carried out in our laboratory on other polyelectrolytes and electrically charged particles in general in order to establish a unified interpretation on the structure of dilute solutions of these solute particles.[31]

Finally we note that the experimental data of the small-angle X-ray scattering (except the molecular weight dependence) can also be described by an isotropic model proposed by de Gennes et al.[34] A detailed check of this model on macroion systems will be reported later, although it obviously cannot be applied to other charged systems.

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Note Added in Proof: Almost complete insensitivity of the position of the peak of the neutron scattering toward salt concentration was reported for a polystyrenesulfonate by Nierlich et al.[23] This is in contradiction with our X-ray scattering data (Figure 2 and Table I). However, the French group observed recently the same salt concentration dependence for the polystyrenesulfonate as ours.

Rinaudo and Milas kindly drew our attention to their recent observation on xanthane showing again insensitivity of the neutron scattering peak toward degree of polymerization, which does not agree with our results described in the present paper. Both their results and ours can be reasonable, however, because xanthane molecules probably assume comparatively stretched conformation as a result of the chain stiffness so that chain-end effect in this case might be much less significant than in loosely coiled macroions (like polyacrylate).

(31) In a recent paper (*Makromol. Chem.* **1977**, *178*, 2429–2353), Dolar et al. have thrown strong doubt on the presence of the lattice structure in polyelectrolyte solutions suggested earlier by us.[7] The SAXS and SANS studies described in this article provide a clear answer to their questioning, indicating that their conclusion is at fault. Furthermore, it is to be noted that the cube-root dependence of the mean activity coefficients has not been claimed by us to hold *always* for all polyelectrolytes, as Dolar et al. seem to believe. As a matter of fact, for example, we observed marked deviation from this dependence for polyglutamate (PGA) and DNA.[32,33] Nonetheless, the neutron scattering shows the presence of an ordering in PGA solution.[13] The cube-root dependence may suggest the presence of an ordered structure, but converses are not always true. Thus, even if one accepts the finding by Dolar et al. that the cube-root relation does not apply to cadmium polystyrenesulfonate, this does not imply the absence of the ordered structure for this particular polymer. The interpretation advanced by Dolar et al. should thus be discarded.

(32) Ise, N.; Okubo, T. *Macromolecules* **1969**, *2*, 401–407.

(33) Okubo, T.; Ise, N. *Macromolecules* **1969**, *2*, 407–411.

(34) de Gennes, P. G.; Pincus, P.; Velasco, R. M. *J. Phys.* (*Paris*) **1976**, *37*, 1461–1472.

(35) Nierlich, M.; Jannink, G., private communication.

(36) Rinaudo, M.; Milas, M., private communication.

Proximity of Metal Ions and Hydrocarbon Side Chains of Chelated α-Amino Acids and Peptides[1]

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Abstract: In order to elucidate the factors responsible for neutral, unbound side-chain conformations in chelates of α-amino acids and peptides, we evaluated rotamer populations about the α–β bond by vicinal proton coupling constant analysis in well-defined complexes of tetragonal, diamagnetic Pd(II). In a dipeptide, for example, the backbone chelates the Pd(II) in two five-membered rings by amino and ionized amide nitrogen and carboxylate oxygen donor atoms. For aromatic phenylalanine or tyrosine side chains in the carboxylate terminal residue of a dipeptide, the mole percentage of the rotamer that directs the side chain over the metal ion rises to about 60% from about 20% in unbound ligand. A similar population increase is also observed in tripeptide complexes of both Pd(II) and diamagnetic Ni(II). Increases in the two rotamers that direct aliphatic side chains toward the metal ion are also observed in complexes of amino acids and peptides of valine and isoleucine. The mole percentages in the complexes are little changed by 80% Me_2SO solvent in place of water. Since several di- and tripeptides contain only one side chain, hydrophobic interactions between side chains cannot be responsible for favoring placement of side chains over the metal ion. There is some precedent for direct metal ion–aromatic side chain interactions in crystal structures. Direct, weak metal ion–aliphatic side chain interactions may be of sufficient energy to affect relative rotamer populations. Alternatively, aliphatic and also aromatic side chains may simply prefer space over a metal ion to a greater interaction with solvent.

What is the disposition of the side chains in chelated α-amino acids and peptides? To what extent do across chelate ring side chain–side chain interactions determine side-chain conformation? Do other kinds of interactions also influence conformation? This paper reports results for hydrocarbon side-chain conformations as deduced from ^1H NMR vicinal coupling constants. Even in the absence of side chain–side chain interactions in the chelated ligands, hydrocarbon side chains are found to favor the conformation that projects them toward the metal ion.

In solution, a lesser difference between the logarithms of the first and second stability constants for Cu^{2+} and phenylalanine compared to alanine (1.3 vs. 1.0), for example, has been interpreted as due to an unusually large second stability constant in the bis(phenylalanine) complex.[3] This result suggests a modest degree of favorable interaction between the two aromatic rings in the bis complex. Some additional stability in the mixed complex of tryptophan and adenosine triphosphate has been assigned to interactions between the two kinds of aromatic rings.[4,5] Favorable side-chain interactions between aromatic bipyridyl or 1,10-phenanthroline and aliphatic amino acid side chains have also been

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(3) Martin, R. B. *Met. Ions Biol. Syst.* **1979**, *9*, 1–39.

(4) Sigel, H.; Naumann, C. F. *J. Am. Chem. Soc.* **1976**, *98*, 730.

(5) Mitchell, P. R.; Prijs, B.; Sigel, H. *Helv. Chim. Acta* **1979**, *62*, 1723.

0002-7863/80/1502-7906$01.00/0

proposed to occur in mixed complexes.[6] There is, however, evidently no crystal structure which shows positive intramolecular interactions between two neutral side chains of chelated amino acids or between one side chain and another aromatic ligand such as 2,2′-bipyridyl.

Less than supposed van der Waals' contact distances found in several crystal structure determinations have led to suggestions of weak attractive interactions between aromatic side chains and transition-metal ions chelated at the α-amino and carboxylate groups of amino acids. Examples include glycyl-L-leucyl-L-tyrosine[7] and a bis complex of tyrosine[8] where the plane of the aromatic ring makes a small angle with the Cu^{2+} chelate plane. Less than expected van der Waals' contact differences occur between the γ and δ carbons of a tyrosine ring and the Hg of CH_3Hg^+ in a 1:1 complex[9] and Pd^{2+} in a bis complex.[10] In none of these complexes is the phenolic group coordinated. In a glycyl-L-tryptophan complex Cu^{2+} is sandwiched between the two indole rings.[11] The indole ring nitrogen is not involved in covalent coordination. Closer than van der Waals' contact distances are also found between Cu^{2+} and two aromatic ring positions in the bis complex of *N*-benzylproline.[12] Thus attractive interactions have been inferred between the aromatic side chains and transition-metal ions of several electronic configurations that are chelated at the α-amino and carboxylate groups of amino acids.

The factors responsible for hydrocarbon side-chain conformations of chelated amino acids and peptides in solution are apt to be subtle. They may not be strong enough to be easily recognized in stability constant comparisons. NMR chemical shifts of protons shielded by aromatic side chains are another approach. There is an angular dependence between the aromatic and the required, observed, second side chain. Due to its through space nature a chemical shift may occur in the observed side chain without stacking and without positive interactions with the aromatic group. Though the energies contributing to a preferred side conformation may be weak, they may still be significant in their ability to favor one side-chain geometry over others available in the absence of such interactions. It is this geometric aspect that we investigate directly in this paper by comparing the conformations in the complexed ligand to that of free ligand by analysis of proton vicinal coupling constants in nuclear magnetic resonance spectroscopy. An advantage of the vicinal coupling constant approach is that a second side chain is not required and the conformation of a single side chain may be determined. Indeed, it is the ability to examine a single side-chain conformation that gives rise to a perhaps surprising result.

For the measurement of vicinal coupling constants in complexes, a diamagnetic metal ion is required. We have used Pd(II) complexes of amino acids and dipeptides and Pd(II) and Ni(II) complexes of tripeptides. All of these systems have been extensively characterized previously by several techniques in this laboratory.[13] $PdCl_4^{2-}$ in the presence of an equimolar amount of dipeptide titrates 2 equiv of base by pH 4, corresponding to deprotonation of ammonium and amide hydrogens.[14,15] The resulting complex consists of a terdentate dipeptide forming two five-membered rings chelated via amine nitrogen, deprotonated amide nitrogen, and carboxylate oxygen donor atoms. The fourth position about the strongly tetragonal Pd^{2+} is occupied by either H_2O or Cl^-; OH^- is not bound in these solutions until pH >8. All the results reported in this paper were obtained between pH 4 and 8. Equimolar solutions of tripeptides and $PdCl_4^{2-}$ titrate 3 equiv of base to form a quadridentate tripeptide chelated via amine nitrogen, two deprotonated amide nitrogen, and a carboxylate oxygen donor atom.[14,15] Equimolar solutions of tripeptides and Ni^{2+} after titration of 3 equiv of base form a similar complex wherein the Ni^{2+} is tetragonal and diamagnetic.[16-18] In none of these systems does cis–trans isomerism compromise the interpretation. Thus di- and tripeptides form relatively rigid multidentate chelates about a diamagnetic tetragonal metal ion. The disposition in space of appropriately chosen side chains attached to the α-carbon attom of an amino acid residue in the chelated peptide may be deduced by coupling constant analysis in ^1H NMR spectroscopy. Our choice of side chains is limited by the ability to perform a conformational analysis on side chains with an α and one or two β hydrogens that have not undergone destructive splitting by other hydrogens.

Experimental Section

Amino acids and peptides of the best quality available from Sigma Chemical Company were used without further purification. K_2PdCl_4, (en)$PdCl_2$, and (en)$Pd(D_2O)_2(NO_3)_2$ were used as sources of Pd(II); the last two were prepared as described earlier.[19,20] $Ni(ClO_4)_2 \cdot 6H_2O$ was used as the source of Ni(II). Complexes were prepared at 0.1 M concentration in D_2O for ^1H NMR spectra. ^1H NMR spectra were recorded on a 90-MHz Varian EM-390 spectrometer at a probe temperature of 34 °C with *tert*-butyl alcohol as internal reference. The three spin ABC coupling constant analysis was performed by using the program LAOCN3. Though often quoted to 0.01 Hz for computational purposes, coupling constants are reliable to only 0.1 Hz.

Results

Substituted ethanes such as occur in α-amino acids with one α- and two β-hydrogens give rise to proton magnetic resonance spectra of 5–12 lines due to a three-spin ABX- or ABC-type system. These spectra are time averaged over three predominant staggered rotamers, designated for the purpose of labeling and expressing mole fractions as *t*, *g*, and *h*, as illustrated in Figure 1. The bulky carboxylate and R groups are anti (trans) in the *t* rotamer, gauche in the *g* rotamer, and also gauche in the most hindered *h* rotamer, where all three substituent groups and all three carbon bound hydrogens are in adjacent positions. Of the two β-hydrogens, in the labeling of Figure 1 proton H_B is usually found at higher field than H_A.[21-24] When the ^1H NMR spectra exhibit a sufficient number of lines, observed vicinal, three-bond, proton spin coupling constants J_{AC} and J_{BC} may be individually determined and related to the mole fractions of each of the three rotamers and to the vicinal parameters J_G and J_T for gauche and anti positions of proton H_C with respect to H_A and H_B.

$$J_{AC} = tJ_G + gJ_T + hJ_G \quad (1)$$

$$J_{BC} = tJ_T + gJ_G + hJ_G \quad (2)$$

For some spectra only the sum of J_{AC} and J_{BC} may be determined, and from the previous two equations

$$2J_{av} = J_{AC} + J_{BC} = J_G(1 + h) + J_T(1 - h)$$

From eq 1 and 2 and with $t + g + h = 1$, it may be shown that the rotamer mole fractions are given by

$$t = (J_{BC} - J_G)/(J_T - J_G)$$

$$g = (J_{AC} - J_G)/(J_T - J_G)$$

(6) Fischer, B. E.; Sigel, H. *J. Am. Chem. Soc.* **1980**, *102*, 2998.
(7) Franks, W. A.; van der Helm, D. *Acta Crystallogr., Sect. B* **1970**, *B27*, 1299. van der Helm, D.; Franks, W. A. *J. Am. Chem. Soc.* **1968**, *90*, 5627.
(8) van der Helm, D.; Tatsch, C. E. *Acta Crystallogr., Sect. B* **1972**, *B28*, 2307.
(9) Alcock, N. W.; Lampe, P. A.; Moore, P. *J. Chem. Soc., Dalton Trans.* **1978**, 1324.
(10) Sabat, M.; Jezowska, M.; Kozlowski, H. *Inorg. Chim. Acta* **1979**, *37*, L511.
(11) Hursthouse, M. B.; Jayaweera, S. A. A.; Milburn, H.; Quick, A. *J. Chem. Soc., Dalton Trans.* **1975**, 2569.
(12) Aleksandrov, G. G.; Struchov, Y. T.; Kurganov, A. A.; Rogozhin, S. V.; Davankov, V. A. *J. Chem. Soc., Chem. Commun.* **1972**, 1328.
(13) Martin, R. B. *Met. Ions Biol. Syst.* **1974**, *1*, 129.
(14) Wilson, E. W., Jr.; Martin, R. B. *Inorg.* Chem. **1970**, *9*, 528.
(15) Pitner, T. P.; Wilson, E. W., Jr.; Martin, R. B. *Inorg. Chem.* **1972**, *11*, 738.
(16) Martin, R. B.; Chamberlin, M.; Edsall, J. T. *J. Am. Chem. Soc.* **1960**, *82*, 495.
(17) Mathur, R.; Martin, R. B. *J. Phys. Chem.* **1965**, *69*, 668; **1971**, *75*, 4066.
(18) Chang, J. W.; Martin, R. B. *J. Phys. Chem.*, **1969**, *73*, 4277.
(19) Lim, M. C.; Martin, R. B. *J. Inorg. Nucl. Chem.* **1976**, *38*, 1911, 1915.
(20) McCormick, B. J.; Jaynes, E. N.; Kaplan, R. I. *Inorg. Synth.* **1972**, *13*, 216.
(21) Martin, R. B.; Mathur, R. *J. Am. Chem. Soc.* **1965**, *87*, 1065.
(22) Espersen, W. G.; Martin, R. B. *J. Phys. Chem.* **1976**, *80*, 741.
(23) Casey, J. P.; Martin, R. B. *J. Am. Chem. Soc.* **1972**, *94*, 6141.
(24) Martin, R. B. *J. Phys. Chem.* **1979**, *83*, 2404.

$$h = (J_T + J_G - 2J_{av})/(J_T - J_G)$$

Thus the rotamer mole fractions may be estimated from the observed vicinal coupling constants J_{AC} and J_{BC} if sufficiently reliable values of the J_G and J_T parameters are known. Values of $J_G = 2.4$ Hz and $J_T = 13.3$ Hz have been suggested as especially applicable to amino acid side chains.[24] The values may be reduced slightly by electronegativity corrections for serine, and the valine and isoleucine side chains. Since the extent of any reduction is uncertain, the above values are utilized in all cases. Reduction in the J_T and J_G parameters would have the effect of decreasing slightly the mole percentage of rotamer *h* for the affected amino acid side chains. No qualitative arguments are altered by the choice of J_G and J_T values.

As can be seen in Figure 1, only in rotamer *h* will the side chain R group at 8 o'clock be directed over a metal ion chelated between the amino and carboxylate groups in the 10 and 6 o'clock positions, respectively.

Valine possesses two methyl substituents on the β-carbon. There is only one α- and one β-hydrogen. Without loss of generality it is convenient to consider hydrogen H_A in Figure 1 as having undergone substitution by a methyl group. Then the coupling constant determined experimentally is J_{BC} and the population of rotamer *t* is given by

$$t = (J_{BC} - J_G)/(J_T - J_G)$$

Only the sum of rotamers *g* and *h* may be determined from $g + h = 1 - t$. For valine, rotamer *t* possesses anti α- and β-hydrogens while in rotamers *g* and *h* these two hydrogens are gauche to one another. Similarly for isoleucine with an ethyl R group in Figure 1, a methyl group is viewed as replacing hydrogen H_A in Figure 1. Analysis of the coupling constants and rotamer populations about the valine and isoleucine side chains is identical.

Table I tabulates the results obtained in this research. For each ligand is listed the J_{AC} and J_{BC} coupling constants for the free ligand and for its Pd^{2+} complex as deduced by computer fitting from its ^1H NMR spectra. On the right hand side of the table are the mole percentages of each rotamer *t*, *g*, and *h*, as depicted in Figure 1, for the free ligand and its Pd^{2+} complex. In all cases except one results for the anionic form of the free ligand are given. For these ligands with neutral side chains the rotamer mole percentages do not depend significantly on ionic form. Results in Table I for Gly-Tyr are in close agreement with another report.[25] The upper half of Table I contains results for phenylalanine and tyrosine side chains while the lower half contains results for isoleucine and valine side chains. Thus entries for Val-Phe and Phe-Val both appear twice in Table I, with results for the Phe side chain in the upper half and the Val side chain in the lower half. Results for Val-Phe and Gly-Val were also obtained in about 80% Me_2SO with little change in coupling constants from the results in water.

Discussion

For phenylalanine and tyrosine side chains in the amino acid or in the carboxylate terminal residue of a dipeptide, the results of Table I indicate a pronounced increase in the population of rotamer *h* (Figure 1) in the Pd^{2+} complex compared to the free ligand. Rotamer *h* uniquely directs the side chain toward the metal ion. The increase in population in rotamer *h* from about 20% to about 60% in the Pd^{2+} complex is at the expense of rotamer *t*; the population of rotamer *g* is relatively unaffected by complex formation. Similar results are obtained for tetragonal Ni^{2+} complexes. The slightly greater mole percentage of rotamer *h* for the Ni^{2+} complexes may be due to its weaker tendency to form tetragonal complexes or to its smaller effective ionic radius of 0.49 nm compared to 0.64 nm for Pd^{2+}.[26]

The rotameric populations of the aromatic side chains of chelated ligands appear to divide into three categories. The mole percentages of rotamer *h* are 59–73% for a peptide aromatic side chain not in the amino terminal residue, 41–50% for aromatic side chains in amino acids, and 22–36 (50)% for peptide aromatic side chains in an amino terminal residue. There are only four instances of the last category in Table I. The mole percentages of rotamer *h* are 50% for the Ni^{2+} complex of Phe-Gly-Gly, 32 and 36% for the Pd^{2+} complexes of Phe-Gly-Gly and Phe-Val, and 22% for the Pd^{2+} complex of Phe-Phe (amino terminal). In all instances but the very last, the mole percentages of rotamer *h* exceed those of unbound ligand. For the Phe-Phe complex steric hindrance evidently reduces the amino terminal rotamer *h* mole percentage to 22%, while the carboxylate terminal percentage of 61% is in the "normal" range. The low mole percentages of rotamer *h* for amino terminal aromatic amino acids generally are consistent with the conclusion of relatively high side chain mobility drawn from the low magnitudes of the visible circular dichroism spectra of tetragonal metal ion complexes of peptides with bulky side chains in the amino terminus, which alone is coordinated to the metal ion via a tetrahedral amino nitrogen.[3,14,18,27]

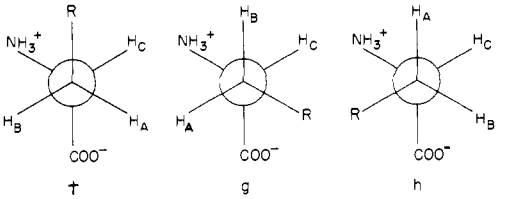

Figure 1. Three staggered rotamers of α-amino acid with two β-hydrogens H_A and H_B.

Because valine and isoleucine possess only one α- and one β-hydrogen, it is not possible to resolve the sum of the rotamer *g* and *h* mole percentages into their component contributions. This limitation is of little importance, however, because both rotamers *g* and *h* dispose an aliphatic group toward the chelated metal ion. Only in rotamer *t* is a hydrogen disposed toward the metal ion. Upon formation of a Pd^{2+} complex the percentages of the sum $g + h$ increase and that of rotamer *t* decreases. The reduction in rotamer *t* from about 30% in the free ligand to less than 10% in the chelated ligand occurs irrespective of whether the isoleucyl or valyl side chain occurs in the free amino acid or amino or carboxylate terminal positions of di- and tripeptides.

Thus for both the aromatic side chains of phenylalanine and tyrosine and the aliphatic side chains of isoleucine and valine, conformations which dispose the side chains to take up a position over the metal ion are markedly more favored in a chelated than unbound ligand. The favoring is not limited to aromatic side chains but also occurs with aliphatic ones.

What are the main interactions responsible for the conformation of hydrocarbon side chains in chelated amino acids and peptides? Table I indicates that the population of the predominant rotamer (*h*) that disposes the side chain over the metal ion is significantly enhanced over its population in the free ligand. Several interactions need to be considered in accounting for the side-chain conformation in chelated amino acids and peptides. Stacking between two aromatic ligands requires good reach and a favorable geometry. These requirements are not met by any examples in Table I: the two aromatic side chains of the Phe-Phe interact unfavorably. Hydrophobic interactions between two aromatic, two aliphatic, or an aliphatic and aromatic side chain may occur as water seeks to reduce its exposure to hydrophobic groups. Chelated ligands with a valyl and another hydrophobic side chain yield coupling constants and rotameric populations similar to chelated ligands with only a single valyl side chain. It is also likely that valyl and isoleucyl side chains are not long enough to interact appreciably with another side chain. Moreover, the rotamer mole percentages are little changed when water is replaced by 80% Me_2SO. For all these reasons, even in the cases where two hydrophobic side chains occur, it does not seem that hydrophobic interactions play a significant role in determining conformation in these complexes.

(25) Kozlowski, H.; Jezowska, M. *Chem. Phys. Lett.* **1977**, *47*, 452.
(26) Shannon, R. D. *Acta Crystallogr., Sect. A* **1976**, *A23*, 751.
(27) Tsangaris, J. M.; Martin, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4255.

Table I. Coupling Constants and Rotamer Mole Percentages

	ligand[a]		Pd^{2+} complex[b]		ligand[a]			Pd^{2+} complex[b]		
	J_{AC}	J_{BC}	J_{AC}	J_{BC}	*t*	*g*	*h*	*t*	*g*	*h*
(en) Phe	5.23	7.34	5.6		45	26	29	59		41
(en) Tyr	6.24	7.97	4.82	5.39	51	35	14	27	22	50
Gly-Phe	4.95	8.56	5.49	3.35	57	23	20	9	28	63
Val-Phe	4.99	8.75	4.58	4.42	58	24	18	19	20	61
Val-Phe[c]			4.40	4.36				18	18	64
Gly-Tyr	4.84	8.65	5.53	2.98	57	22	20	5	29	66
Gly-Phe, amide	5.95	9.09	5.47	3.17	61	33	6	7	28	65
Gly-Phe-Gly	5.53	8.90	5.48 (5.48)	3.13 (3.04)	60	29	12	7 (6)	28 (28)	65 (66)
Gly-Gly-Phe	4.86	8.06	5.15 (5.17)	4.14 (2.92)	52	23	26	16 (5)	25 (25)	59 (70)
Gly-Gly-Tyr	4.86	7.91	4.99 (3.80)	3.56 (3.96)	51	23	27	11 (14)	24 (13)	66 (73)
Phe-Phe, COO^-	5.08	8.03	5.40	3.63	52	25	24	11	28	61
NH_2	5.74	7.32	5.06	8.28	45	31	24	54	24	22
Phe-Val	5.65	7.23	3.64	8.14	44	30	26	53	11	36
Phe-Gly-Gly	7.0		3.71 (5.1)	8.45	84		16	56	12	32 (50)
Gly-Ser	3.64	6.54	2.90	3.20	38	11	51	7	5	88
(bpy)Ileu		5.1		3.2	25	75		7	93	
(en)Ileu		5.1		3.4	25	75		9	91	
Gly-Ileu		5.8		2.8	31	69		4	96	
Gly-Val		5.6		3.4	29	71		9	91	
Gly-Val[c]				3.6				11	89	
Phe-Val		5.8		2.9	31	69		5	95	
Gly-Gly-Val		5.6		4.5 (3.2)	29	71		19 (7)	81 (93)	
Val-Val, COO^-		5.7		3.2	30	70		7	93	
NH_2		5.8		3.0	31	69		6	94	
Val-Phe		5.6		3.1	29	71		6	94	
Val-Phe[c]				3.5				10	90	
Val-Gly		6.1		2.7	34	66		3	97	
Val-Gly-Gly		6.2		3.0 (3.0)	35	65		6 (6)	94 (94)	

[a] All L-amino acids and anionic ligands except for Gly-Ser which is cation. [b] Tetragonal Ni(II) complex values in parentheses. [c] 80% Me_2SO solvent.

Most of the ligands listed in Table I possess only a single hydrophobic side chain so the stabilization of rotamer *h* cannot be due to intramolecular hydrophobic interactions between two side chains. The favoring of rotamer *h* for aromatic side chains may be due to an apparent attractive interaction with Pd^{2+}, as suggested from the crystal structures mentioned in the introduction. It is also evident from Table I that the nonaromatic valyl and isoleucyl side chains occupy similar space over the metal ion as the aromatic side chains. The reason that single aliphatic, nonaromatic side chains prefer space in the direction of the metal ion is not clear. Attractive interactions between metal ions and aliphatic groups is not a popular notion. Though weak, such interactions may tip the relatively sensitive energy balance among the three rotamers. In an accurate crystal structure of a *trans*-bis(1-methylcytosine) complex of tetragonal, dichloro Pd^{2+} there are unusually short intramolecular hydrogen contacts between an amino hydrogen on each ligand and Pd^{2+} to give rise to a very distorted octahedral structure.[28] Though bound to carbon atoms of lesser electronegativity than nitrogen, the hydrogens of aliphatic groups may participate in a similar interaction. Finally, there is the possibility that aliphatic and also aromatic side chains simply prefer "vacant" space over a metal ion to a greater interaction with solvent. Resolution in each case of relative contributions from this "indirect" effect from direct interactions of metal ions and hydrocarbon side chains remains for further inquiry. Whatever the reason for the observed disposition of hydrocarbon side chains over the chelated metal ion, the tendency presumably also exists in cases of two hydrophobic side chains, so that hydrophobic interactions between them may only be a minor contributor to their placement.

(28) Sinn, E.; Flynn, C. M., Jr.; Martin, R. B. *Inorg. Chem.* **1977**, *16*, 2403.