absence of thermal motion. Similar features had been observed in molybdenum acetate,[7] but not in chromium acetate,[6] in accordance with MO calculations.

This accumulation is difficult to interpret, since it apparently does not involve the d orbitals of chromium. The d_{z^2} orbital population, computed from the CI wave function, is 1.003 e. This is practically identical with the average d-orbital population in the promolecule, which is 1 e. Moreover, on the theoretical map, the peak is located at only 0.34 Å from the nucleus. At such a short distance, an effect due to a small contraction of the 3s and/or 3p shells cannot be excluded. It is interesting to notice that these external peaks have been observed only for systems that are insensitive to axial coordination.[7]

The most significant feature of the experimental deformation density in the metal region (Figure 6a) is the lack of density in the direction of the ligands. There is no significant difference between the Cr–N and Cr–O directions within about 1 Å from Cr, and the two directions have thus been averaged for the calculation of the curves of Figure 7a. The figure shows that the difference is very large compared to its esd and points thus to a much lower occupancy of $3d_{x^2-y^2}$ than of $3d_{xy}$. Its low occupancy enables $d_{x^2-y^2}$ to work as an acceptor orbital for the oxygen and nitrogen lone pairs in dative σ bonds.

This character is common to all systems displaying a quadruple metal–metal bond. However, the population of the $d_{x^2-y^2}$ orbital is markedly higher for $Cr_2[H_2P(CH_2)_2]_4$ than for $Cr_2(O_2CH)_4$ and $Mo_2(O_2CH)_4$. From less than 0.25 e for the tetraformates, the computed $d_{x^2-y^2}$ population jumps to 0.57 e for $Cr_2[H_2P(CH_2)_2]_4$. This is probably specific to the $H_2P(CH_2)_2$ ligand, since the carbon lone pair is much higher in energy than the oxygen lone pair and therefore induces a stronger interaction with the empty $d_{x^2-y^2}$ metal orbital.

A character that is more specific to the "supershort" Cr–Cr bond is the existence of a ligand–metal–metal angle significantly bigger than 90° (about 104° for $Cr_2[H_2P(CH_2)_2]_4$[18]). This angle induces some interaction between the ligand lone pairs and the π^* orbitals of the metal, which might contribute to the slight increase observed in the overall π population (2.19 e for $Cr_2[H_2P(CH_2)_2]_4$ instead of 2.02 e for $Cr_2(O_2CH)_4$).[35]

Another feature is directly visible on both experimental and theoretical maps (Figures 6a and 8a) in agreement with the results of the population analysis: this is the relatively low population of the d_{xy} orbitals. This population is only 0.88 e for $Cr_2[H_2P(CH_2)_2]_4$ instead of 1.07 e for $Cr_2(O_2CH)_4$ and 1.05 e for $Mo_2(O_2CH)_4$. The density maps derived in the plane that is perpendicular to the metal–metal axis and contains one metal atom (Figure 8a) can be compared with similar maps derived for $Mo_2(O_2CH)_4$[7] in order to visualize the relative lack of d_{xy} population. Both experimental and theoretical maps derived for $Mo_2(O_2CH)_4$ display significant density accumulation in the xy direction. In contrast with this pattern, the corresponding map observed for $Cr_2mhp)_4$ is just "less negative" in the xy than in the $x^2 - y^2$ direction. The theoretical map obtained for $Cr_2[H_2P(CH_2)_2]_4$ appears quite consistent with experiment.[36] It appears difficult to decide whether this lack of d_{xy} population might correspond to some electron migration toward the δ bonding region. The assignment by a Mulliken population analysis of electrons located in this area might indeed become hazardous.[35] The "squared" shape of the central accumulation disk (Figure 8b) denotes an appreciable remainder of δ bonding, in spite of the high weight of the δ^* orbital in the CI expansion. However, similar evidence for δ bonding was found from the density distribution of $Mo_2(O_2CH)_4$ without any depopulation of the d_{xy} orbitals.

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Registry No. $Cr_2(MPh)_4$, 67634-82-6; $[(CH_3)_2P(CH_2)_2]_4Cr_2$, 68525-29-1; Cr, 7440-47-3.

Supplementary Material Available: Listings of observed and calculated structure factors and of the positional and thermal parameters for $Cr_2(mhp)_4$ (20 pages). Ordering information is given on any current masthead page.

(35) However, the presence of a diffuse d orbital in the basis set of chromium makes less reliable the space partitioning associated with the Mulliken population analysis. Small changes in the *d*-orbital population must therefore be analyzed with caution.

(36) Four small peaks can be characterized in the xy direction at 0.33 Å from the Cr nuclei (Figure 8a). These small and sharp peaks are expected to vanish in a "X-X" distribution, because of thermal motion and limited resolution. That was not the case for the relatively extended accumulations obtained for $Mo_2(O_2CH)_4$.[7]

Pentacyanoferrate(II) Complexes of Amino Acids

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Abstract: The electronic spectra and the kinetic and thermodynamic properties of an extensive series of (amino acid)-pentacyanoferrate(II) complexes have been investigated in aqueous solution. The spectra of the complexes containing aminocarboxylate ligands are similar to that of $Fe(CN)_5NH_3^{3-}$, with Dq estimated to be ~ 0.233 μm^{-1}. For the methionine, histidine, and methionine sulfoxide complexes, Dq values are 0.239, 0.248, and 0.286 μm^{-1}, respectively. The rates of formation of the complexes are 240–370 M^{-1} s^{-1} for zwitterionic amino acids and 18–30 M^{-1} s^{-1} for mononegatively charged and 9 M^{-1} s^{-1} for dinegatively charged α-aminocarboxylate ligands (25 °C and $\mu = 0.10$ M). The specific rates increase as the number of C–C bonds separating the coordination site from the carboxylate group is increased. The kinetic and thermodynamic properties (dissociation rate, stability constant, reduction potential) of each (amino acid)pentacyanoferrate depend strongly on the donor/acceptor nature of its amino acid ligating group. The imidazole group of histidine is unique in the sense that it stabilizes both iron(II) and iron(III) states ($K_{II} = 5.9 \times 10^5$; $K_{III} = 1.1 \times 10^6$ M^{-1}).

Amino acids occupy a special place in the coordination chemistry of transition-metal ions.[2-5] Although many complexes of amino acids are described in the literature, most of them are chelate species involving α-aminocarboxylate binding. Not enough

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attention has been paid to the problem of specific coordination, which refers to the interaction of metal complexes with the ligating side groups of amino acids. The subject is of fundamental importance, because most transition-metal ions are bound to proteins by these residues, rather than by the α-aminocarboxylate groups that make up the peptide chain.

The pentacyanoferrate(II) ion is a useful probe for investigating the properties of specific groups in amino acids and peptides. The $Fe(CN)_5^{3-}$ group typically binds only one ligand, thereby forming a well-behaved series of $Fe(CN)_5L^{n-}$ complexes.[6-10] The reactions generally are rapid, owing to the lability of the coordinated water molecule in the starting complex,[11] $Fe(CN)_5H_2O^{3-}$. The properties of the products, however, are strongly dependent on the nature of L. Whereas the complexes with oxygen donors are labile, those with π acceptors are often inert. Moreover, in common with heme centers, pentacyanoferrate(II) has a high affinity for imidazoles and thioethers, forming stable complexes with histidine[7,8] and methionine.[12] In the present paper we report the results of extensive studies of the electronic spectra, substitution kinetics, and electrochemical properties of pentacyanoferrate(II) complexes with amino acids. A subsequent communication will deal with the preparation of derivatives in which $Fe(CN)_5^{3-}$ is attached to horse heart cytochrome *c*.[13]

Experimental Section

Glycine and β-alanine, from Carlo Erba, L-methionine and L-histidine, from Aldrich, L-tyrosine, DL-tryptophan, L-glutamic acid, DL-phenylalanine, L-leucine, and DL-serine, from Matheson, L-cystine from Fisher, L-valine and L-arginine, from Inlab, and L-lysine from Sigma were used as supplied. Methionine sulfoxide was obtained by controlled hydrogen peroxide oxidation of methionine, as described by Toennies and Kolb.[14] Methionine sulfone was prepared following the procedure of Rheinboldt and Giesbrecht.[15] Dimethyl sulfoxide (Me_2SO) and the usual inorganic reagents were high purity samples obtained from various suppliers. Isonicotinamide (Aldrich) was recrystallized from aqueous solution after treatment with activated charcoal and described by Shepherd.[16] *N*-Methylpyrazinium iodide was prepared from pyrazine (Aldrich, gold label) and methyl iodide, following the procedure of Bahner and Norton.[17]

Samples of $Na_3Fe(CN)_5NH_3 \cdot 3H_2O$ were prepared from sodium nitroprusside by a standard procedure.[18] The compound was recrystallized several times by saturating an aqueous solution containing ca. 3 M NH_3, under argon, at room temperature, and cooling overnight in a freezer maintained at 0 °C. The pure solid was collected on a filter, washed many times with 80% ethanol, and stored for 3 days in the presence of calcium chloride under low pressure (ca. 50 mmHg). The yellow crystalline material was stored in the dark at 0 °C and used within 6 months. Excessive drying leads to slow removal of both H_2O and NH_3. Sample decomposition is accelerated in the presence of light and humidity, producing a greenish product that exhibits complex kinetic behavior. Anal. Calcd for $Na_3Fe(CN)_5NH_3 \cdot 3H_2O$: C, 18.42; N, 25.78; H, 2.77. Found: C, 18.66; N, 25.86; H, 2.78.

Solutions of the aquopentacyanoferrate(II) complex were always freshly prepared by dissolving $Na_3Fe(CN)_5NH_3 \cdot 3H_2O$ in argon-saturated water to yield concentrations usually smaller than 10^{-4} M. The complex can be generated in a quantitative way in very dilute solutions by aquation of $Fe(CN)_5NH_3^{3-}$. At concentrations higher than 0.3 mM, however, the equilibrium between $Fe(CN)_5NH_3^{3-}$ and $Fe(CN)_5H_2O^{3-}$ species cannot be neglected. Although the equilibrium can be shifted by removing NH_3 with appropriate buffers (e.g., acetate or phosphate), formation of dimeric species[19] such as $Fe_2(CN)_{10}^{6-}$ apparently becomes increasingly important under such conditions. The concentration of aquopentacyanoferrate(II) can be determined spectrophotometrically by addition of the *N*-methylpyrazinium ion (MPz), thereby forming the stable, deep blue $Fe(CN)_5MPz^{2-}$ complex (ϵ(655 nm) = 12.3×10^3 M^{-1} cm^{-1}).

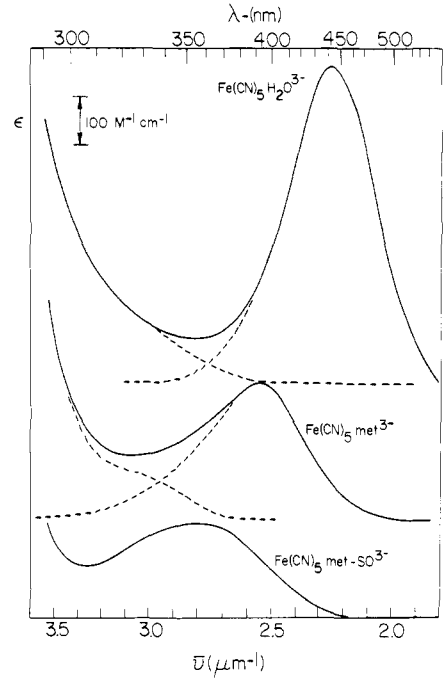

Figure 1. Electronic absorption spectra of selected $Fe(CN)_5L^{3-}$ complexes in aqueous solutions at 25 °C.

The pentacyanoferrate(II) complexes of the several amino acids were always freshly prepared in aqueous solution and kept in the dark under an argon atmosphere. The concentrations of the amino acids were in excess (10–100 times) to avoid competing reactions involving the small amounts of free NH_3 introduced by the starting $Fe(CN)_5NH_3^{3-}$ complex. When concentrated solutions were required, NH_3 was eliminated by vigorous argon bubbling for several hours.

Rapid kinetics were measured on a Durrum Model D-110 stopped-flow apparatus, equipped with a Kel-F flow system. Generally, the solutions of the amino acids were prepared at the appropriate ionic strength and mixed with aqueous solutions containing exclusively the aquopentacyanoferrate(II) complex. All the kinetics were performed under pseudo-first-order conditions. Using more concentrated solutions of the iron complex (e.g., 3×10^{-4} M), it is possible to detect a second, slower reaction ($t_{1/2} \sim 40$ s), indicating the presence of $Fe(CN)_5NH_3^{3-}$. The isomerization kinetics were investigated by using the 5-s time scale of the stopped-flow instrument. In this case, isomeric mixtures, that were generated in a thermostated syringe were mixed with a solution of the ligand (Me_2SO) from another syringe; the decay of the labile isomer was then studied as a function of the concentration of the auxiliary ligand.

Visible and UV spectra were recorded on Cary 14 and 219 spectrophotometers fitted with thermostated cell compartments. Cyclic voltammetric measurements were performed with a PAR 173 potentiostat and a 175 universal programmer. A platinum electrode was employed for measurements of the potentials of the pentacyanoferrate(II) complexes of amino acids, with Ag/AgCl (1 M KCl) as the reference and platinum foil as the auxiliary electrode.

Results and Discussion

Amino acids, having the general formula $RCH(NH_2)CO_2^-$, form two classes of ligands for coordination with pentacyanoferrate(II). In the first class, R is not expected to bind very effectively to $Fe(CN)_5^{3-}$ under the conditions we have used. R may be *neutral* e.g., H in glycine (gly), $(CH_3)_2CH$ in valine (val), $(CH_3)_2CHCH_2$ in leucine (leu), $C_6H_5CH_2$ in phenylalanine (phe),

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Table I. Ligand Field Parameters for Pentacyanoferrate(II) Complexes with Amino Acids and Related Ligands[a]

L	λ_{max}, nm	ϵ_{max}, M^{-1} cm^{-1}	$\bar{\nu}$, μm^{-1}	Dt, μm^{-1}	Dq_L, μm^{-1}
H_2O	444	660	2.25	0.0969	0.184
	330[b]	~100	3.05		
NH_3	396	450	2.52	0.0657	0.233
gly	396	450	2.52	0.0657	0.233
β-ala	396	430	2.53	0.0649	0.234
ε-lys	395	380	2.53	0.0649	0.234
$RCH(NH_2)CO_2^-$ [c]	397	450	2.52	0.0664	0.232
met	391	270	2.56	0.0620	0.239
	325[b]	~100	3.10		
imidazole	383	430	2.61	0.0560	0.248
his	383	435	2.61	0.0560	0.248
Me_2SO	352	210	2.84	0.0297	0.290
met-SO	355	200	2.82	0.0324	0.286

[a] The absorption band listed for each complex is attributed to $^1A_1 \rightarrow {}^1E(1)$ unless noted otherwise; $Dt = 0.628(Dq_{CN} - Dq_L)$ with $Dq_{CN} = 0.338$ μm^{-1} (ref 23). [b] Shoulder, $^1A_1 \rightarrow {}^1A_2$. [c] Arg, trp, tyr, cyst, phe, leu, val, met-SO_2, ser, glu.

$HOCH_2$ in serine (ser), $C_8H_6NCH_2$ in tryptophan (trp), and $CH_3SO_2CH_2CH_2$ in methionine sulfone (met-SO_2); *anionic*, e.g., $^-O_2CCH_2CH_2$ in glutamate (glu), $^-OC_6H_4CH_2$ in tyrosine (tyr), and $^-O_2CH(NH_2)CH_2SSCH_2$ in cystine (cyst); or *cationic*, e.g., $^+NH_2C(NH_2)NHCH_2CH_2CH_2$ in arginine (arg).

In the other class, R is expected to bind strongly to $Fe(CN)_5^{3-}$: this group includes $CH_3SCH_2CH_2$ in methionine (met); $CH_3SOCH_2CH_2$ in methionine sulfoxide (met-SO); $C_3N_2H_3CH_2$ in histidine (his); and $H_2NCH_2CH_2CH_2CH_2$ in lysine (lys).

Electronic Spectra. The lowest energy band in the spectrum of each of the $Fe(CN)_5L^{n-}$ complexes is assigned to the $^1A_1 \rightarrow {}^1E(1)$ transition (Figure 1). The Dt and Dq_L values given in Table I are based on a standard ligand field analysis,[20-22] taking $^1A_1 \rightarrow {}^1A_2$ to be 3.10 μm^{-1} ($\sim {}^1A_{1g} \rightarrow {}^1T_{1g}$ for $Fe(CN)_6^{4-}$).[23]

The Dq values for most amino acids are virtually the same as that of NH_3. Because the carboxylate group is close to H_2O in the spectrochemical series,[24] we can rule out coordination by this group to $Fe(CN)_5^{3-}$. Analogously, the Dq values for the histidine and methionine sulfoxide ligands are identical with those for imidazole and Me_2SO, respectively, providing evidence for the nature of the coordinating group in those amino acids. The same approach does not establish the donor atom in the methionine complex, as in this case the Dq value is very close to that for NH_3. However, as will be shown later, the kinetics and electrochemical data leave no doubt that methionine is bound to $Fe(CN)_5^{3-}$ through its sulfur atom. The presence of a sulfur–iron bond is responsible for the red color of the oxidized complex; the spectrum of this complex features a S→Fe charge-transfer transition at ~505 nm (ϵ = 500 M^{-1} cm^{-1}). Charge-transfer bands of this sort are not observed in the spectra of the NH_3[25] and amino carboxylate pentacyanoferrate(III) complexes, which are all alike. However, they are prominent in the spectra of pentacyanoferrate(III) complexes containing SCN^- and N_3^-.[26]

Formation Kinetics. In the presence of an excess of amino acid, the kinetics of formation of the complexes are described by a first-order rate law for at least two half-lives.

$$Fe(CN)_5H_2O^{3-} + aa^{n-} \xrightarrow{k_f} Fe(CN)_5(aa)^{(3+n)-} + H_2O$$

$$\frac{d[Fe(CN)_5H_2O^{3-}]}{dt} = \frac{d[Fe(CN)_5(aa)^{(3+n)-}]}{dt} = k_{obsd}[Fe(CN)_5H_2O^{3-}] \quad (1)$$

The specific rates, k_f, were obtained from plots of k_{obsd} vs. the amino acid concentration (Figure 2). For each complex, the study was performed at five different temperatures in the range 10–33 °C in order to evaluate the activation parameters. The ionic strength was kept at 0.10 M with lithium perchlorate. In some cases it was varied from 0.05 to 1.0 M for comparison purposes. The final pH for the reactions with the amino acids in zwitterionic form was approximately 8, but for the reactions with the anionic ligands the pH was around 11.5. The specific rates and the corresponding activation parameters are given in Table II.

In a recent study the pK_a of $Fe(CN)_5H_2O^{3-}$ was estimated to be 7.86.[27] However, the following results are not consistent with

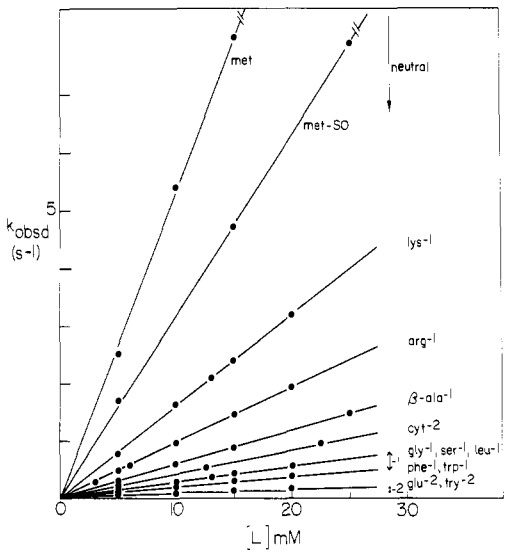

Figure 2. Dependences of the observed rate constants for substitution reactions of $Fe(CN)_5H_2O^{3-}$ on amino acid concentration (25 °C, μ = 0.100 M, lithium perchlorate).

Table II. Specific Rates and Activation Parameters for the Reactions of $Fe(CN)_5H_2O^{3-}$ with Amino Acids and Related Ligands[a]

L	μ, M	k, M^{-1} s^{-1} (at 25 °C)	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/(mol deg)
NH_3	0.10	365	14.7	2.4
Me_2SO[b]	1.00	240	15.4	4
	0.10	370		
met-SO	0.10	308	14.7	2.0
imidazole[c]	0.10	240	15.2	3
	1.00	212		
his[c]	0.10	315	15.4	5
	0.50	233		
	1.00	184		
met[d]	0.10	535	16.7	10
lys^-	0.10	160[e]	14.1	1
met^-	0.10	169	17.6	11
his^- [c]	0.10	91[e]		
met-SO^-	0.10	102[e]	14.5	1.0
arg^-	0.10	96	15.7	−1.0
β-ala^-	0.050	54		
	0.10	57	14.3	−2.4
	0.50	76		
$cyst^{2-}$	0.10	37.5	15.5	2.6
met SO_2^-	0.10	43.2	14.1	−4.1
gly^- [c]	0.10	28.0	14.7	−3
	0.50	41.0		
	1.00	46.		
ser^-	0.10	24.0	14.6	−2.6
leu^-	0.10	29.0	14.6	−2.6
val^-	0.10	30.0	14.6	−2.5
phe^-	0.10	20.0	14.6	−3.3
trp^-	0.10	18.0	14.8	−3.1
glu^{2-}	0.10	9.0	15.5	−2.0
tyr^{2-}	0.10	9.0	15.7	−1.0

[a] Conditions. pH 8–9 for neutral ligands; pH 11.5 for anionic amino acids; ionic strength adjusted with $LiClO_4$. [b] Reference 28. [c] Reference 8. [d] Reference 12. [e] Composite rate.

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this pK_a value. With Me_2SO as the ligand,[28] the specific rates of substitution in $Fe(CN)_5H_2O^{3-}$ are (in M^{-1} s^{-1}) 382 (pH 5.6), 382 (pH 6.80), 379 (pH 8.80), 378 (pH 11.9), and 382 (pH 13), with no inflection at all around pH 7 or above. In acidic solutions there is a systematic decrease of k_f, e.g., 310 (pH 3.23), 187 (pH 2.5), 58 (pH 2.0), and 11.4 M^{-1} s^{-1} (pH 1), owing to protonation of the cyanides, with a pK_a of ~ 2.50.[29,30]

For β-alanine binding, the specific rates (M^{-1} s^{-1}, 25 °C, μ = 0.10 M, β-alanine buffer) are 57, 62, 60, 59, 57, and 60 at pH 8.7, 9.3, 10.1, 10.3, 11.0, and 11.7, respectively. Our results indicate that the pK_a of the coordinated water molecule in $Fe(CN)_5H_2O^{3-}$ is higher than 13. There are many reasons to believe that the pK_a cannot be as low as 7.86.[31] One of the most compelling is the observation that the oxidized complex, $Fe(CN)_5H_2O^{2-}$, exhibits a pK_a of 8.4,[32] and lowering the oxidation state of the metal should increase the pK_a of the coordinated water molecule. In this context it should be noted that the pK_a of the H_2O in $Ru(NH_3)_5H_2O^{3+}$ is 4.1, but it increases to 13.1 when the complex is reduced to the 2+ state.[33] By analogy it is reasonable to suggest a pK_a as large as 17 for $Fe(CN)_5H_2O^{3-}$.

Part of the problem may be associated with the equilibrium of dissociation of amminepentacyanoferrate(II):

$$Fe(CN)_5NH_3^{3-} + H_2O \rightleftharpoons Fe(CN)_5H_2O^{3-} + NH_3 \quad (2)$$

The reaction has been investigated spectrophotometrically[34] from the concomitant changes in the absorption of $Fe(CN)_5H_2O^{3-}$ and $Fe(CN)_5NH_3^{3-}$ at 445 and 396 nm, respectively, with an isosbestic point at 408 nm. Unfortunately, the process can be confused with an apparent deprotonation of $Fe(CN)_5H_2O^{3-}$, owing to the pH dependence of the spectra. The assignment of the absorption band at 396 nm to $Fe(CN)_5OH^{4-}$, however, is not reasonable, because OH^- is usually lower than H_2O in the spectrochemical series (e.g., $Dq_{OH^-}/Dq_{H_2O} = 0.94$[24]); thus it would be surprising if the spectrum of $Fe(CN)_5OH^{4-}$ were similar to that of $Fe(CN)_5NH_3^{3-}$ (λ_{max} is estimated to be $\sim$455 nm for $Fe(CN)_5OH^{4-}$).

It is likely, therefore, that $Fe(CN)_5H_2O^{3-}$ is not deprotonated to any significant extent over the pH range 5–13. Small amounts of $Fe(CN)_5NH_3^{3-}$ and dimeric species (which may be present eventually) can be neglected, because they react[34,35] much slower than $Fe(CN)_5H_2O^{3-}$ and do not interfere in the kinetics of formation of the amino acid complexes.

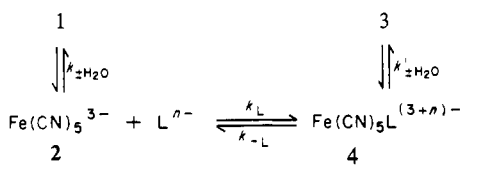
Previous studies have shown[8,9,11,28] that the specific rates of the substitution reactions of $Fe(CN)_5H_2O^{3-}$ with neutral ligands are very similar (240–400 M^{-1} s^{-1}); they do not depend, for example, on the nature and basicity of the donor atom in the entering group. The presence of several coordination sites in the entering ligand increases the rate constant systematically, as expected on statistical grounds. Examination of previous data shows that the zwitterionic amino acids typically behave as neutral ligands (Table II). For the zwitterionic histidine and methionine sulfoxide ligands, the imidazole and sulfoxide groups coordinate to pentacyanoferrate(II) at comparable rates. However, zwitterionic methionine reacts twice as fast as its sulfoxide analogue or histidine.

Coordination of mononegative ligands (e.g., CN^- and NO_2^-) takes place with second-order rate constants that are about 10 times smaller than those for neutral ligands. Typical values are reported to be 30–40 M^{-1} s^{-1} at μ = 1.0 M[36] or 20–30 M^{-1} s^{-1} at μ = 0.10 M. For glycinate, the specific rate has been reported to be 28 M^{-1} s^{-1} (25 °C, μ = 0.10 M).[8] Data set out in Table II show that several related amino acids (serine, leucine, phenylalanine, tryptophan, valine, and methionine sulfone) react with specific rates comparable to that of glycine. The activation enthalpies for the reactions involving these ligands are not very different from those for neutral ligands; however, the activation entropies of the former reactions are systematically more negative (than those for the neutrals).

The behavior of cystine (k_f = 37.5 M^{-1} s^{-1}), β-alanine (k_f = 57 M^{-1} s^{-1}), and arginine (k_f = 96 M^{-1} s^{-1}) is intermediate between that of neutral and mononegative ligands (Figure 2). In the case of cystine, this is explained readily in terms of the presence of two coordinating amino groups in the molecule. On the other hand, arginine is electrically neutral, but there are positive and negative charges at opposite ends of the molecule. The slightly anionic behavior of the ligand appears to be imposed by the proximity of the coordinating amino group to the carboxylate. The β-alanine ligand, which is mononegative, provides an important example of the dependence of the rate constant on the distance of the coordinating site to the carboxylate group. In comparison with glycine, each C–C bond separating the carboxylate and the coordinating group decreases k_f by ca. 30 M^{-1} s^{-1}.

Mononegative amino acids having several nonequivalent sites for coordination with aquopentacyanoferrate(II) (e.g., histidine, methionine, methionine sulfoxide, and lysine) also fall in the intermediate region separating the neutral ligands in Figure 2. The evaluation of the individual constants for each specific site of coordination is not simple; such evaluation will be attempted in a later section (isomerization reactions). Finally, as expected for dinegative ligands, glutamate and tyrosinate react much slower with aquopentacyanoferrate(II) than do mononegative amino acids (rate constants are $\sim$9 M^{-1} s^{-1}).

The rates of formation of the $Fe(CN)_5$(amino acid)$^{(3+n)-}$ complexes are very sensitive to charge distributions in the amino acids. Such rate behavior can be rationalized in terms of a dissociative scheme, analogous to that proposed by Eigen and Wilkins:[37] **1–2–4** and **1–3–4** refer to the S_N1 (or D) and S_N1-IP (D-IP) mechanisms, respectively.



In the dissociative mechanism, **1–2–4**, the rate-determining step is represented by k_{-H_2O}. The observed rate law, assuming a steady-state approximation for the $Fe(CN)_5^{3-}$ intermediate, can be expressed by eq 3 (k_{H_2O} includes the solvent activity, and k_L[L] $\ll k_{H_2O}$). For a limiting situation, where k_L represents a diffusion-controlled process, the effect of interionic interactions can be estimated[38] as

$$k_{obsd} = \frac{k_{-H_2O}}{k_{H_2O}} k_L[L] \quad (3)$$

$$k_{L(-)} = k_L \frac{\delta}{e^{\delta} - 1} \quad (4)$$

where

$$\delta = \frac{Z_A Z_B e^2}{\epsilon k T a(1 + ka)} \qquad k^2 = \frac{8\pi N e^2 \mu}{1000 \epsilon k T}$$

The rate constants k_L and $k_{L(-)}$ refer to the neutral and anionic ligands, whereas all other terms have their conventional meanings.[38] According to this model, an interaction distance of ap-

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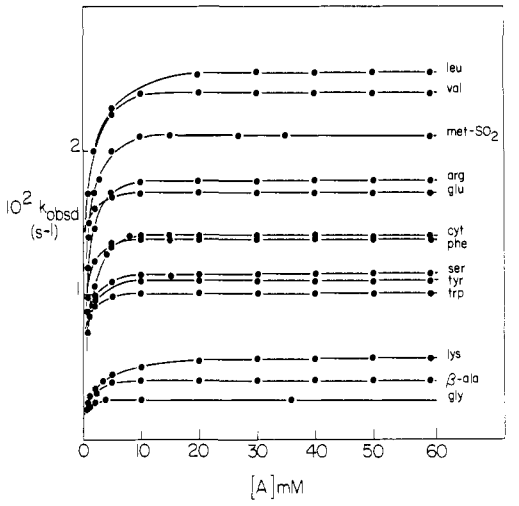

Figure 3. Dependences of the observed rate constants for the dissociation of the $Fe(CN)_5$(amino acid)$^{(3+n)-}$ complexes on the concentration of the added ligand (isonicotinamide or Me_2SO) at 25 °C (μ = 0.100 M, lithium perchlorate).

proximately 4 Å is required to explain a 10-fold decrease in specific rate in going from a neutral to a mononegative ligand. Such a distance is unreasonable, because it is smaller than the radius of the pentacyanoferrate(II) complex.

In the ion-pair mechanism (**1–3–4**), the rate-determining step (k'_{-H_2O}) is preceded by outer-sphere association of the reactants. Neglecting the reverse step (**4–3**), the observed rate law is given by

$$k_{obsd} = \frac{K_{IP}k'_{-H_2O}[L]}{1 + K_{IP}[L]} \quad (5)$$

An ion-pair mechanism has been proposed to account for the reaction between $Fe(CN)_5H_2O^{3-}$ and $Co(NH_3)_5(Me_2SO)^{3+}$ that yields a dimethyl sulfoxide bridged complex;[39] such a mechanism explains the observation that k_{obsd} saturates at high concentrations of the Me_2SO complex. Analogous saturation behavior is not expected for the amino acids, because the product K_{IP}[L] should be much smaller than unity. In this case, eq 5 becomes

$$k_{obsd} = K_{IP}k'_{-H_2O}[L] \quad (6)$$

The charges of the reactants are expected to influence the association constant K_{IP} to a major extent, rather than k'_{-H_2O}. To estimate this effect, we have calculated K_{IP} with the aid of eq 7,

$$K_{IP} = \frac{4\pi Na^3}{3000}e^{\delta} \quad (7)$$

where δ has the same meaning as in eq 4. Then, assuming that the ratio between the kinetic constants for a neutral and an electrically charged amino acid is given by the corresponding ratio of K_{IP}, it is possible to evaluate the distance of interaction within the ion pair (5.8 and 7.0 Å for the glycine and β-alanine outer-sphere complexes). By subtraction of the ionic radius of $Fe(CN)_5^{3-}$ ($\sim$4.5 Å), an estimate of the effective radius for the amino acid ligand is obtained. Such estimates are much more reasonable than those based on diffusion-controlled rates.

In the interpretation of the activation parameters for the ion-pair mechanism, it is worth mentioning that outer sphere association is usually controlled by entropic factors. For example, for a series of outer-sphere complexes between $Fe(CN)_5L^{3-}$ and $Co(NH_3)_5X^{3+}$, the typical values reported[40] for K_{IP} are about 450 M^{-1}, with $\Delta H_{IP} \sim 0$ and $\Delta S_{IP} \sim 12$ cal mol^{-1} deg^{-1}. Analogously, the association of $Fe(CN)_5H_2O^{3-}$ with anionic amino acids is expected to give $\Delta S_{IP} < 0$. It is our view that the negative activation entropies associated with the reactions with anionic ligands are attributable to outer-sphere association.

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Table III. Specific Rates and Activation Parameters for the Dissociation of $Fe(CN)_5L^{3-}$ Complexes

L	donor group	pK_a	k_d, s^{-1} (at 25 °C)	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/(mol deg)
leu$^-$	α-NH_2	9.60	2.60×10^{-2}	22.9	10.7
val$^-$	α-NH_2	9.62	2.40×10^{-2}	22.9	11.5
met-SO_2^-	α-NH_2		2.10×10^{-2}	22.0	6.9
arg$^-$	α-NH_2	5.04	1.80×10^{-2}	22.5	9.1
NH_3 [b]	NH_3	9.24	1.75×10^{-2}	22.5	7.9
glu^{2-}	α-NH_2	9.67	1.70×10^{-2}	22.7	9.3
cyst^{2-}	α-NH_2	9.85	1.40×10^{-2}	23.7	12.2
phe$^-$	α-NH_2	9.24	1.37×10^{-2}	23.4	11.7
ser$^-$	α-NH_2	9.15	1.14×10^{-2}	23.7	11.7
tyr^{2-}	α-NH_2	9.10	1.10×10^{-2}	23.7	11.7
trp$^-$	α-NH_2	9.39	1.00×10^{-2}	23.7	11.5
lys$^-$	ϵ-NH_2	10.53	5.4×10^{-3}	22.5	6.7
β-ala$^-$	β-NH_2	9.87	4.0×10^{-3}	22.9	7.4
gly$^-$ [b]	α-NH_2	9.76	2.7×10^{-3}	23.2	6.9
CH_3NH_2 [b]	α-NH_2	10.63	2.9×10^{-3}	23.0	7.0
imidazole [c]	imid	7.1	1.33×10^{-3}	24.2	10.
his [c]	imid	6.1	5.3×10^{-4}	25.2	11.
met [d]	S		4.4×10^{-4}	27.7	18.9
Me_2SO [e]	S		7.5×10^{-5}	26.3	11.
met-SO	S		1.5×10^{-4}	26.3	12.0

[a] Conditions: μ = 0.100 M ($LiClO_4$); pH 8–9 for neutral ligands; pH 11.5 for anionic amino acids; reactants were dmso, isonicotinamide, and *N*-methylpyrazinium ion, and the rate constants were measured at saturation. [b] Reference 34. [c] Reference 8. [d] Reference 12. [e] Reference 28.

Ligand Exchange Kinetics. Ligand exchange in $Fe(CN)_5L^{n-}$ is much slower than the substitution of coordinated water in $Fe(CN)_5H_2O^{3-}$. The rates are strongly dependent on the nature of the leaving group (L); but they are completely independent of the properties of the entering ligand (Y). The kinetics were investigated under pseudo-first-order conditions, in the presence of excess concentrations of L and Y. Typical plots of the observed rate constants vs. the concentration of Y are shown in Figure 3.

The following mechanism is proposed for the Y/L exchange process (where L dissociation must necessarily follow the **4–3–1** pathway):

$$Fe(CN)_5L^{3-} \underset{k_L}{\overset{k_{-L}}{\rightleftharpoons}} Fe(CN)_5H_2O^{3-} + L$$

$$Fe(CN)_5H_2O^{3-} + Y \underset{k_{-Y}}{\overset{k_Y}{\rightleftharpoons}} Fe(CN)_5Y^{3-}$$

where

$$\frac{-d[Fe(CN)_5L]}{dt} = \frac{d[Fe(CN)_5Y]}{dt} = k_{obsd}[Fe(CN)_5L^{3-}]$$

and

$$k_{obsd} = \frac{k_{-L}k_Y[Y] + k_{-Y}k_L[L]}{k_Y[Y] + k_L[L]} \quad (8)$$

When the concentration of Y is increased, the k_Y[Y] terms predominate over the k_L[L] analogues in eq 8 and k_{obsd} reduces to k_{-L}. Therefore, the rates of dissociation of the coordinated amino acids in the pentacyanoferrate(II) complexes are obtained directly from the saturation plots (Figure 3). As [Y] decreases, k_{obsd} is expected to approach $k_{-Y} = k_{-isonic} = 7.3 \times 10^{-4}$ s^{-1}.[6]

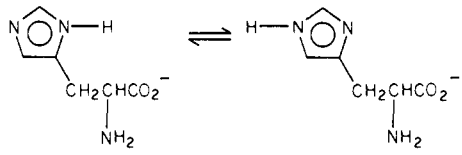
The rate constants and the activation parameters determined for saturation conditions are given in Table III for the several amino acids and related ligands. Because k_{-L}, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ are independent of the entering ligand (e.g., Me_2SO, MPz^+, and isonicotinamide), a limiting dissociative mechanism is established (the $\Delta S^{\ddagger}$ values are positive, as expected). A similar mechanism also has been proposed for reactions involving substituted pyridines as leaving groups based on measurements of activation volumes in solution.[41]

Table IV. Kinetic Data for Isomerization Reactions

kinetic constants	his	met	met-SO	lys
$k^f = k_X + k_Y$, M^{-1} s^{-1}	91[a]	169	102	160
$k_X = k_{NH_2}$, M^{-1} s^{-1}	30[b]	29	25	30[b]
k_Y, M^{-1} s^{-1} [c]	61	140	77	130
k_{isom}, s^{-1} [d]	8.4×10^{-3}	2.1×10^{-2}	1.9×10^{-2}	
$k_{-X} = k_{-NH_2}$, s^{-1}	1.2×10^{-2}	2.5×10^{-2}	2.5×10^{-2}	2.5×10^{-2}
k_{-Y}, s^{-1} [c]	5.2×10^{-4}	3.0×10^{-4}	1.6×10^{-4}	5.4×10^{-3}
$k_{-Y} = k_{-N(3)}$, s^{-1} [e]	1.1×10^{-1}			

[a] Reference 8. [b] Estimated by comparison with analogous α-aminocarboxylate complexes. [c] Y refers to the N(1)-imidazole, thioether, sulfoxide, and ε-amino groups in his, met, met-SO, and lys, respectively. [d] $k_{isom} = k_Y k_{-X}/(k_X + k_Y)$. [e] N(3) refers to the sterically hindered isomer of the his complex.

Isomerization Reactions. In alkaline solution, methionine, methionine sulfoxide, and lysine each possess two different potential donor atoms for binding to pentacyanoferrate(II). The tautomeric forms of histidine,



can coordinate in three different ways, through the N(1), N(3), and amino groups. In all these cases, a mixture of isomers is obtained with pentacyanoferrate(II), the composition depending on the relative rates of formation. With X and Y designations for the isomers, the observed rate constant for the parallel reactions:

$$Fe(CN)_5H_2O^{3-} + X\text{–}Y^- \xrightarrow{k_X} Fe(CN)_5(X\text{–}Y)^{4-} + H_2O$$

$$Fe(CN)_5H_2O^{3-} + Y\text{–}X^- \xrightarrow{k_Y} Fe(CN)_5(Y\text{–}X)^{4-} + H_2O$$

becomes

$$k_{obsd}{}^f = (k_X + k_Y)[X\text{–}Y] \quad (9)$$

For thermodynamic equilibrium, isomer X, which is more labile, should isomerize to Y, which is the stable form. The isomerization reaction can be observed in all these cases. The conversion of the labile form to the inert one is quantitative in the histidine, methionine, and methionine sulfoxide complexes, and almost complete in the case of lysine.

The kinetics may be analyzed in terms of the following scheme:

$$Fe(CN)_5(X\text{–}Y)^{4-} \underset{k_{-X}}{\rightleftharpoons} Fe(CN)_5H_2O^{3-} + X\text{–}Y^-$$

$$Fe(CN)_5H_2O^{3-} + X\text{–}Y^- \xrightarrow{k_Y} Fe(CN)_5(Y\text{–}X)^{4-}$$

where

$$\frac{d[Fe(CN)_5(Y\text{–}X)^{4-}]}{dt} = k_{obsd}{}^{isom}[Fe(CN)_5(X\text{–}Y)^{4-}]$$

and

$$k_{obsd}{}^{isom} = \frac{k_Y k_{-X}}{k_X + k_Y} \quad (10)$$

It is apparent from eq 9 that the isomerization rates are independent of the concentration of the amino acid ligand. As a result, it is relatively difficult to evaluate the kinetic constants involved in k_{obsd}. However, if we introduce an auxiliary ligand A (e.g., dimethyl sulfoxide), it will complete with the amino acid during the formation and isomerization processes. In this case, it is possible to show that

$$k_{obsd}{}^f = (k_X + k_Y)[X\text{–}Y] + k_A[A] \quad (11)$$

and $k_{obsd}{}^{isom}$ becomes

$$k_{obsd}{}^{isom} = \frac{k_{-X}(k_Y[X\text{–}Y] + k_A[A])}{(k_X + k_Y)[X\text{–}Y] + k_A[A]} \quad (12)$$

Therefore,

$$k_{obsd}{}^f k_{obsd}{}^{isom} = k_{-X}(k_Y[X\text{–}Y] + k_A[A]) \quad (13)$$

The slope and intercept of a plot of $k_{obsd}{}^f$ vs. [A] give k_A and $k_X + k_Y$, respectively (eq 11). With k_A determined, a plot of the product $k_{obsd}{}^f k_{obsd}{}^{isom}$ vs. [A] (eq 13) gives k_{-X} and k_Y (and k_X from eq 11).

This approach has been employed successfully to extract the kinetic parameters for the methionine complex.[12] For the methionine sulfoxide system, we have employed a variation of the above method, using an adaptation of a two-step mixing system in the stopped-flow instrument. The procedure, as described in the experimental section, involves introduction of a large excess of auxiliary ligand into the mixture of complexes shortly after formation (e.g., 30 s). Under the conditions employed ([A] saturation), $k_{obsd}{}^{isom} = k_{-X}$; k_X and k_Y then are readily obtained from eq 9 and 11.

The results are given in Table IV. For the histidine complex, with the assumption $k_{NH_2} = 30$ M^{-1} s^{-1} (and use of an isomerization constant of 8.4×10^{-3} s^{-1}),[8] k_{-NH_2} was evaluated. The results show that the NH_2 ($k_d = 1.2 \times 10^{-2}$ s^{-1}) and the sterically hindered N(3) isomers ($k_d = 0.109$ s^{-1}) are much more labile than the N(1) form ($k_d = 5.2 \times 10^{-4}$ s^{-1}). Analogously, in the methionine and methionine sulfoxide series, the FeS form is about 2 orders of magnitude more inert than the $FeNH_2$ isomer.

General Trends in the Substitution Kinetics. Several generalizations about the kinetics of pentacyanoferrate(II) substitution reactions can be extracted from the data given in Tables II–IV. The behavior of amino acids in zwitterionic form is comparable to that of related neutral ligands (e.g., imidazole,[8] pyridine,[11] dimethyl sulfoxide,[28] NH_3). This holds for k_f (240–400 M^{-1} s^{-1}), $\Delta H^{\ddagger}$ (14–16 kcal/mol), and $\Delta S^{\ddagger}$ (2–7 cal/(mol deg)) values. For the anionic amino acids, the rates depend on distance, as illustrated in Figure 4. Calculations, assuming the dissociative ion-pair

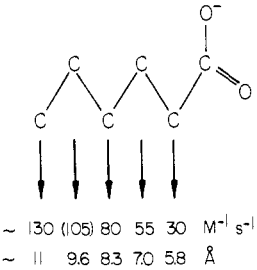


Figure 4. Variation of typical second-order rate constants for the reactions of amino acids with $Fe(CN)_5H_2O^{3-}$ as a function of the localization of the coordinating groups in the chain: d is the interaction distance calculated for the ion pair.

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(42) Our K_{III} value for imidazole accords closely with that reported by Shepherd et al. (Johnson, C. R.; Shepherd, R. E.; Marr, B.; O'Donnell, S.; Dressick, W. *J. Am. Chem. Soc.* **1980**, *102*, 6227).

Table V. Thermodynamic Data for $Fe(CN)_5L^{2-/3-}$ Complexes

L	$E_{1/2}$, (mV vs. NHE)	K_{II}, M^{-1}	ΔH, kcal/mol	ΔS, cal/(mol deg)	K_{III}, M^{-1}
H_2O	370	1			1
leu^-	330	1.1×10^3	−8.3	−13.9	5.3×10^3
val^-	330	1.2×10^3	−8.3	−14.0	5.9×10^3
$met\text{-}SO_2^-$	360	2.1×10^3	−7.9	−11.0	3.1×10^3
arg^-	*b*	5.3×10^3	−6.8	−10.1	
NH_3^-	340	2.1×10^4	−7.8	−10.3	6.8×10^4
glu^{2-}	340	5.3×10^2	−7.2	−11.3	1.7×10^3
$cyst^{2-}$	350	2.7×10^4	−8.2	−9.6	5.8×10^4
phe^-	350	1.5×10^3	−8.8	−15.0	3.3×10^3
ser^-	355	2.1×10^3	−9.1	−14.3	3.8×10^3
tyr^{-2}	345	8.2×10^2	−8.0	−12.7	2.2×10^3
trp^-	345	1.8×10^3	−8.9	−14.6	4.8×10^3
$lys^-(\epsilon)$	330	2.4×10^4	−8.4	−5.7	1.1×10^5
$\beta\text{-}ala^-$	340	1.4×10^4	−8.6	−9.8	4.5×10^4
gly^-	360	1.1×10^4	−8.5	−9.9	1.6×10^4
imidazole	340	1.8×10^5	−9.1	−7.0	5.8×10^5
his	355	5.9×10^5	−9.8	−6.0	1.1×10^6
met	575	1.2×10^6	−11.0	−7.9	4.1×10^2
Me_2SO	850	4.9×10^6	−10.9	−7.0	3.7×10^{-2}
met-SO	870	2.1×10^6	−11.6	−10.0	7.1×10^{-3}

[a] Conditions: 25 °C; $\mu = 0.10$ M. [b] Irreversible cv.

mechanism, indicate that K_{IP} increases systematically with the distance separating $Fe(CN)_5H_2O^{3-}$ and the anionic ligand. The average distance separating the carboxylate anions may be estimated from the theoretical values of K_{IP} by assuming an approximate radius of 4.5 Å for $Fe(CN)_5H_2O^{3-}$ in close contact with the coordinating groups. The results (the average internal distances) suggest that to a very large degree the amino acids are extended in a linear chain conformation.

As predicted by the K_{IP} model, the presence of cationic residues (e.g., in arginine) increases k_f (e.g., from 30 to 96 M^{-1} s^{-1}), whereas anionic residues (e.g., in glutamate and tyrosine) act oppositely ($k_f = 9$ M^{-1} s^{-1}). Neutral residues of several sizes (e.g., in phenylalanine, leucine, valine, tryptophan, methionine) exert little effect on the kinetics of formation involving the α-aminocarboxylate group. Apparently, local steric effects are negligible in the kinetics of formation of the amino acid complexes. The rates are determined mainly by outer-sphere association and solvent exchange within the ion pair.

The data for the dissociation reactions provide a good description of the behavior of the amino acids as monodentate ligands. Because steric effects influence the metal–ligand bond strengths in the series of α-aminocarboxylates as well as in the N(1) isomer of the histidine complex, the dissociation rates are affected in a predictable manner.

Electrochemical Behavior. The cyclic voltammograms of the pentacyanoferrate(II) complexes with amino acids exhibit quasi-reversible behavior, with cathodic and anodic peaks of nearly the same intensity separated by 60–65 mV. The concentrations employed in the experiments were typically 4×10^{-3} M, except in the case of $Fe(CN)_5H_2O^{3-}$, where the concentration was kept as low as possible (10^{-4} M) to minimize dimerization.

The half-wave potentials ($E_{1/2}$) are given in Table V. Because the diffusion coefficients ($\sim(4\text{–}7) \times 10^{-6}$ cm^2 s^{-1}) of the oxidized and reduced species differ by less than 20%, the $E_{1/2}$ values are the same (within experimental error) as the formal reduction potentials ($E^{\circ\prime}$).

The values of the reduction potentials for all the α-aminocarboxylate complexes are virtually the same (~340 mV). The imidazole and histidine complexes also exhibit similar E° values; however, the methionine and methionine sulfoxide complexes are quite distinct, having reduction potentials of 575 and 870 mV, respectively. The comparisons (imidazole and histidine; dimethyl sulfoxide and methionine sulfoxide; NH_3 and the whole series of aminocarboxylate ligands) show that the electrochemical behavior of each complex is dominated by the nature of its functional group.

The stability constants given in Table V for the pentacyanoferrate(II) complexes were calculated from the kinetic data for the formation and dissociation reactions. Also in Table V are the stability constants of the oxidized complexes,[42] which were calculated from the measured electrochemical potentials and the following redox cycle:

$$\begin{array}{ccc} Fe(CN)_5H_2O^{2-} + L & \overset{K_{III}}{\rightleftharpoons} & Fe(CN)_5L^{2-} + H_2O \\ +e \uparrow\downarrow & & \uparrow\downarrow +e \\ Fe(CN)_5H_2O^{3-} + L & \overset{K_{II}}{\rightleftharpoons} & Fe(CN)_5L^{3-} + H_2O \end{array}$$

where

$$E^{\circ\prime}_{Fe(CN)_5L^{2-/3-}} = E^{\circ\prime}_{Fe(CN)_5H_2O^{2-/3-}} + \frac{RT}{F} \ln \frac{K_{II}}{K_{III}} \quad (14)$$

Whereas the trends in K_{II} are determined by the acceptor properties of the ligands, the opposite holds for the oxidized complexes. Interestingly, imidazole appears to behave as a fair π-acceptor as well as a moderately strong σ-donor ligand, because it stabilizes both oxidation states of pentacyanoferrate.

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Registry No. $Fe(CN)_5(H_2O)^{3-}$, 18497-51-3; $Fe(CN)_5(gly)^{4-}$, 70739-30-9; $Fe(CN)_5(\beta\text{-ala})^{4-}$, 83560-70-7; $Fe(CN)_5(\epsilon\text{-lys})^{4-}$, 83560-71-8; $Fe(CN)_5(arg)^{4-}$, 83560-72-9; $Fe(CN)_5(trp)^{4-}$, 83560-73-0; $Fe(CN)_5(tyr)^{5-}$, 83560-74-1; $Fe(CN)_5(cyst)^{5-}$, 83560-75-2; $Fe(CN)_5(phe)^{4-}$, 83560-76-3; $Fe(CN)_5(leu)^{4-}$, 83560-77-4; $Fe(CN)_5(val)^{4-}$, 83560-78-5; $Fe(CN)_5(met\text{-}SO_2)^{4-}$, 83560-79-6; $Fe(CN)_5(ser)^{4-}$, 83560-80-9; $Fe(CN)_5(glu)^{5-}$, 83560-81-0; $Fe(CN)_5(met)^{3-}$, 83560-82-1; $Fe(CN)_5(Im)^{3-}$, 60105-88-6; $Fe(CN)_5(his)^{3-}$, 60105-82-0; $Fe(CN)_5(met\text{-}SO)^{3-}$, 83572-88-7.