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Nuclear Magnetic Resonance Studies of Configuration and Ligand Conformation in Paramagnetic Octahedral Complexes of Nickel(II). III. Amino Acid and Mixed Ethylenediaminediacetic Acid–Amino Acid Complexes

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Proton nmr spectroscopy has been used to investigate the following phenomena in octahedral paramagnetic nickel(II) chelates: (a) the glycinate ring conformation in simple methyl-substituted glycine complexes, (b) variation in coordination sites in the potentially tridentate ligands aspartic (asp), glutamic (glu), and α,β-diaminopropionic (dap) acids, and (c) stereochemical properties, including stereoselective coordination, of Ni(EDDA)$(H_2O)_2$ and several mixed Ni(EDDA)(Z) complexes, where Z is one of the above amino acids or ethylenediamines. The large contact shift variation observed for CH_2 (or C–H) protons of glycinate rings indicates substantial deformation from planarity with extreme equatorial protons 100–150 ppm downfield from extreme axial protons. The following values for the thermodynamic properties of the $k \rightarrow k'$ equilibrium in Ni$(H_2O)_4$(sar)$^+$ (sar = sarcosine) were determined from the temperature dependence of the contact shifts of CH_2 protons: $\Delta H = 0.4 \pm 0.1$ kcal mol^{-1}, $\Delta G°$(at 34°) $= 0.5 \pm 0.1$ kcal mol^{-1}, $\Delta S = -0.35 \pm 0.01$ eu. Tridentate coordination is indicated in 1:1 complexes of asp and dap, but bidentate coordination prevails in Ni(glu)$(H_2O)_4$, and all three ligands are bidentate in Ni(EDDA)(Z). Coordination stereospecificity in Ni(EDDA)(Z) is not great for these ligands. This is discussed in terms of interactions within Z and interactions between Z and the asymmetric background of *trans*-Ni(EDDA).

Introduction

Pratt and Milner's 1962 paper demonstrated the feasibility and suggested several interesting applications of proton nmr studies of paramagnetic nickel(II) complexes.[2] Although subsequent work has been extensive, much of it has concerned tetrahedral complexes and the tetrahedral $\rightleftarrows$ square-planar equilibrium.[3] Thus, the full potential of such investigations for structural, stereochemical (both configuration and ligand conformation), equilibrium, and kinetic analysis of octahedral complexes has not been realized. We have recently used this technique to evaluate conformational equilibria in complexes of substituted ethylenediamines.[4] In this and two other papers, we present the results of similar detailed studies of several other octahedral nickel(II) complexes. This paper is concerned with 1:1 complexes of amino acids and with mixed 1:1:1 amino acid–EDDA–Ni(II) complexes. Separate papers treat complexes of IDA, MIDA, and NTA[5] and of the three closely related hexadentate aminocarboxylate ligands EDTA, PDTA, and CyDTA.[6]

In this paper, the data for 1:1 complexes of methyl-substituted glycines are introduced as evidence for significant distortion from planarity of the five-membered ring of chelated glycinates. In their classic paper on the conformational analysis of metal chelates, Corey and Bailar[7] concluded that the glycinate ring is approximately planar and that the distinction between substituents (like the methyl of alanine) in the axial–equatorial sense is inappropriate. Extensive X-ray data for amino acid chelates generally support this picture, but there is always the question of the appropriateness of solid-state structure determinations for the description of corresponding species in solution.[8] The dihedral angle dependence of contact shifts in glycinate fragments, established on the basis of the spectra of 1:1 complexes of methyl-substituted glycines, is then employed to establish coordination sites in complexes of the three potentially tridentate amino acids aspartic (asp), glutamic (glu), and α,β-diaminopropionic (dap) acids. Finally, the stereochemical properties of mixed EDDA–amino acid complexes of the same amino acids are analyzed on the basis of their spectra. The spectra of such complexes permit convenient and rapid determination of equilibrium isomer distributions which are closely related to conformational preferences of interacting ligands.[8,9] Relatively rapid equilibration in these systems overcomes the principal objection to some earlier studies of these phenomena in stable diamagnetic Co(III) complexes, namely, that conclusions regarding stereospecific coordination have often been drawn from the isomer distribution of isolated products, which may not reflect the thermodynamic equilibrium composition of the system.[10]

Experimental Section

Reagents.—Reagent grade amino acids (Nutritional Biochemical Corp.), H_2EDDA (K & K Laboratories, Inc.), and anhydrous nickel chloride (Alfa Inorganics, Inc.) were used without further purification. Deuterium oxide (99.7% D) was purchased from Columbia Organic Chemicals.

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(2) R. S. Milner and L. Pratt, *Discussions Faraday Soc.*, **34**, 88 (1962).

(3) (a) D. R. Eaton and W. D. Phillips, *Advan. Magn. Resonance*, **1**, 103 (1965); (b) L. Sacconi, *Transition Metal Chem.*, **4**, 199 (1968).

(4) Parts I and II: F. F.-L. Ho and C. N. Reilley, *Anal. Chem.*, **41**, 1835 (1969); **42**, 600 (1970).

(5) Part IV: L. E. Erickson, F. F.-L. Ho, and C. N. Reilley, *Inorg. Chem.*, **9**, 1148 (1970).

(6) Part V: L. E. Erickson, D. C. Young, F. F.-L. Ho, J. B. Terrill, S. R. Watkins, and C. N. Reilley, in preparation.

(7) E. J. Corey and J. C. Bailar, Jr., *J. Am. Chem. Soc.*, **81**, 2620 (1959).

(8) A. M. Sargeson, *Transition Metal Chem.*, **3**, 303 (1966).

(9) R. D. Gillard and H. M. Irving, *Chem. Rev.*, **65**, 603 (1965).

(10) D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *J. Am. Chem. Soc.*, **89**, 5133 (1967).

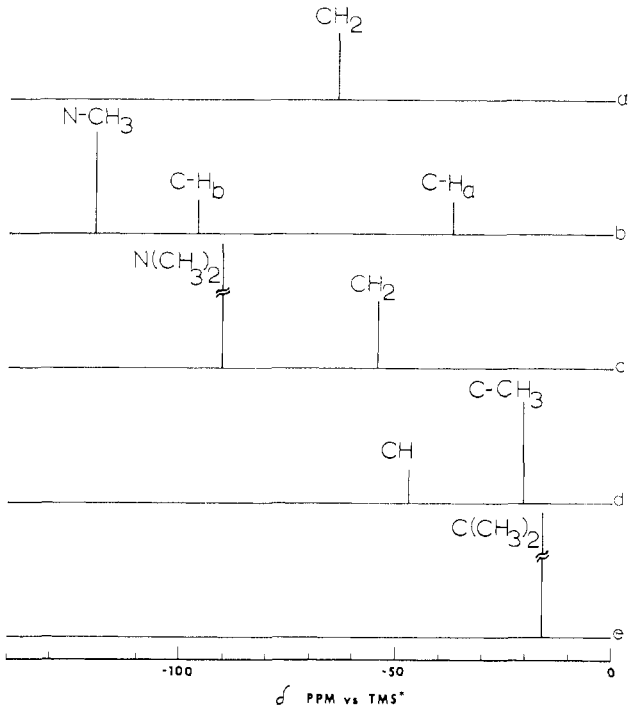


Figure 1.—Schematic nmr spectra of 1:1 nickel(II) complexes of the simple amino acids glycine (a), sarcosine (b), N,N-dimethylglycine (c), L-alanine (d), and C,C-dimethylglycine (e).

Preparation of Samples.—Stock solutions of amino acids (0.10 or 0.50 *M*) and $NiCl_2$ (0.50 *M*) were used to prepare small quantities of nmr samples. In a typical sample preparation, 2.0 ml of $NiCl_2$ solution was added to a 100-ml round-bottom flask. The calculated volume of 0.50 *M* amino acid and additional acid or base (as 0.100 *N* HCl or NaOH) if necesary were then added, and the solution was rotary evaporated to dryness at 50°. To reduce the size of the HDO peak further, the dried solid was usually treated with 1–2 ml of D_2O and evaporated to dryness again before dissolving in 2.0 ml of D_2O. The final concentration of each solution was, thus, ~0.5 *M* (actually 0.5 mol/l. of D_2O), but the ligand:metal ratio was accurately known.

Mixed EDDA–amino acid complexes were prepared in a similar way. However, a solution of Ni(EDDA) was prepared before the amino acid was added. The deep blue Ni(EDDA) solution was prepared by adding 1 mmol of H_2EDDA followed by 2 mmol of NaOH to 1 mmol of $NiCl_2$ in H_2O.

The pH of each D_2O solution was subsequently measured on a Corning research pH meter equipped with a Fisher combination electrode. Sodium 3-(trimethylsilyl)-1-propanesulfonate, abbreviated as TMS*, was added as solid to provide an internal reference for chemical shift measurement.

Nmr Measurements.—The proton spectra were obtained with a Varian HA-100 spectrometer at 100 MHz. The spectrometer was equipped with a V-4333 variable-temperature probe and a V-6040 temperature controller. The recording procedure and temperature measurements have been described earlier.[4]

Results

Schematic nmr spectra of D_2O solutions of nickel complexes of simple α-amino acids with a 1:1 ratio of metal to ligand anion are shown in Figure 1. The simple amino acids are (a) glycine (gly) and the methyl-substituted glycines, (b) sarcosine (sar), (c) N,N-dimethylglycine (dmg), (d) L-alanine (ala), and (e) α-aminoisobutyric acid (or C,C-dimethylglycine, abu). The assignment of peaks, which follows from a comparison of the five spectra and the relative areas of peaks within each spectrum, agrees with previous assignments given for Ni(II) and corresponding similar Co(II) complexes.[2,11] In general, the extent of downfield (more negative) shift decreases with number of bonds between Ni and the observed proton (*i.e.*, N–CH_3 < CH_2 (average) < C–CH_3) while N-methyl substitution increases the average shift of CH_2 protons slightly. The variation in methylene (or C–H) protons shifts requires consideration of the glycinato ligand ring conformation.

The nickel(II) complex of glycine gives a single sharp signal at −64 ppm for the CH_2 protons. Milner and Pratt observed that the single resonance for the methylene protons in the glycine complex could mean either a planar glycinato ring or a distorted ring with rapid conformational interchange of the two forms designated k and k′ (Figure 2) analogous to the corresponding en complexes. The data for methyl-substituted glycines and our previous studies of substituted ethylenediamines[4] suggest the latter explanation. The methylene protons in a given glycinato conformation are in different environments. For example, proton H_b in the k conformer is in a pseudo-equatorial position nearly *trans* to the Ni. On the basis of our studies of en complexes,[4] the pseudo-equatorial protons would be expected to appear at a lower field. However, because of the fast conformational transition (k ⇄ k′), H_b is exchanging between pseudo-equatorial and pseudo-axial environments. Consequently, no "pure" pseudo-equatorial (or "pure" pseudo-axial) proton is observed. Equally important to the appearance of the observed nmr spectrum is the relative population of the conformers. Complete averaging of H_a and H_b to produce a single resonance could occur only if k and k′ were equally populated. This is the case for complexes of glycine and the symmetrically substituted glycines, N,N-dimethylglycine (Figure 1c) and C,C-dimethylglycine (Figure 1e). In the last two instances, both methyl substituents are also completely averaged to give a single resonance.

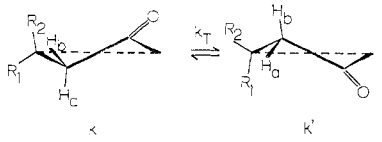


Figure 2.—Conformational representation of chelated glycinates as viewed in the Ni–Ni–O plane.

If the glycine is not symmetrically substituted, as in the case of sarcosine (N-methylglycine), k and k′ could be unequally populated. For sarcosine ($-R_1$ is $-CH_3$), k should be favored since $-CH_3$ is in a pseudo-equatorial position which would lead to less steric interaction with the axial coordinating group of the metal ion as well as with the groups within the glycinato ring (*i.e.*, the neighboring $-CH_2-$). As a result, the observed spectrum of the complex is dominated by the contribution of conformer k. Therefore, of the

(11) C. C. McDonald and W. D. Phillips, *J. Am. Chem. Soc.*, **85**, 3736 (1963).

two CH_2 resonance lines observed (Figure 1b), the one at lower field (−96 ppm) is assigned to H_b. The H_a proton would possess more axial character and appear upfield (−37 ppm) of H_b. However, the center of the $-CH_2-$ doublet remains close to that of the single resonance observed for glycine and somewhat downfield from that of the dmg complex.

For the same reason, the glycinato ring of alanine (C-methylglycine) probably has some preference for the conformation in which $-CH_3$ is pseudo-equatorial. The methyne proton is expected to be found more frequently in an axial position, and the corresponding signal, therefore, appears somewhat upfield from the average methylene proton of the symmetrically substituted glycines. However, it is not as far upfield as the more axial proton in $Ni(sar)(H_2O)_4^+$, so the conformational preference is apparently not as great.

The approach used to obtain the thermodynamic parameters for the $k \rightleftarrows k'$ equilibrium in $Ni(sar)(H_2O)_4^+$ is identical with that used for the analysis of conformational equilibria in en complexes.[4] The contact shift separation of two methylene protons in the sarcosine complex is related to the free energy difference ΔG° between the two extreme conformations, k and k′, by

$$\frac{T(\delta_{bb'} - \delta_{aa'})}{K_b - K_a} = \frac{2}{1 + e^{-\Delta G^\circ/RT}} - 1 \qquad (1)$$

where $\delta_{bb'}$ and $\delta_{aa'}$ are the observed contact shifts for the b proton (more downfield) and the a proton (more upfield), respectively, at a given temperature; K_i (i = b, a) is the composite constant quantity derived from the expression of McConnell and Chesnut[12,13]

$$\delta_i T = -A_i \left\{\frac{\gamma_e}{\gamma_H}\right\} \frac{g\beta S(S+1)}{6Sk} \equiv K_i \qquad (2)$$

with all symbols carrying their usual significance.[12] It can be seen from eq 1 that if $\Delta G^\circ \approx 0$, then $\delta_{bb'} \approx \delta_{aa'}$, which is the case of a single resonance line (CH_2) for a glycinato ring with equal conformational population.

Since the conformational equilibrium depends on temperature, a measurement of the contact shifts $\delta_{bb'}$ and $\delta_{aa'}$, as a function of temperature, could lead to determ nation of the thermodynamic properties of the system. Such data for the sarcosine and glycine complexes are summarized in Table I. It is seen from Table I that all resonances shift upfield smoothly with increasing temperature, but the downfield methylene proton of the sarcosine ligand shifts the fastest. The phenomenon of linear upfield shift of the contact interaction with temperature (degrees Kelvin) is anticipated from the Curie behavior as described by eq 2. However, if this were the only effect, the product of contact shift and temperature (δT) should be independent of temperature. Such a plot is shown in Figure 3.

(12) H. M. McConnell and D. B. Chesnut, *J. Chem. Phys.*, **28**, 107 (1958).

(13) R. H. Holm, A. Chakravorty, and G. O. Dudek, *J. Am. Chem. Soc.*, **86**, 379 (1964).

TABLE I

TEMPERATURE DEPENDENCE OF CONTACT SHIFTS[a] OF 1:1 NICKEL(II) COMPLEXES OF GLYCINE AND SARCOSINE

Temp, °K	Glycine	Sarcosine		
		$-CH_2-$		
	CH_2	H_a	H_b	CH_3
303	−60.7			
307	...	−33.8	−93.4	−118.0
315	−58.4	−33.6	−90.8	−114.8
325	−56.7	−33.3	−87.0	−111.0
335	−55.0	−32.5	−83.5	−108.3
346	−53.3	−32.0	−80.5	−105.3
358	...	−31.6	−77.5	−101.9
367	−50.5			

[a] In ppm downfield from the diamagnetic free ligand, chemical shifts of $-CH_2-$ and $-CH_3$ in free ligand being −3.60 and −2.70 ppm from TMS*, respectively.

Points on lines 1 and 4 are, respectively, the measured data from the downfield and upfield signals of the methylene protons of sarcosine. Line 2 represents the shift of the average of these two resonances with temperature. Points on line 3 are from the single resonance of the glycine complex. Only lines 2 and 3 give the expected horizontal line. The downfield methylene proton (points on line 1) shows a far faster upfield shift and gives a positive deviation from that described in eq 2, while the upfield methylene proton gives a negative deviation. These deviations can be understood

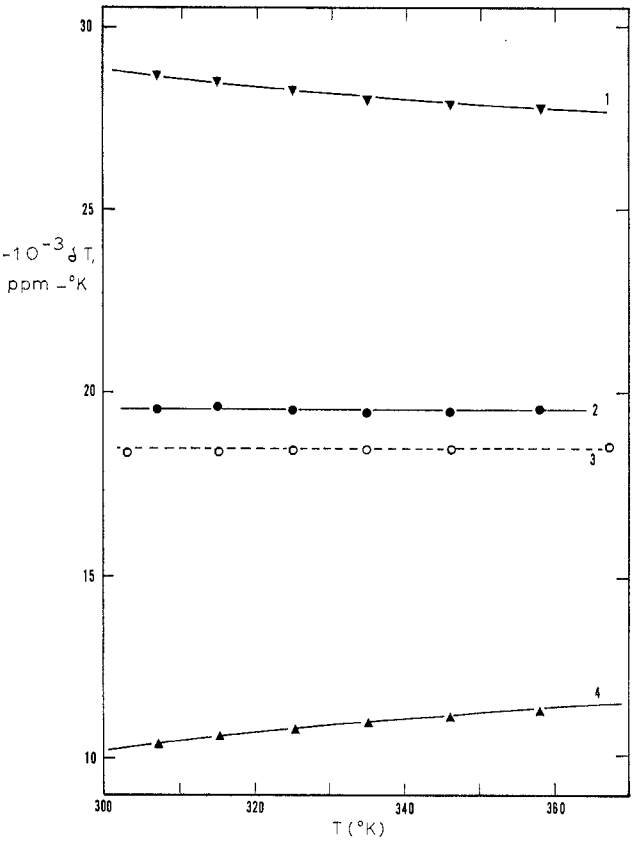


Figure 3.—Temperature dependence of (δT) for 1:1 complexes of sarcosine and glycine. Lines 1 and 4 correspond to the downfield and upfield CH_2 peaks of the sarcosine complex, respectively, line 2 corresponds to the center of the sarcosine CH_2 doublet, and line 3 corresponds to the single CH_2 peak of the glycine complex.

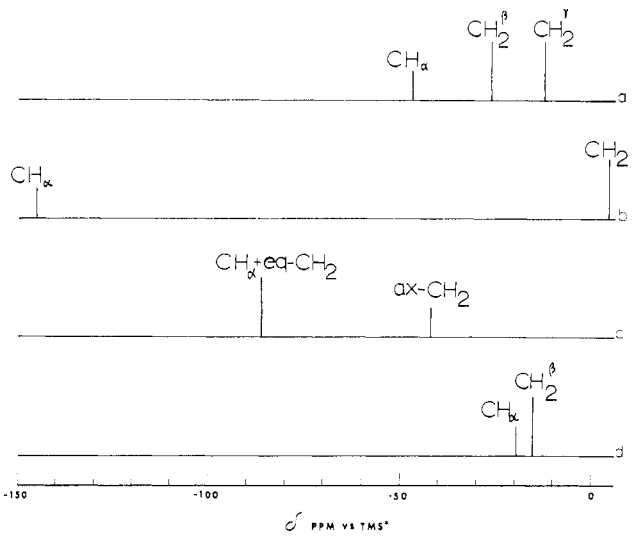


Figure 4.—Schematic nmr spectra of 1:1 complexes of the trifunctional amino acids: (a) L-glutamic, (b) L-aspartic, (c) α,β-diaminopropionic (anion), (d) α,β-diaminopropionic (zwitterion).

readily from a shift of conformational equilibrium with temperature. The less favored conformer (say k′, with R_1 being CH_3 and R_2 being H in Figure 2) could be increasingly populated with a rise in temperature and the proton H_b would, accordingly, have more axial character. This would yield the additional upfield shift for the H_b resonance in excess of that predicted from Curie behavior. The result is the positive deviation. For the same reason, the upfield H_a signal should give a slower upfield shift (negative deviation). Thus, to describe the temperature dependence of the data, the conformational equilibrium parameter is necessary, as described by eq 1.

This can be derived from the simple fundamental relations

$$\delta_{bb'} = f_b\delta_b + f_{b'}\delta_{b'}$$

$$f_b = \frac{1}{1 + e^{-\Delta G^\circ/RT}}$$

where $\delta_{bb'}$ is the observed contact shift of proton b, averaging from environment b (in conformer k) with mole fraction f_b and b′ (in conformer k′) with mole fraction $f_{b'}$. After substituting $f_b + f_{b'} = 1.0$ and $K_i = \delta_i T$ (i = b or b′), one has

$$\delta_{bb'}T = K_a + (K_b - K_a)\frac{1}{1 + e^{-\Delta G^\circ/RT}} \quad (3)$$

Similarly, one can have eq 4 for the upfield proton H_a.

$$\delta_{aa'}T = K_b - (K_b - K_a)\frac{1}{1 + e^{-\Delta G^\circ/RT}} \quad (4)$$

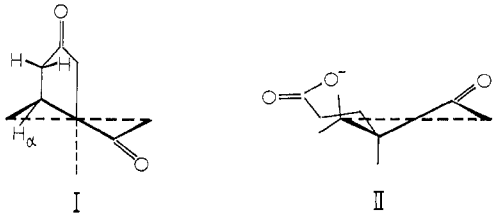
The difference of eq 3 and 4 is just that given in eq 1.

The measurement of δ_b and δ_a of a "frozen" conformation is not possible due to the rapid interconversion of the two extreme forms even at the lowest temperatures available. However, δ_i and K_i at room temperature have been assessed in the following way. First, a set of δ_a values in steps upfield from $\delta_{aa'}$ (−33.8 ppm at room temperature) was selected. For each value of δ_a, ΔG° at each temperature was calculated using eq 1 and data in Table I. Then a least-squares procedure was employed to fit ΔG° *vs.* T data, using the relationship $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$, assuming that ΔH° and ΔS° are independent of temperature. It was found that the standard deviation of ΔG° *vs.* T decreased as δ_a was adjusted upfield away from $\delta_{aa'}$ and reached a minimum at $\delta_a = +10 \pm 5$ ppm (and, accordingly, $\delta_b = -137 \pm 5$ ppm). With this set of δ_i at the ambient probe temperature of 34°, the conformational free energy change (in cal/mol) can be expressed: $\Delta G^\circ = 400 - 0.35T$. This relation of ΔG° to temperature and eq 3 and 4 were used to draw lines 1 and 4 in Figure 3. The close fit with experimental data is evident.

Complexes with glu, asp, and dap.—Although these amino acids all are potentially tridentate ligands, the 1:1 nickel(II) complexes of glu and asp give very different nmr spectra, and the 1:1 complex of dap is very sensitive to protonation (Figure 4). Thus, these complexes are particularly clear examples of the effects of changes in coordination site on spectral parameters.

For asp and glu complexes, the relative intensities of peaks is sufficient to permit the spectral assignments indicated in Figure 4. The most striking difference between the two is the large difference in α-proton shift with that proton occurring at −145 ppm in the asp complex and −45 ppm in the glu complex. In addition, the CH_2 signal of asp is shifted upfield slightly (to +5 ppm *vs.* −2.5 ppm for the free ligand) while the two CH_2 peaks of glu are shifted downfield to −27 and −13 ppm (*vs.* −2.2 and −1.9 ppm for the free ligand). These data are consistent w.th tridentate coordination for asp and bidentate (amino-α-carboxyl) coordination for glu.

Both α-proton and methylene proton shifts support the structures shown in I and II for the L-asp and L-glu



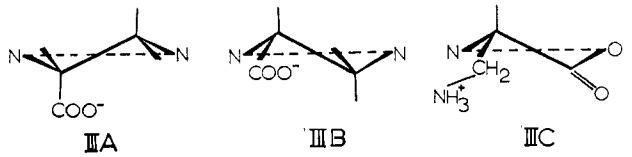
I II

complexes, respectively. The extreme downfield shift for C–H for asp requires an extreme equatorial position for H_α in the five-membered glycinate-type ring. By contrast, the relatively small shift of H_α of glutamate rules out a similar structure for the glu complex. The shift (−45 ppm), in fact, corresponds closely to that of H_α in the 1:1 alanine complex and suggests that the bulky $-CH_2-CH_2-CO_2^-$ group has some preference to occupy an equatorial position in the five-membered glycinate ring. Structure II for the glu complex would also yield the observed attenuation of CH_2 proton contact shift with a number of intervening bonds,[2,14] while structure I is required to explain the

(14) R. J. Fitzgerald and R. S. Drago, *J. Am. Chem. Soc.*, **90**, 2523 (1968).

observed upfield shift of the CH_2 proton signal of asp. The extent and direction of the latter shift is typical of protons adjacent to a Ni-coordinated carboxyl somewhat isolated from delocalization *via* other mechanisms, as noted by Milner and Pratt for the malonate complex of nickel.[2]

For dap complexes, the spectra indicate a change in coordination sites with pH. The spectrum of the 1:1 complex of dap at high pH consists of two peaks at −86 and −42 ppm with relative intensities 2 and 1, respectively. This suggests coordination of both nitrogens and an axial orientation of the carboxyl group preferred (IIIA). This requires that the α proton and one of the CH_2 protons be predominantly equatorial (−86 ppm) while the other CH_2 proton is predominantly axial (−42 ppm). This is the model used by Margerum and Rosen in their kinetic studies of $Ni(dap)^+$.[15] The difference in shifts is, however, not sufficient to rule out some contribution from conformation IIIB. With the addition of 1 mol of HCl, the spectrum consists of two peaks at −19 and −15 ppm with relative intensities 1 and 2, respectively. This is consistent with protonation of the β-NH_2 group and a fairly strong preference for H_α to be axial in the remaining glycinate



ring, as shown in IIIC.

Mixed 1:1:1 EDDA–Amino Acid–Ni Complexes.—The nmr spectrum of the nickel(II) complex of EDDA in aqueous solution, $Ni(EDDA)(H_2O)_2$, is shown in Figure 5a. Four well-resolved peaks are seen in Figure 5a, with each representing two protons. The downfield peaks are assigned to those protons in equatorial (eq) positions in the acetate (ac) and ethylenediamine (en), while those upfield belong to the axial (ax) protons. Furthermore, the extreme upfield peak and the extreme downfield peak are deuterated in 0.02 *M* NaOD at 90°.[16] Therefore, this pair is assigned to the acetate protons and the inner pair to protons of the ethylenediamine ring. The ligand EDDA is tetradentate and could form several geometric isomers with the octahedral nickel ion since the coordinating oxygens of acetate rings would be either in plane or out of plane with respect to the N–Ni–N plane. The simplicity of the spectrum suggests that the complex $Ni(EDDA)(H_2O)_2$ exists mainly in one isomeric form, probably the *trans* form. This agrees with the finding that $Co^{III}(EDDA)$ exists exclusively in the *trans* configuration[17] and ensures that subsequent addition of a bidentate ligand will yield species in which the second ligand occupies sites in plane with the EDDA nitrogen. Spectral assignments for this complex and

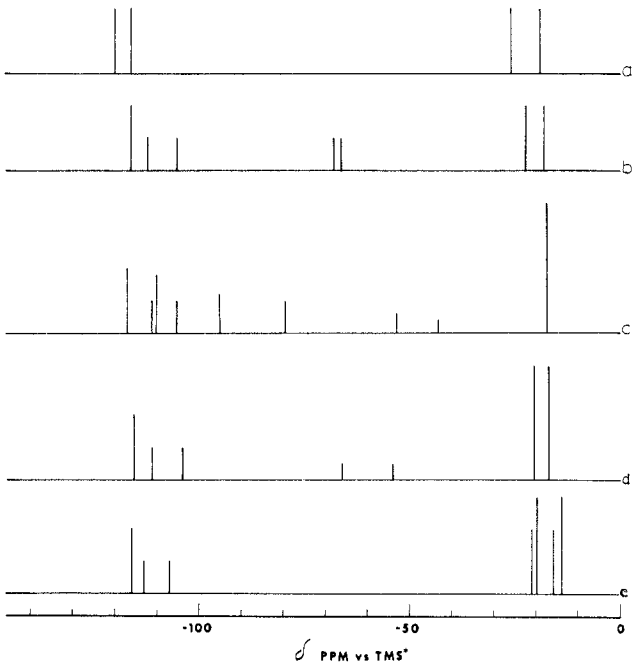


Figure 5.—Schematic nmr spectra of mixed nickel–EDDA–amino acid complexes: (a) $Ni(EDDA)(H_2O)_2$, (b) Ni(EDDA)-(gly)⁻, (c) Ni(EDDA)(sar)⁻, (d) Ni(EDDA)(ala)⁻, (e) Ni-(EDDA)(abu)⁻.

for the mixed complexes shown in Figure 5 are summarized in Table II.

For each of the mixed Ni(Z)(EDDA) complexes, spectra correspond roughly to a superposition of spectra of complexes of Z and EDDA separately—with one important difference: when the α-amino acid (Z) is coordinated in the mixed complex, the amino acid sees the asymmetric background produced by EDDA around the metal ion. This results in nonequivalence for amino acid protons that are equivalent in corresponding 1:1 complexes and the occurrence of diastereoisomers in mixed complexes of asymmetric amino acids. Small changes are also evident in the EDDA portion of the spectrum when Z replaces $2H_2O$. Most notable is a small separation of the two equatorial en peaks which are equivalent in $Ni(EDDA)(H_2O)_2$. Full appreciation of these effects requires a brief consideration of absolute configurations of octahedral complexes.

Although the absolute configurations of compounds of general formula Ni(Z)(EDDA) have not been reported, absolute configurations of *trans*-Co(Z)(EDDA) isomers have recently been reported[17] for the same Z. Since from X-ray data $Ni(en)_3^{2+}$[18] possesses the same absolute configuration as $Co(en)_3^{3+}$,[19] *trans*-Ni(Z)(EDDA) probably can be directly related to the known *trans*-Co(Z)(EDDA) system. Analogous to the cobalt(III) case,[20] *trans*-Ni(Z)(EDDA)⁻ in $\Delta(C_2)$ configuration can be depicted as in Figure 6 (where the lower acetate ring is omitted for picture clarity). In Figure 6, the conformations of en, ac, and

(15) D. W. Margerum and H. M. Rosen, *J. Am. Chem. Soc.*, **89**, 1088 (1967).
(16) J. B. Terrill and C. N. Reilley, *Inorg. Chem.*, **5**, 1988 (1966).
(17) J. I. Legg and D. W. Cooke, *ibid.*, **4**, 1576 (1965).
(18) L. N. Swink and M. Atoji, *Acta Cryst.*, **13**, 639 (1960).
(19) K. Nakatsu, M. Shiro, Y. Saito, and H. Kuroya, *Bull. Chem. Soc. Japan*, **30**, 158 (1957).
(20) J. I. Legg, D. W. Cooke, and B. E. Douglas, *Inorg. Chem.*, **6**, 700 (1967).

TABLE II

CONTACT SHIFTS AND SPECTRAL ASSIGNMENTS OF MIXED EDDA–AMINO ACID COMPLEXES OF NICKEL

Complex	Contact shift[a]	Integrated area	Assignment[b]
Ni(EDDA)(H_2O)$_2$	−19	2	ac
	−26	2	en
	−116	2	en
	−120	2	ac
Ni(EDDA)(gly)	−18	2	ac
	−23	2	en
	−66	1	CH_2 (gly)
	−68	1	CH_2 (gly)
	−105, −112	2	en
	−116	2	ac
Ni(EDDA)(sar)	−18	4	ac, en
	−43	0.4	CH_2 (sar)
	−53	0.6	CH_2 (sar)
	−80	1	CH_2 (sar)
	−95	1.2	CH_3 (sar)
	−110	1.8	CH_3 (sar)
	−105, −111	2	en
	−117	2	ac
Ni(EDDA)(dmg)	−15	4	ac, en
	~−76	8 (vb)	CH_2, CH_3
	−116	4	ac, en
Ni(EDDA)(ala)	−17	3.5	ac, $^1/_2$ (CH_3)
	−21	3.5	en, $^1/_2$ (CH_3)
	−54	0.5	CH (ala)
	−66	0.5	CH (ala)
	−104, −111	2	en
	−116	2	ac
Ni(EDDA)(abu)	−14	3	CH_3
	−16	2	ac
	−20	3	CH_3
	−21	2	en
	−107, −113	2	en
	−116	2	ac

[a] In ppm downfield from the internal reference TMS*. [b] ac and en designate protons of the acetate and ethylenediamine rings of the EDDA ligand, respectively.

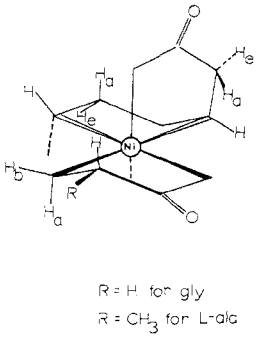


Figure 6.—Structure of mixed *trans*-Ni(EDDA)(amino acid) complexes indicating ring conformations and the axial–equatorial nature of C–H protons. The lower acetate ring has been omitted for clarity.

glycinato rings are k, k′, and k′, respectively. The axial and equatorial nature of ac and en protons of EDDA is noted explicitly. Although the conformations of the ac and en rings of EDDA are fixed by the *trans* coordination, the glycinate ring of Z can, of course, also exist in the k conformation. The effects of substitution on this k $\rightleftarrows$ k′ equilibrium should be evident in the contribution of Z to the spectrum of the mixed-ligand complex. In particular, under equilibrium conditions, when Z is optically pure (say, L), the equilibrium ratio of Δ,L to Λ,L should be sensitive to the conformational preference (k *vs.* k′) of Z.

As noted earlier, for the symmetric ligands glycine and C,C-dimethylglycine (abu), the effect of the asymmetric EDDA background is simply to produce a nonequivalence of otherwise equivalent protons. Thus, gly gives rise to a barely resolved equal-intensity doublet at −66 and −68 ppm for the two CH_2 protons (*vs.* −64 ppm for the 1:1 complex), and abu has two equal-intensity peaks at −14 and −20 ppm, which can be assigned to the two kinds of C–CH_3 protons (*vs.* −17 ppm for the 1:1 complex). For the third symmetric substituted glycine, dmg, very broad peaks were observed at about −20, −80, and −115 ppm, with extensive overlap of the latter pair. This possibly results from interchange of dmg ions between Ni atoms at a rate sufficient to produce severe line broadening.[21]

When optically active L-alanine is coordinated in the mixed complex, the two diastereoisomers designated Δ,L (shown in Figure 6 with R equal to CH_3) and Λ,L could be formed. The presence of two isomers is revealed clearly by the alanine portion of the spectrum (Figure 5d), which consists of two small peaks at −54 and −66 ppm for the single methyne proton and two large peaks at −17 and −21 ppm for the CH_3 protons. The latter overlap peaks of axial en and ac protons of EDDA. Relative intensities of both methyne and methyl peaks for the two isomers are nearly equal, indicating equal concentrations of the two diastereoisomers and no stereospecific coordination for L-alanine in this system.

Although alanine does not appear to coordinate stereospecifically, some degree of stereospecific coordination is observed for sarcosine. The spectrum of Ni(EDDA)(sar)$^-$ (Figure 5c) can be accounted for in terms of two isomers in about a 3:2 ratio. Like the other mixed complexes, the sarcosine contribution to the total spectrum appears in the same region as in the corresponding 1:1 complex. The two peaks at −43 and −53 ppm are, therefore, assigned to "axial" CH_2 protons of coordinated sarcosine; the larger peak at −80 ppm apparently represents the overlap of corresponding "equatorial" protons. A similar ratio holds for the two methyl peaks, but the overlap with EDDA peaks in the −100 to −120 ppm region is too extensive to permit quantitative estimates from this portion of the spectrum.

Mixed 1:1:1 EDDA Complexes with glu, asp, and dap.—Spectra of these complexes are shown in Figure 7, and complete spectral assignments are summarized in Table III. The contribution from EDDA in the spectrum of these mixed complexes again closely resembles its contribution in the simpler mixed complexes of *trans*-Ni(Z)(EDDA). It is, therefore, believed also to act as a tetradentate ligand in mixed complexes with these amino acids, which all have three donor sites.

The Z portions of the spectra of these complexes are particularly interesting. Since glutamate normally

(21) This is also observed in Ni(NTA)$_2^{4-}$. See ref 5.

TABLE III
CONTACT SHIFTS AND SPECTRAL ASSIGNMENTS OF MIXED EDDA–AMINO ACID AND –DIAMINE COMPLEXES OF NICKEL

Complex	Contact shift[a]	Integrated area	Assignments[b]
Ni(EDDA)(glu)	−12	2	$CH_2(\gamma)$
	−19	4	$CH_2(\beta)$ + ac
	−26	2	en
	−46	1	$CH(\alpha)$
	−104, −111	2	en
	−116	2	ac
Ni(EDDA)(asp)	−20	2	ac
	−26	2	en
	−31	2	$CH_2(\beta)$
	−38	1	$CH(\alpha)$
	−105, −110	2	en
	−116	2	ac
Ni(EDDA)(dap)	−17	6	ac + en + dap (ax)
	−111	2	en
	−126	2	ac
	−154	1	dap (eq)
Ni(EDDA)(en)	−17	4	ac + en
	−95	4	ethylene
	−111	2	en
	−126	2	ac
Ni(EDDA)(pn)	−18	7	ac + en + CH_3
	−30	2	pn (ax)
	−111	2	en
	−126	2	ac
	−150	1	pn (eq)

[a] In ppm downfield from the internal reference TMS*. [b] ac and en designate protons of the acetate and ethylenediamine rings of the EDDA ligand, respectively.

functions as a bidentate ligand, its spectrum in the mixed complex (Figure 7a) is not expected to be significantly different from that of its 1:1 complex (Figure 5a). In fact, the agreement is very good. However, with aspartate and α,β-diaminopropionate, drastic spectral differences are observed between 1:1 complexes (Figure 4) and mixed 1:1:1 complexes (Figure 7). These changes can be readily accounted for in terms of a shift of these ligands from tridentate to bidentate coordination. Thus, the shift of the methyne proton of aspartate increases from −145 ppm in its tridentate state (II) to −38 ppm in the mixed complex, a shift consistent with bidentate chelation *via* amino and α-carboxyl groups with its $CH_2CO_2^-$ fragment having some preference for the equatorial position in the mixed complex. The small upfield shift of CH_2 protons observed in Ni(L-asp)$(H_2O)_3$ also changes to a downfield shift in the mixed complex (+5 → −30 ppm), reflecting the breaking of the O–Ni bond.

Similarly, dap in the mixed complex apparently coordinates through two nitrogens with a strong preference for the conformation in which the CO_2^- is equatorial (IIIB). The single equatorial ring proton can be identified with the peak at −154 ppm while the two axial dap proton signals overlap peaks from axial protons of en and ac groups of EDDA to produce a broad unresolved peak centered at −16 ppm. The spectral assignment given for *trans*-Ni(EDDA)(dap)$^-$ is further supported by spectra of Ni(EDDA)(en) and Ni(EDDA)-(pn) (Figure 7d and e). For all three complexes, the low-field EDDA pattern consists of two peaks at about −110 and −125 ppm, while the upfield EDDA peaks

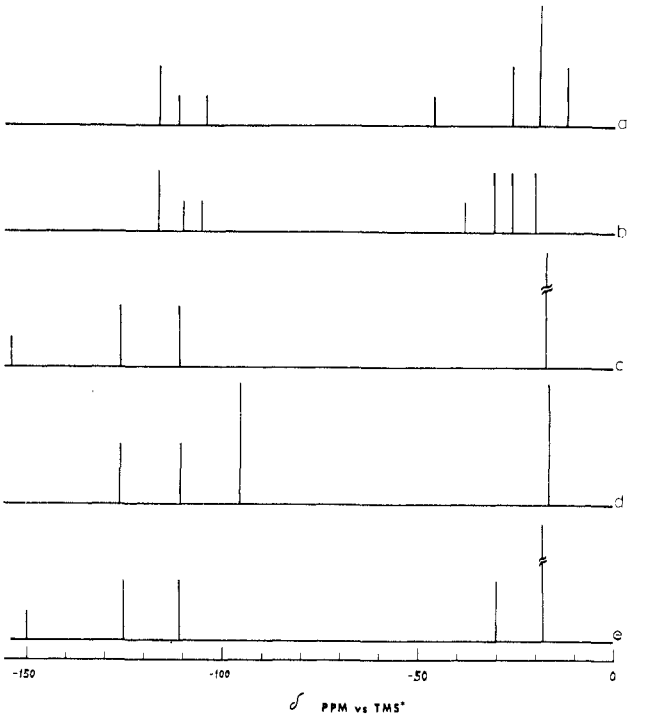
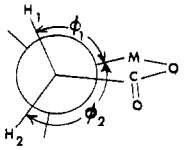


Figure 7.—Schematic nmr spectra of mixed nickel–EDDA–amino acid and –diamine complexes: (a) Ni(EDDA)(L-glu)$^{2-}$, (b) Ni(EDDA)(L-asp)$^{2-}$, (c) Ni(EDDA)(dap)$^-$, (d) Ni(EDDA)-(en), (e) Ni(EDDA)(pn).

are unresolved. Deuteration at high pH shows that the acetate proton peak is the one at −110 ppm. This seems to be typical of species with four coplanar nitrogens and differs from that observed for mixed amino acid complexes for which the en CH_2 protons gave two peaks at about −112 and −105 ppm. The en CH_2 protons of Ni(EDDA)(en) give rise to a single peak at −95 ppm, very similar to their shift in Ni(en)$(H_2O)_4^{2+}$, and the pn portion of the spectrum of Ni(EDDA)-(pn) corresponds closely to that of Ni(pn)$(H_2O)_4^{2+}$. Furthermore, the pn portion of the spectrum of Ni-(EDDA)(pn) closely resembles that of Ni(EDDA)-(dap)$^-$. The extreme downfield (equatorial) shift of one pn or dap proton indicates a strong preference for the CH_3 of pn and the CO_2^- of dap in Ni(EDDA)-(dap)$^-$ to assume an equatorial position leaving only one equatorial proton. By contrast, as noted earlier, in the corresponding 1:1 complexes, the carboxyl group apparently has a strong tendency to be axial (IIIA), but the methyl still strongly prefers the equatorial position.

Discussion

Glycinate Ring Conformations and Proton Contact Shifts.—Although our approach has been essentially empirical, the ability of a relatively simple model to account for ligand contact shifts in a large number of complexes provides strong support for our two principal conclusions: (1) that five-membered chelated glycinate rings are considerably distorted from planarity and (2) that the contact shifts of CH_2 (or CH) protons reflect the extent of this distortion as measured by the dihedral angle (ϕ) between Ni and H in an Ni–N–C–H fragment (IV). The difference between



IV

extreme axial and extreme equatorial shifts calculated for $Ni(sar)(H_2O)_4^+$ (147 ppm) has considerable uncertainty and may be subject to unrecognized systematic errors. Perhaps the −100-ppm axial–equatorial difference actually observed for the relatively inflexible acetate fragment of chelated EDDA is a better measure of the extreme axial–equatorial difference in a chelated glycinate ring. Furthermore, N substitution, for example, tends to reduce the average shift of both CH_2 protons so a single value cannot be assigned to all substituted glycines. Nevertheless, the downfield shift of equatorial protons greatly exceeds that of axial protons so that the more downfield peak of two glycinate protons can be reliably assumed to be in a more equatorial environment ($\phi_2 > 120°$).

If the dihedral angle dependence of the contact shift in the glycinate ring parallels that of coordinated en, the distortion from planarity should be comparable for the two kinds of rings since $\delta_e - \delta_a$ is ~150 ppm in both cases.[4] This suggests the desirability of a reexamination of the parameters included in the conformational analysis of chelated glycinate rings. The approach introduced in this paper could be used to determine the thermodynamic parameters for the k ⇄ k′ equilibrium for comparison with calculated values. In summary, the values obtained for $Ni(sar)(H_2O)_4^+$ are $\Delta G° = 0.5 \pm 0.1$ kcal mol^{-1}, $\Delta H° = 0.4 \pm 0.1$ kcal mol^{-1}, and $\Delta S° = -0.35 \pm 0.01$ eu at 34°.

While this paper was in preparation, Pratt and Smith[22] reported a study of nickel(II) complexes of iminodiacetic acid and several related ligands which form five- and six-membered chelate rings. Consistent with our results, they conclude that the contact shift of ligand protons in these σ-bonded complexes depends on the dihedral angle between Ni–N–C and N–C–H planes in a manner similar to that of the vicinal proton–proton spin-coupling constant in H–C–C–H fragments. Apparently, as Golding has suggested,[23] the Fermi contact interaction, which is responsible for proton–proton spin coupling in ethane fragments, is also responsible for the contact shifts observed in these σ-bonded nickel complexes. A detailed theoretical analysis of the problem is certainly called for.

With these empirical demonstrations of the dihedral angle dependence of contact shifts in Ni(II) complexes, nmr spectroscopy provides still another approach to the conformational analysis of chelated ligands. The dihedral angle dependence of vicinal proton–proton spin-coupling constants in H–C–C–H or H–C–N–H fragments[24] and the less well-established dihedral angle dependence of vicinal metal (*e.g.*, platinum-195)–proton spin-coupling constants in M–N–C–H fragments[25] permits conformational analysis of diamagnetic complexes, while the contact shift fills the same role in paramagnetic (at least Ni(II)) complexes.

Stereospecific Coordination and Preferred Ligand Conformation in Ni(EDDA)(Z).—The degree of stereospecific coordination by Z in Ni(EDDA)(Z) or similar complexes (as measured by the Δ:Λ ratio) is generally considered to be closely related to the conformational preference of Z. However, the relationship is not always straightforward. The steric interactions which lead to a preferred conformation for Z could result from interactions between Z and the rest of the complex or from interactions intrinsic to Z itself. Stabilization of one conformation by hydrogen bonding to the solvent should be included in the latter category.[26] For purpose of discussion, it is instructive to consider the following general cases. (1) Z strongly prefers one conformation when coordinated; interaction between Z and the rest of the complex is strong. Δ:Λ should be (a) much different from 1 unless (b) the two effects operate in opposite directions. (2) Z strongly prefers one conformation, but interaction between Z and the rest of the complex is negligible. Δ:Λ should be about 1. (3) Z has little or no intrinsic conformational preference, but interaction between Z and the rest of the complex is substantial. Δ:Λ could be much different from 1. (4) Z has little or no intrinic conformational preference, nor are interactions between Z and the rest of the complex significant. Δ:Λ should be about 1.

Examination of the Z spectrum of symmetric Z's permits some evaluation of intra- *vs.* interligand interactions. The background asymmetry of the rest of the complex could lead to some conformational preference for Z. This in turn could result in contact shift differences in otherwise identical protons. The very small difference in gly proton shifts in Ni(EDDA)(gly) indicates that the interaction between chelated gly and the rest of the complex is similar for k and k′ conformations. This suggests that whether the EDDA N–H proton is eclipsed by H_b of glycine or not (Figure 6) is not significant in determining the glycinate conformation; *i.e.*, the NH_2 protons have little influence on the conformation of Z. Thus, any conformational preference of Z must result from differential steric (or electrostatic) interactions between the ligand R group and the two EDDA acetate groups. Clearly a very bulky R group could more readily approach the upper acetate group (Figure 6) which bends back away from R than the lower acetate group whose chelation plane intersects the line of approach of R as k → k′. This probably accounts for the comparatively large relative difference (−20 and −14 ppm) in methyl proton shifts for C,C-dimethylglycine. Presumably, the more downfield peak corresponds to the methyl group which is equatorial in the preferred conformation (k).

This argument can be extended to the asymmetric

(22) L. P. Pratt and B. B. Smith, *Trans. Faraday Soc.*, **65**, 915 (1969).
(23) R. M. Golding, *Mol. Phys.*, **7**, 561 (1964); see also M. Wicholas and R. S. Drago, *J. Am. Chem. Soc.*, **91**, 5964 (1969).
(24) B. B. Smith and D. T. Sawyer, *Inorg. Chem.*, **7**, 922 (1968).
(25) L. E. Erickson, J. W. McDonald, J. K. Howie, and R. P. Clow, *J. Am. Chem. Soc.*, **90**, 6371 (1968).
(26) K. N. Raymond, P. W. K. Corfield, and J. A. Ibers, *Inorg. Chem.*, **7**, 842 (1968).

ligands ala and sar. The preferred conformation for L-ala should be k′ (CH_3 equatorial) for the Δ configuration and k for the Λ configuration. Thus, the correct spectral assignments must be the following: for Δ,L: H_α, −66 ppm (more equatorial); CH_3, −17 ppm (more axial); for Λ,L: H_α, −54 ppm; CH_3, −21 ppm. Since the concentrations of the two isomers are essentially equal, and the methyne proton shifts indicate only slight conformational preference, Ni(EDDA)(L-ala) should probably be considered an example of case 4.

Although NH_2 proton–EDDA interactions have little conformational influence, the N–CH_3 of sarcosine probably has considerable influence in the isomer distribution of Ni(EDDA)(sar)$^-$. The tendency for the CH_3 to be equatorial, as in Ni(sar)$(H_2O)_4^+$, no doubt determines the preferred conformation. Very likely, interaction with the N–H proton of EDDA results in some decrease in this preference compared to the corresponding 1:1 complex. This is reflected in a decrease in the H_b–H_a shift difference from ∼60 to ∼30–40. However, this conformational preference is still sufficient to produce the observed 3:2 ratio of diastereoisomers. Thus, Ni(EDDA)(sar)$^-$ is an example of case 1b in the previous scheme. The conformational preference of sar is less than it is in a symmetric environment.

The data for the diamine mixed complexes can also be examined in terms of this scheme. For the en portion of the spectrum of Ni(EDDA)(en), a single peak is observed at −94 ppm, very close to its position in Ni(en)$(H_2O)_4^{2+}$. This again implies very weak interaction between NH_2 protons and the EDDA framework, as observed for chelated glycine. However, for Z = pn or dap, the situation is very different. The tendency for R to be equatorial is apparently so great by virtue of intraligand interactions that it probably assumes that conformation whether the configuration is Δ or Λ. Since NH_2 proton interactions are so small, this probably corresponds to case 2 with stereospecificity negligible. Unfortunately, no isomer ratio could be determined from the nmr spectra of these complexes since the spectra are consistent with either a single isomer or with overlap of peaks from the two isomers.

Comparison of Ni(EDDA)(Z) and Similar Co(III) Complexes.—Table IV summarizes data on coordination stereospecificity for the Ni(EDDA)(Z) complexes reported in this paper and analogous Co(III) complexes. Although the two types of complexes are certainly not identical, the asymmetric background provided by two ens or by dien (*trans* coordinated) should be quite comparable to that provided by *trans* coordinated EDDA.

For the L-ala complexes, there appears to be no stereospecific coordination for either type of complex.[10] By contrast, whereas sar coordination is reported to be completely stereospecific in Co(en)$_2$(sar)$^{2+}$,[27] we find only a 3:2 ratio for Ni(EDDA)(sar)$^-$.

The observation that coordination in Co(en)$_2$(N-meala)$^{2+}$ is also completely stereospecific[28] suggests the desirability of examining Ni(EDDA)(N-meala)$^-$. The interaction of adjacent methyl groups assures that an essentially single conformation will prevail for a given N-meala fragment. However, the synthesis of this complex has not yet been completed, nor have we investigated Ni(EDDA)(val)$^-$ whose analogous complex Co(en)$_2$(L-val)$^{2+}$ shows about a 1.7:1.0 stereospecificity ratio.[10]

TABLE IV
STEREOSPECIFICITY OF COORDINATION IN Ni(EDDA)(Z) AND ANALOGOUS Co(III) COMPLEXES

Complex	Diastereoisomer ratio	Ref
Co(en)$_2$(L-ala)$^{2+}$	∼1	10
Ni(EDDA)(L-ala)$^-$	∼1	This work
Co(en)$_2$(sar)$^{2+}$	Very large	27
Ni(EDDA)(sar)$^-$	1.5	This work
Co(en)$_2$(N-meala)$^{2+}$	Very large	28
Co(en)$_2$(L-val)$^{2+}$	1.7	10
Co(dien)(asp)$^+$	Some	30
Ni(EDDA)(L-asp)$^{2-}$	Uncertain (see text)	This work
Co(en)$_2$(L-glu)$^+$	Very large	29
Ni(EDDA)(L-glu)$^{2-}$	Uncertain (see text)	This work
Ni(EDDA)(L-dap)$^-$	Uncertain (see text)	This work

The coordination stereospecificity of L-glu in Co(en)$_2$(L-glu)$^+$ also appears to be great[29] suggesting that the relatively small degree of stereospecificity observed for Co(dien)(L-asp)$^+$ [30] is in error. However, our data for Ni(II) complexes are ambiguous. The single peaks observed for the different ligand protons support stereospecificity while the methyne proton shifts suggest no strong conformational distortion of the glycinate ring.

The "Ring-Opening Shift."—One relatively minor observation that has important implications for structural and kinetic studies of any multidentate ligand containing acetate fragments (*e.g.*, IDA, EDTA) is the substantial downfield shift (∼30 ppm) observed for the CH_2 protons of L-asp in going from tridentate Ni(L-asp) (Figure 4b) to bidentate Ni(EDDA)(L-asp)$^{2-}$ (Figure 7b). Since no significant shift differences were observed for protons of the analogous pair of L-glu complexes, this shift can be attributed to the breaking of the Ni–O bond. In general, apart from conformational effects, spin delocalization through nitrogen produces a downfield shift with rapid attenuation with an increased number of intervening bonds, but coordination through a carboxyl oxygen produces a small upfield shift (probably *via* a spin-polarization mechanism).[2] Thus, for example, it should be readily possible to determine on the basis of its effect on the acetate CH_2 contact shift whether a reagent displaces a given coordinated acetate oxygen.

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(27) (a) D. A. Buckingham, S. F. Mason, A. M. Sargeson, and K. R. Turnbull, *Inorg. Chem.*, **5**, 1649 (1966); (b) J. F. Blount, H. C. Freeman, A. M. Sargeson, and K. R. Turnbull, *Chem. Commun.*, 324 (1967).

(28) M. Saburi, M. Homma, and S. Yoshikawa, *Inorg. Chem.*, **8**, 367 (1969).

(29) (a) J. H. Dunlop, R. D. Gillard, N. C. Payne, and G. B. Robertson, *Chem. Commun.*, 874 (1967); (b) J. H. Dunlop and R. D. Gillard, *J. Chem. Soc., A*, 1469 (1967).

(30) J. I. Legg and D. W. Cooke, *J. Am. Chem. Soc.*, **89**, 6854 (1967).