Metal Ion–Purine Interactions: Preparation and Study of some Metal Complexes of 8-Ethyl-xanthine and 8-Ethyl-3-methyl-xanthine

J. M. SALAS-PEREGRIN*, E. SANCHEZ-MARTINEZ and E. COLACIO-RODRIGUEZ

Department of Inorganic Chemistry, Faculty of Sciences, Granada University, 18071 Granada, Spain

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Abstract

The interactions of 8-ethyl-xanthine (8EH) and 8-ethyl-3-methylxanthine (3MEH) with Cu(II), Pd(II), Ag(I) and Au(III) ions in aqueous medium were studied, and the isolated complexes characterized by means of ^{1}H NMR and IR as well as elemental analyses. Reactions occur over a wide pH range, with the purine bases acting as a monoanion, in molecular or protonated forms.

Introduction

Studies of purine–metal ion interactions have become one of the main topics in the research of bioinorganic chemistry [1–6]. Among the purine bases, xanthine occurs as minor constituent in tRNA and the methyl-substituted derivatives of this base have been utilized as model compounds for nucleosides [7–8].

A number of metal complexes of xanthine derivatives have been studied in detail, especially those in which theophylline acts as a ligand [9–18]. However, studies over the interactions between metal ions with substituted xanthines in the 8 position are scanty [19–20].

We are interested in the study of metal–xanthine and metal–methylated xanthine derivatives complexes, both in solution and in the solid phase. In our earliest publications we reported the stability constants of binary complexes of xanthine, theophylline, theobromine, 3,8-dimethylxanthine and 1,3,8-trimethyl xanthine in solution with various metal ions [21–22], and the thermal and spectroscopic studies of a number of isolated complexes in the solid phase [16–17, 20, 23–26]. In this paper we report the preparation and characterization of two 8-alkylated xanthine derivatives, the 8-ethylxanthine (8EH) and 8-ethyl-3-methyl-xanthine (3MEH), and the preparation of copper(II), silver(I), gold(III) and palladium(II) complexes with these derivatives.

Experimental

Preparations

8-ethyl-xanthine and 8-ethyl-3-methylxanthine were prepared according to Speer and Raymond [27].

Ag(8E)·2H₂O and Ag(3ME)

A hot solution of 8-ethylxanthine (5.6×10^{-4} mol) or 8-ethyl-3-methylxanthine (5.2×10^{-4} mol) in about 250 ml of water was mixed with a solution of $AgNO_3$ (8.3×10^{-4} mol or 5.2×10^{-4} mol, respectively) in the minimum amount of water. In both cases a white precipitate was immediately obtained, which was washed with water and ethanol. *Anal.* Calcd. for $Ag(C_7H_7N_4O_2)\cdot 2H_2O$: C, 26.01; H, 3.41; N, 17.34; Ag, 33.41; Found: C, 25.85; H, 3.46; N, 16.57; Ag, 32.92. *Anal.* Calcd. for $Ag(C_8H_9N_4O_2)$: C, 31.90; H, 2.99; N, 18.61; Ag, 35.86; Found: C, 31.47; H, 3.07; N, 18.13; Ag, 35.39.

Cu(8E)₂(NH₃)₂·2H₂O and Cu(3ME)₂(NH₃)₂·4H₂O

4.2×10^{-4} mol and 1.3×10^{-4} mol of $Cu(NO_3)_2\cdot 3H_2O$ are dissolved in aqueous NH_4OH. To these solutions 5.6×10^{-4} mol of 8-ethylxanthine and 1.3×10^{-4} mol of 8-ethyl-3-methylxanthine, dissolved in the minimum amount of water, were added under stirring. From the resulting solutions, blue-gray and brown precipitates were obtained respectively. Both precipitates were washed with aqueous NH_4OH and ethanol and dried with ethylic ether. *Anal.* Calcd. for $Cu(C_7H_7N_4O_2)_2(NH_3)_2\cdot 2H_2O$: C, 34.18; H, 4.88; N, 28.48; Cu, 12.92; Found: C, 34.12; H, 4.67; N, 28.35; Cu, 12.24. *Anal.* Calcd. for $Cu(C_8H_9N_4O_2)_2(NH_3)_2\cdot 4H_2O$: C, 34.56; H, 5.76; N, 25.20; Cu, 11.43; Found: C, 34.89; H, 5.07; N, 24.97; Cu, 10.66.

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*Author to whom correspondence should be addressed.

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Pd(8EH)₂Cl₂·H₂O and Pd(3MEH)₂Cl₂·2H₂O

To a suspension of $PdCl_2$ (5.6×10^{-4} mol) in 50 ml of water was added, with stirring and heating, 1 ml of HCl 12 N. When all the $PdCl_2$ was dissolved 6.8×10^{-4} mol of 8-ethylxanthine or 1.1×10^{-3} mol of 8-ethyl-3-methylxanthine were added. In both cases a pale yellow precipitate was soon isolated, and this was washed with water and ethanol. *Anal.* Calcd. for $Pd(C_7H_8N_4O_2)_2Cl_2 \cdot H_2O$: C, 30.24; H, 3.24; N, 20.16; Pd, 19.16; Found: C, 31.36; H, 3.17; N, 19.48; Pd, 18.58. *Anal.* Calcd. for $Pd(C_8H_{10}N_4O_2)_2Cl_2 \cdot 2H_2O$: C, 31.92; H, 3.99; N, 18.62; Pd, 17.69; Found: C, 31.70; H, 3.61; N, 17.93; Pd, 17.56.

(3MEH₂)(AuCl₄)·H₂O

To a solution of tetrachloroauric acid (5.9×10^{-4} mol) in about 20 ml of water was added a solution of 8-ethyl-3-methylxanthine (4.8×10^{-4} mol) in the minimum amount of water and 2 ml of HCl 6 M. The resulting solution was heated under stirring during 2 h. After two days at room temperature a precipitate of yellow needles appeared. The precipitate was washed with ethanol and dried with ether. *Anal.* Calcd. for $(C_8H_{11}N_4O_2)(AuCl_4) \cdot H_2O$: C, 17.39; H, 2.36; N, 10.14; Cl, 25.72; Au, 35.69; Found: C, 18.14; H, 2.58; N, 10.97; Au, 35.69.

Methods

The determination of the acidity constants of both xanthine derivatives was carried out by potentiometric titration using a Radiometer TTT-60. The measurements were performed at 20, 25, 30, 40 and 50 °C. The ionic strength was adjusted to 0.1 mol $\times$ l^{-1} with potassium nitrate.

The IR spectra were taken with a Perkin-Elmer 4250 instrument. NMR spectra were recorded on a Hitachi-Perkin-Elmer R-600 FT NMR spectrometer, using DMSO-d_6 as solvent and TMS as internal standard. Microanalyses of C, H and N were performed in the Institute of Bio-organic Chemistry, C.S.I.C. (Barcelona).

Results and Discussion

8-Ethylxanthine and 8-Ethyl-3-Methylxanthine

To establish the structures of the compounds prepared we used both IR and ^1H NMR spectrometry. The most significative IR and UV bands for these purine bases are collected in Table I, where the ^1H NMR chemical shifts for these purine bases are also shown. The assignations of Table I were obtained from the literature data for other analogous compounds [28–31].

In aqueous solutions, 8EH and 3MEH can be considered as being weak dibasic acids. The acid dissociation constants of both purine bases were calculated by standard [32] methods. The values of the acidity constants obtained at various temperatures are presented in Table II. The pK values obtained for 8EH and 3MEH are similar to those reported by Izzat *et al.* [33] and Colacio-Rodríguez [34] for other analogous purine bases. On the other hand and in agreement with several other authors [35, 36], the first dissociation process can be assigned to proton loss binding to nitrogen atoms N_7 while K_2

TABLE I. Spectral Data for 8EH and 3MEH.

	8EH	3MEH	Band Assignment
IR data (cm^{-1})	3150s	3150s	ν(N–H)
	2990s	3010s	ν(N–H)
	2800w	2820w	ν(C–H)
	1700vs^a	1685vs^a	ν(C=O)
	1570s	1590s	ν(C=C)
	1515s	1540s	ν(C=N)
	1385s	1375s	ν(C–N)
Electronic spectra (nm)	270 (log ϵ = 3.9; pH = 5.3)	275 (log ϵ = 4.1; pH = 5.4)	π–π^*
	200 (log ϵ = 4.9; pH = 5.3)	202 (log ϵ = 4.4; pH = 5.4)	π–π^*
H NMR chemical shifts (δ)	12.80	13.10	N_7–H
	10.60	11.00	N_1–H
	11.40	–	N_3–H
	–	3.30	N_3–CH_3
	2.60	2.70	–CH_2–^{q}
	1.20	1.30	–CH_3^{t}

^{a}Wide band. ^{q}Quadruplet. ^{t}Triplet.

TABLE II. Proton Dissociation Constants and the Corresponding Thermodynamic Parameters; (Ionic Strength = 0.1 M (KNO_3)).

Ligand	pK_a at [a]					ΔH (Kj × mol^{-1})	ΔS (j × K^{-1} × mol^{-1})	ΔG (25 °C) (kJ × mol^{-1})
	20	25	30	40	50 °C			
8EH	7.70	7.52	7.42	7.23	–	+39.2	−13.6	+43.2
	10.03	9.97	9.85	9.62	–	+36.6	−68.2	+56.9
3MEH	8.74	8.66	8.60	8.50	8.35	+22.6	−90.0	+49.4
	9.88	9.95	9.70	9.58	9.38	+37.0	−65.7	+56.6

[a] Standard deviations for pK_a values is ±0.01.

values correspond to loss of the protons binding to N_1 (3MEH) and N_3 (8EH).

The corresponding thermodynamic constants for the ionization of 8EH and 3MEH are also listed in Table II. In both cases the enthalpy changes for the first proton dissociation are endothermic and the entropy changes are negative. The trend is the same for the second dissociation of the two ligands. The values are similar to those found by Christensen *et al.* [33, 37] for the dissociation processes of xanthine and other purine bases.

From values of pK_1 and pK_2 the distribution diagrams of the different ionic forms can be obtained as a function of pH (Fig. 1).

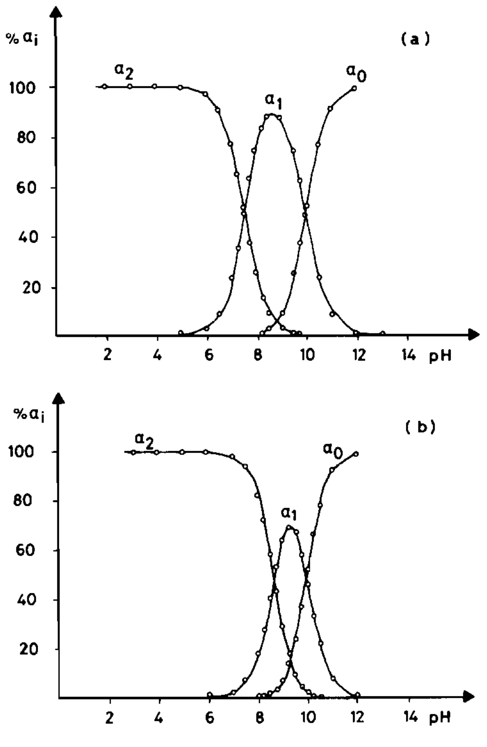


Fig. 1. Distribution diagrams of ionic forms for: (a) 8EH; (b) 3MEH.

Binding Sites and Complex Formation

8-Ethylxanthine and 8-ethyl-3-methylxanthine exhibit different potential binding sites, hence complex formation between 8EH and 3MEH with metal ions could occur in a number of ways, depending mainly on the pH of the medium. For establishing the molecular structure of the prepared complexes we used IR spectroscopy and ^1H NMR spectrometry.

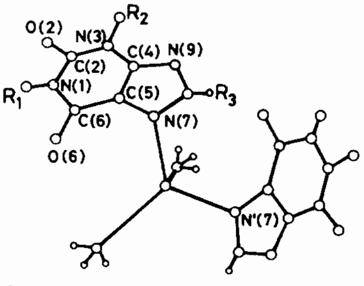
Copper Complexes

In a previous work [38] we examined the thermal behaviour of the complexes $Cu(8EH)_2(NH_3)_2 \cdot 2H_2O$ (I) and $Cu(3ME)_2(NH_3)_2 \cdot 4H_2O$ (II). The TG and DSC curves of these complexes are very similar and display the presence of water of crystallization and coordinated ammonia (endothermic effects at 91 °C and 189 °C (I) and 80 °C and 184 °C (II)). Further support for this is provided by the IR spectra of both complexes: the IR spectra of compound I show two bands at 3400 cm^{-1} and 3330 cm^{-1}, which are not present in the IR spectrum of 8EH, and which can be assigned to ν(O–H) and ν(N–H) of water and ammonia respectively. These bands appear in the IR spectrum of compound II at the same wavelength. On the other hand, we have registered the IR spectra of I and II using polyethylene as dispersive medium to identify any bands with significant M–N stretching character. We found two new bands at 245 and 225 cm^{-1} (I) and 430 and 230 cm^{-1} (II), that could be assigned to ν(Cu–N) (bands at 245, 225 and 230 cm^{-1}) and ν($Cu–NH_3$) (band at 430 cm^{-1}) [19].

For complex (I) the band corresponding to ν-($Cu–NH_3$) is obscured by adsorption bands of the ligand.

In the 1700–1600 cm^{-1} range, the spectra of I and II display bands at 1665 cm^{-1} (I) and 1670 cm^{-1} (II); we have assigned these bands at ν(C=O). These bands are shifted toward lower wavelengths, by 35 and 15 cm^{-1} respectively (see Table I), which is a clear indication of the existence of interactions of the hydrogen bonding type between carbonyl groups and the water or ammonia molecules. Analogous shifts occur for the bands due to ν(C=C) and ν(C=N), which is usual in metal complexes of purine bases when these act as anionic ligands [34].

Based on these data we suggest for the structure of the complexes **I** and **II** the one presented below:



8EH: R_1, R_2 = H; R_3 = CH_2-CH_3
3MEH: R_1 = H; R_2 = CH_3; R_3 = CH_2-CH_3

Palladium Complexes

For complexes $Pd(8EH)_2Cl_2 \cdot H_2O$ (**III**) and $Pd(3MEH)_2Cl_2 \cdot 2H_2O$ (**IV**), magnetic measurements suggest a square planar configuration, in agreement with IR spectra. Thus, the bands at 325 cm^{-1} (**III**) and 330 cm^{-1} (**IV**) are due to stretching vibrations of the Pd–Cl bonds, the chlorine atoms being at the *trans* position. The positions of these bands are in agreement with bibliographic data [39, 40]. Likewise, the IR spectra of the complexes **III** and **IV** are very similar to the IR spectra of the free ligands, showing only very small shifts in the bands due to ν(C=O); ν(C=C) and ν(C=N), which suggests a coordination of the ligand in the molecular form.

In the ^1H NMR spectra of the complexes **III** and **IV** all the signals are strong shifted to lower field relative to those of the free ligands. Thus, for complex **III** these signals appear at 1.80 ppm ($-CH_3$) 3.60 ppm ($-CH_2$); 11.5 ppm (N_1-H); – 12.6 ppm (N_7-H) and 14.5 ppm (N_3-H), while for **IV** all signals are shifted 0.3 ppm to lower field in relation with their position in the H NMR spectrum of 3MEH. These shifts are similar to the shifts observed upon complexation through nitrogen at N-9 position in related compounds [41].

Silver Complexes

The IR spectra for the complexes $Ag(8E) \cdot 2H_2O$ (**V**) and Ag(3ME) are quite unlike those observed for the free ligands, the region of major change being that below 1500 cm^{-1}. Thus, IR spectrum of **V** shows as more significative, a band at 3400 cm^{-1} due to ν(O–H) of the water of crystallization. These molecules are removed in one step (endothermic effect at 91 °C in its DSC curve). Likewise, with the deprotonation of the ligand only a single band assigned to ν(N–H) remains (band at 3130 cm^{-1}). On the other hand, the IR spectrum of **V** shows a shift to lower wavelength of the band due to ν(C=O), (1665 cm^{-1}) which can be due to the interaction of this group with the water molecules. Finally, the IR spectrum of **V** shows at 225 cm^{-1} a new band that we have tentatively assigned to ν($Ag-N_7$).

The IR spectrum of **VI** did not show bands that can be assigned to ν(O–H). At 1680, 1580 and 1515 cm^{-1} there are bands due to ν(C=O), ν(C=C) and ν(C=N), respectively, which are slightly shifted to lower wavelength in relation to the position of these bands in the IR spectrum of free 3MEH. Likewise, we have examined the IR spectrum of **VI** in the 500–200 cm^{-1} range to identify any bands with significant Ag–N stretching character, and we found a new band at 250 cm^{-1} that could be due to ν($Ag-N_7$).

The poor solubility of the complexes **V** and **VI** in the solvents used (DMSO-d_6 and D_2O) prevented us from obtaining H NMR spectra; however, IR data suggest for both complexes that these ligands are bonded to Ag(I) through N-7. Due to its low solubility, a polymeric structure in which ligands should be bonded through N-7 and N-9 atoms is also possible [42, 43].

Gold Complexes

When 8EH and 3MEH react with $HAuCl_4$ in acid medium (HCl), only the compound $(3MEH_2)(AuCl_4) \cdot H_2O$ (**VII**) is isolated. For 8EH the chlorhydrated purine base is more insoluble and precipitates.

The IR spectrum of **VII** shows at 3580 and 3510 cm^{-1} two bands assigned to ν_{as}(OH) and ν_s(OH), considered to be water of crystallization. Likewise, in the 3200–2800 cm^{-1} region there are several bands that can be assigned to ν(N–H) and ν(C–H), while in the 1750–1300 cm^{-1} range the most significant bands appear at 1705 cm^{-1} (ν(C=O)), 1650 cm^{-1} ($\delta_{as}(H_2O)$); 1590 cm^{-1} (ν(C=C)); 1565 cm^{-1} (ν(C=N)); 1445 cm^{-1} (δ(C–H)); 1400 cm^{-1} (δ(C–H)) and 1350 cm^{-1} (ν(C–N)). In the above assignments the displacements to higher wavenumber of the signals corresponding to ν(C=O) and ν(C=N) in relation with their position in the IR spectrum of 3 MEH are considered important. The displacement to higher wavenumber of ν(C=N) is a consequence of the protonation of the 3MEH in the N-9 atom, because the protonation increases the electronic density in the carbon atom adjacent to the protonated nitrogen [44]. This has also been observed in other analogous compounds of the type $(LH_2)(AuCl_4)$ (where LH = theophylline, 3,8-dimethylxanthine, caffeine and 1,3,8-trimethylxanthine) [17]. In these compounds the negative charge of the square planar $AuCl_4^-$ ion is neutralized by a protonate purine base. In our case, the square planar nature of $AuCl_4^-$ ion is corroborated by magnetic measurements (the compound is diamagnetic) and IR data (IR spectra of this compound show a single band due to ν(Au–Cl) at 355 cm^{-1}).

References

1 G. L. Eichhorn, in G. L. Eichhorn (ed.), 'Inorganic Biochemistry', Elsevier, Amsterdam, 1973, p. 1191.
2 D. J. Hodgson, *Prog. Inorg. Chem., 23,* 211 (1977).
3 L. G. Marzilli, *Prog. Inorg. Chem., 23,* 255 (1977).
4 R. W. Gellert and P. Bau, in H. Sigel (ed.), 'Metal Ions in Biological Systems, Vol. 8', Marcel Dekker, New York, 1979, p.1.
5 R. B. Martin and Y. H. Mariam, in H. Sigel (ed.), 'Metal Ions in Biological Systems, Vol. 8', Marcel Dekker, New York, 1979, p. 57.
6 L. G. Marzilli, T. J. Kistenmacher and G. L. Eichhorn, in T. G. Spiro (ed.), 'Nucleic Acid–Metal Ion Interactions', Wiley, New York, 1980.
7 J. R. Lusty and P. F. Lee, *Inorg. Chim. Acta, 91,* L47 (1984).
8 L. G. Marzilli, T. J. Kistenmacher and C. H. Chang, *J. Am. Chem. Soc., 95,* 7505 (1973).
9 T. J. Kistenmacher, D. J. Szalda and L. G. Marzilli, *Inorg. Chem., 14,* 1626 (1975).
10 T. Sorrell, L. G. Marzilli and T. J. Kistenmacher, *J. Am. Chem. Soc., 98,* 2181 (1976).
11 D. J. Szalda, T. J. Kistenmacher and L. G. Marzilli, *Inorg. Chem., 15,* 2783 (1976).
12 T. J. Kistenmacher, D. J. Szalda, C. Chiang, M. Rossi and L. G. Marzilli, *Inorg. Chem., 17,* 2582 (1978).
13 M. S. Zitzman, R. R. Krebs and W. J. Bridsall, *J. Inorg. Nucl. Chem., 40,* 571 (1978).
14 S. D. Rothenberger, M. S. Zitzman and W. J. Bridsall, *J. Inorg. Nucl. Chem., 43,* 1673 (1981).
15 M. Biangini Cingi, *Transition Met. Chem., 4,* 221 (1979).
16 E. Colacio-Rodríguez, J. M. Salas-Peregrin, M. P. Sánchez-Sánchez and A. Mata-Arjona, *Thermochim. Acta, 66,* 245 (1983).
17 E. Colacio-Rodríguez, J. M. Salas-Peregrin, R. López-Garzón and J. D. López-González, *Thermochim. Acta, 71,* 139 (1983).
18 E. Colacio-Rodríguez, J. M. Salas-Peregin and M. A. Romero-Molina, *Rev. Chim. Miner., 21,* 123 (1984).
19 E. Colacio-Rodríguez, J. D. López-González and J. M. Salas-Peregrin, *Can. J. Chem., 61 (11),* 2506 (1983).
20 J. M. Salas-Peregrin, E. Colacio-Rodríguez, F. Girela-Vilchez and M. Roldán, *Thermochim. Acta, 80,* 323 (1984).
21 E. Colacio-Rodríguez, J. M. Salas-Peregrin, J. D. López-González and C. Valenzuela-Calahorro, *An. Quím., 80B,* 49 (1984).
22 J. M. Salas-Peregrin, E. Colacio-Rodríguez, M. Moreno-Carretero and J. D. López-González, *An. Quím. 80B,* 167 (1984).
23 J. M. Salas-Peregrin, E. Colacio-Rodríguez, M. A. Romero, Molina and M. P. Sánchez-Sánchez, *Thermochim. Acta, 69,* 313 (1983).
24 E. Colacio-Rodríguez, J. D. López-González and J. M. Salas-Peregrin, *J. Thermal. Anal., 28,* 3 (1983).
25 E. Colacio-Rodríguez and J. M. Salas-Peregrin, *Thermochim. Acta, 74,* 45 (1984).
26 E. Colacio-Rodrìguez, J. M. Salas-Peregrin, M. A. Romero-Molina and R. López-Garzón, *Thermochim. Acta, 76,* 373 (1984).
27 J. H. Speer and A. L. Raymond, *J. Am. Chem. Soc., 75,* 114 (1953).
28 E. R. Blout and M. Fields, *J. Am. Chem. Soc., 72,* 479 (1950).
29 D. Lichtenberg, F. Bergmann and Z. Neiman, *J. Chem. Soc. C:, 10,* 1939 (1971).
30 L. M. Twanmoh, H. B. Wood and J. S. Driscoll, *J. Heterocycl. Chem., 10 (2),* 187 (1973).
31 R. Savoie, J. J. Jutier, L. Prizant and A. Beauchamp, *Spectrochim. Acta, Part A:, 38,* 561 (1982).
32 J. M. Degorre, A. Delannoy, J. Hennion and J. Nicole, *Bull. Soc. Chim. Fr.,* 471 (1979).
33 R. M. Izatt, J. J. Christensen and J. H. Rytting, *Chem. Rev., 71,* 439 (1971).
34 E. Colacio-Rodríguez, *Thesis,* University of Granada, 1983.
35 L. F. Cavalieri, J. Fox, A. Stone and N. Chang, *J. Am. Chem. Soc, 76,* 1179 (1954).
36 F. Bergmann, D. Lichtenberg and Z. Neiman, 'The Jerusalem Symposia on Quantum Chemistry and Biochemistry, Vol. IV', 1972.
37 J. J. Christensen, J. H. Rytting and R. M. Izzat, *Biochemistry, 9,* 4907 (1970).
38 J. M. Salas-Peregrin, E. Colacio-Rodríguez and E. Sánchez-Martínez, *Thermochim. Acta,* in press.
39 P. Chang Kong and F. D. Rochon, *Can. J. Chem., 59,* 3293 (1981).
40 A. A. Danopoulos and S. M. Paraskewas, *Inorg. Chim. Acta, 55,* 141 (1981).
41 E. Colacio-Rodríguez, J. M. Salas-Peregrin, M. A. Romero-Molina, E. Sánchez-Rodrigo and M. Nogueras-Montiel, *Inorg. Chim. Acta, 79,* 250 (1983).
42 L. Prizant, M. J. Olivier, R. Rivest and A. L. Beauchamp, *J. Am. Chem. Soc., 101,* 2765 (1979).
43 P. I. Vestues and E. Sletten, *Inorg. Chim. Acta, 52,* 269 (1981).
44 V. Adam, A. Grimison and G. Rodríguez, *Tetrahedron, 23,* 2513 (1967).