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Synthesis of Tetracyano(*S*-2-aminomethylpyrrolidine) and Tetracyano(2-aminomethylpiperidine) Complexes of Fe(II) and Co(III): Stereochemistry and Comparison of Spectroscopic Properties of Isoelectronic Structures

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Sodium tetracyano((*S*)-2-aminomethylpyrrolidine = *S*-pyrda)ferrate(II) and -cobaltate(III) and tetracyano(2-aminomethylpiperidine = pipda)ferrate(II) and -cobaltate(III) were prepared. These complexes afforded well-separated ^{1}H NMR spectra sufficient to delineate their structures in solution. The major conformation of the coordinated pyrda and pipda differs in the condensation mode of the five-membered chelate ring and the heterocycles, i.e. *cis*- and *trans*-, respectively, this leads to the different orientation of the heterocycle of the diamines. The comparison of the ^{1}H and ^{13}C chemical shifts and the electronic structure is described from the viewpoint of the isoelectronic structures with different electric charges.

Tetracyano(diamine) chelates of iron(II) and cobalt(III) are diamagnetic and offer a good example of isoelectronic compounds.[1] The unsymmetrical coordination geometry of these compounds provides well-separated ^{1}H NMR spectrum. Therefore the effects of the charge on the metal ion on the electronic and NMR spectra can be evaluated using these compounds. Recently an antineoplasmic effect was shown to be provided by the platinum complexes with 2-aminomethylpyrrolidine but the efficacy was reported to be poor for the corresponding 2-aminomethylpiperidine.[2—8] The stereochemistry of these 2-aminomethyl-azacycloalkane coordinated to metal ions is interesting for the analysis of clinical efficacy. The coordination of 2-aminomethyl-azacycloalkane to metal ions can in principle occur either by *cis*- and *trans*-fusion between the azacycloalkane ring and the five-membered chelate rings (Chart 1). Furthermore, the stereochemistry of these chelates is rich because of the puckering of the five-membered chelate rings: The alkyl group can extend in either equatorial or axial directions. The stereochemistry of the chelate formed by these diamines has been the subjects of several studies.[9—14] But those studies were undertaken when high magnetic field NMR spectrometers were not available and the details about the conformations of these 2-aminomethyl-azacycloalkanes on coordination have not been obtained.

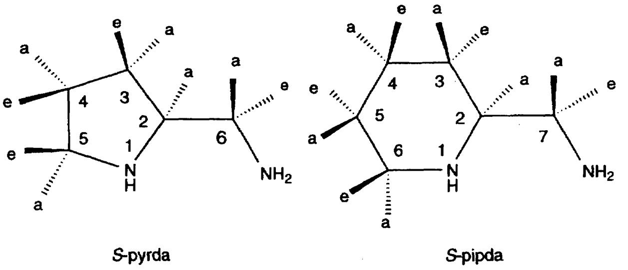

Chart 1.

The synthesis and characterization of the title compounds are undertaken to investigate the stereochemistry by using NMR spectroscopy as well as optical spectrometry.

Experimental

(*S*)-2-Aminomethylpyrrolidine was prepared by reduction of L-proline amide with $LiAlH_4$ by the method of Saburi et al.[15] Bp 52 °C (11 mmHg, 1 mmHg = 133.322 Pa). 2-Aminomethylpiperidine was prepared from 2-aminomethylpyridine by reduction.[16] Bp 78—85 °C (20.5—27.5 mmHg, 2.73×10^{3}—3.67×10^{3} Pa). $K_3[Co(CN)_5Br]$ was prepared by the method of Adamson.[17]

$Na_2[Fe(CN)_4(S\text{-pyrda})]\cdot H_2O$ (1). A solution of *S*-pyrda (7.50 g, 0.0749 mol) in methanol (25 cm^3) was added to a solution of $Fe(ClO_4)_2\cdot 6H_2O$ (9.20 g, 0.0254 mol) in methanol (16 cm^3) under nitrogen. To the resultant mixture, an aqueous solution of sodium cyanide (4.90 g, 0.100 mol in 12 cm^3 of water) was added with vigorous stirring. After this was stirred for 1 h the resutant mixture was concentrated to near dryness, and water (5 cm^3) and methanol (25 cm^3) were added to dissolve the product. Undissolved material was removed by filtration and ethanol (60 cm^3) was added to the filtrate. Separated yellow crystals were collected on a filter, washed with ethanol (40 cm^3) and ether (30 cm^3), successively, and stored in vacuo. Yield, 7.31 g (88.8%). Found: C, 33.26; H, 4.06; N, 26.04%. Calcd for $Na_2[Fe(CN)_4(C_5H_{12}N_2)]\cdot H_2O$: C, 33.36; H, 4.35; N, 25.93%. $\nu_{C\equiv N}$ 2040, 2050 cm^{-1}.

$Na_2[Fe(CN)_4(pipda)]\cdot 3.5H_2O\cdot 0.5NaClO_4$ (2). A solution of pipda (5.74 g, 0.0503 mol) in methanol (20 cm^3) was added to a solution of $Fe(ClO_4)_2\cdot 6H_2O$ (6.08 g, 0.0168 mol) in methanol (15 cm^3) under nitrogen. After this was stirred for 30 min, an aqueous solution of NaCN (3.29 g, 0.0671 mol) in 10 cm^3 of water was added dropwise to the vigorously agitated tris(2-aminomethylpiperidine)iron(II) solution formed in situ. Yellow precipitates that formed during the addition of NaCN were redissolved with further addition of NaCN. The resulting yellow-brown mixture was concentrated under reduced pressure to yield a viscous oil. To the residue, water (3 cm^3) and methanol (10 cm^3) were added to triturate successively. Undissolved material was removed by filtration. Ethanol (20 cm^3) was added to the filtrate, and the mixture was left at room temperature for 2 d. Yellow crystals that formed were collected on a filter and washed with ethanol (40 cm^3) and ether (20 cm^3). The crystals were stored in vacuo. Yield, 4.65 g (62.3%). Found: C, 27.08; H, 4.72; N, 19.09%. Calcd for $Na_2[Fe(CN)_4(C_6H_{14}N_2)]\cdot 3.5H_2O\cdot 0.5NaClO_4$: C, 27.03; H, 4.76; N, 18.91%. $\nu_{C\equiv N}$ 2040 cm^{-1}.

Na[Co(CN)$_4$(*S*-pyrda)]·0.5H$_2$O (3). Into an aqueous solution of $Na_2[Co(CN)_5Br]$, *S*-pyrda was added and the mixture was heated at 80 °C for 6 h. The mixture was concentrated with a rotatory evaporator to an oily residue. Ethanol (50 cm^3) was added and the separated white precipitates were extracted with methanol (33 cm^3). The filtrate and the extract were combined and concentrated again. The residue was dissolved in water (10 cm^3) and put on an anion exchange column (Dowex 1X8, 65 mm×35 mmϕ) and developed with 0.2 M HCl (1 M = 1 mol dm^{-3}). The fractions that had absorbance between 0.020 and 0.132 at 340 nm was collected and concentrated to dryness. This was dissolved in 20 cm^3 of water, neutralized with 0.1 M NaOH, filtered, and concentrated again. The residue was dissolved in 3 cm^3 of ethanol. Isopropyl ether was added to the mixture until it became turbid and the mixture was left for 1 week. Separated crystals were collected on a filter and washed with small amount of an equal-volume mixture of methanol and ethanol. Yield, 104 mg (6.3%). Found: C, 37.21; H, 5.04; N, 28.51%. Calcd for $Na[Co(CN)_4(C_5H_{12}N_2)]\cdot 0.5H_2O$: C, 36.62; H, 4.43; N, 28.47%.

H$_3$O[Co(CN)$_4$(pipda)]·CH$_3$OH (4). This was prepared by the method described above with pipda instead of *S*-pyrda and the neutralization with NaOH solution was not done. Yield, 0.137 g (8.3%). Found: C, 39.42; H, 6.31; N, 25.32%. Calcd for $H_3O[Co(CN)_4(C_6H_{14}N_2)]\cdot CH_3OH$: C, 40.25; H, 6.45; N, 25.60%.

^{1}H NMR spectra were obtained with a JEOL GX-400 with sodium 3-trimethylsilyl-1-propionate-2,2,3,3-d_4 as an internal standard. ^{13}C NMR spectra were recorded with a JEOL alpha 500 spectrometer with dioxane (67.40 ppm) as an internal standard. Electronic spectra were recorded with a Shimadzu UV-2200 spectrophotometer and CD spectra were recorded with a JASCO J20 dichrograph. Infrared spectra were measured with a JASCO spectrophotometer using KBr disks.

Results and Discussion

The electronic and CD spectra of aqueous solutions of $[Fe(CN)_4(S\text{-pyrda})]^{2-}$ (**1**) and $[Co(CN)_4(S\text{-pyrda})]^-$ (**3**) are shown in Fig. 1. The absorption maxima corresponding to the first and the second absorptions for the Fe(II) complexes are typical to this class of compounds: 25.7×10^3 cm^{-1} (ε = 425 M^{-1} cm^{-1} and 32.7 (565) for **1** and 25.4 (401) and 31.3 (366) for $[Fe(CN)_4(pipda)]^{2-}$ (**2**).[18,19] The tetracyano(diamine)ferrate(II) complexes show spectroscopic properties analogous to the cobalt(III) complexes owing to its low-spin d^6 configuration.[1] The absorption bands of the cobaltate(III) complexes appeared in a region higher in energy than the ferrate(II) complexes. The first absorption bands appeared at 28.2×10^3 cm^{-1} (ε = 192 M^{-1} cm^{-1}) and 34.7 (117) for $[Co(CN)_4(pipda)]^-$ (**4**). The Fe(II) and Co(III) complexes of the *S*-pyrda, **1** and **3**, show that the visible CD components almost mirror those of the 1*R*,2*R*-*trans*-cyclohexanediamine = *R*-chxn complexes, $[Fe(CN)_4(R\text{-chxn})]^{2-}$ and $[Co(CN)_4(R\text{-chxn})]^-$ of which the signs of CD components are negative ($\Delta\varepsilon$ = −0.18 at 22.2×10^3 cm^{-1} for the Fe(II) complex and $\Delta\varepsilon$ = −0.09 at 24.8×10^3 cm^{-1} for the Co(III) complex) and positive ($\Delta\varepsilon$ = +0.51 at 26.0×10^3 cm^{-1} for the Fe(II) complex and $\Delta\varepsilon$ = +1.01 at 28.6×10^3 cm^{-1} for the Co(III) complex) for the first absorption band.[1] The CD spectra of *cis*- and *trans*-isomers of *trans*-$[CoCl_2(S\text{-pyrda})]^+$ have been reported to show small positive and large negative bands for the Ia($^1A_{1g}\rightarrow{}^1E_g$) and a positive component for Ib($^1A_{1g}\rightarrow{}^1A_{2g}$).[10] The application of Yamatera theory[20] shows that the transitions of these chloro and cyano compounds occur in the reverse order in the visible region.[1] In these d^6 metal chelates, the origin of the Cotton effect is solely the conformation of the chelate ring and the sign of the Cotton effect is intrinsic to the nature of each transition. The CD components of the *R*-chxn complexes arise from the asymmetric conformation of the five-membered chelate ring, λ. The fact that the CD spectra of the *S*-pyrda complexes is almost a mirror image of the *R*-chxn shows that the conformation of the five-memberd chelate ring is δ and the asymmetry at the secondary amine site contributes little to the CD. The asymmetry of the secondary amine contributes considerably to CD strength when the alkyl substituent of the secondary amine takes an equatorial orientation.[21] In the case of *S*-pyrda complexes, the alkyl substituent is in the axial orientation.

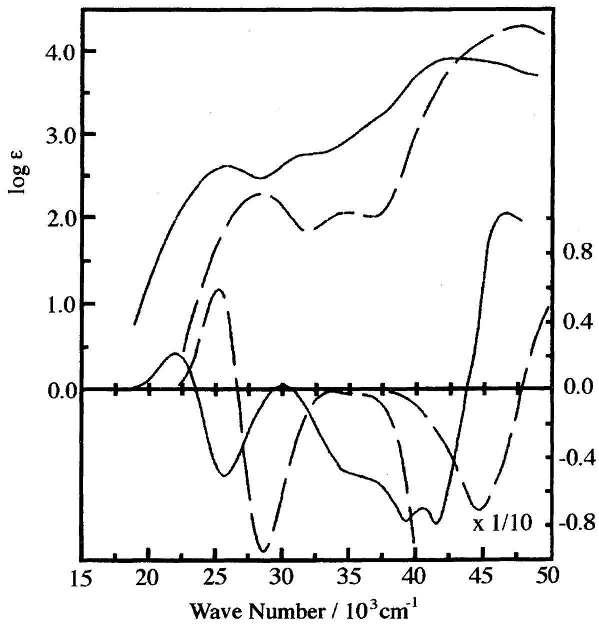

Fig. 1. Absorption and CD spectra of aqueous solution of $[Fe(CN)_4(S\text{-pyrda})]^{2-}$ (—) and $[Co(CN)_4(S\text{-pyrda})]^-$ (- - -).

The five-membered chelated rings and the pyrrolidine ring are fused with *cis*-condensation for *S*-pyrda complexes but the five-membered chelated rings and the piperidine ring can be fused with *cis*- and *trans*-condensation for *S*-pipda com-

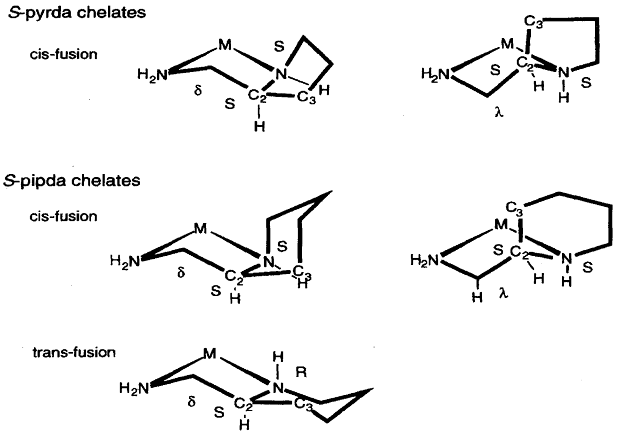

Fig. 2. Schematic representation of coordination mode of *S*-2-aminomethylpyrrolidine (*S*-pyrda) and *S*-2-aminomethylpiperidine (*S*-pipda) to metal ions.

plexes, as shown schematically in Fig. 2. The secondary amine changes to an asymmetric center on coordination to metal ions. Two distinct conformations have been reported for *S*-pyrda (or *R*-pyrda) coordinated to platinum(II). The X-ray crystallography of [Pt(*S*-mandelato)(*S*-pyrda)][22] and [Pt(*R*-pyrda)(CBDCA = cyclobutane-1,1′-dicarboxylato)][23] showed that the former have an equatorially attached C_3 carbon but the latter has the axially attached C_3 carbon on the five-membered chelate ring. These differences arise from the combination of the chelate ring and the absolute configuration (*S* or *R*) around the asymmetric C_2 carbon. The former have the set of $S\lambda/R\delta$ while the latter have $S\delta/R\lambda$. Although the ^{1}H NMR spectra of these complexes have not been reported, the structure represents the one imposed by crystal packing and the structure in solution may differ from them.

Figure 3 shows the 400 MHz ^{1}H NMR spectra of **1** and **2** in D_2O. All C–H appeared in the region between 1.4 and 3.25 ppm. The assignment was done by $\{^1H\}$ decoupling measurements. The key signals are those appearing at 2.70 and 2.23 ppm for **1**. The latter is a sharp triplet that shows the participation of ^2J and $^3J_{\mathrm{Hax-Hax}}$ and the absence of $^3J_{\mathrm{Hax-Heq}}$ nor $^3J_{\mathrm{Heq-Heq}}$. This allows us to assign this signal to H_{6a}. The double doublet at 2.70 ppm is assigned to H_{6e} because this has the coupling with H_{6a} and H_2. The key signals for **2** are those appearing at 2.79 and 2.09 ppm. The latter is a sharp triplet that suggests that the participation of the ^2J and $^3J_{\mathrm{Hax-Hax}}$ coupling and the absence of $^3J_{\mathrm{Hax-Heq}}$ nor $^3J_{\mathrm{Heq-Heq}}$. This allows us to assign this signal to H_{7a}. The sharp narrow coupling at 2.79 ppm disappeared on irradiation at the triplet at 2.30 ppm while this signal became a singlet with small coupling constants due to $^3J_{\mathrm{Hax-Heq}}$ or $^3J_{\mathrm{Heq-Heq}}$ on irradiation at H_{7a}. The signal at 2.79 ppm was assigned to H_{7e} and the signal at 2.30 ppm was assigned to H_{2a}. These considerations lead to the assignments of all the signals listed in Table 1.

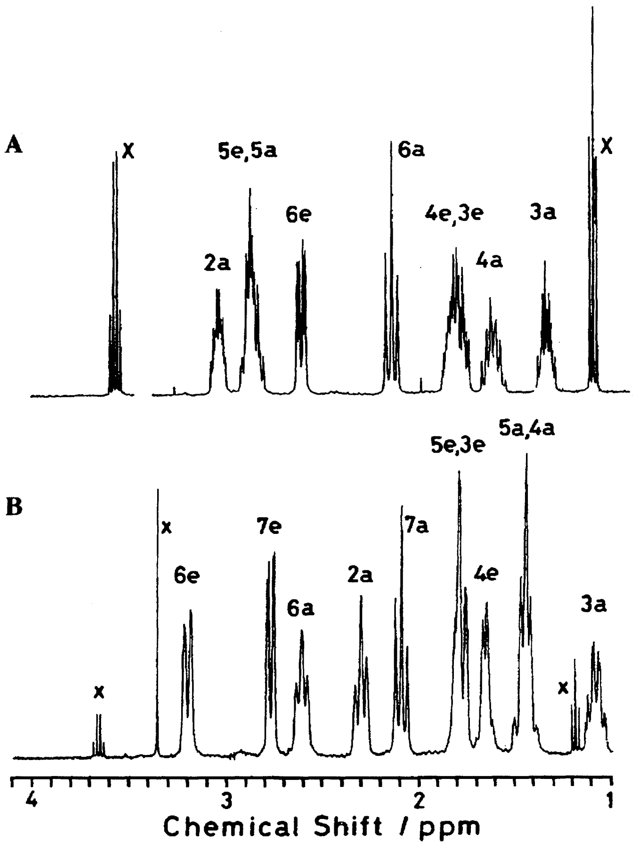

Fig. 3. 400 MHz ^{1}H NMR spectra of $[Fe(CN)_4(S\text{-pyrda})]^{2-}$ (A) and $[Fe(CN)_4(S\text{-pipda})]^{2-}$ (B). The peaks with × are due to ethanol and methanol.

Table 1. Chemical Shifts of Tetracyanoferrate(II) and Tetracyanocobaltate(III) of *S*-pyrda and pipda

Diamine nucleus	*S*-pyrda Chemical shift/ppm			pipda Chemical shift/ppm		
	$\delta_{(\mathrm{Fe^{II}})}$	$\delta_{(\mathrm{Co^{III}})}$	Δ_2	$\delta_{(\mathrm{Fe^{II}})}$	$\delta_{(\mathrm{Co^{III}})}$	Δ_2
H_{2a}	3.13	3.48	0.35	2.30	2.68	0.38
H_{3a}	1.43	1.60	0.17	1.08	1.31	0.23
H_{3e}	1.88	1.99	0.11	1.77	1.86	0.08
H_{4a}	1.71	1.86	0.15	1.44	1.47	0.03
H_{4e}	1.93	2.03	0.10	1.81	1.83	0.02
H_{5a}	2.94	3.09	0.15	1.44	1.63	0.19
H_{5e}	2.99	3.16	0.17	1.66	1.71	0.05
H_{6a}	2.23	2.56	0.33	2.61	2.82	0.21
H_{6e}	2.70	2.92	0.22	3.20	3.37	0.17
H_{7a}				2.09	2.42	0.33
H_{7e}				2.79	2.91	0.12
C_2	62.5	64.5	2.0	63.2	65.8	2.6
C_3	27.2	27.2	0.0	29.2	28.1	−1.1
C_4	27.7	26.7	−1.1	24.2	23.3	−0.9
C_5	52.2	52.9	0.7	27.8	26.8	−1.0
C_6	48.5	50.1	1.6	51.8	52.9	1.1
C_7				49.3	50.2	0.9

The corresponding cobalt(III) complex gave spectra similar to those of the ferrate(II) complexes and the assignments of ^{1}H and ^{13}C resonances were done using ^{1}H–^{1}H and ^{1}H–^{13}C COSY spectra. The data are given in Table 1 also.

The coupling constants among protons within the five-membered chelated rings are consistent with the structure with the orientation of H_{2a} being axial and the carbon atoms (C_3) of heterocycles attached in equatorial orientation for both ligands: The coupling constants of H_2 with H_{6a} and H_{6e} for **1** are 11.1 and 4.6 Hz and the coupling constants of H_2 with H_{7a} and H_{7e} for **4** are 12.5 and 3.8 Hz, but the carbon atoms (C_5 and C_6) attached to the secondary amine are in axial and equatorial orientation for *S*-pyrda and pipda, respectively. Thus in **2** and **4**, the five membered chelate ring and piperidine ring is *trans*-fused.

An inspection of Table 1 finds two characteristics about chemical shift: the difference in chemical shift between protons attached to the same carbon atom, Δ_1, and the difference in chemical shift between Co(III) and Fe(II) complex, Δ_2, for the corresponding protons. The former characteristic is that the axial proton resonates at a higher magnetic field than equatorial one for the couple sharing the common carbon. The magnitude of Δ_1 is larger for Fe(II) complexes than Co(III) complexes and is larger for the pipda complexes than *S*-pyrda complexes. This difference is presumably caused by the anisotropy of the C–N bond and C–C bond or metal nitrogen bond. The small Δ_1 for H_{5a} and H_{5e} for **1** and **3** show the conformational fluctuation of the *S*-pyrda complexes.

The difference, Δ_2, shows that the resonance of ^1H of Co(III) complex appeared in the field lower than that of Fe(II) complex as expected from the deshielding effect. Large Δ_2 were observed at the sites near to the metal ions, and Δ_2 differ for two protons (axial and equatorial) bonded to the common carbon atom. Substantial differences are found between the pairs of H_{3a} and H_{3e}, H_{5a} and H_{5e} for the pipda complexes but the difference between the axial and equatorial protons attached to the same carbon is reduced for the *S*-pyrda complexes. The magnitude of Δ_2 is larger for axial protons than for equatorial ones. This may be because the anisotropy caused by the single bonds is more effective for Fe(II) complexes than Co(III) complexes.

On the other hand, the chemical shift of ^{13}C is different from that of ^1H. Though the carbon showed a difference in chemical shifts for the carbons near the metal ion, upfield shifts were observed for two (for *S*-pyrda complex) and three (for pipda complex) carbons in heterocycles.

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