnetic inequivalence of the purine $N{-}CH_3$ groups and also indicates that the two purines have different chemical environments. Other important ^1H NMR spectroscopic features are a broad signal at δ = 13.21 ppm, suggesting that the N7 purine atom is protonated, and a resonance at δ = 11.38 ppm that cannot easily be assigned, even though an N7 purine imidazolic proton seems a realistic assignment for this low-field shifted resonance.[1,20] Recording the ^1H NMR spectrum at different temperatures in $CDCl_3$ points



6



7

Scheme 6

towards the existence of a temperature dependent equilibrium for **7**. Notably, while the N−CH_3, pyridine and PPh_3 signals do not vary significantly with the temperature in the -60 to +60 °C range, the two low-field signals at δ = 11.38 and 13.21 ppm are lost at higher temperatures. This fact suggests that complex **7** encompasses an equilibrium between two different species. Recording the ^{1}H NMR spectrum of **7** in [D_5]pyridine further corroborates this finding as the proton spectrum contains only two signals in the purine N−CH_3 region (δ = 3.14 ppm for N1−CH_3; δ = 3.29 ppm for N3−CH_3) while the N7−H signals are no longer evident. By slow evaporation of the [D_5]pyridine solution orange crystals are obtained, which display IR and ^{1}H NMR ($CDCl_3$) spectra identical to those of the original compound **7**.[21]

In order to determine the structure of the palladium compound **7** and to collect important geometrical information on this class of compounds, an X-ray analysis has been carried out on a single crystal. The diffraction study showed that a dinuclear palladium complex and nine water molecules form the asymmetric unit cell. Four water molecules are located in a precise position of the lattice while the remaining five are disordered. An ORTEP drawing of the complex is shown in Figure 1 with the atomic numbering scheme. Details of crystal data and relevant information are summarized in Table 1.

Each metal atom in **7** displays a distorted square-planar coordination with the triphenylphosphane molecule located *cis* to a pyridine N atom and *cis* to the S atom of an 8-

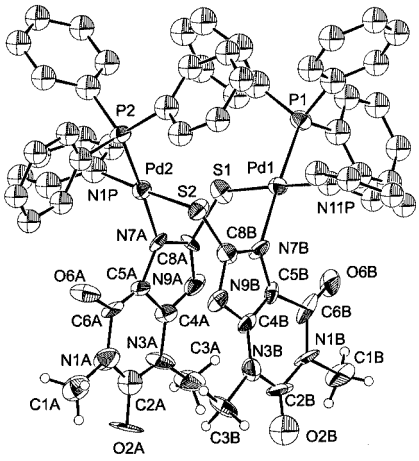


Figure 1. ORTEP drawing of **7**

Table 1. Summary of crystal data for [Pd(μ-*S*,*N*-8-BTT)-(PPh_3)Py]$_2$·9H_2O (**7**)

Formula	$C_{60}H_{52}N_{10}O_4S_2P_2Pd_2$·9$H_2O$
Mol. wt.	1478.18
T, K	296
λ, Å (Mo-K_α radiation)	0.71073
Crystal dimen., mm	0.25 × 0.15 × 0.11
Cryst. syst.	Monoclinic
space group	Cc
a, Å	22.178 (5)
b, Å	17.612 (5)
c, Å	19.575 (5)
β, °	117.656 (5)
V, Å^3	6772 (3)
Z	2
ρ_{calcd}, g/cm^{-3}	1.402
Abs coeff/mm^{-1}	0.705
F(000)	2820
θ range	1.55−25.00
Total no. of reflns	5943
No. of unique reflns	4267
R,[a] %	0.0701
R_w,[b] %	0.1661
Goodness of fit	1.117

[a] $R = \sum||F_0| - |F_c||/\sum|F_0|$. [b] $R_w = [\sum w(|F_0| - |F_c|)^2/\sum wF_0^2)]^{1/2}$.

TT^{2-} ligand. A *trans*-located N7 imidazolic atom from a second 8-TT^{2-} ligand completes the coordination polyhedron about each palladium atom. A remarkable feature of the present structure is that each palladium atom is linked by two different molecules of purine, i.e. each purine ligand in the dimeric structure binds two different palladium atoms, the first one using the S-atom and the second one through the imidazolic N7 atom. Thus, an eight-membered ring containing Pd1-S1-C8A-N7A-Pd2-S2-C8B-N7B and featuring a boat geometry is formed (Figure 2). For both metals, the square-planar coordination deviates slightly from planarity (Pd1, rms deviation 0.024; Pd2, rms deviation 0.070), the largest deviation being 4.15(69)° Å (for

Pd1) and 3.87(81)° Å (for Pd2). The dihedral (OR torsion) angle between the palladium planes is 71.00(31)°.

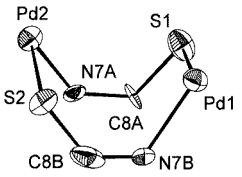


Figure 2

The two purine molecules are practically planar (the torsional angles between the imidazolic and pyrimidinic mean planes are: 3.10(1.34)°, (molecule A); and 4.12(1.24)°, (molecule B) and also non parallel to one another [angle between imidazolic mean plane of A and B purine molecules: 16.12(45)°], while the exocyclic groups do not show any significant deviation from the plane containing the purine ligand.

The bond lengths between palladium and the NNSP donor set are similar for both metal atoms, the largest difference being only 0.0423(399) Å between the N7A−Pd2 and N7B−Pd1 bond length. The analysis of the coordination distances showed the well-known *trans*-effect exerted by the P atoms. In fact, the longer P−Pd separation [P1−Pd1: 2.2655(75) Å] is opposite to the shorter N7 metal distance [N7B−Pd1: 2.0601(190) Å] and vice versa [P2−Pd2: 2.2863(77) Å; N7A−Pd2 2.1024(209) Å]. The distances N(pyridine)−Pd, and S−Pd are similar for both metal centres [N11P−Pd1: 2.0791(92) Å; N1P−Pd2: 2.0791(100) Å]. The two Pd−N(pyridine) distances are longer than the covalent Pd−N bond length (1.98 Å) and are even longer than the Pd−N bond lengths of other Pd−N(pyridine) complexes (1.98−2.04 Å) according to a search in the Cambridge Structural Database,[22] although they are similar to those found in palladium complexes in which pyridine is *trans* to an alkyl C atom.[23] Palladium complexes featuring a coordination sphere containing N, S, P and N atoms are unknown, and therefore no comparative information is available to discuss the *trans*-effect seen in **7** in detail.

A final comment relevant to the Pd1−Pd2 separation [4.1364(70) Å], is that this distance excludes any significant bonding interactions between the two metal centres. The rest of the bond lengths and angles are similar to those found in other N(7)-bonded purine complexes,[6,24] and do not deserve any additional comments.

Conclusions

The mild oxidation of 8-thiotheophylline (8-TTH_2) with I_2 leads to the formation of **1**, a new thiopurine derivative containing two theophylline units bonded through the C8 carbon atoms by a S−S bridge. Reaction of **1** with *cis*-[$PdCl_2(PPh_3)_2$] gives **6** in which two palladium atoms are likely to be bridged by two chlorides and each metal is additionally coordinated to one PPh_3 group and to the deprotonated thiol group of the 8-thiotheophylline ligand. It is conceivable that PPh_3 released from the *cis*-[$PdCl_2(PPh_3)_2$], is responsible for the cleavage of the S−S bond in **1**. Complex **6** reacts with pyridine to give the dimetallic complex **7** which was authenticated by X-ray methods. In the latter complex two palladium atoms are held together by two molecules of 8-TT^{2-} through the N7 and S atom. Each metal completes a square-planar coordination by using one PPh_3 and one pyridine molecule. The bonding pattern of the thiotheophyllinate anion in **7** is without precedent and represents a remarkable and curious coordination mode of purine derivatives. The process leading to **7** has been rationalised and likely proceeds via nucleophilic substitution of the two chloride bridges and subsequent deprotonation of the 8-TTH^- by pyridine.

The experimental results suggest: a) The coordination of the present thiopurine occurs through the S-atom; b) phosphane metal complexes, like the palladium one used in this work as the starting material, may be biologically relevant due to their capacity of easily dissociating the phosphane ligand, which, in turn, may react with disulfide groups of sulfur-containing proteins resulting in the cleavage of the S−S bridges. Although the solubility of the present palladium complexes do not allow any possible application in medicinal chemistry, this kind of study, possibly extended to other nucleobases and/or to different transition metal complexes and phosphanes, is important because it can bring about new metal-nucleobase interactions. Current studies are in progress in our laboratories in order to verify whether the use of palladium and platinum complexes, stabilised by water soluble phosphanes, may lead to the synthesis of metal-purine derivatives of higher solubility in biological conditions.

Experimental Section

All reagents were of analytical grade and were used without further purification. The complexes *cis*-[$PdCl_2(PPh_3)_2$],[6] $Na_2[PdCl_4]$ and the ligand 8-thiotheophylline[25] (8-TTH_2) were prepared as described previously. All reactions were routinely performed under argon by using standard Schlenk-tube techniques. Deuterated solvents for NMR spectroscopic measurements were dried over molecular sieves (4 Å). ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker AVANCE DPX 300 spectrometer. Peak positions are relative to tetramethylsilane (^1H, $^{13}C\{^1H\}$) and were calibrated with respect to the residual protonated solvent (^1H) or to the solvent resonance ($^{13}C\{^1H\}$). The $^{31}P\{^1H\}$ NMR spectra are given with respect to external 85% H_3PO_4 in D_2O with downfield values taken as positive. Infrared spectra were recorded on KBr discs on a IR-ATI Mattson Infinity Series. Elemental analyses (C, H N, S) were performed on a Fisons Instruments EA 1108 elemental analyser. GC/MS analyses were carried out using a Varian GC/MS Saturn 3 gas chromatograph-ion-trap mass spectrometer, using a stationary phase column DB-5MS (J&W Scientific,Folsom, Ca, USA), 30 m × 0.25 mm I.D. × 0.25 μm film thickness. Melting points were measured on a BÜCHI 530 instrument.

Synthesis of *S,S*-Bis(8-thiotheophylline) [1, 8-$BTTH_2$]: The ligand **1** was prepared by stirring 8-thiotheophylline (8-TTH_2) (1.00 g,

5.0 mmol) with KOH (0.28 g, 4.8 mmols) in EtOH (20 mL) for 30 min. Further addition of I_2 (1.32 g, 5.2 mmol) at room temperature, and reflux for 6 hours gave **1** as a pale yellow powder that was filtered off, washed with H_2O (2 × 2 mL), EtOH (2 × 2 mL) and finally vacuum dried. Yield: 1.37 g, 65%. m.p.: 294−295 °C. $C_{14}H_{14}N_8O_4S_2$ (422.44): calcd. C 39.8, H 3.3, N 26.5, S 14.2; found C 41.2, H 3.4, N 24.6, S 14.0. M.p.: 294−295 °C. IR: ν(N−H) 3115−2660 cm^{-1} (br. w.); ν(C6=O) 1717 (s); ν(C2=O) 1640 (s). ^1H NMR (22 °C, [D_6]DMSO): δ = 3.33 (s, N1-CH_3), 3.56 (s, N3-CH_3), 4.67 (w, N7−H) ppm. $^{13}C\{^1H\}$ NMR (22 °C, [D_6]DMSO): δ = 27.5 (N1-CH_3), 29.8 (N3-CH_3), 112.2 (C5), 146.9 (C4), 148.80 (C8), 151.0 (C6), 154.8 (C2) ppm.

Synthesis of the Potassium Salts of 8-Thiotheophyllinate [2, K_2(8-TT)] and *S,S*-Bis(8-thiotheophyllinate) [3, K_2(8-BTT)]: 8-TTH_2 (for **2**; 5 mmol, 1 g) or 8-$BTTH_2$ (for **3**; 2.5 mmol, 1 g) was introduced, via a dropping funnel, to a solution of KOH (0.27 g. 4.8 mmol) in EtOH (10 mL); a white precipitate immediately separated. The mixture was stirred and refluxed for 2 hours, slowly cooled down to room temperature, the precipitate filtered off, washed with two portions (2 mL) of cold EtOH and, finally, dried under vacuum.
2: Yield: 0.86 g, 60%. $C_7H_6K_2N_4O_2S$ (288.41): calcd. C 29.1, H 2.1, N 19.4, S 11.1; found C 29.1, H 2.3, N 19.2, S 10.9. IR: ν(C6=O) 1672 cm^{-1} (s); ν(C2=O) 1631 (s); ν(C=C) + ν(C=N) 1526, 1518, 1553, 1445. ^1H NMR (22 °C, CD_3OD): δ = 3.25 (s, N1-CH_3), 3.41 (s, N3-CH_3) ppm.
3: Yield: 0.87 g, 70%. $C_{14}H_{12}K_2N_8O_4S_2$ (498.62): calcd. C 33.7, H 2.4, N 22.5, S 12.9; found C 33.5, H 2.5, N 22.2, S 12.5. IR: ν(C6=O) 1687 cm^{-1} (s); ν(C2=O) 1631 (s); ν(C=C) + ν(C=N) 1565, 1525, 1454. ^1H NMR (22 °C, CD_3OD): δ = 3.36 (s, N1-CH_3), 3.51 (s, N3-CH_3) ppm.

Synthesis of the Pyridinium Salt of *S,S*-Bis(8-thiotheophyllinate) [4, $(PyH)_2$(8-BTT)]: Pyridine (5 mL) was added to a vigorously stirred suspension of **1** (0.5 g, 1.18 mmol) in EtOH (15 mL). The yellow solution obtained was stirred for 2 h at room temperature and concentrated to ca. 5 mL. The addition of pentane (10 mL) gave a pale yellow precipitate that was filtered off, washed twice with pentane (5 mL) and dried under vacuum. The crude yellow powder thus obtained contained some pyridine and did not give reproducible elemental analyses. Nevertheless, an analytically pure compound was obtained by recrystallisation from hot EtOH.

An in situ NMR spectroscopy experiment in which **1** (20 mg, 0.0047 mmol) was dissolved in [D_5]pyridine (0.5 mL) showed that **4** was the only product formed. Yield: 0.24 g, 35%. $C_{24}H_{22}N_{10}O_4S_2$ (578.62): calcd. C 49.8, H 3.8, N 24.2, S 11.1; found C 49.4, H 4.2, N 23.8, S 10.7. IR: ν(PyN-H) 3110 cm^{-1} (w.); ν(C6=O) 1718, 1704 (s); ν(C2=O) 1644 (s); ν(C=C)+ν(C=N) 1594, 1547, 1485 (s). ^1H NMR (22 °C, [D_5]pyridine): δ = 3.43 (s, N1-CH_3, 6 H), 3.70 (s, N3-CH_3, 6 H), 8.67−7.72 (m, Py, 20 H) ppm.

Reaction of 1 with PPh_3 in Ethanol: A suspension of **1** (0.5 g, 1.18 mmol), KOH (0.07 g, 1.25 mmol) and PPh_3 (0.62 g, 2.34 mmol) in EtOH (5 mL) was refluxed for 3 hours. The resulting colourless solution was kept at room temperature overnight to leave a pale yellow precipitate, which was filtered off, washed with cold EtOH and vacuum dried. NMR spectroscopy and elemental analysis allowed us to confirm that this compound is **2** (Yield: 0.44 g, 65%). A second crop of **2** was obtained from the mother liquor. Total yield: 0.52 g, 76%.

An in situ NMR spectroscopy experiment (0.5 mL CD_3OD, T = 50 °C) showed that O=PPh_3 and an insoluble white precipitate, which was separated and identified as **2**, were formed during the reaction of **1** (0.017 g, 0.04 mmol) with KOH (0.003 g, 0.05 mmol) and PPh_3 (0.025 g, 0.09 mmol).

Reaction of 1 with PPh_3 in DMSO or Dioxane. Synthesis of 8-Phenylthiotheophylline [(5), 8-PhTTH]: Compound **1** (0.5 g, 1.18 mmol) and PPh_3 (0.65, 2.48 mmol) were added to 5 mL of DMSO (or dioxane). The suspension was stirred at 30 °C for 1 h and then heated to 50 °C for 2 h. The addition of heptane (15 mL) to the hot solution yielded a pale yellow precipitate that was filtered off, washed with pentane (2 × 10 mL) and vacuum dried. The crude compound was recrystallised twice from hot EtOH to give analytically pure yellow microcrystals of **5**.

In situ NMR spectroscopy monitoring of this reaction ([D_6]DMSO, T = 60 °C) confirmed that the only soluble compound formed was **5**. Yield: 0.17 g, 30%. $C_{25}H_{22}N_4O_2PS$ (473.51): calcd. C 63.4, H 4.7, N 11.8, S 6.8; found C 63.2, H 4.5, N 11.6, S 6.5. IR: ν(N−H) 3200−2620 cm^{-1} (br. w.); ν(C6=O) 1690 (s); ν(C2=O) 1642 (s). ^1H NMR (22 °C, [D_6]DMSO): δ = 3.15 (s, N1-CH_3, 3 H), 3.35 (s, N3-CH_3, 3 H), 7.24−7.65 (m, Ph, 5 H), 11.33 (w, N7−H, 1 H) ppm. $^{13}C\{^1H\}$ NMR (22 °C, [D_6]DMSO): δ = 27.7 (N1-CH_3), 29.8 (N3-CH_3), 104.3 (C5), 129.1−133.8 (m, Ph), 149.9 (C4), 151.1 (C2), 151.6 (C6), 170.3 (C8) ppm. $^{31}P\{^1H\}$ NMR (22 °C, [D_6]DMSO): δ = 27.5 ppm.

Synthesis of [Pd(PPh_3)(μ-Cl)(8-TT)]$_2$ (6). Method A: Compound **1** (0.1 g, 0.24 mmol) was added to a solution of KOH (0.028 g, 0.5 mmol) in EtOH (20 mL). After 5 min, *cis*-[$PdCl_2(PPh_3)_2$] (0.350 g, 0.50 mmol) was added to the reaction mixture to yield a red orange suspension. This was left for 30 min at room temperature and then heated to reflux for 2 hours. A red orange precipitate formed, which was filtered off, washed twice with EtOH (5 mL) and air dried. Yield: 0.27 g, 91%.

Method B: A solution of $Na_2[PdCl_4]$ (0.06 g, 0.20 mmol) in 5 mL of water was added at room temperature to a suspension of PPh_3 (0.131 g, 0.5 mmol), 1 (0.05 g, 0.12 mmol) and KOH (0.012 g, 0.2 mmol) in 15 mL of EtOH. The mixture was stirred at room temperature for 1 h and then refluxed for 2 h. The red orange precipitate of 6 was isolated as described above. Yield: 0.1 g, 70%.

Method C: One equivalent of **3** (or **4**) was reacted in refluxing EtOH with two mol equivalents of *cis*-[$PdCl_2(PPh_3)_2$] (or $Na_2[PdCl_4]$ and PPh_3 in a 1:2 molar ratio). After 1 h the precipitate was separated, washed and dried as described previously. Yield: 73%.

Method D: Reaction of one equivalent of **2** with a stoichiometric amount of *cis*-[$PdCl_2(PPh_3)_2$] (or 1 $Na_2[PdCl_4]$ + 2 PPh_3) in refluxing EtOH, gave **6** as a red orange precipitate within 1 h. The compound was separated, washed and dried as described previously. Yield: 73%.

$C_{50}H_{44}Cl_2N_8O_4P_2Pd_2S_2$ (1230.76): calcd. C 48.8, H 3.6, N 9.1, S 5.2; found C 48.5, H 3.8, N 9.2, S 4.9. IR: ν(N7 H) 3059−2790 cm^{-1} (w); ν(C6=O) 1673 (s); ν(C2=O) 1625 (s); ν(C=C) + ν(C=N) 1583, 1535, 1520 (s); δ(Ph−H) 740, 703, 688, 516, 507.

In Situ Reaction of 1 with *cis*-[$PdCl_2(PPh_3)_2$] in CD_3OD: Compound **1** (30 mg, 0.071 mmol), *cis*-[$PdCl_2(PPh_3)_2$] (100 mg, 0.142 mmol) and CD_3OD (0.5 mL) were placed into a 5-mm NMR tube maintained at 20 °C. A $^{31}P\{^1H\}$ NMR spectrum was immediately acquired, showing only the resonance due to the starting metal complex *cis*-[$PdCl_2(PPh_3)_2$]. The temperature was then raised to 50 °C causing the separation of a red orange solid within 6 h. Formation of O=PPh_3 was observed by $^{31}P\{^1H\}$ NMR spectroscopy and GC-MS analysis. The red precipitate was separated,

Table 2. Selected bond lengths (Å) and angles (°) for $[(8\text{-BzTT})_2\text{-Pd}(PPh_3)_2]_2$ (**7**)

Pd1−N11P	2.079(9)
Pd1−N7B	2.10(2)
Pd1−P1	2.266(8)
Pd1−S1	2.294(8)
Pd2−N7A	2.060(19)
Pd2−N1P	2.087(10)
Pd2−P2	2.286(8)
Pd2−S2	2.301(8)
P1−C121	1.796(13)
P1−C101	1.824(13)
P1−C111	1.857(13)
P2−C201	1.847(12)
P2−C211	1.821(12)
P2− C221	1.842(13)
S1−C8A	1.76(2)
S2−C8B	1.73(3)
N7A−C8A	1.38(3)
N7A−C5A	1.40(3)
C8A−N9A	1.34(3)
N7B−C8B	1.29(3)
N7B−C5B	1.34(3)
C8B−N9B	1.44(3)
N11P−Pd1−N7B	85.3(8)
N11P−Pd1−P1	94.7(5)
N7B−Pd1−P1	176.4(6)
N11P−Pd1−S1	178.4(5)
N7B−Pd1−S1	93.3(7)
P1−Pd1− S1	86.7(3)
N7A−Pd2−N1P	85.6(7)
N7A−Pd2−P2.	176.7(6)
N1P−Pd2−P2	94.7(5)
N7A−Pd2−S2	93.4(5)
N1P−Pd2−S2	175.7(5)
C8A−S1−Pd1	106.2(8)
C8B−S2−Pd2	103.1(10)
C8A−N7A−Pd2	129.8(15)
C5A−N7A−Pd2	127.8(16)
N9A−C8A−N7A	113.5(18)
N9A−C8A−S1	127.0(17)
N7A−C8A−S1	119.5(17)
C4A−N9A−C8A	107(2)
C8B−N7B−Pd1	123.5(17)
C5B−N7B−Pd1	128.5(17)
N7B−C8B−N9B	114(2)
N7B−C8B−S2	128(2)
N9B−C8B−S2	118(2)
C4B−N9B−C8B	99(2)

washed with two portions (0.5 mL) of CH_3OH and vacuum dried. This residue was dissolved in $[D_6]$DMSO (0.5 mL) and $^{31}P\{^1H\}$ NMR spectroscopy confirmed that it was **6**.

Synthesis of $[Pd(PPh_3)Py(\mu\text{-S,N-8-TT})]_2\cdot 9H_2O$ (7): Compound **6** (0.15 g, 0.12 mmol) was introduced into a vessel containing acetonitrile (5 mL). The temperature was kept at 50 °C and pyridine (1 mL) was then added. The red orange solution obtained from this was left to stand at room temperature. Orange prismatic crystals were obtained by slow evaporation of the solvent. Yield: 0.05 g, 30%. $C_{60}H_{52}N_{10}O_4P_2Pd_2S_2\cdot 9H_2O$ (1478.05): calcd. C 48.7, H 4.8, N 9.5, S 4.3; found C 49.0, H 5.1, N 9.2, S 4.1. IR: ν(C6=O) 1673 cm^{-1} (s); ν(C2=O) 1625 (s); ν(C=C) + ν(C=N) 1603, 1521 (s); δ(Ph−H) 762, 696, 534, 514, 491. ^1H NMR (22 °C, $CDCl_3$): δ = 3.14, 3.22 (s, N1-CH_3, 3 H), 3.40, 3.52 (s, N3-CH_3, 3 H), 7.18−7.70 (m, Ph, 5 H), 7.18−8.62 (m, Py, 5 H), 11.40 (s, 1 H), 13.23 (w, 1 H) ppm. $^{31}P\{^1H\}$ NMR (22 °C, $CDCl_3$): δ = 27.35 ppm. ^1H NMR (22 °C, $[D_5]$pyridine): δ = 3.14 (s, N1-CH_3, 6 H), 3.29 (s, N3-CH_3, 6 H), 7.02−7.70 (m, Ph, 5 H), 7.02−7.78 (m, Py, 5 H) ppm. $^{31}P\{^1H\}$ NMR (22 °C, $[D_5]$pyridine): δ = 36.18 ppm.

In Situ Reaction of 6 with $[D_5]$pyridine: Compound **6** (35 mg, 0.028 mmol) was placed into an NMR tube and $[D_5]$pyridine (0.5 mL) was added. Dissolution took place after heating at 50 °C to give a red orange solution. $^{31}P\{^1H\}$ NMR spectroscopic monitoring showed the presence of several compounds with **7** being the most abundant (82%). Formation of $O{=}PPh_3$ or PPh_3 was not observed. Compound **7** was precipitated as an orange microcrystalline solid by addition of acetonitrile (2 mL).The compound was confirmed by IR and NMR spectroscopy. The identification of the secondary compounds that accompany the formation of **7** was not attempted.

X-ray Crystallography: Crystals suitable for the X-ray diffraction study were obtained from a solution of **7** in acetonitrile/pyridine (1:1) by slow evaporation. Data were collected at 293 K on a Stoe-Siemens AED diffractometer, using graphite-monochromatised Mo-K_α radiation (λ = 0.71069 Å). The unit cell parameters were obtained from least-squares refinement of 32 well-centred reflections ($12.5° < \theta < 15.9°$). The data were collected by the ω − 2θ scan mode ($1.55° < 2\theta < 25°$) and were corrected for Lorentz and polarisation effects as well as for absorption effects. Details of crystal data and relevant information are summarised in Table 1. The structure was solved using the Sir97 program.[26] In the final refinement the SHELX-96 program[27] was used and in the graphic representation the ORTEP program.[28] Refinement was done by full-matrix least-squares calculations, initially with isotropic thermal parameters. In the final refinement, all purine non-hydrogen atoms and water oxygen atoms were refined anisotropically, whereas purine hydrogen atoms were placed at their calculated positions and then refined isotropically. All of the phenyl rings were treated as rigid bodies with D_{6h} symmetry and C−C distances fixed at 1.39 Å. No significant peaks were detected in the final least-squares cycles. Selected bond lengths and angles are listed in Table 2.

CCDC-194639 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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