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Iron(III) Complexes of Sodium 2-Pyridinecarboxaldehyde Dithiocarbazonate, a Possible Chelating Agent for the Treatment of Iron Overload

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The 1:2 complexes of iron(III) with sodium 2-pyridinecarboxaldehyde dithiocarbazonate of the formula $Fe(PD)_2X$ *(where PD is 2-pyridinecarboxaldehyde dithiocarbazonate anion, and* $X^- = Cl^-$, NO_3^-, N_3^- *and* NCS^-*) have been prepared by interaction of iron(III) ions with NaPD (1:2), in the presence of an appropriate anion. They show molar conductance values of 33.0 to 55.2 mhos* cm^2 mol^{-1} *in DMF solution. These data indicate that the anions of* $Fe(PD)_2X$ *are associated in the first coordination sphere of Fe(III) to a different extent in DMF solution. The ultraviolet-visible absorption spectral data of* $Fe(PD)_2X$ *in DMF solution also support the different extent of coordination of anions to Fe(III). The* $Fe(PD)_2X$ *complexes in the solid state have low spin iron(III) with* μ_{eff} *values varying from 1.95 to 2.35 BM. The EPR data of the iron(III) complexes in frozen DMF also support their low-spin nature. These data also show that all complexes have rhombic symmetry except the azide complexes which have axial symmetry. The EPR and infrared spectral data of iron(III) complexes also suggest that the anions of these complexes are associated in the first coordination sphere of iron(III) in the solid state. The association of anions in the* $Fe(PD)_2X$ *complexes may suggest their geometry to be capped octahedron or pentagonal bipyramid. It has been suggested that one of the most important factors for efficiently removing iron from iron loaded mice is the formation of kinetically inert low-spin iron(III) complexes between iron(III) ions and tridentate chelating agents in the ratio of 1:2.*

Introduction

Spingarn and Sartorelli [1] have synthesized several tridentate ligands such as sodium pyrazinecarboxaldehyde dithiocarbazonate, pyrazinecarboxaldehyde thiosemicarbazone and pyrazinecarboxaldehyde 2′-hydrazinylhydrazone. These ligands remove significant amounts of iron from iron loaded mice. Sodium pyrazinecarboxaldehyde dithiocarbazonate is more efficacious than desferroxamine in reducing the degree of saturation of transferrin by iron. It is also more active than desferroxamine in removing iron from ferritin. Sodium 2-pyridinecarboxaldehyde dithiocarbazonate is similar in structure to sodium pyrazinecarboxaldehyde dithiocarbazonate except that the latter has one extra nitrogen atom in the aromatic ring than the former. It is expected that this extra nitrogen of sodium pyrazinecarboxaldehyde dithiocarbazonate is not involved in binding to iron(III) when a 1:2 complex is formed between iron(III) and this ligand. Sodium 2-pyridinecarboxaldehyde dithiocarbazonate as tridentate ligand will form a 1:2 complex between iron(III) and this ligand. This complex seems to be structurally similar to the 1:2 complex between iron(III) and sodium pyrazinecarboxaldehyde dithiocarbazonate. Therefore, we report here the synthesis and physical studies of 1:2 complexes of formula $Fe(PD)_2X$ (where $X^- = Cl^-$, NO_3^-, N_3^- and NCS^-) between iron(III) and sodium 2-pyridinecarboxaldehyde dithiocarbazonate(NaPD).

Experimental

Materials

Ferric chloride and carbon disulphide were purchased from Polyform, India. Hydrazine hydrate and 2-pyridinecarboxaldehyde were purchased from B.D.H., England, and Koch-Light, England, respectively. Other chemicals used were of the highest grade commercially available.

Sodium 2-pyridinecarboxaldehyde dithiocarbazonate (abbreviated as NaPD and its anion with −1 charge as PD) was prepared by warming 2-pyridinecarboxaldehyde (0.04 mol) and sodium dithiocarbazinate (0.05 mol) [1] in 70% ethanol at 50 °C for 5 to 10 minutes. The mixture was cooled and filtered to yield an orange solid (decomposed at 241–243 °C), which is highly soluble in water.

$Fe(PD)_2NO_3$

$FeCl_3$ (1 mmol) was dissolved in distilled water containing a small quantity of dilute HCl to avoid

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hydrolysis of ferric ions. NH_4OH (1:1) solution was added in slight excess to give a precipitate of $Fe(OH)_3$. The $Fe(OH)_3$ precipitate was washed with distilled water till free from chloride ions. This $Fe(OH)_3$ precipitate was dissolved in the minimum required quantity of dilute HNO_3. A solution of NaPD (2 mmol) in distilled water was added to it. A dark green pricipitate was obtained. This precipitate was filtered, washed with distilled water and methanol, and finally dried in a desiccator over anhydrous calcium chloride.

$Fe(PD)_2Cl$

A $FeCl_3$ (1 mmol) solution was mixed with a solution of NaPD (2 mmol) in doubly distilled water. A dark green precipitate was obtained. This precipitate was filtered, washed with distilled water and methanol, and finally dried in a desiccator over anhydrous calcium chloride.

$Fe(PD)_2NCS/N_3$

This complex was prepared by the synthetic method used for $Fe(PD)_2Cl$ except that 25 mmol of $KNCS(NaN_3)$ was added in $FeCl_3$ solution.

The analytical data for $Fe(PD)_2X$ (where $X^- = Cl^-, NO_3^-, N_3^-$ and NCS^-) are given in Table I.

TABLE I. Analytical and Molar Conductance Data of $Fe(PD)_2X$[a].

Complex	Analysis, found (calcd.)%				Molar conductance in mhos cm^2 mol^{-1} at 27 °C[b, c]
	C	H	N	Fe	
NaPD	38.0 (38.35)	2.9 (2.37)	19.0 (19.16)	–	–
$Fe(PD)_2Cl$	34.4 (34.75)	2.2 (2.50)	17.2 (17.37)	11.38 (11.54)	33.0
$Fe(PD)_2NO_3$	32.3 (32.95)	2.8 (2.37)	19.0 (19.21)	11.01 (10.94)	39.3
$Fe(PD)_2N_3$	34.0 (34.29)	2.5 (2.47)	25.6 (25.71)	11.37 (11.25)	55.2
$Fe(PD)_2NCS$	35.4 (35.57)	2.3 (2.39)	19.3 (19.36)	11.13 (10.98)	55.0

[a] $X^- = Cl^-, NO_3^-, N_3^-, NCS^-$. [b] After incubating 1×10^{-3} solutions of complexes for a week at 27 °C. [c] Cell constant = 0.0749 cm^{-1}.

Physical Measurements

Iron in the iron(III) complexes was estimated by a Varian Techtron Atomic Absorption Spectrophotometer 6 against standard solutions of ferric chloride, which were standardised by the EDTA titration method [2]. The iron complex was decomposed using concentrated nitric acid followed by Analar grade hydrochloric acid. The final solution was evaporated to dryness and the residue was dissolved in doubly distilled water containing one drop of concentrated hydrochloric acid to prepare the solution for atomic absorption measurement.

Other physical measurements were carried out as described previously [3].

Results and Discussion

The iron(III) complexes of the formula $Fe(PD)_2X$ (where $X^- = Cl^-$, NO_3^-, N_3^- and NCS^-) have been prepared by interacting solutions of Fe(III) and NaPD in the ratio of 1:2 in the presence of an appropriate anion. They are insoluble in petroleum ether, benzene, carbon tetrachloride, chloroform, acetone, ethanol, methanol and water. They are soluble in dimethylformamide (DMF) and dimethyl sulphoxide, but a small quantity of insoluble material, possibly elemental sulphur, was left behind. The iron content in DMF solution was determined by atomic absorption spectroscopy after removing the DMF and decomposing the complexes as described earlier.

The molar conductances of the iron(III) complexes in DMF solution are given in Table I. These molar conductance values vary from 33.0 to 55.2 mhos cm^2 mol^{-1} after incubation for a week at 27 °C. These values fall below the range of 1:1 electrolytes in DMF solution [4]. This indicates that the anions are associated in the first coordination sphere of iron(III) to different extents in DMF solution.

The electronic absorption maxima (λ_{max}) and their extinction coefficients (ϵ_{max}) of iron(III) complexes and free ligand in DMF solution are given in Table II. They show differences in number, positions and extinction coefficients of absorption maxima. These differences can also be interpreted in terms of different extents of association of anions in the first coordination sphere of iron(III) in DMF solution. The absorption bands of iron(III) complexes observed between 12,000 and 30,000 cm^{-1} can be tentatively assigned [5]. The bands above 27,000 cm^{-1} can be assigned to ligand $\pi \rightarrow \pi^*$ transitions. The bands between 20,000 and 22,000 cm^{-1} can be assigned to charge transfer, probably $d \rightarrow \pi^*$ transitions. The bands between 12,000 and 17,000 can be assigned to d–d transitions.

The magnetic moments (μ_{eff}) of the iron(III) complexes in the polycrystalline state calculated from their magnetic susceptibility data at room temperature are given in Table III. The μ_{eff} values range between 1.84 and 2.38 BM, and can be interpreted in terms of low-spin iron(III) complexes [6]. These polycrystalline iron(III) complexes show a broad strong EPR signal centred at a g value of 2.00 to 2.11 and another weak signal at higher field due to g anisotropy. The g values of these complexes obtained

TABLE II. Electronic Absorption Maxima and Their Extinction Coefficients of $Fe(PD)_2X^a$ in DMF.

Complex	λ_{max} (cm^{-1})	ϵ_{max}
NaPD	29,940	7,107
	24,876	6,502
	20,833	332
$Fe(PD)_2Cl$	27,778	11,456
	21,739	4,582
	15,667	1,632
	12,048	745
$Fe(PD)_2NO_3$	27,778	1,171
	21,739	481
	15,625	132
	12,048	341
$Fe(PD)_2N_3$	27,778	9,284
	20,833	3,772
	12,469	537
$Fe(PD)_2NCS$	29,412	10,872
	21,739	3,723
	16,129	1,013
	12,107	506

[a] $X^- = Cl^-, NO_3^-, N_3^-$ and NCS^-.

TABLE III. Magnetic Moment and EPR Data of $Fe(PD)_2X^a$.

Complex	Magnetic moment μ_{eff} (BM) (298 K)	EPR data (77 K)	
		in DMF[b]	in solid
$Fe(PD)_2Cl$	2.21	$g_x = 1.999$	$g = 2.108^c$
		$g_y = 2.114$	2.001
		$g_z = 2.151$	
$Fe(PD)_2NO_3$	2.27	$g_x = 1.999$	$g = 2.108^c$
		$g_y = 2.114$	2.002
		$g_z = 2.154$	
$Fe(PD)_2N_3$	2.35	$g = 1.997$	$g = 2.110^c$
		$g_1 = 2.117$	2.000
$Fe(PD)_2NCS$	1.95	$g_x = 2.064$	$g = 2.103^c$
		$g_y = 2.114$	2.001
		$g_z = 2.151$	

[a] $X^- = Cl^-, NO_3^-, N_3^-$ and NCS^-. [b] Molar concentration $\simeq 6 \times 10^{-4}$ *M*. [c] A major broad signal with peak to peak width varying from 120 to 160 Gauss.

by their EPR data are given in Table III. These signals may be due to concentration broadening of low-spin iron(III) complexes having axial or rhombic symmetry [7]. The concentration broadening in these iron(III) complexes has been further confirmed by taking their EPR spectra in frozen DMF solution. The g values obtained from frozen solution EPR spectra are also given in Table III. The iron(III) complexes have axial symmetry in the azide complex and rhombic symmetry in the nitrate, chloride and thiocyanate derivatives. These EPR data also suggest that the iron(III) complexes are low-spin with association of anions in the first coordination sphere of iron(III) in the solid state.

The selective infrared spectra of free ligand and its iron(IIII) complexes in the solid state (KBr) in the range of 4000 to 400 cm^{-1} are discussed below. The higher frequency band of free ligand at 3122 cm^{-1} can be assigned to ν(NH) vibration of the imine group [8]. The bands at 1610 and 1588 cm^{-1} can be assigned to ν(C=N) vibrations. The band at 1520 cm^{-1} can be assigned to $\nu(C\overset{\cdots}{-}N)$ vibration [9]. The band at 1000 cm^{-1} is assigned to ν(C=S) vibration [10, 11]. The bands at 568 and 410 cm^{-1} in the free ligand can be assigned to in-plane pyridine ring deformation and out-of-plane pyridine ring deformation, respectively [9]. The infrared band at 3122 cm^{-1} of the free ligand is broadened and shifted to lower frequency in the iron(III) complexes due to hydrogen bonding of the imine group with lattice water. The ν(C=N) vibrations are observed at 1633–1645 and 1600–1610 cm^{-1} in the iron(III) complexes. The $\nu(C\overset{\cdots}{-}N)$ vibration is observed at 1505–1515 cm^{-1} in the iron(III) complexes. The iron(III) complexes show two ν(C=S) vibrations at 950–963 and 1017–1028 cm^{-1} [11]. The bands at 568 cm^{-1} and at 410 cm^{-1} of the free ligand are shifted to 615–622 and 452–458 cm^{-1} respectively in the iron(III) complexes [9]. These data suggest that the ligand behaves as tridentate with two nitrogen atoms and one sulphur atom coordinating to Fe(III) in the iron(III) complexes.

The bands at 1380, 830 and 695 cm^{-1} in NO_3^- ion in KNO_3 are absent in the $Fe(PD)_2NO_3$ complex. This suggests that the NO_3^- ion is coordinating to iron(III) in the above complex [9]. The ν_a(NNN) vibration of the azide ion in $Fe(PD)_2N_3$ complex is present at 2066 cm^{-1} whereas the N_3^- ion in NaN_3 shows the ν_a(NNN) vibration at 2128 cm^{-1} [12]. This indicates that the azide ion is coordinated to iron(III). The thiocyanate ion in $Fe(PD)_2NCS$ shows ν(CN) at 2070 cm^{-1} as compared to ν(CN) of ionic thiocyanate at 2053 cm^{-1}. This can be interpreted in terms of nitrogen atoms of the thiocyanate ion coordinating to iron(III) in the thiocyanate complex. Thus, the anions of the $Fe(PD)_2X$ in the solid state are associated in the first coordination sphere of iron(III) in the iron complexes.

A similar association of anions of low-spin $Fe(DMT - H)_2X$ and $Fe(PT - H)_2X$ complexes (where DMT – H is the anion of diacetyl monoxime thiosemicarbazone and PT – H is the anion of 2-pyridinecarboxaldehyde thiosemicarbazone, and $X^- = Cl^-$, NO_3^-, N_3^-, NCS^- and NO_2^-) has previously been observed [3, 12], and is further supported by Mössbauer studies of $Fe(DMT - H)_2X$ in the solid state [13]. These complexes and the $Fe(PD)_2X$ complexes seem to form seven coordinate geometry such as capped octahedron or pentagonal bipyramid in the solid state.

Diacetyl monoxime thiosemicarbazone, 2-pyridinecarboxaldehyde thiosemicarbazone and sodium pyridinecarboxaldehyde dithiocarbazonate form 2:1 complexes with iron(III), which are low-spin and, thus, substitutionally inert [15]. Similar 2:1 complexes of pyrazinecarboxaldehyde thiosemicarbazone and sodium pyrazinecarboxaldehyde dithiocarbazonate with iron(III) [1] are expected to be low-spin and substitutionally inert, whereas desferroxamine forms a six coordinate high-spin iron(III) complex [16]. Therefore, the formation of low-spin and substitutionally inert complexes between iron(III) and the above tridentate ligands seems to be one of the most important factors for efficiently removing iron from iron loaded mice, ferritin and transferrin by the tridentate ligands. In addition, the chelating agent should be inexpensive, orally administrable, nontoxic, resistant to degradation prior to efficient absorption via the gastrointestinal tract, able to disperse through the blood stream, and bind iron in competition with transferrin [17].

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References

1 N. E. Spingarn and A. C. Sartorelli, *J. Med. Chem., 22,* 1314 (1979).
2 G. Schwarzenbach and H. M. Iring, 'Complexometric Titration', Matheun, London, 1957, p. 77.
3 R. Raina and T. S. Srivastava, *Inorg. Chim. Acta, 67,* 83 (1982).
4 W. J. Geary, *Coord. Chem. Rev., 7,* 81 (1971).
5 M. J. M. Campbell, *Coord. Chem. Rev., 15,* 309 (1975).
6 J. Lewis and R. G. Wilkins (Eds.), 'Modern Coordination Chemistry', Interscience, New York, 1960, p. 407.
7 B. A. Goodman and J. B. Raynor, *Adv. Inorg. Chem. Nucl., 13,* 136 (1970).
8 J. R. Dyer, 'Absorption Spectroscopy of Organic Compounds', Prentice–hall, N.J., 1965, pp. 22–57.
9 K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds', 3rd Ed., Wiley–Interscience, New York, 1977.
10 M. A. Ali, S. H. Livingstone and D. J. Phillips, *Inorg. Chim. Acta, 5,* 119 (1971).
11 D. Coucouvanis, *Prog. Inorg. Chem., 26,* 424 (1979).
12 J. C. Bailar, Jr., H. J. Emeleus, R. S. Nyholm and A. F. Trotman-Dickenson (Eds.), 'Comprehensive Inorganic Chemistry', Pergamon, Oxford, 1973, Vol. 2, p. 286.
13 R. Raina and T. S. Srivastava, *Indian J. Chem., 21A,* 490 (1982).
14 R. Raina, T. S. Srivastava, S. Joglekar and S. N. Shringi, *Inorg. Chim. Acta, 76,* L197 (1983).
15 F. Basolo and R. G. Pearson, "Mechanism of Inorganic Reactions', 2nd Ed., Wiley-Interscience, New York, 1967, pp. 141–145.
16 K. N. Raymond, *Adv. Chem. Series, 162,* 33 (1977).
17 D. A. Brown and M. V. Chidambaram, in 'Metal Ions in Biological Systems', Vol. 14, H. Sigel, Ed., Marcel Dekker, New York, 1982, p. 165.