Preparation and Properties of Trisodium Pentacyano(isonicotinohydrazide)ferrate(II) Hexahydrate and the Kinetics of its Substitution Reactions †

By **Miguel A. Blesa,* Irene A. Funai,** and **Pedro J. Morando,** Departamento de Fisicoquímica, Facultad de Farmacia y Bioquímica, Universidad Nacional de Buenos Aires, Argentina
José A. Olabe,*‡ and **Pedro J. Aymonino,** Cátedra de Química Inorgánica, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Argentina
Guillermo Ellenrieder, Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicades (INIFTA), La Plata, Argentina

The preparation, spectral properties (visible, i.r., and n.m.r.), and conductivity of the title complex $Na_3[Fe(CN)_5(inh)]\cdot 6H_2O$, containing isonicotinohydrazide bound through the pyridine nitrogen atoms, are described. The rate of formation of $[Fe(CN)_5(inh)]^{3-}$ from $[Fe(CN)_5(OH_2)]^{3-}$ and inh in aqueous solution at 25 °C is 3.25×10^2 dm^3 mol^{-1} s^{-1} and the rate of release of inh from the complex is 7.3×10^{-4} s^{-1}, with $\Delta H^\ddagger = 108$ kJ mol^{-1} and $\Delta S^\ddagger = 59.8$ J K^{-1}mol^{-1}. These parameters are very close to values reported for the corresponding isonicotinamide complex.

ISONICOTINOHYDRAZIDE, $NC_5H_4\cdot CO\cdot NHNH_2$ (inh), is an important drug in the treatment of pulmonary tuberculosis, due to its ability to inhibit the growth of *Mycobacterium tuberculosis*. In the past, studies were made of inh complexes with Cu^{2+} and other dipositive ions,[1-3] prompted in part by the reports that the copper complexes showed an enhanced bacteriostatic activity both *in vitro* [1] and *in vivo*.[2] Thus, a series of complexes was studied in which the metal ions were bound to the hydrazide moiety, either as the hydrazide or the hydrazone anion. These complexes included 1 : 1 and 2 : 1 (ligand: metal) chelates. The stability constants reported for the 1 : 1 complexes ranged from log K 4.14 for Mn^{II} (ref. 3*f*) to 8.0 (ref. 3*b*) or 10.0 (ref. 3*f*) for Cu^{II}, usually determined by potentiometric titrations of the proton released on co-ordination. The possibility of co-ordination through the pyridine nitrogen has received little attention.[3g] In this paper we show that, with the $[Fe(CN)_5(OH_2)]^{3-}$ ion, the importance of such interaction may be equal or greater than complex formation through the hydrazide moiety. This result is especially relevant as it points to a close similarity of inh with other pyridine derivatives, such as pyridinecarboxylic acids and amides, and other substances related to vitamin B_6. The influence of inh on the metabolism of vitamin B_6 is well known.[4a] The $[Fe(CN)_5(OH_2)]^{3-}$ ion, which contains low-spin Fe^{II}, is a good simple model for iron in some biological systems. In this context, it is interesting to note that binding of nicotinic acid to leg haemoglobin has been suggested as a possible mechanism of regulation of the oxygen affinity of this monomeric hemo-protein.[4b]

Previously,[5] we reported the reaction of inh with $[Ru(NH_3)_5(OH_2)]^{2+}$ in solution. Now we report the characterization of $Na_3[Fe(CN)_5(inh)]\cdot 6H_2O$, in which the iron is bound to the pyridine nitrogen, together with some structural and kinetic properties of this ion in solution.

EXPERIMENTAL

Analytical reagents were used as provided unless otherwise stated. Isonicotinohydrazide was a gift from Gerardo Ramón Laboratories, Bs. As., and was recrystallized according to standard techniques. Iodometric titration [6] showed that the purified substance contained not less than 99% inh. The salt $Na_3[Fe(CN)_5(NH_3)]\cdot 3H_2O$ was prepared following literature techniques,[7] and its purity was checked through the absorption coefficient of its band at 398 nm.

Preparation of $Na_3[Fe(CN)_5(inh)]\cdot 6H_2O$.—To a slurry of 3 g of $Na_3[Fe(CN)_5(NH_3)]\cdot 3H_2O$ in 86% (v/v) aqueous methanol, an excess (two to ten times) of inh was added with continuous stirring. After gentle heating (not exceeding 60 °C) during 2 h, formation of soluble $Na_3[Fe(CN)_5(inh)]$ was achieved; the solution was cooled and 98% ethanol was added. The solid inh complex precipitated as a brick-red powder, which was filtered off, washed with ethanol and diethyl ether, and dried over $CaCl_2$.

Analyses.—Elementary analyses were by the Department of Organic Chemistry, Facultad de Farmacia y Bioquímica, Bs. As. {Found: C, 26.7; H, 3.5; N, 22.3. Calc. for $Na_3[Fe(CN)_5(inh)]\cdot 6H_2O$: C, 26.4; H, 3.8; N, 22.4%}. Sodium was determined by flame photometry (Found: 14.0. Calc. 13.8%). The inh in the complex was titrated by iodometry in potassium hydrogencarbonate. No interference from the reaction of I_2 with cyanide released from the complex [8] was observed. Previous separation from the $[Fe(CN)_5]^{3-}$ moiety was unnecessary, even though I_2 establishes a redox equilibrium with iron(II) cyanide which is oxidized to the iron(III) derivatives. The standard redox potential for the complex is

---

† Presented in part at the 6th Argentine Congress of Pharmacy and Biochemistry, Mar del Plata, 1975 and the 10th Panamerican Congress of Pharmacy and Biochemistry, Punta del Este, 1975.

‡ *Present Address:* Departamento de Polít. Científ. y Tecnológ., Universidad Nacional de Luján.

[1] E. Sorkin, W. Roth, and H. Erlenmeyer, *Helv. Chim. Acta*, 1952, **35**, 1736.

[2] W. O. Foye and R. N. Duvall, *J. Amer. Pharm. Assoc.*, 1958, **47**, 285.

[3] (*a*) A. Albert, *Experientia*, 1953, **9**, 370; (*b*) *Nature*, 1956, **177**, 525; (*c*) A. Doadrio, *Anales Real Acad. Farm.* (*Madrid*), 1968, 261; (*d*) A. Doadrio and A. García-Carro, *Anales Fis. y Quim.* (*Madrid*), 1966, 329; (*e*) G. R. Supp, *Analyt. Chem.*, 1968, **40**, 981 and refs. therein; (*f*) K. Nagano, H. Kinoshita, and Z. Tamura, *Chem. Pharm. Bull.* (*Tokyo*), 1963, **11**, 999; (*g*) K. Nagano, H. Kinoshita, and A. Hirakawa, *ibid.*, 1964, **12**, 1198, 1207.

[4] (*a*) T. M. McCane, K. Deuschle, and W. McDermot, *Amer. Rev. Tuberc. Pulmonary Diseases*, 1957, **76**, 1100; V. Zamboni and E. Fachinelli, *Giorn. ital. Chemioterap.*, 1954, **1**, 638; (*b*) C. A. Appleby, B. A. Wittenberg, and J. B. Wittenberg, *Proc. Nat. Acad. Sci. U S.A.*, 1973, **70**, 564.

[5] M. A. Blesa and M. C. Geldstein, submitted for publication to *J. Inorg. Nuclear Chem.*

[6] U.S. Pharmacopaea, 16th Revision, p. 369.

[7] D. J. Kenney, T. P. Flynn, and J. B. Gallini, *J. Inorg. Nuclear Chem.*, 1961, **20**, 75.

[8] W. C. Crouse, D. A. Bennett, and D. W. Margerum, *React. Kin. Cat. Letters*, 1974, **1**, 135.

ca. 0.50 V (see below), and for I^-–$[I_3]^-$ under our conditions the potential is *ca.* 0.51 V. On addition of $[S_2O_3]^{2-}$, however, $[I_3]^-$ disappeared only when sufficiently large amounts of $[S_2O_3]^{2-}$ had been added to react with all the I_2 except that consumed in the oxidation of the hydrazide group. The end-point of the titration was a transition from red to green (Found for inh: 27.2. Calc.: 27.4%). The water content of the complex was determined by thermal gravimetric analysis (t.g.a.), as in previous work[9] (Found: 20.8. Calc. 21.6%).

Structural Determinations.—Ultraviolet–visible, i.r., and ^1H n.m.r. spectra, as well as thermal and electrical conductivity data, were obtained as described previously.[8] The molar conductivity (Λ) was 370 S cm^2 mol^{-1}; this value corresponds to a 1 : 3 electrolyte[10] and excludes the possibility of deprotonation of the ligand (as its tautomer, the hydrazonic acid) yielding a quadrivalent complex anion.

Kinetics.—The rate of formation of $[Fe(CN)_5(inh)]^{3-}$ from $[Fe(CN)_5(OH_2)]^{3-}$ and inh was followed on a Durrum–Gibson model D-110 stopped-flow spectrophotometer. The increase in absorbance at 437 nm was followed at 25 °C and I = 1 mol dm^{-3} (NaCl). The ion $[Fe(CN)_5(OH_2)]^{3-}$ was generated *in situ* by aquation of $[Fe(CN)_5(NH_3)]^{3-}$. The rate of release of inh from $[Fe(CN)_5(inh)]^{3-}$ was followed in a Hitachi–Perkin-Elmer 139 spectrophotometer, recording the decrease in absorbance at 437 nm or the increase in absorbance at 365 nm, in accordance with the stoicheiometry (1).

$$[Fe(CN)_5(inh)]^{3-} + \text{pyridine} \longrightarrow [Fe(CN)_5(py)]^{3-} + \text{inh} \quad (1)$$

In this reaction, the role of pyridine is to scavenge $[Fe(CN)_5(OH_2)]^{3-}$ generated initially (see Discussion section). The kinetic runs were made at constant concentrations of free inh (usually 1.9 × 10^{-3} mol dm^{-3}) and a large excess of pyridine. The pH was kept constant at 8.05 ($Na_2B_4O_7\cdot10H_2O$–HCl) and the ionic strength was 1 mol dm^{-3} (NaCl). This reaction was studied over the range 10—35 °C.

RESULTS AND DISCUSSION

Infrared Spectrum of the Solid.—Table 1 presents data obtained in KBr disks and Nujol mulls. The assignments are only tentative and follow previous work.[3g,11-13] The high degree of hydration and hydrogen bonding are responsible for the broadness and intensity of bands in the OH stretching (2 500—3 700 cm^{-1}), HOH deformation (1 565—1 760 cm^{-1}), and H_2O librational regions (<820 cm^{-1}). Peaks and bands due to the $Fe(CN)_5$ and inh moieties protrude from these broad bands. Characteristic peaks of $Fe^{II}(CN)_5$ were found at 2 040 (CN stretching) and 570 cm^{-1}. Bands due to inh were displaced as expected for aromatic nitrogen co-ordination, taking into account the shifts ensuing from protonation of the free ligand;[3g] thus, the ring-breathing band at 995 cm^{-1} in free inh (KBr disk, our own measurements) shifted towards the blue on complex formation[3g] (*cf.* ref. 14). Bonding of inh to Fe through the terminal NH_2 can be excluded because of the absence of a new band in the 1 160—1 380 region.[3g] Enolization of the C=O group can also be excluded in view of the near coincidence of the C=O stretching in the complex and in free inh (1 663 cm^{-1} in our spectra).

TABLE 1

Infrared spectrum of $Na_3[Fe(CN)_5(inh)]\cdot6H_2O$

Assignment	Wavenumber (cm^{-1})	Comments
ν(OH)	3 440 (h)	steep fall from 3 700
ν(NH)	3 300 (h)	vs, br long tail (3 215—2 500)
ν(CH)	3 215 (sh)	
ν(CN)(A_1)[a]	2 090m	
ν(CN)(E)	2 049	
		(2 036 Nujol)vs
Amide I ν(CO)	*ca.* 1 660 (h)	s, br
$\delta(NH_2)$	*ca.* 1 619 (h)	
Amide II [δ(NH) + ν(CN)]	*ca.* 1 537 (h) *ca.* 1 516 (sh)	m, br
ν(ring)	1 482w 1 410m	
Amide III [δ(NH) + ν(CN)]	1 325 1 311 (sh)	w, br
δ(CH)	1 223w	
$\rho(NH_2)$[δ(CH)?]	1 123vw, br	
ν(ring)	1 018w	
ν(NN)?	978vw, br	
γ(CH) $\omega(NH_2)$	853w	
ν(ring) Amide V?	762w	br
γ(CH)?	*ca.* 680 (h)	
$Fe(CN)_5$	570s[b]	
	530	
	491	
	462	
	418	
	388	
	348	

ν = Stretching, δ = deformation, ρ = rocking, γ = out-of-plane deformation, ω = wagging; vs = very strong, s = strong, m = medium, w = weak, vw = very weak, br = broad, h = hump, sh = shoulder.

[a] Equatorial or axial A_1 mode (see E. L. Varetti and P. J. Aymonino, *Inorg. Chim. Acta*, 1973, **7**, 597). [b] Either FeC stretching or FeCN bending (see ref. 11 and work reported therein).

Electronic Spectrum in Solution.—Like other similar Fe^{II} pentacyanides,[11,15] $[Fe(CN)_5(inh)]^{3-}$ showed an intense metal-to-ligand $t_{2g} \rightarrow \pi^*$ charge-transfer transition in the visible, centred at 437 nm (ε 4.7 × 10^3 dm^3 mol^{-1} cm^{-1}). The corresponding isonicotinamide complex ($\lambda_{max.}$ 435 nm, ε 4.6 × 10^3 dm^3 mol^{-1} cm^{-1}) and other iron(II) pentacyanides behave similarly.[11] The position of the maximum is in agreement with the electron-attracting properties of the $C(O)NHNH_2$ substituent. Intraligand transitions, $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$, were found at 220 (ε 1.67 × 10^4 dm^3 mol^{-1} cm^{-1}) and 264 nm (shoulder, $\varepsilon_{app.}$ 5.5 × 10^3 dm^3 mol^{-1} cm^{-1}); $t_{2g} \rightarrow \pi^*$ (CN) must contribute to some extent in this region. For the free protonated ligand, the maxima are at 212 (ε 5.0 × 10^3)

---

[9] J. A. Olabe and P. J. Aymonino, *J. Inorg. Nuclear Chem.*, 1974, **36**, 1221.

[10] S. Glasstone, 'An Introduction to Electrochemistry,' Van Nostrand, New York, 1942.

[11] J. A. Olabe and P. J. Aymonino, *J. Inorg. Nuclear Chem.*, 1976, **38**, 2922.

[12] D. Prevorsek, *Bull. Soc. chim. France*, 1958, 795.

[13] N. O. Katz, J. A. Olabe, and P. J. Aymonino, submitted for publication to *J. Inorg. Nuclear Chem.*

[14] N. S. Gill, R. H. Nuttal, D. E. Scaife, and D. W. A. Sharp, *J. Inorg. Nuclear Chem.*, 1961, **18**, 79; N. N. Greenwood and K. Wade, *J. Chem. Soc.*, 1960, 1130.

[15] H. E. Toma and J. M. Malin, *Inorg. Chem.*, 1973, **12**, 1039.

and 265 nm (ε 5.4 × 10^3 dm^3 mol^{-1} cm^{-1});[16] $t_{2g} \rightarrow \pi^*$ in $[Fe(CN)_6]^{4-}$ is at 218 nm.[17]

^{1}H *N.M.R. Spectrum.*—The two quartets of free inh [in D_2O: α protons, 8.78 p.p.m.; β protons, 7.76 p.p.m., referred to DSS, according to our own measurements in a 12% solution (*cf.* ref. 18)] changed into doublets for the complex, the α-proton signal moving downfield by 0.50 p.p.m. and the β-proton signal shifting upfield by 0.16 p.p.m. Similar behaviour is observed in other $[Fe(CN)_5L]^{3-}$ ions.[12,18] The shift in the β position is related to the magnitude of the π back donation,[19] and inh fits neatly in the sequence. Malin *et al.*[19] tentatively attributed the downfield shift of the α protons to the ' paramagnetic ' anisotropy of Fe^{II} and to electric fields in the $Fe(CN)_5$ moiety. However, on inspection of the data reported,[19] it is possible to see an approximate correlation between the magnitude of the shift and the electron-attracting properties of the substituents. This suggests that an additional effect might be present, namely a change in the local distribution of the electron density in the co-ordinated heterocycle as several substituents are introduced at the γ position. By way of conjugative effects, the best electron-attracting groups would remove from the α position some of the increased electron density arising from donation by the $Fe(CN)_5$ moiety, producing a deshielding effect which would add to other contributions.

Kinetics of Formation of $[Fe(CN)_5(inh)]^{3-}$.—The solids described by Hofmann[20] as containing $Na_3[Fe(CN)_5(OH_2)]$ are not a good source of $[Fe(CN)_5(OH_2)]^{3-}$ in solution as they are contaminated by various (large) amounts of the dimer $Na_6[Fe_2(CN)_{10}]$.[21,22] In fact, $[Fe(CN)_5(OH_2)]^{3-}$ is not very stable in solution, and large discrepancies regarding its spectral properties are found in the literature. Most recent studies agree that the maximum at 440 nm is attributable to this ion, whilst the dimeric ion $[Fe_2(CN)_{10}]^{6-}$ and $[Fe(CN)_5(OH_2)]^{2-}$ both absorb at *ca.* 390 nm.[21,23,24] In an effort to avoid complications, we followed the procedure of Toma and Malin,[23a] generating the aqua-ion by dissolving the sodium salt of the ammine complex, $Na_3[Fe(CN)_5(NH_3)]\cdot 3H_2O$ and using a fresh solution for each run. The stability constant of $[Fe(CN)_5(NH_3)]^{3-}$ is of the order of 10^4 dm^3 mol^{-1},[25] so that at not too high pH values the dissociation is complete when at sufficiently low concentrations. Thus, at pH 7 and $c = 10^{-4}$ mol dm^{-3}, at equilibrium there should be only 1% of $[Fe(CN)_5(NH_3)]^{3-}$. This equilibrium is established rapidly, with a first-order rate constant $k = 1.75 \times 10^{-2}$ s^{-1},[26] so that it is essentially complete in a few minutes.

The dimerization equilibrium has been reported to be pH dependent, with an equilibrium constant of 83 dm^3 mol^{-1} at pH 10 and 10 °C.[22] Although there are no data available at other pH values, if we take this value as a guide, not more than 1% dimer is expected to be present when the concentration of the aqua-complex is $\leqslant 10^{-4}$ mol dm^{-3}. Furthermore, the dimerization is slow at low concentrations: Emschwiller[22] reported a rate constant of dissociation to the monomer of 3×10^{-5} s^{-1} at 10 °C; from this and the equilibrium constant, the dimerization rate constant should be 2.5×10^{-3} dm^3 mol^{-1} s^{-1}, yielding a half-life $t_{\frac{1}{2}} = 100$ h when $c = 10^{-3}$ mol dm^{-3}.

In spite of these considerations, the oscilloscope traces of the increase in absorbance at 437 nm showed two distinct reactions, taking place at very different rates. The faster reaction was second order (first order in complex, first order in inh concentration), with a rate constant $k_f = 3.25 \times 10^2$ dm^3 mol^{-1} s^{-1} (see Table 2); this reaction is easily identified as the formation of the inh complex [equation (2)]. Toma and Malin[23a] and later

$$[Fe(CN)_5(OH_2)]^{3-} + inh \longrightarrow [Fe(CN)_5(inh)]^{3-} + H_2O \quad (2)$$

Bradic *et al.*[27a] discussed features of analogous reactions with other heterocycles, which proceed by way of a dissociative mechanism [equations (3) and (4)]. As

$$[Fe(CN)_5(OH_2)]^{3-} \underset{k_{H_2O}}{\overset{k_{-H_2O}}{\rightleftharpoons}} [Fe(CN)_5]^{3-} + H_2O \quad (3)$$

$$[Fe(CN)_5]^{3-} + L \xrightarrow{k_1} [Fe(CN)_5L]^{3-} \quad (4)$$

shown in Table 3, values of k_f are sensitive only to the charge borne by the ligand, and it is accepted that the measured second-order rate constants should be interpreted as $k_f = k_{-H_2O}k_1/k_{H_2O}[H_2O]$. In no case have deviations from second-order kinetics, due to saturation, been detected.[23a,27] The agreement of the value found for inh and for other uncharged amines is excellent and leaves no doubt that the faster reaction measured is (2).

TABLE 2

Rate constants for the reaction between aquated $[Fe(CN)_5(NH_3)]^{3-}$ and inh at 25 °C, $I = 1$ mol dm^{-3}, and pH 8.0

$10^5[Fe(CN)_5(NH_3)^{3-}]$ / mol dm^{-3}	[inh] / mol dm^{-3}	$10^{-2}k_f$ (fast reaction) / dm^3 mol^{-1} s^{-1}	10^2k (slow reaction) / s^{-1}
0.50	5×10^{-2}	3.30	1.36
0.76	1×10^{-1}	2.68	1.44
0.76	5×10^{-2}	3.08	1.57
0.76	1×10^{-2}	3.11	1.75
3.8	5×10^{-2}	3.26	1.55
5.0	5×10^{-3}	3.17	1.86
5.7	1.5×10^{-1}	2.80	1.67

k_f(average) = 3.25×10^2 dm^3 mol^{-1} s^{-1}, k(average) = 1.65×10^{-2} s^{-1}.

---

[16] B. Zommer and J. Szuszkiewicz, *Chem. Anal.* (*Warsaw*), 1969, **14**, 1075, and our own measurements.

[17] H. B. Gray and N. A. Beach, *J. Amer. Chem. Soc.*, 1963, **85**, 2922.

[18] W. Brügel, *Z. Elektrochem.*, 1962, **66**, 159.

[19] J. M. Malin, C. F. Schmidt, and H. E. Toma, *Inorg. Chem.*, 1975, **14**, 2924.

[20] K. A. Hofmann, *Annalen*, 1900, **312**, 1.

[21] G. E. Emschwiller, *Compt. rend.*, 1964, **259**, 4281.

[22] G. E. Emschwiller, *Compt. rend.*, 1967, **265**, 281.

[23] (*a*) H. E. Toma and J. M. Malin, *Inorg. Chem.*, 1973, **12**, 2080; (*b*) S. K. Wolfe, C. Andrade, and J. H. Swinehart, *ibid.*, 1974, **13**, 2567.

[24] H. E. Toma, *Inorg. Chim. Acta*, 1975, **14**, 205.

[25] (*a*) J. Legros, *J. Chim. Phys.*, 1964, **61**, 923; (*b*) M. A. Blesa, J. A. Olabe, and P. J. Aymonino, *J.C.S. Dalton*, 1976, 1196.

[26] H. E. Toma and J. M. Malin, *Inorg. Chem.*, 1974, **13**, 1772.

[27] (*a*) Z. Bradic, M. Pribanic, and S. Asperger, *J.C.S. Dalton*, 1975, 353; (*b*) Z. Bradic, D. Pavlovic, I. Murati, and S. Asperger, *ibid.*, 1974, 344.

TABLE 3

Rate constants, k_f, for the reaction of $[Fe(CN)_5(OH_2)]^{3-}$ with various ligands at 25 °C and I = 1 mol dm^{-3}

Ligand	$\frac{10^{-2}k_f}{dm^3\,mol^{-1}\,s^{-1}}$	Ref.
$[SO_3]^{2-}$	0.033	27*a*
$[CN]^-$	0.38	27*a*
py	3.7	23*a*
Isonicotinamide	3.0	23*a*
inh	3.3	This work
Pyrazine	3.8	23*a*
Ethylenediamine (en)	3.3	25*b*
$[Hen]^+$	6.2	25*b*
Methylpyrazinium	5.5	23*a*

The second trace on the oscilloscope was first order in the complex concentration, with $k = 1.65 \times 10^{-2}$ s^{-1} (see Table 2). There are two possible explanations for this reaction. (*a*) In a reaction parallel to (4), a complex bound to the hydrazide moiety is also formed [equation (5)] at a rate comparable to (4). Later this complex

$$[Fe(CN)_5]^{3-} + inh \longrightarrow [(NC)_5FeNH_2NHC(O)C_5H_4N]^{3-} \qquad (5)$$

reverts at a slower rate to the aromatic nitrogen-bound complex, in a reaction probably controlled by rupture of the Fe–N bond (see below). (*b*) The second reaction is a spurious artifact originating in the complicated equilibria of $[Fe(CN)_5(OH_2)]^{3-}$ in solution. The occurrence of a similar reaction in the ligation of other heterocycles (see for example ref. 23*a*), where no isomers are possible, strongly suggests that the second possibility is much more likely. It should be emphasized that the reported pK_a values of inh (1.85, 3.54, and 10.77 [3b] or 10.0 [28]) enable us to disregard the possibility of complications arising from acid–base equilibria of the free ligand at pH 8.05. Similarly, the stability constant of the ammine complex is too low to identify the slow reaction as the aquation of $[Fe(CN)_5(NH_3)]^{3-}$ which could be present in substantial amounts, even though the rates are very similar.[26] The reported data on the dimer$\rightleftharpoons$monomer equilibrium also do not fit with our results, as the equilibrium should be reached very slowly and be displaced far to the right. In fact, our slow reaction probably involves the iron(III) species $[Fe(CN)_5(OH_2)]^{2-}$ which is easily generated from the corresponding iron(II) species by air oxidation in the presence of catalytic amounts of decomposition products.[24,*]

For our purposes, it is important to establish whether the complex formation takes place through the terminal NH_2 at all. The slowest reaction can be safely disregarded on the above basis. Furthermore, we prepared the hydrazine complex,[13] and this, when placed in water, suffers ' instantaneous ' loss of hydrazine. This result was expected in view of the relation proposed between the pK_a of the conjugated acid of the ligand and the rate of release of aliphatic amines.[26] On the basis of this relation, and using the pK_a of benzohydrazide as an approximation (pK_a 3.27),[28] the release of hydrazine would be expected to take place with $k \sim 56$ s^{-1}. No such process is obvious in our experiments. If a truly dissociative *D* mechanism is accepted, it is necessary to assume that complex formation through NH_2 is kinetically irrelevant, probably because the ligand is released as fast as or faster than water, *i.e.* the actual rate constant is at least ten times higher than the estimate given above.[29] On the other hand, as we have previously pointed out,[25b] it is probable that the mechanism is actually a dissociative interchange I_d, and on this basis long-range π interactions of the type suggested by Toma and Malin [30] would account for a highly favoured mode of co-ordination through aromatic nitrogen. Of course, a direct and fast isomerization after co-ordination cannot be ruled out, although the close similarity in rate constants for inh and isonicotinamide do not suggest differences in this sense. For our present purposes, it is enough to state that the overall evidence points to the non-occurrence of the complex-formation reaction of terminal NH_2, even though previous work [23a,27a] suggested that $[Fe(CN)_5]^{3-}$ should not discriminate between both nucleophiles.

Kinetics of Release of inh from $[Fe(CN)_5(inh)]^{3-}$.—The release of heterocyclic ligands from $[Fe(CN)_5L]^{n-}$ is known to be a dissociative process.[15,25b,27a] In our case, in the presence of excess of pyridine, equations (6)—(8) fully describe the reaction. At low [py], k_1' must be

$$[Fe(CN)_5(inh)]^{3-} \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} [Fe(CN)_5]^{3-} + inh \qquad (6)$$

$$[Fe(CN)_5]^{3-} + H_2O \underset{k_{-H_2O}}{\overset{k_{H_2O}}{\rightleftharpoons}} [Fe(CN)_5(OH_2)]^{3-} \qquad (7)$$

$$[Fe(CN)_5]^{3-} + py \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} [Fe(CN)_5(py)]^{3-} \qquad (8)$$

taken into account, together with k_1, but under conditions where [py] $\gg$ [inh] a saturation region is obtained where $k_{obs.}$ is simply k_{-1}. As the features of the dependence of $k_{obs.}$ on the concentration of the incoming ligand were already fully established,[15,25b,27a] we focused our attention on measuring the kinetic parameters k_{-1}, $\Delta H_{-1}^{\ddagger}$, and $\Delta S_{-1}^{\ddagger}$, related directly to the release of inh from the complex. The results of the kinetic measurements are shown in Table 4. The rate constant is almost identical with the rate constant of release of isonicotinamide (7.3×10^{-4} s^{-1}); [15] furthermore, the activation parameters are also identical within experimental error (see Table 5). Thus, the replacement of H by NH_2 on the amide nitrogen of isonicotinamide does not affect the complexing properties of the aromatic nitrogen. This is reasonable for neutral inh as a ligand. Previous work has related the rates of release of various heterocycles with the π-stabilization energy of the complexes, the basicity of the donor atom, and the charge of the

---

[*] *Note added in proof.* See, however, a paper published after submission of this work: G. Davies and A. R. Garafalo, *Inorg. Chim. Acta*, 1976, **19**, L3.

[28] K. Nagano, H. Tsukahara, H. Kinoshita, and Z. Tamura, *Chem. Pharm. Bull.* (*Tokyo*), 1963, **11**, 797.

[29] H. E. Toma, J. M. Malin, E. Giesbrecht, and E. Fluck, *Inorg. Chim. Acta*, 1975, **14**, 11.

[30] H. E. Toma and J. M. Malin, *J. Amer. Chem. Soc.*, 1972, **94**, 4039.

ligand.[15,25b,26] None of these quantities changes much in going from isonicotinamide to uncharged inh. In a dissociative reaction such as the one under study, the entropy of solvation of the ligand is the important quantity. No effect of the difference in solvation entropy of inh and isonicotinamide on the rate of release of both ligands was observed, indicating that the structure of the solvent near the terminal end of inh is little changed on release of the ligand (or that both ligands suffer similar changes).

TABLE 4

Rate constants for the reaction $[Fe(CN)_5(inh)]^{3-} \longrightarrow [Fe(CN)_5]^{3-} + inh$ at various temperatures, $I = 1$ mol dm^{-3} (NaCl), pH 8.05, and [inh] = $10[Fe(CN)_5(inh)^{3-}]$ {measured as the saturation rate of the reaction of $[Fe(CN)_5(inh)]^{3-}$ with pyridine at high [py]}

$10^4[Fe(CN)_5(inh)^{3-}]$ / mol dm^{-3}	[py] / mol dm^{-3}	θ_c / °C	10^4k / s^{-1}
1.9	0.1	11.0	0.767
3.8	0.1	11.0	0.769
1.9	0.1	14.9	1.39
3.8	0.1	14.9	1.48
1.9	0.1	19.9	3.27
3.8	0.1	19.9	3.32
1.9	0.2	25.0	6.99
1.9	0.1	25.0	7.52
1.9	0.05	25.0	7.25
3.8	0.1	25.0	7.25
1.9	0.1	30.5	15.8
3.8	0.1	30.5	14.9
1.9	0.1	34.5	28.9

TABLE 5

Kinetic parameters for the reaction $[Fe(CN)_5L]^{n-} \longrightarrow [Fe(CN)_5]^{n-} + L$

L	10^4k (25 °C) / s^{-1}	$\Delta H^‡$ / kJ mol^{-1}	$\Delta S^‡$ / J K^{-1} mol^{-1}	Ref.
$[SO_3]^{2-}$	0.57	*ca.* 120	*ca.* 76	25*b*
CNH	0.004 (pH 4.6)			25*a*
Pyrazine	4.2	111	59	15
Isonicotinamide	7.3	109	59	15
inh	7.25	108	59.8	This work
py	11.0	104	46	15
en	51.5	97	38	25*b*
$[Hen]^+$	104	100	50	25*b*
Methylpyrazinium ion	2.8	115	75	15
NH_3	175	93	33	26

Thermodynamic Stability of the inh Complex.—From the ratio of k_f to k_{-1}, the value of the stability constant for the inh complex is found to be 4.6×10^5 dm^3 mol^{-1} almost identical with the value for isonicotinamide (4.0×10^5 dm^3 mol^{-1}). On the basis of the similarities with isonicotinamide, it can also be concluded that $E^\ominus$ for Fe^{II}–Fe^{III} should be *ca.* 0.50 V in the inh complex. On the other hand, for heterocycles where the π-stabilization energy and basicity are diverse (*e.g.* nicotinamide), other values are found. These factors should be taken into account in situations where competition between inh and other heterocycles for metallic moieties might be of importance. In this context, the behaviour of inh towards $[Fe(CN)_5]^{3-}$ is strikingly different from its behaviour towards aqua-ions. The complexes of inh with dipositive aqua-ions have been much studied and in these cases large differences in behaviour between inh and isonicotinamide exist.[3g] The possibility of complex formation *in vivo* through the pyridine nitrogen should not be disregarded, and even simultaneous interactions of both donor centres with metallic ions are possible.[31]

We thank Professor S. Lamdan, Gerardo Ramón Laboratories, Bs. As., for the gift of inh, the Department of Organic Chemistry (Facultad de Farmacia y Bioquímica, Bs. As.) for the elementary analysis, Professor Dra. R. A. Corral for the n.m.r. spectra, and CONICET and UBA for partial support.

[6/768 *Received*, 21*st April*, 1976]

---

[31] M. A. Blesa, unpublished work.