ν_3, none of the common calculations can be performed to test the validity of adopting an octahedral crystal-field model[28,29] and, consequently, one cannot tell whether the low B value reflects some special character of $[Ni(tren\text{-}py)]^{2+}$ with respect to the tris species or whether it is just an artifact of a model inappropriately applied.

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The Kinetics of Reaction of Nickel(II) Ion with a Variety of Amino Acids and Pyridinecarboxylates

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Abstract: The rate constants for the formation of the mono complex of nickel(II) with 22 different ligands have been determined by the stopped-flow method. The ligands studied included amino acids, polyamino carboxylates, peptides, and pyridinecarboxylates. The zwitterion form is shown to be extremely unreactive, and this striking result is discussed. The reactivity of the monoprotonated forms of pyridine-2-carboxylate and pyridine-2,6-dicarboxylate and the diprotonated EDTA and CyDTA is ascribed to the presence of small amounts of the neutral form with the proton associated with the carboxylate. An expected correlation of formation rate constant with the charge of the ligand is observed. Small deviations of some ligands are discussed in terms of the detailed structure of these ligands in solution.

The generally accepted mechanism[1] for the formation of many inner-sphere metal complexes $ML^{(n-m)+}$ involves exchange of the ligand L for a molecule of water of the inner coordination sphere of the metal within the outer-sphere complex $M_{aq}{}^{n+}L^{m-}$.

$$M_{aq}{}^{n+} + L_{aq}{}^{m-} \underset{}{\overset{K_{os}}{\rightleftharpoons}} M_{aq}{}^{n+}L^{m-} \underset{k_r}{\overset{k_{H_2O}}{\rightleftharpoons}} ML^{(n-m)+} + H_2O \quad (1)$$

The process is dominated by the value of k_{H_2O}, and the results of a large number of studies of the kinetics of formation of metal complexes, particularly those of nickel(II), with a wide variety of ligands lend strong support to this mechanism.[2] The more recent tendency has therefore been to investigate the finer details of complex formation. This includes a study of the effects of charge and structure of the ligand, already coordinated as well as entering, on the rate and mechanism of the formation reaction.[3-8] The difference in five- and six-membered chelate formation[4,5] and the nature of the donor atoms[6-8] are among the structural factors which have been investigated.

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In the present study we are concerned with the kinetics of reaction, over a range of pH, of nickel(II) ion with 22 ligands, which are listed with their abbreviations in Table I. Nearly all of the ligands contain one or more amino and/or carboxylate groups as part of aliphatic or heterocyclic systems. The aim is to have available, for comparative purposes, the reaction rate constants for a variety of ligands under a uniform set of conditions. We were hoping thus to examine the effect of (a) charge and its distribution in the ligand and (b) donor atom protonation on the mechanistic behavior.

Experimental Section

Materials. Commercial products of the highest quality available were used. Aminomalonic acid was prepared by hydrolysis of the ester (Aldrich)[9] and piperidine-2,6-dicarboxylate by hydrogenation of pyridine-2,6-dicarboxylate.[10]

Kinetic Experiments. Standard solutions of ligands, lutidine and acetate buffers, and sodium nitrate were prepared by weight. Nickel ion concentration was estimated by EDTA titration, and sodium perchlorate solutions were prepared by mixing standardized solutions of sodium carbonate and perchloric acid. A very small optical density change accompanied the formation of the mono complexes of the aliphatic ligands, but these reactions were attended by pH changes (eq 2), which were used to follow the progress of the reaction. An added buffer (2,6-lutidine, $pK \sim 6.7$, or acetate, $pK \sim 4.8$) limited the pH change to a small one, about 0.2 unit, which was registered with an appropriate indicator (bromothymol blue, $pK \sim 6.8$, λ 620 mμ, or methyl orange, $pK \sim 3.5$, λ 510 mμ). In detail, nickel nitrate solution (10^{-3}–10^{-1} M, buffered $\sim 10^{-2}$ M at ionic strength 0.3 M with added $NaNO_3$ (or $NaClO_4$ for uv work)) was mixed with ligand solution (10^{-4}–10^{-3} M, buffered $\sim 10^{-2}$ M,

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Table I. Kinetic Data for the Formation of Nickel(II) Mono Complexes at 25° and Ionic Strength 0.30 M

Reacting form of ligand	Ligand abbreviation[a]	pK_a	k, M^{-1} sec^{-1}	ΔH^*, kcal mole^{-1}
$^+NH_3CH_2CH_2NH_2$	en	7.5, 10.5	5.9×10^2	10.4
			6.7×10^2 [b]	
$NH_2CH_2CONH_2$	ga	8.1	2.2×10^3	
$NH_2CH_2COO^-$	gly	9.7	2.2×10^4	11.4
$^+NH_3CH_2CH(NH_2)COO^-$	dap	6.6, 9.5	1.9×10^3	
$^+NH_3(CH_2)_2CH(NH_2)COO^-$	dab	8.1, 10.4	2.8×10^3	
$^+NH_3(CH_2)_3CH(NH_2)COO^-$	orn	8.5, 10.7	2.0×10^3	
$^+NH_3(CH_2)_4CH(NH_2)COO^-$	lys	9.1, 10.7	4.4×10^3	
$NH_2COCH_2CH(NH_2)COO^-$	aspNH_2	8.8	8.7×10^3	
$NH_2CH_2CONHCH_2COO^-$	digly	8.1	3.6×10^3	
			2.1×10^4 [c]	
$NH_2CH_2(CONHCH_2)_2COO^-$	trigly	8.0	3.7×10^3	
			8.0×10^3 [c]	
$NH_2CH_2(CONHCH_2)_3COO^-$	tetragly	8.0	4.2×10^3	
$NH(CH_2COO^-)_2$	IDA	9.3	8.8×10^4	
			4.5×10^4 [d]	
$IDAH^-$			7.7×10^{-2} [d]	
$^-OOCCH_2CH(NH_2)COO^-$	asp	9.6	3.9×10^4	
$NH_2CH(COO^-)_2$	ama	9.0[e]	3.4×10^5	
$(CH_2)_2N_2(CH_2COO^-)_4(H^+)$	EDTA	6.2, 10.3	1.9×10^5	
			2.0×10^5 [f,g]	
			1.0×10^6 [h]	
$EDTA\ H_2^{2-}$			3.0×10^3	
			8.0×10^2 [f]	
			2.0×10^3 [g]	
$C_6H_{10}N_2(CH_2COO^-)_4(H^+)$	CyDTA	6.1	1.9×10^5	
			3.6×10^5 [i]	
$CyDTAH_2^{2-}$			8.0×10^3	
2-Aminomethylpyridine	amp	8.6	8.6×10^3	
amp H^+			35	
2-Picolinamide	pad		1.3×10^3	12.4
Pyridine-2-carboxylate	pyc	1.6, 5.4	2.6×10^4	14.4
pyc H^+			~30	
Pyridine-2-acetate	pya	5.6[e]	1.0×10^4	11.4
Pyridine-2,6-dicarboxylate	pydic	2.1, 4.7	6.3×10^4	12.4
			2.4×10^4 [i]	9.1[i]
pydic H^+			5.0×10^3	
Piperidine-2,6-dicarboxylate	pidic	3.1, 10.1	5.1×10^4	

[a] Abbreviation refers to least protonated species; *i.e.*, $^+NH_3CH_2CH_2NH_2$ is enH^+. [b] G. A. Melson, Ph.D. Thesis, Sheffield, 1962, I = 1.0. [c] Reference 3, I = 0.15 M. [d] Reference 20, I = 1.25 M. [e] This work. [f] N. Tanaka and Y. Sakuma, *Bull. Chem. Soc. Japan*, **32**, 578 (1959), I = 0.1. [g] D. W. Margerum and B. A. Zabin, *J. Phys. Chem.*, **66**, 2214 (1962), I = 0.1. [h] T. R. Bhat, D. Raahamma, and J. Shankar, *Inorg. Chem.*, **5**, 1132 (1966), I = 0.5; G. A. Rechnitz and Z.-F. Lin, *Anal. Chem.*, **39**, 1406 (1967), I = 0.01. [i] D. W. Margerum, P. J. Menardi, and D. J. Lanes, *Inorg. Chem.*, **6**, 283 (1967), I = 0.1. [j] Data for the formation of the bis (see text).

at ionic strength 0.3 M and containing indicator 5×10^{-5} M if necessary) in a glass–lucite stopped-flow apparatus. The pH of the experiment was taken as the mean of the pH at the beginning and end. The latter part of the kinetic trace was used to give excellent first-order plots from which $k_{obsd} = 0.693/t_{1/2}[Ni^{2+}]$ was computed. Complex formation was complete with the concentrations of reactants used. No pH change accompanies the nickel reaction with pad, pyc, pya, or pydic in neutral solution, but these reactions could be easily followed directly at 260–280 mμ. Those with EDTA and CyDTA were followed at 240 mμ. The result by the indicator method (pH 4.1–3.9) agreed well with that obtained by direct observation (pH 4.0) in the case of the Ni^{2+}–pyc system. For the few experiments at pH $\leq$3.0 no buffers were required. The collected results are shown in Table I. For en and gly, determination of ΔH^* required knowing K_a values for various temperatures, and this introduced significant errors in the values for the activation parameters (±2.5 kcal mole^{-1}). For the other cases cited, ΔH^* values are ±1 kcal mole^{-1} and ΔS^* values are ±3 eu. A summary of kinetic data is given in Table II.

Results

All the reactions were first order in nickel ion, which was always held in excess and in sufficiently high concentration to ensure pseudo-first-order kinetics and complete formation of the mono complex. A protonated form of the ligand predominates in the pH range of the studies, which was 6–7 for the aminocarboxylates, 4–5 for EDTA and CyDTA, and 2–5 for the pyridine derivatives. With the majority of ligands this is the monoprotonated form which we represent as LH^+. Reaction with Ni^{2+} to produce the chelate NiL^{2+} is then considered to occur as in eq 2. If the

$$\begin{aligned} LH^+ &\rightleftharpoons L + H^+ \qquad K_a = [L][H^+]/[LH^+] \\ LH^+ + Ni^{2+} &\longrightarrow NiL^{2+} + H^+ \qquad k_1 \\ L + Ni^{2+} &\longrightarrow NiL^{2+} \qquad k_2 \end{aligned} \tag{2}$$

half-life for reaction is $t_{1/2}$ using excess nickel, it can be shown that

$$\frac{0.693}{t_{1/2}[Ni^{2+}]} = k_{obsd} = \frac{(k_1[H^+] + k_2K_a)}{K_a + [H^+]}$$

or

$$k_{obsd}\frac{(K_a + [H^+])}{[H^+]} = k_1 + \frac{k_2K_a}{[H^+]} \tag{3}$$

With the diamines the diprotonated form LH_2^{2+} predominates, but the treatment of data is analogous now with $K_a = [LH^+][H^+]/[LH_2^{2+}]$. Plots of $k_{obsd}(K_a + [H^+])[H^+]^{-1}$ against $[H^+]^{-1}$ are shown in Figures 1 and 2 for the ligands studied. From (3), the intercept gives a value for k_1, and the slope equals k_2K_a. Except for the

Table II. Kinetic Data

Ligand	[Ni²⁺], M	Temp, °C	pH	k_{obsd}, M^{-1} sec^{-1}
en	0.01	25.0	7.0–6.8	120
	0.025	25.0	6.5–6.3	45
	0.10	25.0	6.0–5.8	13
	0.025	35.0	6.3–6.1	95
	0.025	45.0	6.8–6.6	202
ga	0.01	25.0	7.0–6.9	170
	0.01	25.0	6.8–6.6	130
	0.10	25.0	6.7–6.5	100
	0.10	25.0	6.3–6.0	29
	0.10	25.0	6.0–5.8	17
gly	0.01	25.0	7.0–6.8	36
	0.015	25.0	6.7–6.5	21
	0.025	25.0	6.5–6.3	11
	0.10	25.0	6.0–5.8	3.7
	0.01	35.0	6.8–6.6	97
	0.01	9.0	7.2–7.0	8.2
dap	0.01	25.0	7.0–6.9	1500
	0.20	25.0	6.7–6.5	970
	0.25	25.0	6.5–6.3	685
	0.10	25.0	6.0–5.8	312
dab	0.01	25.0	7.0–6.7	140
	0.055	25.0	6.6–6.5	90
	0.10	25.0	6.0–5.8	17
orn	0.01	25.0	7.0–6.8	52
	0.05	25.0	6.7–6.5	23
	0.10	25.0	6.0–5.9	6.3
lys	0.01	25.0	7.0–6.8	30
	0.10	25.0	6.7–6.5	14
	0.10	25.0	6.0–5.8	3.7
aspNH₂	0.01	25.0	7.0–6.8	110
	0.01	25.0	6.7–6.5	56
	0.10	25.0	6.0–5.8	14
digly	0.01	25.0	7.1–6.9	290
	0.05	25.0	6.7–6.5	110
	0.10	25.0	6.4–6.3	76
	0.10	25.0	6.0–5.8	40
trigly	0.01	25.0	7.1–6.9	420
	0.01	25.0	6.8–6.6	230
	0.10	25.0	6.1–5.9	44
tetragly	0.01	25.0	7.1–6.9	426
	0.01	25.0	6.9–6.7	298
	0.10	25.0	6.5–6.3	106
IDA	0.01	25.0	7.0–6.8	435
	0.01	25.0	6.8–6.6	200
	0.01	25.0	6.6–6.4	124
	0.10	25.0	6.0–5.8	54
	0.10	25.0	5.0–4.8	2.8
asp	0.01	25.0	7.0–6.8	74
	0.01	25.0	6.7–6.5	40
	0.10	25.0	6.2–6.0	13
	0.05	25.0	5.9–5.7	6.4
ama	0.025	25.0	7.0–6.8	2800
	0.01	25.0	6.8–6.6	1700
	0.01	25.0	6.6–6.4	1300
	0.01	25.0	6.3–6.1	770
	0.025	25.0	6.0–5.8	270
EDTA	0.001[a]	25.0	5.0	1.6×10^4
	0.001[a]	25.0	4.6	8.0×10^3
	0.001[a]	25.0	4.0	4.4×10^3
CyDTA	0.001[a]	25.0	5.0	2.2×10^4
	0.001[a]	25.0	4.7	1.6×10^4
	0.001[a]	25.0	4.0	9.3×10^3
amp	0.01	25.0	7.0–6.8	190
	0.01	25.0	6.8–6.6	120
	0.01	25.0	6.3–6.1	65
	0.10	25.0	6.0–5.8	51
pad	0.01	4.0	7.0	140
	0.01	25.0	7.0	1300
	0.01	25.0	6.0	1500
	0.01	36.0	7.0	3000
pyc	0.001[a]	1.0	7.0	2.2×10^3
	0.001[a]	15.0	7.0	8.8×10^3
	0.001[a]	25.0	7.0	2.6×10^4
	0.01[a]	25.0	5.0	8.9×10^3
	0.002[a]	25.0	5.0	1.0×10^4
	0.002[a]	25.0	4.8	7.5×10^3
	0.01[a]	25.0	4.6	7.1×10^3
	0.002[a]	25.0	4.6	5.9×10^3
	0.002[a]	25.0	4.3	3.8×10^3
	0.01[a]	25.0	4.0	2.3×10^3
	0.01[a]	25.0	3.0	2.7×10^2
	0.10[a]	25.0	2.3	62 (74)[b]
	0.10[a]	25.0	1.7	30 (48)[b]
pya	0.001[a]	3.0	7.0	1.8×10^3
	0.001[a]	17.0	7.0	4.7×10^3
	0.001[a]	25.0	7.0	1.0×10^4
pydic	0.001[a]	1.0	7.0	8.9×10^3
(formation	0.001[a]	16.0	7.0	3.0×10^4
of mono)	0.001[a]	25.0	7.0	6.3×10^4
	0.001[a]	25.0	4.3	4.0×10^4
	0.001[a]	25.0	4.0	2.2×10^4
	0.001[a]	25.0	3.6	1.2×10^4
	0.001[a]	25.0	2.9	7.4×10^3
				(8.6×10^3)[b]
	0.001[a]	25.0	2.5	4.1×10^3
				(5.8×10^3)[b]
pydic		0.5[d]	7.0	7.1×10^3
(formation		9.5[c]	7.0	1.0×10^4
of bis)		14.0[d]	7.0	1.7×10^4
		20.0[c]	7.0	1.8×10^4
		25.0[d]	7.0	2.4×10^4
		30.0[c]	7.0	3.1×10^4
pidic	0.01	25.0	7.1–6.9	39
	0.01	25.0	6.8–6.6	17
	0.10	25.0	6.2–6.0	5.9

[a] Ligand concentration 10^{-4} M. [b] When corrected for small amount of nonreactive diprotonated form. [c] Using $\sim 4.0 \times 10^{-5}$ M Ni(pydic)$(H_2O)_3$ and 3.8×10^{-4} M pydic. [d] Using $\sim 5 \times 10^{-5}$ M Ni(pydic)$(H_2O)_3$ and 2.5×10^{-4} M pydic.

ligands en, dap, EDTA, CyDTA, pyc, and pydic, $K_a \ll [H^+]$ and the y function of the figures approximates to k_{obsd}. The calculation of k_2 requires a knowledge of K_a, and these values have been mainly taken from the literature.[11] The values chosen are given in Table I and were measured in conditions as close to those of the kinetic studies ($I = 0.3$) as possible. The calculated values for k_2 will obviously depend on the chosen pK_a, but an examination of the literature[11] for several well-studied amino acids shows remarkably little variation in the value with a variety of conditions and a number of investigators. For example, with gly at 20°, values for pK_a include 9.6 ($I = 0.001$), 9.8 ($I = 0.5$), and 9.8 ($I = 1.0$). Furthermore, small differences in rate constants will not be emphasized. Some previous kinetic results are available and are incorporated in Table I. Considering the difference in conditions, the agreement in general is excellent. Of special significance is the close correspondence between our results (by flow methods) when the reacting form of ligands is in small concentration and those obtained by temperature-jump techniques[3] when the reacting form is a substantial proportion of the ligand species present. This observation also applies to our experiments with the pyridine derivatives, where because of the high stability of the complex and the weak basicity of the ligand a wide range of pH could be studied. The rate constant for the nonprotonated form obtained

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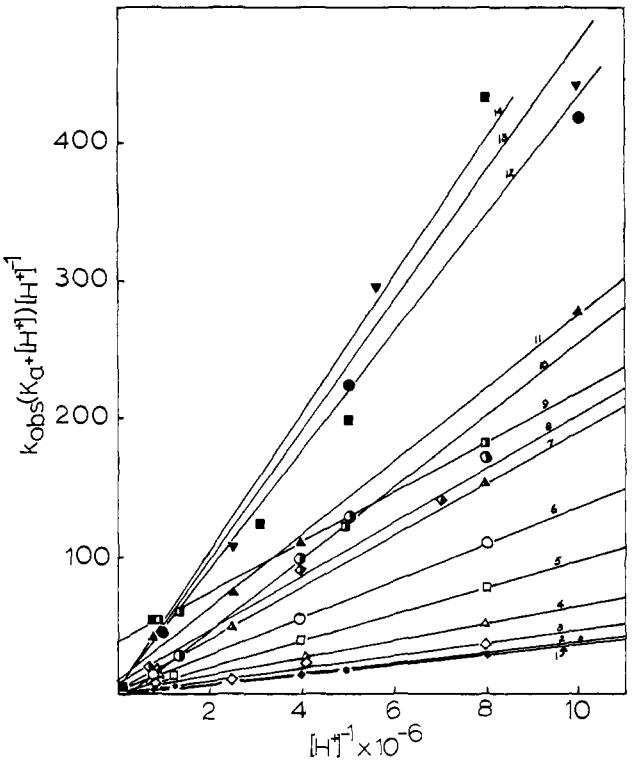

Figure 1. $k_{obsd}(K_a + [H^+])[H^+]^{-1}$ as a function of $[H^+]^{-1} \times 10^{-6}$ for the reaction of Ni^{2+} with the following ligands: pidic, ●, 1; lys, ◆, 2; gly, ◇, 3; orn, △, 4; asp, □, 5; $aspNH_2$, ○, 6; en, ▲, 7; dab, ◑, 8; amp, ◧, 9; ga, ◑, 10; digly, ▲, 11; trigly, ●, 12; tetragly, ▼, 13; IDA, ■, 14.

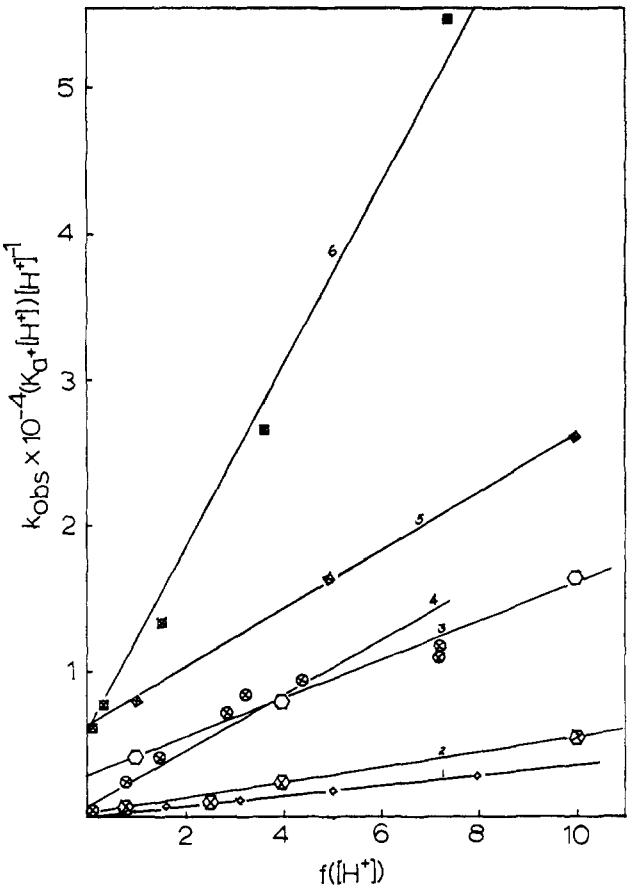

Figure 2. $k_{obsd} \times 10^{-4}(K_a + [H^+])[H^+]^{-1}$ as a function of $[H^+]^{-1} \times 10^{-6}$ for the ligands ama, ◇, 1, and dap, ⊗, 2; $[H^+]^{-1} \times 10^{-4}$ for the ligands EDTA, ○, 3, and CyDTA, ⊕, 5; and $K_a[H^+]^{-1} \times 20$ for the ligands pyc, ⊗, 4, and pydic, ⊠, 6.

directly without recourse to pK_a values agreed well with that obtained indirectly in the more acid region.

Discussion

Examination of the stability constants of the nickel complexes suggests that the majority of the ligands studied here act in a bidentate fashion. There is now strong evidence that in neutral solution the amide or peptide residue coordinates with nickel through the oxygen donor atom so that a weak chelate is completed by $-NH_2$ coordination.[12,13] The first two members of the series dap, dab, orn, and lys act as terdentate ligands. As an increasing number of methylene groups separate the amino functions, large-membered rings would be formed and orn and lys almost certainly become bidentate. There is evidence that in alkaline solution orn can coordinate through all donor atoms (even with a seven-membered ring) while the lys–nickel complex may be polymeric.[14] It is believed that IDA, ama, pydic, and pidic also function as terdentate ligands, while EDTA and CyDTA are five- or six-coordinate. The consistency of the results with a variety of ligands strongly suggests that with the reacting form of the ligand the rate-controlling step is the production of the first metal–donor atom bond and that this is followed by rapid single- or multiple-ring chelation. This is in agreement with previously expressed ideas on the mode of chelation of nickel(II) with such ligands,[3-5] as well as with 2,2′-bipyridine[6] and polyamines.[15,16]

Nonreactivity of the Protonated Ligand. The most striking feature of the study is the unreactivity of the protonated form of aliphatic amino carboxylates (and here we specifically refer to protonation involving the amino acid grouping). This is shown by the low value, which is indistinguishable experimentally from zero, for the intercept of the majority of linear plots shown in Figures 1 and 2. This behavior is duplicated by another type of N, O donor system involving the peptide linkage and represented by ga, digly, trigly, and tetragly, where again the form $^+NH_3CH_2CONHR$ (R = H, or peptide residues) is at least 10^3-fold less reactive than the neutral form, NH_2CH_2CONHR. The variation of $k_{obsd}(K_a + [H^+])[H^+]^{-1}$ with the inverse *first* power of $[H^+]$ for the dap, dab, orn, and lys series shows that the predominant reactive form is monoprotonated and is therefore $^+NH_3(CH_2)_nCH(NH_2)COO^-$ rather than $NH_2(CH_2)_nCH(NH_3^+)COO^-$. This is in agreement with pK_a and nmr data; for example, for lys the form involving protonation of the α-NH_2 group comprises only about 15% of the two monoprotonated forms.[17,18]

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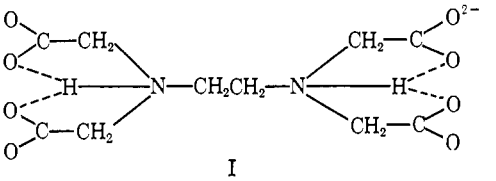
(14) G. R. Brubaker and D. H. Busch, *Inorg. Chem.*, **5**, 2110 (1966).
(15) D. W. Margerum, D. B. Rorabacher, and J. F. G. Clarke, Jr., *ibid.*, **2**, 667 (1963).
(16) The possibility that the inverse proton concentration dependence (Figures 1 and 2) arises from a mechanism of the kind $LH^+ + Ni \rightleftarrows NiL' + H^+ \rightarrow NiL + H^+$, in which the slow step involves ring closure ($NiL' \rightarrow NiL$), tends to be ruled out by consideration of probable values of the rate constants involved.
(17) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1961, p 447.
(18) F. Taddei and L. Pratt, *J. Chem. Soc.*, 1553 (1964).

The drastic reduction of the rate of complexing which attends monoprotonation of the amino carboxylate ligands has been noted previously by several workers but not specifically commented upon. The reaction of glycine and alanine with nickel(II) and cobalt(II) was studied on the basis of only the anionic form reacting,[3-5] and recently Pearlmutter and Stuehr[19] were able to measure even by flow methods the high rate constant for the Cu^{2+}–glycine reaction (4.0×10^9 (mono) and 4.0×10^8 (bis) at 25°) by working at pH 3–4, thus drastically reducing the concentration of reacting species. The rate constants for reaction of IDA^{2-} and $IDAH^-$ with nickel(II) are 4.5×10^4 and 7.7×10^{-2} M^{-1} sec^{-1} at 25° ($I = 1.25$), respectively.[20] The corresponding rate constants for NTA^{3-} and $NTAH^{2-}$ are 4.8×10^5 and 7.5 M^{-1} sec^{-1}, showing once again an almost 10^5 difference in reactivity.[21] This pronounced difference in behavior is not shared by the non- and monoprotonated forms of related chelating ligands. Thus, the rate constant for reaction of enH^+ with Ni^{2+} is about 10^2 less than that calculated for en (4×10^4 M^{-1} sec^{-1}),[2] and a somewhat similar difference attends the reaction of amp and $ampH^+$ (Table I) and bipy and $bipyH^+$ [22] with Ni^{2+}, some of the difference undoubtedly residing in the unfavorable electrostatic effect for the protonated ligand. Similarly, $HOOC \cdot COO^-$ and $HOOCCH_2COO^-$ have an even closer reactivity, compared with the corresponding dianionic forms, toward nickel(II).[23] This makes particularly significant the inertness of $^-OOCCH(NH_3^+)COO^-$ and $^-OOCCH_2$-$CH(NH_3^+)COO^-$ where, even with the favorable disposition of carboxylate groups, the presence of the NH_3^+ group prevents chelation.

In seeking the cause for this striking effect, we note that the dipolar ion (zwitterion) is the major monoprotonated form of aliphatic amino acids, approximately 10^5 larger in amount than the uncharged form.[17] Since coordination cannot occur through primary attachment to the RNH_3^+ group (consider, for example, the zero intercept for reaction of enH_2^{2+} in Figure 1, and the nonreactivity of NH_4^+ ion[8]), the first step of coordination must occur through the $-COO^-$ grouping of the amino acid. This is certainly a labile arrangement with the breaking rate constant likely to be very much greater than the combined process of H^+ ionization from the $-NH_3^+$ residue and ring closure. The over-all rate constant would then the very much less than that for coordination of $NH_2CH_2COO^-$ where these unfavorable situations do not arise. The Ni–O bond formed with the amide and peptide linkage will be extremely labile so that ring closure following Ni–O bond formation will also be difficult with the protonated form of these ligands. Another contributory factor to the unreactivity of the zwitterion may be the necessity to break down the strong intramolecular interactions (which may be electrostatic or hydrogen bonding in nature) which are believed to occur in the zwitterion form of the α-amino acids and α-aminopolycarboxylic acids.[24] Infrared evidence has been used to indicate that, even with the polycarboxylates such as $NTAH^{2-}$, all the available carboxylate groups interact in an equivalent manner with the single protonation site.[24] Thus with these ligands also, intramolecular ring formation of the protonated form must be broken before coordination can occur.[25] Irrespective of the *modus operandi* of the effect, the fact that H_2EDTA^{2-} (and H_2CyDTA^{2-}) reacts with nickel(II) with a relatively high rate constant is interesting, since this diprotonated form approximates two joined halves of the unreactive $IDAH^-$ and has a suggested structure (I) with protonation at the N atoms.[24,26] This result could be explained by the inclusion in equilibrium with I of a small



I

amount, difficult to detect otherwise, of a form in which one or, less likely, two carboxylate groups have the proton associated with them, and which thus contains a free nitrogen able to coordinate in the first step.

When complexing by the polyamines is considered, however, the Ni–NH_2 bond formed is relatively stable to bond dissociation, and the completion of the ring with proton elimination occurs readily. Reinforcing evidence for this idea is the fact that $^+N(CH_3)_3CH_2CH_2$-NH_2 reacts with nickel with a rate constant (4×10^2) similar to that of enH^+ (6×10^2 M^{-1} sec^{-1} at 25°).[27] It is not as easy to see why the monoprotonated dicarboxylates react so easily, since intramolecular hydrogen-bonded structures also appear to exist with the half-neutralized malonic acids.[28] However, it should be remembered that the –COOH grouping, unlike $-NH_3^+$, is capable of coordination even as a first step.

Pyridinecarboxylates. The unreactivity of the zwitterion form is also seen in the saturated pyridine system, pidic (Figure 1). However, with the heterocyclic derivative, pydic, an appreciable value for k_1, the reaction rate constant for the protonated form, is obtained (5×10^3 M^{-1} sec^{-1}), while with the monocarboxylate pyc examination of the data *at low pH* indicates a small but definite residual rate constant for $k_1 \simeq 30$ M^{-1} sec^{-1}. We ascribe these rate constants to the presence of reactive forms II and III, in equilibrium with the zwitterion form.

If rate constants for reaction of II and III are assumed to be 2.6×10^4 (as in pyc) and 1.3×10^3 M^{-1} sec^{-1}

(19) A. F. Pearlmutter and J. Stuehr, *J. Am. Chem. Soc.*, **90**, 858 (1968).

(20) T. J. Byadelek and A. H. Constant, *Inorg. Chem.*, **4**, 833 (1965).

(21) T. J. Byadelek and M. L. Blomster, *ibid.*, 3, 667 (1964).

(22) J. C. Cassatt and R. G. Wilkins, unpublished experiments, find second-order rate constants of 2.0×10^3 and 26 M^{-1} sec^{-1} at 25°, respectively.

(23) G. H. Nancollas and N. Sutin, *Inorg. Chem.*, **3**, 360 (1964), have found that for $Ni^{2+} + C_2O_4^{2-} \rightarrow NiC_2O_4$ $k_{25}° = 7.5 \times 10^4$ M^{-1} sec^{-1}, and for $Ni^{2+} + HC_2O_4^- \rightarrow NiC_2O_4 + H^+$, $k_{25}° = 5 \times 10^3$ M^{-1} sec^{-1}. F. P. Cavasino, *J. Phys. Chem.*, **69**, 4380 (1965), measured $Ni^{2+} + CH_2(CO_2)_2^{2-}$, $k_{25}° = 7.0 \times 10^4$ M^{-1} sec^{-1}, and $Ni^{2+} + CH_2(CO_2)_2H^-$, $k_{25}° = 3.1 \times 10^3$ M^{-1} sec^{-1}, all at $I = 0.1$.

(24) D. Chapman, D. R. Lloyd, and R. H. Prince, *J. Chem. Soc.*, 3645 (1963).

(25) The small but definite rate constants for reaction of $NTAH^{2-}$ and $IDAH^-$ may in fact result from the presence of the small amount of the neutral form ($\sim 10^{-3}$%) in which the proton is associated with the carboxylate group and which therefore may be considered to be reactive.

(26) G. Schwarzenbach and H. Ackermann, *Helv. Chim. Acta*, **30**, 1798 (1947); R. J. Kula, D. T. Sawyer, S. I. Chan, and C. M. Finley, *J. Am. Chem. Soc.*, **85**, 2930 (1963).

(27) J. C. Cassatt and R. G. Wilkins, unpublished temperature-jump experiments.

(28) H. B. Evans and J. H. Goldstein, *Spectrochim. Acta*, **24A**, 73 (1968).

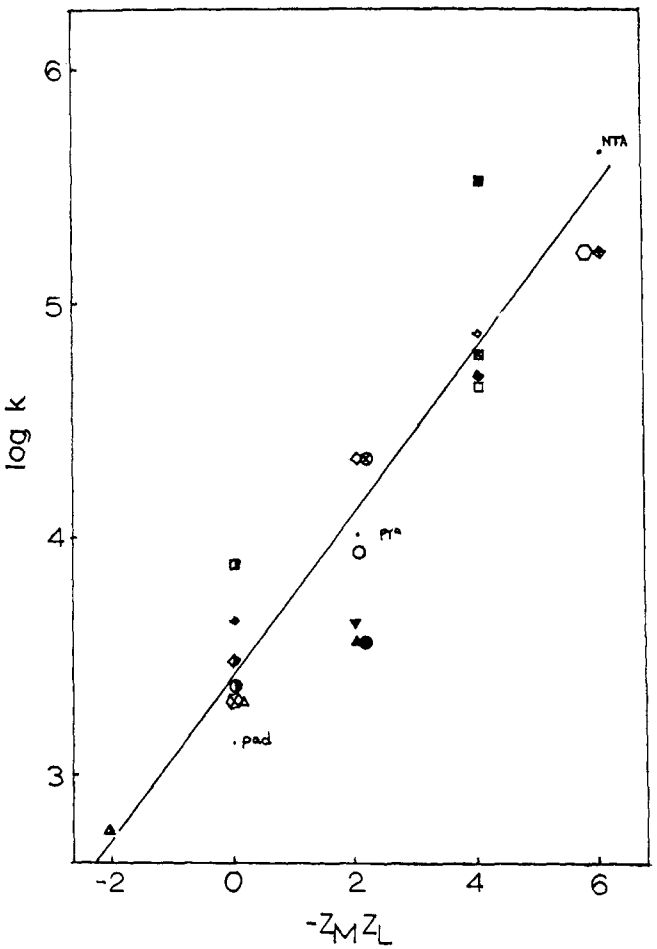
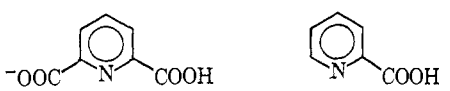


Figure 3. Log k as a function of $-Z_MZ_L$ for the ligands whose symbols are listed in Figures 1 and 2 and for pad, pya, and NTA.

(as in pad) then 25 and 2%, respectively, of the nonzwitterion forms, in equilibrium with the corresponding zwitterions, would account for the reactivity of the monoprotonated species. In agreement with these



II III

findings, spectral and pK_a data indicate that the isoelectric form of pyc contains approximately 5% of the uncharged form.[29] Consideration of pK_a values leads us to expect larger amounts of II, as found by our results, although no information on this point is presently available. With the wide separation of pK_a values in the alicyclic compound pidic, the nonzwitterion form would be expected to occur only in extremely small quantities (as with the aliphatic amino acids), and the nonreactivity of the protonated form is thus understood.

The Effect of Charge Product on the Ligation Rate. On the basis of mechanism 1, the second-order formation rate constant k (usually values of k_2 from (2)) is equal to $K_{os}k_{H_2O}$. In addition, K_{os} is related to the charge of the reactants, Z_M and Z_L, by expression 4,[30]

$$\ln K_{os} = \ln K_0 - Z_MZ_Le^2/aDkT \quad (4)$$

where K_0 is the association constant of two uncharged particles in solution, e is the electronic charge, a is the distance of closest approach of the ions, D is the solvent dielectric constant, and T is the temperature. Thus, since k_{H_2O} appears only slightly dependent on ligand structure

$$\log k = \log (K_0k_{H_2O}) - \frac{Z_MZ_Le^2}{2.3aDkT} \quad (5)$$

We have accumulated sufficient data to enable us to make a plot of log k against $(-Z_MZ_L)$ (Figure 3). The linear plot is obtained using "simpler" ligands with the charge present being reasonably localized. From the slope, a value for a = 8.5 Å is obtained which is somewhat higher than that usually encountered with ion pairing. The figure also contains appropriate data for the larger and more complex amino acids and peptides, and their deviation from the general plot needs mention. The values of k for digly, trigly, and tetragly are close to one another, and to that of the neutral ga and NH_3,[2] and are significantly reduced from that of gly. This suggests the relative unimportance of a negatively charged carboxylate group removed from the eventual coordination site. On the other hand, although dap and dab would be expected to act as neutral species because of the near proximity of the positive and negative charges, it may have been thought that orn and lys would have been nearer glycine in reactivity. The fact that this is not so suggests the NH_3^+ grouping is twisted around and approaches closely the negative center in orn and lys, a behavior already suggested on the basis of ORD curves of these amino acids in different pH.[31]

In one particularly favorable case (pydic), we have measured the formation rate constant at different temperatures for the *bis* species. This value is slightly less than that for the formation of the *mono* species at 25°. In this instance, therefore, the negatively charged carboxylated groups do not tend to loosen the hydration shell and increase k_{H_2O}, as has been observed in particular cases[3-5] but is not apparently a general phenomenon.[8] The formation of the bis species is attended by an appreciably lower ΔH^* value, however, offset by a less positive ΔS^*.

We are continuing our studies, examining other types of amino acids which contain, for example, the imidazole residue. Preliminary results indicate an interesting complexity in behavior.

Acknowledgment. We are grateful for a National Science Foundation Grant (GP 1963 and 5671) and a Du Pont Teaching Fellowship which supported this work.

(29) R. W. Green and H. K. Tong, *J. Am. Chem. Soc.*, 78, 4896 (1956); H. P. Stephenson and H. Sponer, *ibid.*, 79, 2050 (1957).

(30) G. H. Nancollas, "Interactions in Electrolyte Solutions," Elsevier Publishing, Co., Amsterdam, 1966, p 17.

(31) L. I. Katzin and E. Gulyas, *J. Am. Chem. Soc.*, 86, 1655 (1964).