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Note

Palladium phosphine complexes from 8-(thio)-theophylline, 8-(methylthio)-theophylline and 8-(benzylthio)-theophylline

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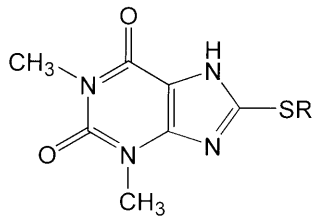
Abstract

A series of palladium(II) complexes have been synthesized and characterized to examine the coordination chemistry of several 8-thio-purine derivatives: 8-(thio)-theophylline (8-TTH_2), 8-(benzylthio)-theophylline (8-BzTTH) and 8-(methylthio)-theophylline (8-MTTH). All of the complexes have been studied by IR and multinuclear (^1H, ^{31}P, ^{13}C NMR) spectroscopy. A representative example of a Pd complex, [*cis*-Pd(8-$BzTT)_2(PPh_3)_2$], has been authenticated by X-ray crystallography. In this complex square-planar coordination about palladium occurs through two deprotonated N7 purine atoms *cis* to each other, and two triphenylphosphine phosphorus atoms. In this paper, we present and discuss details of the synthesis, characterization and structural properties of the novel complexes. The synthesis and the characterization of 8-(benzylthio)-theophylline (8-BzTTH), a new organic ligands based on the molecular skeleton of 8-thio-purine, and a new procedure to obtain 8-(methylthio)-theophylline (8-MTTH) are also presented.

Keywords: Crystal structures; Palladium complexes; Purine base complexes

1. Introduction

Studies on the interactions of metal ions with purine and pyrimidine bases are of paramount importance in bioinorganic chemistry due to the central role that these compounds have in the chemistry of nucleic acid derivatives [1]. Purines are multidentate ligands exhibiting a variety of potential donor groups and consequently behave as effective ligands for a wide range of metal ions. In fact, in addition to the N donor atoms, and to the carboxylate group, it has recently been shown that purine bases can even bind through C atoms. In particular, it has been demonstrated that the C(8) site in caffeine can efficiently coordinate to $[Ru(NH_3)_3Cl_2]$ [2a], $[Os(NH_3)_5]$ [2b] and 9-(2-(2-aminoethylamino)ethyl)adenine [3] with $[RuCl_2(DMSO)_2]$. In order to study this very rare kind of interaction between purine bases and metals, that could be of biological relevance, the synthesis of new examples of complexes exhibiting the C8–metal interaction is of interest and largely desirable. In this regard, our group has recently shown a novel route to C8



R= H: 8-(Thio)-theophylline, 8-TTH_2
R= CH_3: 8-(Methylthio)-theophylline, 8-MTTH
R= CH_2Ph: 8-(Benzylthio)-theophylline, 8-BzTTH

Scheme 1.

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coordination of theophylline under mild conditions [4] by previous coordination of 8-(methylthio)-theophylline (8-MTTH), a 8-thio-purine base similar to those found in retinal rod photoreceptors [5], to palladium.

In order to obtain more information about the chemical properties of 8-thio purine derivatives we have studied the reactivity of [*cis*-$PdCl_2(PPh_3)_2$] with 8-(thio)-theophylline (8-TTH_2), 8-(methylthio)-theophylline (8-MTTH) and 8-(benzylthio)-theophylline (8-BzTTH) (Scheme 1).

2. Experimental

All reagents were of analytical grade and were used without further purification. [*cis*-$PdCl_2(PPh_3)_2$] [4] and the ligand 8-TTH_2 were prepared as described previously [6]. The ligand 8-MTTH was synthesized as described in the literature [6] or with the improved procedure described below. Deuterated solvents for NMR measurements were dried over molecular sieves (0.4 nm). ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker AVANCE DRX 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). 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 analysis (C, H, N, S) were performed on a Fisons Instruments EA 1108 elemental analyser.

2.1. X-ray crystallography

The crystal used for X-ray work ($0.25 \times 0.15 \times 0.11$ mm) was obtained from a solution of [*cis*-Pd(8-BzTT)$_2$(PPh_3)$_2$] (**5**) in $CHCl_3$ by slow evaporation of the solvent. Data were collected at 294 K on a Stoe–Siemens AED diffractometer, using graphite-monochromatized Mo Kα radiation ($\lambda = 0.71069$ Å). The unit cell parameters were obtained from least-squares refinement of 25 well-centered reflections ($5 < \theta < 15°$). The data were collected by the $\omega - 2\theta$ scan mode ($1.52 < 2\theta < 19.96°$) and were corrected for Lorentz and polarization effects and for absorption.

The compound crystallizes in the monoclinic system, space group $P2_1/c$, with $a = 13.434(5)$, $b = 20.783(5)$, $c = 21.091(5)$ Å, $\beta = 92.96(5)°$, $U = 5881(3)$ Å^3, $Z = 4$, $D_c = 1.348$ g cm^{-3} and $\mu = 0.495$ mm^{-1}. 5438 unique reflections were collected ($2\theta_{max} = 40$, $h = 0$–12, $k = 0$–19, $l = -20$ to 20). Due to the poor statistics of the weak reflections, 2385 reflections with $|F| > 2\sigma(F)$ were included in the calculations.

In the final refinement, all purine non-hydrogen atoms were refined anisotropically and purine hydrogen atoms (except phenyl hydrogen) were placed at calculated positions and then were refined isotropically.

The final $R(F_o)$ value was 0.0987 [$R(F_o)_{all\ data} = 0.2302$, $wR(F_o) = 0.1726$, $wR(F_o)_{all\ data} = 0.2235$].

The structure was solved using the SIR97 program [7]. In the final refinement the SHELX-96 program was used [8] and in the graphic representation the ORTEP program was used [9].

2.2. Preparation

2.2.1. Synthesis of 8-MTTH (*1*) and 8-BzTTH (*2*)

The two ligands **1** and **2** were prepared using a similar procedure. CH_3Br (0.5 g, 5.3 mmol) or $PhCH_2Br$ (0.9 g, 5.3 mmol) (8-MTTH or 8-BzTTH, respectively) was added to a suspension of KTTH in 20 ml of EtOH, which is generated in situ by reaction of TTH_2 (1 g, 5 mmol) with 1 equiv. of KOH (0.28 g, 5 mmol). After 6 h refluxing, the precipitated obtained was filtered out, washed with H_2O (2×2 ml), EtOH (2×2 ml) and finally air dried.

(**2**) 8-BzTTH.

Yield (**1**): 76%.

Yield (**2**): 83%; m.p. 277–278°C.

2.3. Synthesis of the complex DMSO·[PdCl(8-TTH)$_2$(DMSO)(PPh_3)] (*3*)

Reaction of 8-TTH_2 (0.1 g, 0.5 mmol) with KOH (0.028 g, 0.5 mmol) and [*cis*-$PdCl_2(PPh_3)_2$] (0.35 g, 0.5 mmol) in 20 ml of EtOH at reflux yielded a red–orange precipitate, which was filtered out, washed with two portions of cold EtOH and air dried. By slow evaporation of a solution of this red powder in DMSO, red microcrystals were obtained, which were filtered out, washed with two portions (2 ml) of EtOH and air dried.

Yield: 44% from 8-TTH_2.

2.4. Synthesis of the complexes [PdCl(8-BzTT)(PPh_3)$_2$] (*4*) and [Pd(8-BzTT)$_2$(PPh_3)$_2$] (*5*)

In a similar procedure to that described above for compound **3**, the reaction of 8-BzTTH, KOH and [*cis*-$PdCl_2(PPh_3)_2$] in 1:1:1 and 2:2:1 molar ratios, respectively, gave rise to red–orange (**4**) and orange (**5**) precipitates.

Yield (**4**): 45%.

Yield (**5**): 60%.

2.5. Synthesis of the complex [Pd(8-MTT)$_2$(PPh_3)$_2$] (*6*)

As reported above for **5**, the reaction of 8-MTTH with KOH and [*cis*-$PdCl_2(PPh_3)_2$] in a 2:2:1 molar ratio in refluxed ethanol gave **6** as an orange powder.

Yield: 36% (Tables 2–5).

Table 1
Selected bond distances (Å) and angles (°) for $(8\text{-BzTT})_2Pd(PPh_3)_2$ (**5**)

Pd1–N7B	2.043(16)	C10A–C11A	1.54(2)
Pd1–N7A	2.060(15)	C1B–N1B	1.43(2)
Pd1–P1	2.319(6)	N1B–C2B	1.40(2)
Pd1–P2	2.326(6)	N1B–C6B	1.42(2)
S1–C8A	1.74(2)	C2B–O2B	1.22(2)
S1–C10A	1.779(18)	C2B–N3B	1.38(3)
S2–C8B	1.75(2)	C3B–N3B	1.47(2)
S2–C10B	1.82(2)	N3B–C4B	1.41(3)
C1A–N1A	1.46(2)	C6B–O6B	1.24(2)
N1A–C2A	1.42(3)	C6B–C5B	1.39(3)
N1A–C6A	1.41(2)	C4B–N9B	1.32(2)
C2A–O2A	1.23(2)	C4B–C5B	1.38(3)
C2A–N3A	1.37(3)	C5B–N7B	1.39(2)
C3A–N3A	1.45(2)	N7B–C8B	1.37(2)
N3A–C4A	1.36(2)	C8B–N9B	1.36(2)
C6A–O6A	1.20(2)	C10B–C11B	1.48(2)
C6A–C5A	1.46(3)		
C4A–N9A	1.35(3)		
C4A–C5A	1.38(3)		
C5A–N7A	1.35(2)		
N7A–C8A	1.36(2)		
C8A–N9A	1.37(2)		
N7B–Pd1–N7A	87.1(6)		
N7B–Pd1–P1	169.2(5)		
N7A–Pd1–P1	88.0(4)		
N7B–Pd1–P2	87.4(5)		
N7A–Pd1–P2	168.2(5)		
P1–Pd1–P2	99.1(2)		

3. Results and discussion

3.1. Ligands

The ligands 8-(methylthio)-theophylline (8-MTTH) (**1**) and 8-(benzylthio)-theophylline (8-BzTTH) (**2**) were obtained by reaction of 8-TTH_2 with KOH and $BrCH_3$ with $BrCH_2Ph$ in a 1:1:1 molar ratio.

Compound 8-MTTH was authenticated by comparison of its spectroscopic data with those reported in the literature [6].

NMR experiments alone provide an unequivocal assignment of the structure proposed for 8-BzTTH. Key points of the NMR analysis (^1H NMR) are: a resonance at δ 13.38 ppm, typical of a N–H group [4], the absence of any S–H resonance and the presence of a singlet that can safely be ascribed to a $S–CH_2–$. A perusal of all of these points suggest that the ligand is produced by substitution on the 8-TTH_2 sulfur atom with a benzyl group. The ^{13}C NMR spectrum is in agreement with the formula proposed. In particularly, the C-8 resonance arises (148.7 ppm) in a closer position to that in 8-MTTH (153.0 ppm) than to that in 8-TTH_2 (163.8 ppm). This result suggests that there is a strong influence of the nature of the substituent on the electronic behaviour of the imidazolic ring of the purine base.

3.2. Palladium complexes (*3*, *4*, *5*, *6*)

The ligands 8-TTH_2, 8-MTTH and 8-BzTTH react in EtOH with KOH and $[cis\text{-}PdCl_2(PPh_3)_2]$ to afford a variety of palladium complexes according to the molar ratio between reactants and the particular ligand.

Noticeably, the reaction of 8-TTH_2 with KOH and $[cis\text{-}PdCl_2(PPh_3)_2]$ leads to the formation of a red precipitate (compound **3a**) irrespective of the stoichiometry adopted. The IR spectrum shows a characteristic ν(N–H) purine broad absorption (2780–3250 cm^{-1}) and significant coordinated purine and PPh_3 absorption signals. This red precipitate is practically insoluble in most of the organic and inorganic solvents and only in hot DMSO it exhibits a solubility sufficient to run NMR spectra.

Table 2
Analytical results for the complexes

	Found (calc.) (%)	C	H	N	S
2	$C_{14}H_{14}N_4O_2S_1$	55.8 (55.6)	4.5 (4.6)	17.9 (18.5)	10.0 (10.6)
3	$C_{29}H_{34}N_4O_4S_3ClPPd$	45.5 (45.14)	4.7 (4.44)	6.8 (7.26)	12.8 (12.5)
4	$C_{50}H_{43}N_4O_2SClP_2Pd$	62.3 (62.0)	4.7 (4.5)	5.5 (5.8)	3.1 (3.3)
5	$C_{64}H_{56}N_8O_4S_2P_2Pd$	62.4 (62.3)	4.5 (4.5)	10.1 (9.1)	4.9 (5.2)
6	$C_{52}H_{48}N_8O_4S_2P_2Pd$	57.3 (57.7)	4.2 (4.5)	10.1 (10.4)	5.4 (5.9)

Table 3
^1H parameters (δ in ppm, J in Hz. All spectra recorded in $CDCl_3$, **3** in DMSO-d_6)

	$N1–CH_3$	$N3–CH_3$	N7–H	$S–CH_3$	$S–CH_2$	Ph–	PPh
2	3.24	3.46	13.38		4.49(s)	7.42–7.25	
3	3.14	3.52	11.58			7.29–7.70	
4	3.16	3.25			4.15	7.67–7.23	7.10
5	3.04	3.23			5.20 (AB, $J = 13.39$)	7.41–7.18	6.94–7.08
6	3.25	3.34		2.29			

Table 4
$^{13}C\{^1H\}$ parameters (δ in ppm. All spectra recorded in $CDCl_3$)

	C2	C4	C5	C6	C8	N1–CH_3	N3–CH_3	S–CH_3	S–CH_2	Ph
8-TTH_2 [a]	149.9	139.3	103.5	151.4	163.8	27.7	31.0			
1	150.0	142.2	107.6	151.0	153.0	27.5	29.6	14.0		
2	153.8	137.7	108.3	151.4	148.7	28.2	30.3		36.1	127.9–129.4
3 [b]										
4	154.8	138.5	114.0	151.5	150.2	27.6	29.1		36.3	134.8–126.7
5	155.0	142.2	114.7	150.8	148.4	27.6	28.8		40.8	135.9–126.7
6 [b]										

[a] Included for comparision.
[b] No soluble enough.

At room temperature the $^{31}P\{^1H\}$ NMR spectrum features two distinct resonances, which transform in a single resonance (23.70 ppm) at 60°C. The ^1H NMR spectrum at this temperature shows a broad signal at 11.53 ppm, which is assigned to the H–N7 proton. At lower temperature, when two equilibrating species are present in solution the ^1H NMR spectra shows a single resonance at 11.58 ppm, suggesting that the purine ligands are coordinated to the metal in the same way. Resonances due to $-CH_3$ purine groups match with this supposition. Finally, by slow evaporation of a solution of the red precipitate in DMSO, a red microcrystal (compound **3**) was obtained, which displayed the same spectroscopic behaviour.

The IR spectra of compound **3** shows bands of free and coordinated DMSO molecules (ν(S=O) = 1070, 1022 cm^{-1}). This finding is supported by elemental analysis of this recrystallised compound, which is in accord with Pd(8-TTH)$(DMSO)_2(PPh_3)$Cl composition. These data suggest the composition [Pd(8-TTH)(DMSO)(PPh_3)Cl] DMSO for this compound, with the ligand being coordinated to the metal through the sulfur atom.

Unfortunately, the X-ray structure of the red precipitate **3a** could not be determined, although we can hypothesize from the experimental data that tryphenylphosphine, a ligand and likely a chloride atom are coordinated to the metal. However, we cannot exclude a priori that this compound has a polymeric nature with a chloride atom acting as bridging ligand between two single units of Pd(8-TTH)(PPh_3).

On the other hand, compounds **4** and **5** are obtained when 1 mol of 8-BzTTH reacts with 1 and 1/2 mol of [*cis*-$Cl_2Pd(PPh_3)_2$]. All of the obtained complexes do not show any absorbance assignable to the N7–H stretching vibrations in the infrared spectra. The absence of the N7–H resonance in the ^1H NMR spectra, compared with the free ligand 8-BzTTH, suggests that the ligand coordination site is N7 atom. When a 1:1 molar ratio of 8-BzTTH and [*cis*-$Cl_2Pd(PPh_3)_2$] was used to carry out the reaction, the elemental analysis of the final compound and the integration of the ^1H NMR spectra reveal only one ligand is coordinated to the palladium by substitution of a chloride atom. In this case, the two PPh_3 groups could be *trans* to each other because the ^{31}P NMR spectrum exhibits only a single resonance with a chemical shift similar to those reported for *trans*-PPh_3 palladium complexes [10]. In the synthetic reaction of that compound a *cis* to *trans* isomerization occurs, as previously reported for [*trans*-PdCl(8-MTT)$(PPh_3)_2$] [4]. Moreover, when a 1:2 metal-to-ligand molar ratio is used a complex resulting from the substitution of two chloride atoms by two 8-$BzTT^-$ is obtained. In such a case, the ^1H NMR spectrum shows that S–CH_2– protons of both purine molecules arise as an AB system, which points out two protons that are magnetically different to each other in both molecules. Finally, the PPh_3 resonance in the ^{31}P NMR suggests a *cis*-disposition of the phosphines, as confirmed by X-ray crystallography.

The reactivity of 8-MTTH is similar to that reported above for 8-BzTTH. The crystal structure of [*trans*-PdCl(8-MTT)(PPh_3)] in which only a single chloride atom is substituted has been published previously [4]. Nevertheless, a different complex where both chloride ligands have been replaced (compound **6**) can be obtained by reacting 8-MTTH with KOH and [*cis*-$Cl_2Pd(PPh_3)_2$] in a 2:2:1 molar ratio in refluxed EtOH. In this case, the ^{31}P NMR spectrum suggests a *trans* disposition of the phosphines.

Table 5
$^{31}P\{^1H\}$ parameters (δ in ppm. All spectra recorded in $CDCl_3$, **3** in DMSO-d_6)

	δ (T = r.t.)	δ (T = 60°C)
3	23.77 (29%) 26.98 (71%)	23.76 (100%)
4	21.49	
5	30.94	
6	14.95	

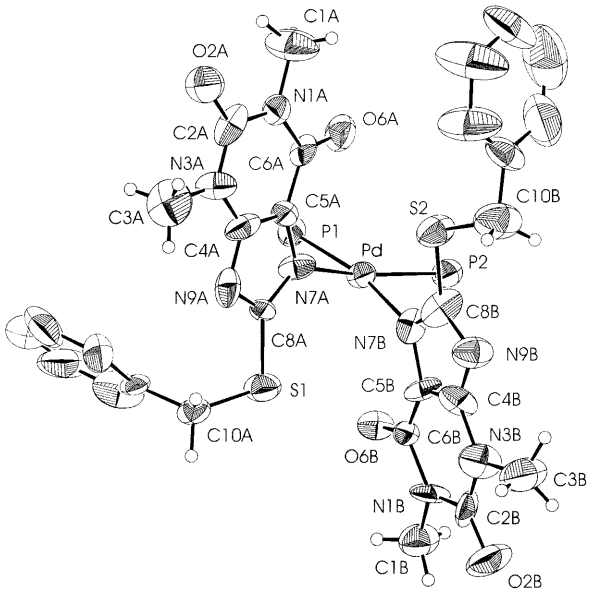

Fig. 1. Molecular diagram of the Complex $(8\text{-BzTT})_2Pd(PPh_3)_2$ (**5**). Triphenylphosphine phenyl groups are not included for clarity.

*3.3. Crystal and molecular structure of $(8\text{-BzTT})_2Pd(PPh_3)_2$ (**5**)*

In order to confirm the structural composition of the palladium derivatives and to collect novel geometrical information on this class of compounds, an X-ray analysis has been carried out on a single crystal of [*cis*-$Pd(8\text{-BzTT})_2(PPh_3)_2$]. An ORTEP drawing of the complex is shown in Fig. 1 with the atomic numbering scheme. A list of selected bond distances and angles appear in Table 1.

In this compound, the palladium(II) atom is coordinated by the phosphorus atoms of two triphenylphosphine molecules and through the N7 atoms of two 8-$BzTT^-$ anions. As anticipated by NMR analysis, the two triphenylphosphine groups are *cis* to each other and *trans* to the two purine ligands. The coordination polyhedron of the metal atom adopts a marked distorted square-planar geometry (P2–Pd–P1 = 99.1(2)°, N7A–Pd–N7B = 87.1(6)°) likely caused by the steric repulsion between the two triphenylphosphine ligands. The two purine bases show a relative disposition in which their S–CH_2–Ph groups point in opposite directions. The two purine molecules are practically planar (the angle between imidazolic and pyrimidine mean planes being 3.1(6) and 3.1(9)° for A and B purine molecules, respectively), while the exocyclic groups do not show any significant deviation from the purine plane. The two purines are twisted away from the metal coordination mean plane (the angles between the mean planes of A and B purines, and with the Pd mean plane are 76.7(7), 72.5(6) and 76.9(6)°, respectively) in order to minimize the steric repulsion between the bulky triphenylphosphine ligands and the phenyl groups of the purine ligands.

Finally, bond distances and angles are similar to those found in other N(7)-bonded purine complexes [4,11], and there are no significant interactions between molecules.

4. Conclusions

The reactivity in basic media (KOH in EtOH) of a series of thio-theophilline derivatives towards [*cis*-$PdCl_2(PPh_3)_2$] suggests that these compounds present a different behaviour depending on whether or not the sulfur purine atom is substituted. 8-(Thio)-theophylline (8-TTH_2) reacts only through the sulphur S8 atom with the N7 atom not being coordinated. Unlike TTH_2, 8-(methylthio)-theophylline (8-MTTH) and 8-(benzylthio)-theophylline (8-BzTTH) react only through the N7 purine atom. Cleavage of the C8–S bond is never observed. The complexes obtained by reaction with [*cis*-$PdCl_2(PPh_3)_3$] have different stoichiometry depending on the molar ratio of the reactants. In reactions with 8-BzTTH (1:1 molar ratio) and 8-MTTH (in any ratio) [4] *cis–trans* isomerization of the ligands around metal is observed.

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References

[1] (a) B. Lippert, Coord. Chem. Rev. 156 (1997) 275. (b) A. Sigel, H. Sigel (Eds.), Metal Ions in Biological Systems, vol. 32, Marcel Dekker, New York, 1996, p. 1.
[2] (a) H. Krentzien, M.J. Clarke, H. Taube, Bioinorg. Chem. 4 (1975) 143. (b) A. Johnson, L.A. O'Connell, M.J. Clarke, Inorg. Chim. Acta 210 (1993) 151.
[3] C. Price, M.R.J. Elsegood, W. Clegg, N.H. Rees, A. Houlton, Angew. Chem., Int. Ed. Engl. 36 (1997) 1762.
[4] A. Romerosa, J. Suárez-Varela, M.A. Hidalgo, J.C. Avila-Rosón, E. Colacio, Inorg. Chem. 36 (1997) 3784.
[5] M.J. Ruiz, J.W. Karpen, Nature 389 (1997) 289.
[6] K.W. Merz, P.H. Sthal, Arzneim.-Forsch. 15 (1965) 10.
[7] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, A.G. Moliterni, M.C. Burla, G. Polidori, M. Carmalli, R. Spagna, SIR97 Package Program, 1997.
[8] G.M. Sheldrick, SHELX-96, Program for Crystal Structure Determination, University of Göttingen, 1996.
[9] C.K. Johnson, ORTEP: Report ORNL-5318, OAK Ridge national Laboratory, Oak Ridge, TN, 1976.
[10] (a) J. Mason, Multinuclear NMR, Plenum Press, New York, 1987. (b) R. Bruce King, Encyclopedia of Inorganic Chemistry, Wiley, New York, 1994.

[11] (a) E. Colacio, A. Romerosa, J. Ruiz, P. Roman, J.M. Gutierrez-Zorrilla, M. Martínez-Ripoll, J. Chem. Soc., Dalton Trans. (1989) 2323. (b) E. Colacio, A. Romerosa, J. Ruiz, P. Roman, J.M. Gutierrez-Zorrilla, A. Vegas, M. Martínez-Ripoll, Inorg. Chem. 30 (1991) 30. (c) J.D. Orbell, K. Wilkowsli, L.G. Marzilli, T.J. Kistenmacher, Inorg. Chem. (1982) 3478. (d) A.T.M. Marcelis, H.J. Korte, B. Krebs, J. Reedijk, Inorg. Chem. (1982) 4059. (e) W.M. Beck, J.C. Calabrese, N.D. Kottmair, Inorg. Chem. 18 (1979) 176.