Synthesis, Characterization, and Antibacterial Activities of Some Rare Earth Metal Complexes of Pipemidic Acid

Lin YANG,* Dongliang TAO, Xiaoli YANG, Yongfang LI, and Yuming GUO

College of Chemistry and Environmental Science, Henan Normal University; Xinxiang, 453002, P.R. China.
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Eight new solid complexes of pipemidic acid (PPA) with trichlorizated rare earth metals $LaCl_3$, $CeCl_3$, $PrCl_3$, $NdCl_3$, $SmCl_3$, $TbCl_3$, $DyCl_3$, and YCl_3 have been synthesized. The complexes were characterized by elemental analyses, IR, NMR, and molar conductance measurements. The general formulas of the complexes are $[M(PPA)_4]Cl_3$ (M=Ce(III), Pr(III), Nd(III), Sm(III), Tb(III), Dy(III), Y(III)), and $[La(PPA)_4Cl]Cl_2$. At the same time, the antibacterial activities of PPA and four of its complexes were tested. The results show that PPA and its complexes all have inhibitory action against bacteria of *Escherichia coli*, *Bacillus subtilis*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* but not *Staphylococcus aureus*. We compared their antibacterial activities and found that the antibacterial activity of $[La(PPA)_4Cl]Cl_2$ against *S. pneumoniae* is much stronger than that of PPA and the other complexes.

Key words pipemidic acid; rare earth complex; antibacterial activity; IR, ^{13}C-NMR

The interaction of metal ions with drugs administered for therapeutic purposes is a subject of considerable interest.[1—4] It is known that some drugs work by chelation[1] or inhibiting the formation of metalloenzymes.[2] Therefore metal ions might play a vital role during the biological process of drug utilization in the body.

Pipemidic acid (PPA) is a 4-quinoline derivative with the molecular structure shown in Fig. 1. It is well known for its antibacterial activity *via* inhibition of the synthesis of deoxyribonucleic acid. Qiao *et al.* studied complexes of PPA with some transition metals.[5] The results suggested that metal ion coordination might be involved in the antibacterial activity of PPA. We have studied the interaction between some main group metals and PPA.[6] We found that the antibacterial activities of the metal complexes are identical to or less than that of PPA. The interaction of rare earth ions and drugs can produce special antibacterial or anticancer effects.[3] In this investigation, we synthesized and characterized the complexes of La^{3+}, Ce^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Tb^{3+}, Dy^{3+}, and Y^{3+} with PPA. At the same time, the antibacterial activities of $[La(PPA)_4Cl]Cl_2$, $[Pr(PPA)_4]Cl_3$, $[Sm(PPA)_4]Cl_3$, and $[Y(PPA)_4]Cl_3$ were determined. The antibacterial activity of $[La(PPA)_4Cl]Cl_2$ against *Streptococcus pneumoniae* is much greater than that of PPA alone.

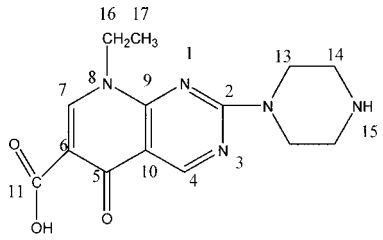

Fig. 1. Structure of PPA

Experimental

The metal chlorides and ligand PPA were obtained from the Beijing Chemical Company (Beijing, PR China). Solvents used in this experiment were of analytical reagent grade. Elemental analysis of carbon, hydrogen, and nitrogen was performed on a Carlo Erba MOD1106 elemental analyzer. After destruction of the organic matter with $HClO_4$, the lanthanides were titrated with EDTA in the presence of a buffer solution (urotropine buffer, pH 5.5) using xylenol orange as an indicator. Chlorine analyses were performed by precipitation as silver chloride. IR spectra were recorded in the range of 4000—400 cm^{-1} as KBr discs on a Nicolet 5DX instrument. The molar conductance of 10^{-3} M solutions in water was measured at room temperature on a DDS-12A conductivity meter. With tetramethylsilane (TMS) as the external standard, ^{13}C-NMR spectra were obtained at room temperature on a Bruker AC-300L spectrometer in D_2O for the complexes and in 0.2 M D_2SO_4 for PPA.

Synthesis of Complexes The solid complexes were prepared by mixing 1.0 mmol of lanthanide chloride in 30 ml of ethanol with 4.0 mmol PPA (1.4 g) in 20 ml of acetic acid. The reaction mixtures were then refluxed in a water bath for 3—4 h to give the precipitate. After cooling to room temperature, the solid complexes were filtered as fine precipitates. The precipitates were washed with acetic acid and then ethanol. Then they were dried and stored in a desiccator containing dry calcium chloride. The yield of the products was about 70%. The complexes were subjected to elemental microanalyses for C, H, N, Cl, and metal ion contents and their structures were confirmed by their IR and ^{13}C-NMR spectra.

Results and Discussion

The complexes were stable at room temperature and soluble in water, but insoluble in ethanol, acetone, and acetic acid. The elemental analyses of the complexes (Table 1) showed that the metal ions form complexes with the composition $[M(PPA)_4Cl]Cl_2$ for La(III), and $[M(PPA)_4]Cl_3$ for Ce(III), Pr(III), Nd(III), Sm(III), Tb(III), Dy(III), and Y(III). The molar conductance of the complexes in water at room temperature was 267 $s \cdot cm^2 \cdot mol^{-1}$ for $[La(PPA)_4Cl]Cl_2$ and varied from 408 to 435 $s \cdot cm^2 \cdot mol^{-1}$ for $[M(PPA)_4]Cl_3$, indicating that the complexes of $[La(PPA)_4Cl]Cl_2$ in water are in the range expected for 1 : 2 electrolytes and the complexes of $[M(PPA)_4]Cl_3$ in water are in the range expected for 1 : 3 electrolytes.[7] The assumed structure of the complexes are presented in Figs. 2, 3.

IR Spectra The IR Spectra of PPA and its two complexes are shown in Figs. 4—6. The important IR spectral bands of PPA and its complexes are presented in Table 2. The IR spectrum of the ligand PPA shows two strong bands at 1619 cm^{-1} and 1640 cm^{-1} which are assigned to the stretching vibration of the carboxylic carbonyl group and ring carbonyl group, respectively.[8,9]

The new bands at 1717—1737 cm^{-1} confirm that the metal ions coordinate with the hydroxy oxygen of the carboxylic

* To whom correspondence should be addressed. e-mail: yxl1997@sohu.com
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Table 1. Analytical Data[a] of the Complexes

Complex	Empirical formula (formula weight)	C %	H %	N %	M %	Cl %	Yield (%)	DT[b]	MC[c]
$[LaL_4Cl]Cl_2$	$C_{56}H_{68}Cl_3N_{20}O_{12}La$ (1458.55)	47.46 (46.12)	4.57 (4.70)	19.42 (19.21)	9.47 (9.35)	7.21 (7.29)	72.3	270	267.65
$[CeL_4]Cl_3$	$C_{56}H_{68}Cl_3N_{20}O_{12}Ce$ (1459.76)	45.98 (46.08)	4.68 (4.70)	18.97 (19.19)	9.45 (9.60)	7.16 (7.28)	65.6	284	408.45
$[PrL_4]Cl_3$	$C_{56}H_{68}Cl_3N_{20}O_{12}Pr$ (1460.55)	45.84 (46.05)	4.59 (4.70)	19.22 (19.18)	9.45 (9.65)	7.09 (7.28)	78.3	289	421.45
$[NdL_4]Cl_3$	$C_{56}H_{68}Cl_3N_{20}O_{12}Nd$ (1463.88)	45.67 (45.95)	4.54 (4.68)	18.45 (19.14)	9.56 (9.85)	7.14 (7.27)	87.2	293	436.46
$[SmL_4]Cl_3$	$C_{56}H_{68}Cl_3N_{20}O_{12}Sm$ (1470.00)	45.43 (45.76)	4.75 (4.66)	18.79 (19.06)	10.14 (10.23)	7.13 (7.24)	86.7	274	431.30
$[TbL_4]Cl_3$	$C_{56}H_{68}Cl_3N_{20}O_{12}Tb$ (1478.57)	45.23 (45.49)	4.55 (4.63)	18.65 (18.95)	10.45 (10.75)	7.04 (7.19)	74.4	294	428.37
$[DyL_4]Cl_3$	$C_{56}H_{68}Cl_3N_{20}O_{12}Dy$ (1482.14)	46.02 (45.38)	4.92 (4.62)	17.80 (18.90)	10.78 (10.96)	7.14 (7.18)	73.3	265	423.09
$[YL_4]Cl_3$	$C_{56}H_{68}Cl_3N_{20}O_{12}Y$ (1408.55)	47.39 (47.75)	4.76 (4.87)	19.76 (19.89)	6.20 (6.31)	7.43 (7.55)	75.6	287	426.53

a) Calculation values in parentheses. L=PPA. *b*) DT=decomposition temperature. *c*) MC=molar conductance ($s \cdot cm^2 \cdot mol^{-1}$).

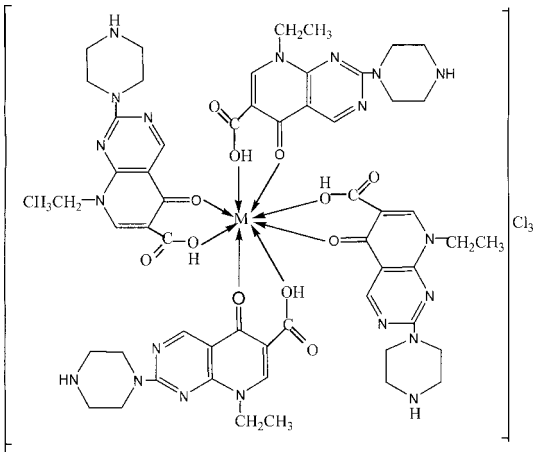

Fig. 2. Proposed Structure of the Complexes (M=Ce, Pr, Nd, Sm, Tb, Dy, Y)

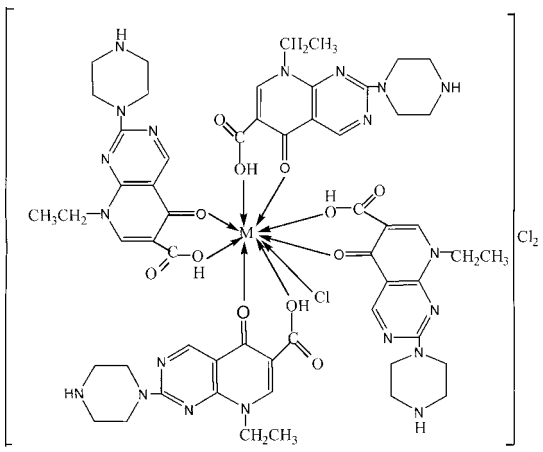

Fig. 3. Proposed Structure of the Complexes (M=La)

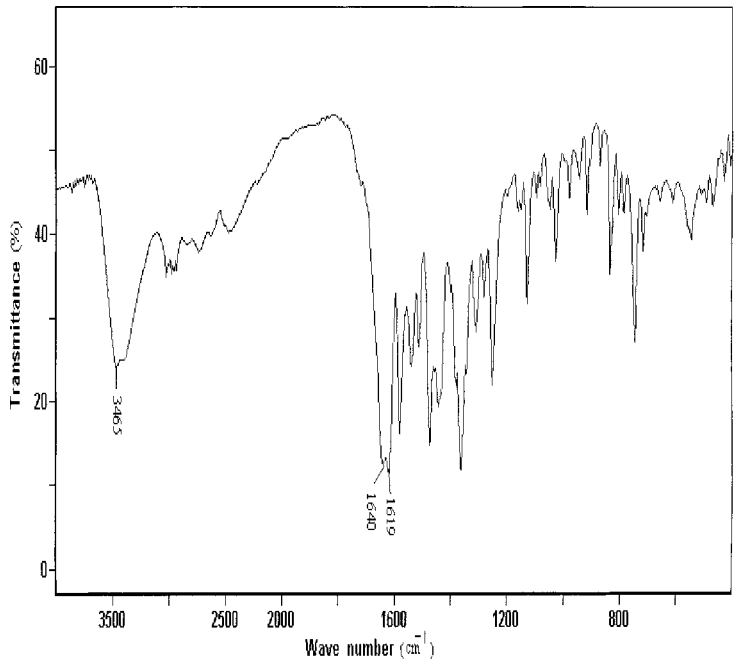

Fig. 4. IR Spectra of PPA

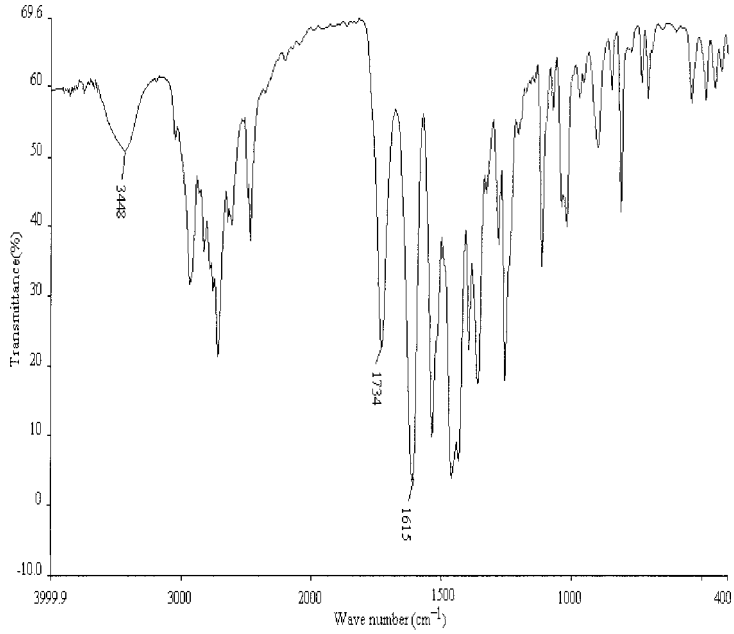

Fig. 5. IR Spectra of $[La(PPA)_4Cl]Cl_2$

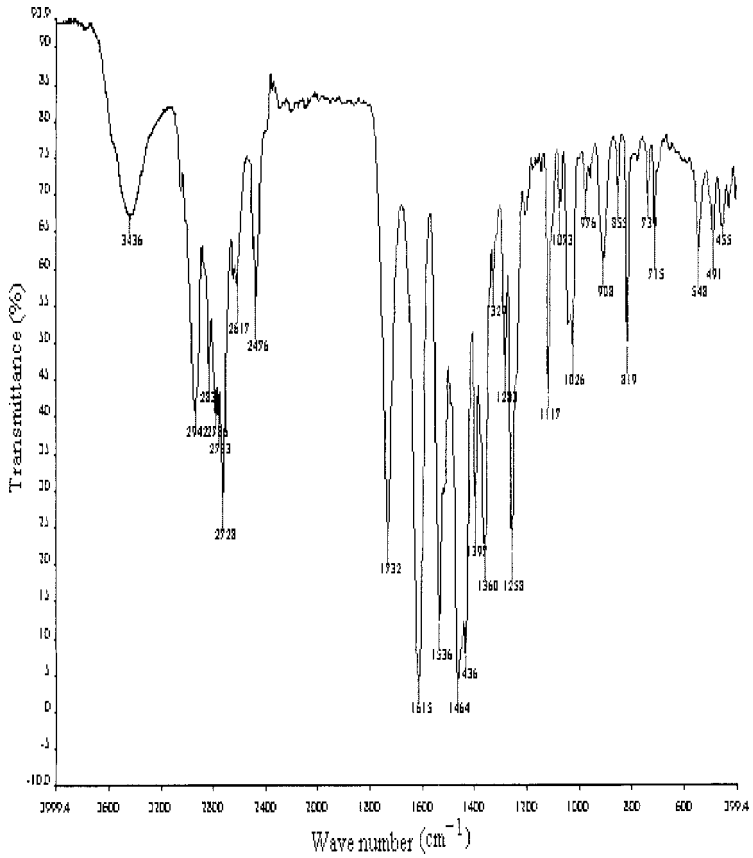

Fig. 6. IR Spectra of $[Pr(PPA)_4]Cl_3$

group, which strengthens the C=O vibration. On complexation, the water of crystallization in PPA is removed, which eliminates the action of the hydrogen bond. Thus ν (C=O) of the carboxylic group is shifted to higher frequency. The ν (C=O) ring vibration at 1640 cm^{-1} and ν (O–H) in the carboxylic group at 3465 cm^{-1} are shifted to lower wave numbers. Since the ν (C=N) and ν (N–H) vibrations change little, we infer that there is no coordination between metal ions and nitrogen atoms. These results indicate that the complexes form a bidentate (chelate) ligand complex in which the metal ions are coordinated to the ring carbonyl oxygen and hydroxy oxygen in the complexes.[10,11]

^{13}C-NMR Spectra To confirm the coordination of the carboxylic oxygen to the metal ion in the complexes, ^{13}C-

NMR spectra were recorded for the ligand PPA and its rare earth complexes. The important chemical shifts for the ligand PPA and the complexes are given in Table 3. The ^{13}C-NMR data indicate that the important chemical shifts for PPA have changed by coordination. Taking the complexes $[La(PPA)_4Cl]Cl_2$ and $[Pr(PPA)_4]Cl_3$ as examples, the prominent feature of the ^{13}C-NMR spectra show downfield shifts of the C5 (ring carbonyl group) and C11 (carboxylic group) resonances from 173.16 ppm and 165.00 ppm for the ligand to 178.55 ppm and 179.86 ppm, respectively, for the complex $[La(PPA)_4Cl]Cl_2$, and to 177.17 ppm and 179.45 ppm, respectively, for the complex $[Pr(PPA)_4]Cl_3$. This indicates coordination through the ring carbonyl oxygen and hydroxy oxygen to the metal ions.[12,13]

Antibacterial Activity The antibacterial activities of ligand PPA and metal complexes against the five bacteria *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *S. pneumoniae* and *Pseudomonas aeruginosa* at 37 °C at pH 7.4 in phosphate buffer *in vitro*[14] are listed in Table 4. The results show that the ligand and its rare earth complexes have inhibitory action against all the bacteria except for *S. aureus*. For the complexes of Pr, Sm, and Y, the antibacterial activities against *E. coli*, *S. aureus*, *B. subtilis*, and *S. pneumoniae* are similar to that of PPA, but are weaker against *P. aeruginosa*. For the complex of La, the antibacterial activities against *E. coli*, *S. aureus*, and *P. aeruginosa*, are similar to that of PPA. However, the antibacterial activity of $[La(PPA)_4Cl]Cl_2$ against *S. pneumoniae* is much greater than that of PPA.

Thus we assume that the coordination of metal ions with PPA varied the conjugated system of PPA and the antibacterial activities changed. In other words, the complexes probably have enhanced activities when they enter bacterial cells to act with DNA *in vivo*.[3,5,15] Furthermore, the solubility of the complexes in water is much higher than that of PPA in water, which will improve drug efficacy. At the same time, the antibacterial activity of the lanthanum complex was the greatest of the complexes studied. This may be related to the ionic radius of La^{3+}, which is the largest of the four ions (La^{3+}, Pr^{3+}, Sm^{3+}, and Y^{3+}). It has been reported that the antibacterial activity of a complex is influenced by its stability. The lower the stability of the complex, the greater the antibacterial activity.[16,17] This is probably because they have more free ions in the solution, which can enhance the cooperative interaction between the metal ions and the ligands. Among the four complexes, the lanthanum complex had the lowest stability because it had the largest ionic radius, and thus it showed greater antibacterial activity than the others. In addition, the lanthanum complex had stronger inhibition against *S. pneumoniae*. This is not only related to the above-described reasons, but also to the character of *S. pneumoniae*.

This study clearly demonstrated how metal ions interact with PPA. PPA interactions with metal ions might have bio-

Table 2. Important IR Spectral Bands of PPA and Its Complexes (cm^{-1})

Compound	ν(C=O) (acid group) (s)	ν(C=O) (ring) (s)	ν(O–H) (m)
$PPA \cdot 3H_2O$	1619	1640	3465
$[La(PPA)_4Cl]Cl_2$	1734	1615	3448
$[Ce(PPA)_4]Cl_3$	1734	1616	3444
$[Pr(PPA)_4]Cl_3$	1732	1615	3436
$[Nd(PPA)_4]Cl_3$	1733	1616	3440
$[Sm(PPA)_4]Cl_3$	1735	1615	3432
$[Tb(PPA)_4]Cl_3$	1733	1615	3408
$[Dy(PPA)_4]Cl_3$	1735	1616	3395
$[Y(PPA)_4]Cl_3$	1734	1615	3447

Table 3. ^{13}C-NMR Spectral Data (δ ppm) of PPA and Its Complexes

Compound	$PPA \cdot 3H_2O$	$[LaL_4Cl]Cl_2$	$[CeL_4]Cl_3$	$[PrL_4]Cl_3$	$[NdL_4]Cl_3$	$[SmL_4]Cl_3$	$[TbL_4]Cl_3$	$[DyL_4]Cl_3$	$[YL_4]Cl_3$
C(2)	155.81	158.13	158.26	158.11	158.24	158.31	158.16	158.34	158.51
C(4)	154.26	153.32	153.26	153.47	153.34	153.69	153.79	153.51	153.27
C(5)	173.16	178.55	210.36	177.17	175.46	179.89	201.13	182.25	179.68
C(6)	108.45	107.34	107.25	107.48	107.61	107.24	107.37	107.41	107.23
C(7)	153.41	151.36	151.40	151.38	151.51	151.42	151.33	151.23	151.18
C(9)	155.26	158.11	158.32	158.09	158.34	158.42	158.17	158.25	158.28
C(10)	108.64	107.66	107.58	107.61	107.72	107.45	107.83	107.59	107.62
C(11)	165.00	179.86	180.29	179.45	179.99	180.56	179.14	178.82	179.56
C(13)	48.61	47.58	47.67	47.60	47.87	47.90	47.56	47.67	47.71
C(14)	42.48	42.39	42.46	42.51	42.45	42.39	42.38	42.42	42.41
C(16)	41.65	40.86	40.52	40.37	40.48	40.65	40.39	40.43	40.54
C(17)	12.89	13.37	13.46	13.57	13.41	13.39	13.52	13.44	13.38

Table 4. Antibacterial Activity of PPA and Its Complexes

Compound	*Escherichia coli*	*Staphylococcus aureus*	*Bacillus subtilis*	*Streptococcus pneumoniae*	*Pseudomonas aeruginosa*
$PPA \cdot 3H_2O$	+++	−	+	+	+
$[LaL_4Cl]Cl_2$	+++	−	+	+++	+
$[PrL_4]Cl_3$	+++	−	+	+	−
$[SmL_4]Cl_3$	+++	−	+	+	−
$[YL_4]Cl_3$	+++	−	+	+	−

"−": no sensitive, D=6 mm; "+": weak sensitive, D<15 mm; "++": middle sensitive, D=15—20 mm; "+++": strong sensitive, D>20 mm. L=PPA.

logical significance. Depending upon the exact location of the metal ion in a biological system, drugs will have very different binding geometries, binding constants, and antibacterial activities, *etc*. This will be important in the various parameters chosen to model drug activity.

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