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Metal Complexes of Alkylating Agents.
V. Complexes of Phosphoramide Mustard Derivatives

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Abstract

Metal complexes of phosphoramide mustard derivatives of $RR'P(O)N(CH_2CH_2Cl)_2$ where R = R' = NH_2 (L_1); R = $-O-P(R')(O)N(CH_2CH_2Cl)_2$ and R' = $N(CH_3)_2$ (L_2) have been prepared. The L_2 ligand is a novel organophosphorus compound. Metal complexes of L_1 include $M(ClO_4)_n(L_1)_x$ where $n = 2$, $x = 4$, M = Cu, Mg; $n = 2$, $x = 5$, M = Co, Ni; $n = 3$, $x = 5$, M = Al; $n = 2$, $x = 6$, M = Ba, Mn; and $MCl_2(L_1)_x$ where $x = 3$, M = Co; $x = 4$, M = Cu. Metal complexes of L_2 include $M(ClO_4)_x(L_2)_x(H_2O)_y$ where $x = 2$, M = Ba, Co, Cu, Mg, Mn, Ni; $x = 3$, M = Al, La and $y = 2, 4, 6$ or 8. Nickel(II) and cobalt(II) complexes of trimethyl phosphonoacetate (TMPA) with stoichiometry $Ni(TMPA)_2(ClO_4)_2 \cdot 3H_2O$ and $Co(TMPA)_2(ClO_4)_2 \cdot 2H_2O$ have also been prepared.

Introduction

Previous papers in this series reported the synthesis of metal complexes of a variety of alkylating agents such as aziridinyl phosphine oxides [1] and aziridinyl phosphine sulfides [2], cyclophosphamide [3], chlorambucil and melphalan [4]. All of these alkylating agents have been used as anticancer agents. In all of the complexes reported thus far, the aziridinyl group or 2-chloroethylamine group attached to the phosphorus remains intact during the formation of the metal complex. In the present work, the metal complexing ability of the phosphoramide mustards shown in Fig. 1 is discussed.

Experimental

Safety

The alkylating agents employed in this work and described herein are all cancer suspect agents. Care should be exercised in their use. Heating and grinding of perchlorate salts should also be avoided due to their potentially explosive nature.

Trimethyl Phosphonoacetate (TMPA)

Trimethyl phosphonoacetate was used as obtained from Lancaster Synthesis Ltd.

Preparation of $[(ClCH_2CH_2)_2N]P(O)(NH_2)_2$ (L_1)

A suspension of bis(2-chloroethyl)amine hydrochloride (Aldrich) (50 g, 280 mmol) was refluxed in freshly-distilled $POCl_3$ (130 ml, excess) for 20 h until a complete solution resulted. The excess $POCl_3$ was then distilled off and the residue was vacuum distilled (boiling point 120 °C at 0.2 mm Hg) to yield 67 g of material which solidified to a solid mass upon cooling (yield = 92%). This material was identified [5] as bis(2-chloroethyl)phosphoramidic dichloride. Ammonia gas was bubbled through a solution of bis(2-chloroethyl)phosphoramidic dichloride (25 g, 96.5 mmol) in 250 ml of $CHCl_3$ for 30 min. Solid L_1 formed which was collected and refluxed in acetone for 10 min before filtering the hot solution and cooling the filtrate to give 16.8 g of L_1 (79.1% yield). *Anal.* Calc. for $C_4H_{12}Cl_2N_3OP$: C, 21.83; H, 5.51; N, 19.10. Found: C, 21.79; H, 5.46; N, 19.17%.

Preparation of $\{[(ClCH_2CH_2)_2N]P(O)[N(CH_3)_2]\}_2O$ (L_2)

Dimethylamine (10.9 ml, 164 mmol) was condensed in an ice-salt bath and dissolved in 25 ml of cold diethyl ether. This solution was then added dropwise to a stirred suspension of bis(2-chloroethyl)phosphoramidic dichloride (21.3 g, 82.2 mmol) in 85 ml of diethyl ether over a 30 min period at 0 °C.

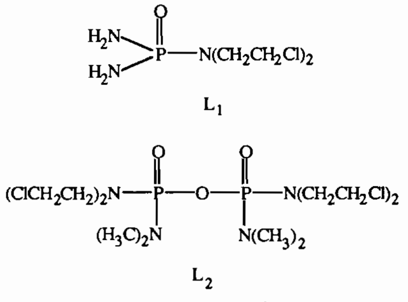

Fig. 1. Structures of L_1 and L_2.

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The resulting mixture was allowed to stand at room temperature overnight before filtering off the dimethylammonium chloride formed. The filtrate was reduced to 21.2 g of an oily residue which was used without further purification since decomposition occurred during vacuum distillation attempts (96.4% yield). The compound was identified as $[(ClCH_2CH_2)_2N]P(O)[N(CH_3)_2]Cl$ by ^1H and ^{13}C NMR. To 33 g (123.4 mmol) of this compound was added dropwise, with stirring, a mixture of 2,6-lutidine (13.22 g, 123.4 mmol) and water (2.2 ml, 123.4 mmol) over a 10 min period in an ice bath. This mixture yielded a solid mass after standing at room temperature overnight which was diluted with diethyl ether and filtered to remove the lutidine hydrochloride. The filtrate was reduced to 24.4 g of an oily residue, washed with petroleum ether, and used without further purification. Characterization of L_2 by IR and NMR data will be discussed later.

Preparation of Complexes of L_1 and L_2

The metal perchlorate complexes of L_1 were all prepared in a similar manner. The hydrated metal perchlorate (1 mmol) was stirred for 1.5 h in a solution of acetone (5 ml), absolute ethanol (5 ml), and triethylorthoformate (2 ml). The triethylorthoformate is used for dehydration of the hydrated metal perchlorate [6]. A slight excess of solid ligand (5 mmol) was added and stirring was continued for an additional 15 min before unreacted ligand was filtered off. When petroleum ether (150 ml) was added to the filtrate, the complexes precipitated as oils or gums. Trituration of these oils and gums with copious amounts of petroleum ether combined with cooling in petroleum ether and vacuum desiccation yielded air-stable complexes of L_1. When anhydrous metal perchlorates or anhydrous metal chlorides were available, the preparation of complexes followed the same procedure except 10 ml of acetone was used in lieu of the acetone/ethanol solution and no triethylorthoformate was required. Only a 3:1 ligand/metal ratio was used for the metal chloride complexes.

Metal complexes of L_2 were obtained by reacting 1 mmol of metal perchlorate in 10 ml of acetone with 3 mmol of ligand dissolved in acetone (usually 1 mmol/ml). The complexes precipitated after addition of diethyl ether (150 ml) as gums which were worked up as described previously. Pumping *in vacuo* usually gave a glass which was washed further with diethyl ether and dried several more hours *in vacuo* to give a solid. The lanthanum complex of L_2 was prepared by dissolving $LaCl_3 \cdot 6H_2O$ (353 mg, 1 mmol) in a solution of acetone (5 ml) and absolute ethanol (3 ml), and then solid $AgClO_4$ (621 mg, 3 mmol) was added to prepare $La(ClO_4)_3$. The AgCl formed was filtered off and 2 ml of triethylorthoformate was added to the filtrate. The resulting solution was stirred for 1 h before an acetone solution of the ligand (3.5 mmol) was added. Diethyl ether was added and the white gum was worked up as before. All of the metal complexes of L_1 are hygroscopic and are soluble in acetone, chloroform and dimethyl sulfoxide.

Elemental Analysis

Carbon, hydrogen, nitrogen, and halogen analyses were performed by Desert Anal, Tucson, AZ.

Infrared Spectra

Spectra were recorded on either a Perkin-Elmer 727 or 1430 infrared spectrometer and samples were prepared as potassium bromide disks, Nujol mulls or run neat.

Nuclear Magnetic Resonance Measurements

^1H NMR spectra were recorded on either a Jeol MH-100 NMR spectrometer or a Jeol FX-90 Fourier Transform NMR spectrometer. ^{13}C NMR spectra were recorded on a Jeol FX-90, an IBM NR-300, or a Bruker AM-400 Fourier Transform NMR spectrometer. ^{31}P NMR data were obtained with an IBM WB-200 spectrometer with an insert containing 86% H_3PO_4 as internal standard. All other samples were recorded at room temperature with tetramethylsilane or the solvent (acetone-d_6, $CDCl_3$, or DMSO-d_6) as the internal standard.

Electron Paramagnetic Resonance Measurements

The EPR spectra were obtained at room temperature and liquid nitrogen temperature on a Varian E-3 EPR spectrometer.

Magnetic Susceptibility Measurements

The Faraday method was used to measure the magnetic susceptibility of L_1 complexes. The measurements were made at 295 K with mercury(II) tetrathiocyanatocobaltate(II) as the reference.

Electronic Spectral Measurements

The visible and near-infrared spectra were obtained using nitromethane or acetone solutions. The spectra were obtained using a Cary Model 14 spectrophotometer with matched 1 and 5 cm cells.

Results and Discussion

Analytical data, colors, percent yield, melting points and P=O stretching frequencies for complexes of L_1 are given in Table 1, and Table 2 lists data for complexes of L_2 and TMPA.

Infrared Spectral Measurements

Infrared analysis has been used to help elucidate the coordination of metal ions. The spectrum of the

TABLE I. Data for complexes of L_1

Compound	Carbon(%)		Hydrogen(%)		Nitrogen(%)		Color	ν(P=O)[a] (cm^{-1})
	calc.	found	calc.	found	calc.	found		
$[Al(L_1)_5](ClO_4)_3 \cdot 4H_2O$	16.02	16.38	4.54	4.62	14.02	13.37	tan	1168
$[Ba(L_1)_6](ClO_4)_2$	17.38	17.35	4.35	4.65	15.20	14.92	white	1158
$[Co(L_1)_5](ClO_4)_2$	17.67	17.90	5.28	4.88	15.46	15.13	blue	1125
$[Cu(L_1)_4](ClO_4)_2 \cdot 2H_2O$	16.30	16.77	4.41	4.42	14.26	14.16	green	1128
$[Li(L_1)_3](ClO_4)$	18.79	18.87	4.70	5.08	16.44	16.47	white	1150
$[Mg(L_1)_4](ClO_4)_2$	17.41	17.85	4.35	4.94	15.23	15.39	white	1090
$[Mn(L_1)_6](ClO_4)_2$	18.30	18.67	4.57	4.97	16.01	16.25	tan	1130
$[Ni(L_1)_5](ClO_4)_2$	17.67	17.61	4.42	5.03	15.46	14.75	green	1155
$[Co(L_1)_3]Cl_2 \cdot 2H_2O$	17.43	17.52	4.84	4.56	15.25	14.98	blue	1165
$[Cu(L_1)_4]Cl_2 \cdot H_2O$	18.60	18.76	4.84	5.10	16.27	14.64	green	1172

[a] ν(P=O) for L_1 is 1180 cm^{-1}. All L_1 complexes were run as KBr pellets and L_1 was run neat.

TABLE 2. Data for complexes of L_2 and TMPA

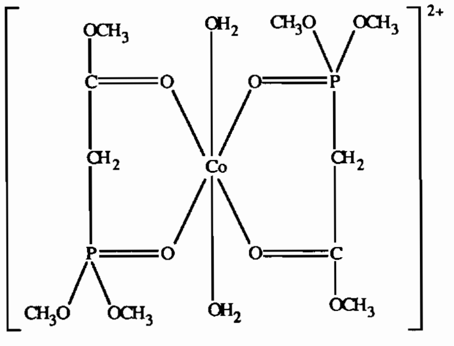
Compound	Carbon (%)		Hydrogen(%)		Nitrogen(%)		Chlorine(%)		Color	Yield (%)	ν(P=O) (cm^{-1})[a]
	calc.	found	calc.	found	calc.	found	calc.	found			
$[Al(L_2)_3](ClO_4)_3 \cdot 8H_2O$	22.62	22.69	5.24	5.14	8.80	8.59	27.88	26.45	tan	39.1	1208
$[Ba(L_2)_2](ClO_4)_2 \cdot 2H_2O$	21.61	21.54	4.50	4.40	8.40	7.89	26.65	26.90	white	23.9	1210
$[Co(L_2)_2](ClO_4)_2 \cdot 2H_2O$	22.96	22.82	4.78	4.94	8.93	8.22	28.31	29.01	blue	83.3	1208
$[Cu(L_2)_2](ClO_4)_2 \cdot 4H_2O$	22.25	22.06	4.94	4.59	8.65	7.92	27.42	27.23	green	16.4	1202
$[La(L_2)_3](ClO_4)_3 \cdot 6H_2O$	21.76	21.52	4.83	4.74	8.46	7.92	26.82	28.06	white	43.8	1190
$[Mg(L_2)_2](ClO_4)_2 \cdot 2H_2O$	23.62	23.83	4.92	5.29	9.18	8.68	29.12	29.45	white	37.6	1215
$[Mn(L_2)_2](ClO_4)_2 \cdot 2H_2O$	23.38	23.76	4.71	4.82	9.09	8.84	28.81	30.49	white	77.8	1200
$[Ni(L_2)_2](ClO_4)_2 \cdot 4H_2O$	22.33	21.79	4.96	5.16	8.68	7.87	27.52	27.95	yellow	80.6	1202
$[Co(TMPA)_2](ClO_4)_2 \cdot 2H_2O$	18.23	18.66	3.95	4.17					pink	63.4	1140(1748) Nujol 1120(1685)
$[Ni(TMPA)_2](ClO_4)_2 \cdot 3H_2O$	17.75	18.15	4.14	4.20			10.50	10.09	green	56.2	1250(1730) Nujol 1115(1682)

[a] ν(P=O) for L_2 is 1242 cm^{-1}, ν(P=O) for TMPA is 1268 cm^{-1}, ν(C=O) for TMPA is 1745 cm^{-1}, ν(C=O) in parentheses. All complexes were run as KBr pellets except where indicated as Nujol.

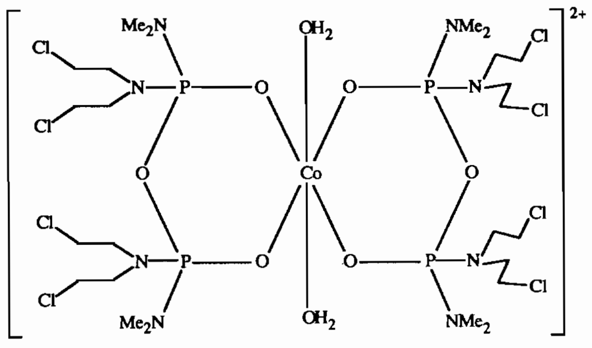
complex was compared with that of the uncomplexed ligand in order to determine the effect of coordination upon the various vibrational frequency modes. The evidence of a band at 1596 cm^{-1} and a very broad band in the 3750–3650 cm^{-1} region is evidence for the presence of water in the complexes [7]. These bands are absent in the anhydrous complexes. Indication of the presence of water in the infrared spectra was taken into account in calculating the stoichiometries shown in Tables 1 and 2. The IR spectra of the perchlorate salts indicate that the perchlorate ions are not coordinated since they have bands at 1100 and 625 cm^{-1} which are characteristic of uncoordinated perchlorate anions [8].

The region of primary importance in phosphine oxide coordination is the phosphoryl stretching frequency which is known to shift to lower frequency upon coordination through the phosphoryl oxygen atom [1, 9, 10]. This shift has been attributed primarily to a decrease in the $d\pi$–$p\pi$ back-bonding from oxygen to phosphorus upon metal coordination to the phosphoryl oxygen atom [11]. All metal complexes of L_1 and L_2 show a P=O shift to lower frequency which is support for coordination of the metal to the phosphoryl oxygen (see Tables 1 and 2).

Complexes of TMPA with Ni(II) and Co(II) were also prepared in order to compare the relative chelating ability of this ligand to that of L_2. The complexes were prepared by the same procedure used for L_2 and data for these complexes are included in Table 2. The colors of the two complexes of TMPA suggest octahedral coordination. When the samples are run as Nujol mulls, both the P=O and the C=O stretching frequencies shift to lower wavenumbers. This supports a bidentate coordination with two ligands coordinated in a square planar geometry and two water molecules in the axial positions (Fig. 2). However, this coordination changes when potassium



$[Co(TMPA)_2]^{2+} \cdot 2H_2O$



$[Co(L_2)_2]^{2+} \cdot 2H_2O$

Fig. 2. Proposed structures for metal complexes of TMPA and L_2.

bromide disks of the complexes are prepared. The simple act of grinding these materials results in color changes to blue and dark green for the cobalt and nickel complexes, respectively, indicative of tetrahedral symmetry. The IR spectra indicate that the metal–carbonyl coordination has now disappeared since the C=O stretching band lies at essentially the same frequency as that of the uncomplexed ligand. Apparently, the metal coordination to the carbonyl oxygen is a relatively weak interaction.

Nuclear Magnetic Resonance Measurements

All of the phosphoramide mustards and their diamagnetic complexes exhibit a complex set of resonances in the δ 3.00–4.00 range. The 2-chloroethylamine ^1H NMR spectrum shows two triplets at 3.40 and 4.00 ppm for the two equivalent sets of α and β protons, respectively. The spectra of the complexes indicate that the ligand is still intact. In acetone-d_6, a peak is present at δ 2.86 and 2.99 for the Ba and Mg complexes, respectively, which integrates for half the value of the mustard region, thereby probably representing the 4 NH_2 protons. The ^{13}C NMR spectra of the Ba, Mg, Al and Li complexes are also almost identical to that of uncomplexed L_1.

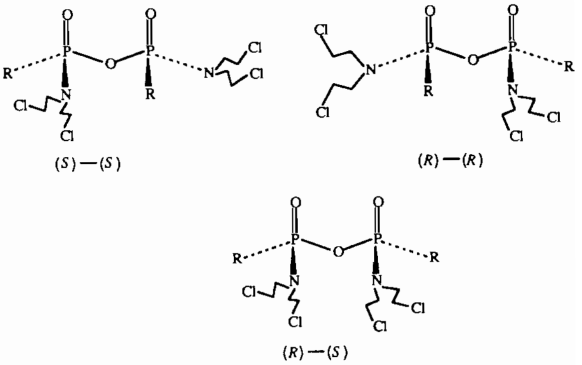


Fig. 3. Stereoisomers.

The ^1H NMR spectrum of L_2 shows two distinguishable sets of resonances in the δ 3.43–3.70 region of the spectrum. Both of these multiplets are basically doublets of triplets, as expected for the methylene protons. The dimethylamino region exhibits a doublet at δ 2.78 (J = 13.3 Hz) from PNC coupling. Another doublet at δ 2.75 (J = 11 Hz) is from an impurity of the precursor, $[(ClCH_2CH_2)_2N]P(O)[N(CH_3)_2]Cl$. Since attempts to vacuum distill L_2 led to decomposition, it was necessary to use an impure product as our ligand. The ratio of the methylene region to the methyl region of the spectrum is 4:3 as expected.

The ^{13}C NMR spectrum of L_2 shows the three expected peaks for the Cα, Cβ and $N(CH_3)_2$ carbon atoms at δ 49.24, 41.54 and 36.32, respectively. Peaks representing the precursor were also present at δ 41.11 and 36.83. The Cα peak is the same for both compounds. The off-resonance spectrum also shows the same general properties. The downfield peak is simply a triplet (J = 53 Hz) centered at δ 48.99. Two other triplets are present at δ 41.46 and 41.06 (J = 60 Hz). Two quartets are present centered at δ 36.60 and 36.10 (J = 50 Hz), also indicative of the presence of the precursor. The spectra of complexes of L_2 are generally more complicated than those of the ligands. The ratio of the methylene region to the methyl region is still 4:3 indicating that the ligand is still intact.

The $^{31}P\{^1H\}$ NMR spectrum of L_2 contains two closely spaced singlets at 10 ppm downfield from H_3PO_4 with a separation of 10.1 Hz. These singlets are attributed to the racemic pair [(*S*,*S*) and (*R*,*R*)] and the *meso* forms (*S*,*R*) shown in Fig. 3. The pattern of two closely spaced singlets has been observed with other symmetrical pyrophosphate compounds in which two of the groups of the phosphorus atoms were dimethylamino and the other two were various alkyl and alkoxy groups [9]. The difference between the peaks in the L_2 spectrum is 10.1 Hz which is in good agreement with previously reported values. We also tentatively assign the upfield peak in the set of singlets to the racemic pair based on conclusions

TABLE 3. Electronic spectral data

Compound	λ_{max} (nm) (cm^{-1})	ϵ
$[Co(L_1)_5](ClO_4)_2$^{a}	623(16051)	68.5
	595(16807)	68.1
	580(17241)	67.2
	550(18182)	51.7
$[Co(L_1)_3]Cl_2\cdot 2H_2O$	663(15083)	449
	638(15674)	395
	615(16260)	326
	590(16949)	285
	580(17241)	252
$[Cu(L_1)_4](ClO_4)_2\cdot 2H_2O$	727(13755)	230
$[Co(L_2)_2](ClO_4)_2\cdot 2H_2O$^{b}	668(14970)	21.1
	592(16892)	12.3
	580(17241)	11.3
$[Ni(L_2)_2](ClO_4)_2\cdot 4H_2O$	1260(7937)	1.7
	782(12788)	2.8
	700(14286)	2.7
	595(16807)	1.3
	427(23419)	12.3

^{a}L_1 complexes run in nitromethane. ^{b}L_2 complexes run in acetone.

from previous optical resolution studies in which a chiral alcohol split the upfield peak into two peaks [12].

Electronic Spectral Measurements

Electronic absorption spectral data obtained for solutions of the complexes in nitromethane or acetone are given in Table 3. The $Co(ClO_4)_2$ complexes of L_1 and L_2 both exhibit spectra indicative of tetrahedral cobalt(II) [13]. Five-coordinate Co(II) complexes are known which show absorption bands in the visible region of the spectra at approximately 12 500 and 20 000 cm^{-1}. Since the spectrum of the Co(II) complex of L_1 is indicative of tetrahedral Co(II), the fifth ligand must occupy a unique position in the crystal lattice which is not the case in solution. The spectrum of the Co(II) complex with L_2 was surprising since L_2 would be expected to be a bidentate ligand even in solution. The likely solution coordination environment of Co(II) is two monodentate L_2 ligands and two water molecules. In contrast to the Co(II) complex of L_2, the Ni(II) complex solution spectrum is that expected for octahedral Ni(II). We assign these absorptions as follows: $^3T_{1g}(P) \leftarrow {}^3A_{2g}$, 427 nm; $^3T_{1g}(F) \leftarrow {}^3A_{2g}$, 782 nm; and $^3T_{2g} \leftarrow {}^3A_{2g}$, 1260 nm [14]. The low molar absorptivities are due to Laporte forbidden transitions. These three absorptions are typical of those reported previously for other tris-Ni(II) complexes of pyrophosphates [9, 10].

Magnetic Susceptibility Measurements

The magnetic data for the paramagnetic complexes of L_1 are listed in Table 4. Complexes of L_2 were too air-sensitive for accurate magnetic susceptibility measurements. The magnetic susceptibility of the Ba(II) complex with L_1 was measured for use as the diamagnetic contribution for the Co(II) and Ni(II) perchlorate complexes of L_1. For the other complexes, tabulated data for substituent diamagnetic corrections were employed [15]. All the magnetic moments fall in the range of moments expected for the particular paramagnetic ion.

Electron Paramagnetic Resonance Measurements

The EPR spectra of the Cu(II) complex of L_1 were recorded at 296 and 77 K. Both spectra are anisotropic as expected for tetragonal Cu(II). The $g_\perp$ and $g_\parallel$ values are 2.07 and 2.42 at 296 K and 2.08 and 2.28 at 77 K, respectively. These g values are similar to those observed for the tetragonal Cu(II) complexes of other phosphoramides [16].

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TABLE 4. Magnetic susceptibility data at 296 K

Compound	χ_M^{a} (x10^6)	Corr. (x10^6)	χ_M' (x10^6)	μ_{eff} (BM) (experimental)	Experimental range
$[Co(L_1)_5](ClO_4)_2$	7741	58.3	7799	4.32	4.1–5.2
$[Co(L_1)_3]Cl_2\cdot 2H_2O$	10325	453	10778	5.08	4.1–5.2
$[Ni(L_1)_5](ClO_4)_2$	3667	58.3	3725	2.99	2.8–4.0
$[Cu(L_1)_4](ClO_4)_2\cdot 2H_2O$	1143	593	1736	2.03	1.7–2.2
$[Mn(L_1)_6](ClO_4)_2$	9687	811	10498	5.00	≈5.9
$[Co(TMPA)_2](ClO_4)_2\cdot 2H_2O$	8884	301	9185	4.71	4.1–5.2

^{a}cgs units.

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