Noncovalent Ligand–Metal and Ligand–Ligand Interactions in Tridentate (Dipeptide)palladium(II) Complexes

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Abstract: The tridentate (Gly-Gly)Pd(H_2O) complex binds a series of aliphatic unidentate amines in the fourth planar coordination position with stability constant logarithms linearly related to pK_a of the amines. This linear relationship is used as a base line for comparisons with other complexes. Aromatic amines show enhanced binding with up to 62% for phenethylamine (2-phenylethylamine) of a closed form that places the aromatic ring near the strongly planar Pd. Thus an aromatic ring–metal ion interaction leads to an enhanced complex stability in aqueous solution. The two tridentate complexes (Gly-Gly)Pd and (Gly-Phe)Pd bind Cl^- and also NH_3 with equal stabilities in the fourth planar position. Both aliphatic and aromatic unidentate amines bind more strongly to the dipeptide complex with a phenylalanine side chain, suggesting a hydrophobic interaction between the phenyl group and hydrocarbon portions of the amines. Both amine proton chemical shifts and phenyl side chain proton vicinal coupling constant analysis in NMR spectroscopy indicate that the interaction is limited to hydrogens on only the first three carbons in the linear amines. Rotamer mole percentages are estimated for seven complex forms in each (Gly-Phe)Pd–amine complex. Transfer of the phenyl side chain to form the (Phe-Gly)Pd complex results in little enhanced amine binding. Tridentate (Gly-Ile)Pd with a secondary butyl side chain exhibits little enhanced binding of aliphatic amines and weak enhancements with aromatic amines. Stability enhancement, defined as the molar ratio of closed to open forms, permits quantification of the results. The order of decreasing interaction energies in the complexes is given by phenyl–aromatic > phenyl–(propyl or larger) > phenyl–ethyl > isoleucyl–aromatic > Pd–aromatic > phenyl–methyl >> Pd–aliphatic ~ isoleucyl–aliphatic ~ 0.

Intramolecular noncovalent interactions between ligands in complexes include hydrogen bonding, hydrophobic, and stacking interactions. In this paper we are concerned with interactions between hydrocarbon portions of ligands that do not participate in hydrogen bonding. Examples of complexes in which intramolecular hydrophobic and stacking interactions occur have been compiled.[1] There is also evidence that both aromatic and aliphatic hydrocarbon portions of ligands tend to occupy space near the metal ion rather than out in solution.[2,3] For brevity we refer to this tendency as a ligand–metal interaction, though a direct favorable hydrocarbon–metal interaction has been shown only for aromatic rings with metal ions by less than van der Waals distances in several crystal structure determinations. One example involving Pd(II) is in the bis(tyrosine) complex where there appears to be an interaction between Pd and C1 and C2 of the tyrosine ring.[4] The phenol group is not involved.

Additional evidence that aromatic and hydrocarbon portions of ligand take up space near the metal ion comes from rotamer analysis about the $\alpha C-\beta C$ bond in amino acid side chains by proton vicinal coupling constant analysis in NMR spectroscopy.[3,5-7] Probably due to its smaller size, planar Ni(II) shows more hydrocarbon side chain interaction than Pd(II) in peptide complexes.[3,6] Since Ni(II) does not readily yield diamagnetic complexes with dipeptides, we use only Pd(II) complexes in this study.

Dipeptide complexes of the diamagnetic Pd(II) possess especially favorable properties for this analysis. The complexes have been well characterized: they are fully formed by pH 4 by deprotonation of both ammonium and amide hydrogens.[8-10] The resulting neutral complex consists of a tridentate dipeptide chelated in two 5-membered rings by an amine nitrogen, deprotonated amide nitrogen, and carboxylate oxygen donor atoms. Both chelate rings reside in the same plane as the strongly planar Pd(II) coordination plane. This well-defined structure provides a framework for introduction of amino acid side chains. The fourth position about the planar Pd(II) is occupied by either H_2O or Cl^-; the ambiguity is resolved in this study.

In this paper we extend application of vicinal coupling constant analysis to find the effect of additional ligand binding on altering amino acid side chain rotamer mole percentages. In addition, direct comparison of complex stability constants permits quantitative assessment of the energies involved in intracomplex hydrocarbon interactions with other ligands and with Pd(II).

Experimental Section

Dipeptides glycyl-L-phenylalanine and L-phenylalanylglycine were purchased from Sigma Chemical Co. and glycyl-L-isoleucine from Cyclo Chemical Co. K_2PdCl_4 was obtained from Alfa Products. The higher amines were purchased from Aldrich Chemical Co. and were greater than 98% pure, except for cyclohexanemethylamine which was 95% pure.

Potentiometric titrations were conducted on an automatic Radiometer titrating system under N_2 at 21 °C. The Radiometer PHM 64 pHmeter with a combined electrode was calibrated with Fisher Scientific Co. pH 4.00 and 7.00 standard buffer solutions. For determination of amine pK_a values solutions were about 50 mM in the amine hydrochloride and titrated with 0.9 M NaOH at an ionic strength of 0.1 M controlled with $NaClO_4$.

Proton NMR spectra were recorded on solutions 25 mM in (dipeptide)Pd in D_2O on a Varian EM 390 spectrometer at 90 MHz and routinely at 34 °C. Ionic strength was controlled to 0.1 M with $NaNO_3$. Some spectra for coupling constant analysis were also taken at 21 °C, the same temperature as the stability constant determinations. The NMR spectra were unaffected by the temperature change. In the complex (Gly-Gly)PdCl a long-range five-bond coupling constant of 1.0 Hz between glycyl methylene hydrogens was confirmed by a double resonance experiment.

Because of Cl^- flow from electrodes used in pH determinations and binding of Cl^- to (dipeptide)Pd, potentiometric experiments were conducted with 1 mM complex in the presence of 20 mM Cl^-. Probably due to slow Pd–Cl^- bond breaking, achieving equilibrium takes several minutes in potentiometric titrations with amine ligands. Therefore, in experiments to determine amine stability constants, seven individual solutions were prepared with 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, and 0.8 equiv of base with 1 mM (dipeptide)Pd, 5 mM amine, and 20 mM NaCl. Ionic strength was adjusted to 0.1 M with $NaClO_4$. Solutions were stirred

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Table I. Amine Basicity Constants and Stability Constants with (dipeptide)Pd(H_2O) Complexes[a]

	pK_a	(Gly-Gly)-Pd(H_2O)	(Gly-Phe)-Pd(H_2O)
ammonia	9.50	6.50	6.53
methylamine	10.88	7.18	7.31
ethylamine	10.95	7.26	7.48
n-propylamine	10.88	7.23	7.53
n-butylamine	10.90	7.23	7.53
n-pentylamine	10.88	7.21	7.48
n-hexylamine	10.89	7.23	7.50
ethanolamine	9.80	6.67	
methoxyethylamine	9.68	6.57	
cyclohexanemethylamine	10.81	7.16	7.44
benzylamine	9.73	6.86	7.03
phenethylamine	10.18	7.26	7.48
3-phenyl-1-propylamine	10.47	7.10	7.42
4-phenyl-1-butylamine	10.72	7.29	7.54

[a] At 0.1 M ionic strength and 21 °C.

overnight and the pH measured at 21 °C. Observed pH values ranged from 4.9 < pH < 7.0. Hydrolysis of the aquo complex does not occur until pH >7. Both a nonlinear least-squares program and the SCOGS program[11] gave identical apparent stability constants. These constants are correced for Cl^- by the equation given at the beginning of the Results section. All amine stability constants reported in this paper refer to (dipeptide)Pd(H_2O). Their relative accuracy is estimated to be ±0.02 log unit.

Results

Though the donor atoms in the three coordination positions furnished by tridentate dipeptides in the Pd(II) complex have been well characterized as amine and deprotonated amide nitrogens and carboxylate oxygen,[8-10] the fourth ligand has remained uncertain in those solutions to which Cl^- has been added either internally as $PdCl_4^{2-}$ or externally as an ionic strength control. Even in supposedly Cl^- free solutions, the Cl^- flow from pH electrodes may affect results in comparing accurately determined stability constants. Therefore, as part of this study, amine stability constant determinations were carried out in the presence of a known excess Cl^- concentration not materially altered by electrode flow. If an accurate stability constant for Cl^- binding to (dipeptide)Pd(II) is available, stability constants of other ligands based on H_2O in the fourth position may then be calculated.

For both tridentate complexes (Gly-Gly)Pd and (Gly-Phe)Pd, the stability constants for Cl^- binding were determined by the intensity change in ultraviolet absorption spectra. For a solution 0.7 mM in (dipeptide)Pd adjusted to 0.1 M ionic strength with $NaClO_4$ at 21 °C, the absorption maxima appear at 329 nm (ϵ 678) for the aquo complex and at 349 nm (ϵ 620) for the Cl^- complex. (When half the complexes bind Cl^- the absorption maximum appears at 338 nm). For a series of 13 Cl^- concentrations from 0 to 0.3 M there is a tight isosbestic point at 341 nm. A nonlinear least-squares fit of absorption intensity at 320, 329, and 365 nm yields log K_{Cl} = 1.90 ± 0.05 for the Cl^- stability constant to both the (Gly-Gly)Pd(H_2O) and (Gly-Phe)Pd(H_2O) complexes. Stability constants for amine binding to (dipeptide)Pd(H_2O) reported in this paper are calculated from $K = K_{app}(1 + K_{Cl}[Cl^-])$, where K_{app} is the apparent stability constant in the presence of a known fixed 20 mM Cl^- concentration.

Column 3 of Table I lists stability constants for a series of unidentate amines to neutral, tridentate (Gly-Gly)Pd(H_2O). Figure 1 shows that when the logarithms of the stability constants for the first 10 amines in Table I are plotted against amine basicity, represented by pK_a in column 2, the points may be fitted by a straight line. The least-squares line through all 10 solid circles is represented by a slope of 0.54 ± 0.02 and a correlation coefficient, r = 0.997. (Since there are four potential acidic protons in NH_4^+ and only three in all the other amines, the point for NH_3 has been shifted by log (4/3) = 0.12 unit to the right in Figure 1.) We conclude that the first 10 amines of Table I interact

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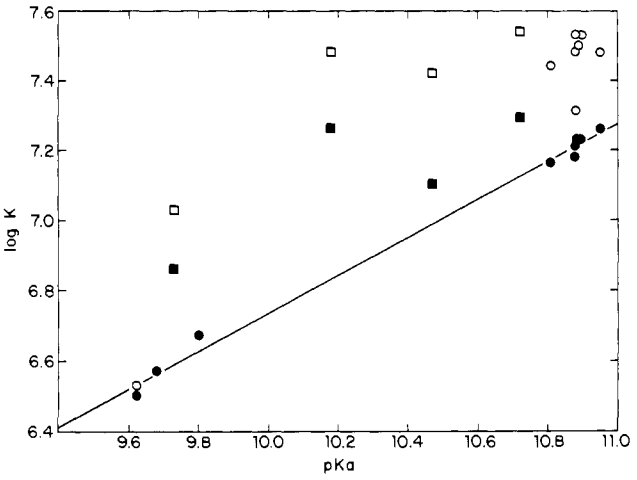

Figure 1. Stability constant logarithms for coordination of unidentate amines to tridentate (dipeptide)Pd(H_2O) complexes vs. amine basicity. Solid circles refer to aliphatic amines with (Gly-Gly)Pd(II) and the least-squares line is drawn for all 10 solid circles (two are superimposed). Four solid squares refer to binding of aromatic amines to (Gly-Gly)Pd. Binding to (Gly-Phe)Pd is represented by open circles for ammonia and seven aliphatic amines and open squares for four aromatic amines.

Table II. Parameters for (Gly-Gly)Pd Metal Interaction with Aromatic Amines and Pentylamine

amine	log K_G	log K_o	log K_{CG}	% closed	log (1 + E_{LM})
H_2NCH_2Ph	6.86	6.59	6.53	47	0.16
$H_2N(CH_2)_2Ph$	7.26	6.84	7.05	62	0.26
$H_2N(CH_2)_3Ph$	7.10	6.99	6.45	22	0.06
$H_2N(CH_2)_4Ph$	7.29	7.13	6.78	31	0.09
$H_2N(CH_2)_4CH_3$	7.21	7.21		0	0

similarly with (Gly-Gly)Pd. Thus the amine group basicity appears as the predominant predictor of metal ion stability of unidentate aliphatic amines to (Gly-Gly)Pd(H_2O).

As shown by the four solid squares in Figure 1, (Gly-Gly)Pd stability constant logs for the last four unidentate amines of Table I, each containing a phenyl group, fall above the least-squares straight line for the aliphatic amines. This result suggests a favorable interaction between the aromatic ring and the metal ion that does not occur with wholly aliphatic amines. While the point for the aromatic benzylamine falls 0.27 log unit above the line in Figure 1, the point for cyclohexanemethylamine of similar geometry and extension falls within 0.01 log unit of the line.

We consider the interaction of the unidentate amines with the tridentate (Gly-Gly)Pd designated MG. The basic form of the amine, A, reacts with MG to form an open complex, AMG, in which the hydrocarbon portion of the amine does not interact with the Pd, and a closed complex, CMG, in which such an interaction occurs.

$$MG + A \rightleftarrows AMG \rightleftarrows CMG$$

The associated equilibrium constants are defined as

$$K_o = [AMG]/[MG][A] \quad (1)$$

$$K_{CG} = [CMG]/[MG][A] \quad (2)$$

The observed stability constant is given by

$$K_G = K_o + K_{CG} \quad (3)$$

We estimate the amount of interacting or closed form in the phenyl-containing amines by comparing the observed stability constants in Table I with those expected from the straight line in Figure 1 and the known amine pK_a. These values are listed in the third column of Table II as log K_o. From the observed stability constant K_G, eq 3 permits calculation of K_{CG}, which appears in the fourth column of Table II. The percentage of

Table III. ^{1}H Chemical Shift Difference of Bound Aliphatic Amines between (Gly-Gly)Pd and (Gly-Phe)Pd Complexes[a]

amine	difference at nth carbon, ppm				
	$n = 1$	$n = 2$	$n = 3$	$n = 4$	$n = 5$
H_2NCH_3	0.269				
$H_2NCH_2CH_3$	0.283	0.256			
$H_2N(CH_2)_2CH_3$	0.314	0.284	0.129		
$H_2N(CH_2)_3CH_3$	0.330	0.294	0.125	0.043	
$H_2N(CH_2)_4CH_3$	0.311				−0.004

[a] 10 mM complex in 0.1 M $NaNO_3$. Positive values correspond to upfield shifts in (Gly-Phe)Pd complex.

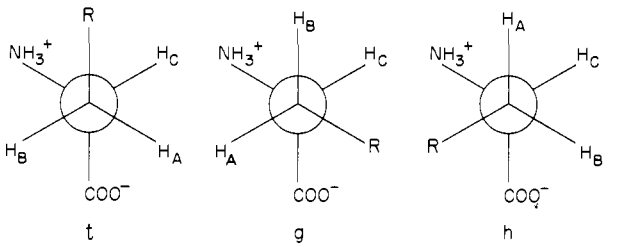

Figure 2. Three staggered rotamers of α-amino acid with two β-hydrogens H_A and H_B.

interacting or closed form is given by $100K_{CG}/K_G$ and appears in the fifth column of Table II. This percentage of closed form is due to a special interaction not present in the non-phenyl-containing amines. It is greatest for phenethylamine with 62% closed form. As indicated by the entries for pentylamine in the last row of Table II, a similar calculation conducted on an aliphatic amine yields 0% closed form. The significance of the last column in Table II awaits the Discussion section.

Coordination of the same unidentate amines was also investigated with (Gly-Phe)Pd, where a phenylalanyl side chain appears in the carboxylate terminal residue of the tridentate dipeptide. Stability constants determined potentiometrically appear in the fourth column of Table I, and the points are plotted as the unfilled circles for aliphatic amines and unfilled squares for aromatic amines in Figure 1. Stability constants for both aliphatic and aromatic amines are larger with (Gly-Phe)Pd than with (Gly-Gly)Pd, suggesting a favorable interaction between the phenylalanyl side chain on the dipeptide and the hydrocarbon portion of the unidentate amines. On the other hand, stability constants for Cl^- and NH_3 are the same for the two dipeptide complexes, suggesting that only an intramolecular interaction produces different stability constants.

Support for a favorable interaction between the phenylalanyl side chain and the hydrocarbon portion of bound unidentate amines is provided by ^{1}H NMR chemical shifts of bound aliphatic amines. In order to elminate shifts due to simple amine coordination, Table III compares the chemical shifts of amines bound to (Gly-Gly)Pd and (Gly-Phe)Pd. All shifts but the last in Table III represent upfield shifts in the bound aliphatic amine protons induced by phenyl group shielding. For all the amines in Table III the greatest upfield shifts are observed for protons bound to the first carbon with protons bound to succeeding carbons showing progressively smaller shifts. Protons bound to the fourth and fifth carbons of butyl- and pentylamine exhibit little or no shift. These results indicate that protons on only up to three carbons in the linear aliphatic amines reside within the phenyl shielding cone in the tridentate (Gly-Phe)Pd complexes. The chemical shift difference observed even for the CH_3NH_2 provides additional proof that the phenylalanyl side chain take up a position over the metal ion.

More details concerning the structures of the (Gly-Phe)Pd–amine complexes may be deduced from a consideration of conformations of both the phenylalanyl side chain of the dipeptide and the bound unidentate amine. The phenylalanyl side chain may take up three different rotamers about the α–β carbon–carbon bond. As before,[3,7] we designate these rotamers and their mole fractions as t, g, and h as shown in Figure 2. The disposition of the Phe side chain is anti to the carboxyl group in rotamer t, anti to nitrogen in rotamer g, and anti to the α-hydrogen in rotamer h. Only in rotamer h is the dipeptide phenyl ring directed toward the metal ion in the tridentate complex. Rotamer h is thus the key rotamer for these considerations.

Table IV. Proton Vicinal Coupling Constants and Rotamer Mole Percentages in (Gly-Phe)Pd Complexes

fourth ligand	J_{AC}, Hz	J_{BC}, Hz	NMR			stabilities		
			h	g	t	h	g	t
Cl^-	5.77	3.30	61	31	8			
NH_3	5.74	3.26	61	31	8			
H_2NCH_3	5.44	3.11	66	28	7	71	23	6
$H_2N(CH_2)_2CH_3$	5.02	2.94	71	24	5	80	16	4
$H_2N(CH_2)_3CH_3$	5.06	2.97	70	24	5	80	16	4
H_2NCH_2Ph	5.46	3.14	65	28	7	74	21	5
$H_2N(CH_2)_2Ph$	5.14	2.94	70	25	5	76	19	5

The one α- and two β-protons of a phenylalanyl side chain give rise to a three-spin ABC-type ^{1}H NMR spectrum, from which the observed vicinal coupling constants J_{AC} and J_{BC} may be extracted. The spectra are time averaged over the three staggered rotamers h, g, and t, illustrated in Figure 2. The rotameric mole fractions may be deduced from the observed vicinal coupling constants by means of the equations

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

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

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

where $J_{av} = (J_{AC} + J_{BC})/2$. Values of $J_G = 2.4$ Hz and $J_T = 13.3$ Hz have been recommended as applicable to amino acid side chains.[12]

Table IV tabulates vicinal coupling constants and rotamer mole percentages (under the columns headed NMR) for the Phe side chain in tridentate (Gly-Phe)Pd complexes with a variety of unidentate ligands in the fourth coordination position. In the unbound Gly-Phe ligand the values are $J_{AC} = 4.95$ Hz, $J_{BC} = 8.56$ Hz, $h = 20\%$, $g = 23\%$, and $t = 57\%$.[3] Coordination of Gly-Phe as a tridentate ligand to Pd(II) results in a dramatic increase in rotamer h mole percentage from 20% in the free ligand to 61% in both the Cl^- and NH_3 complexes of Table IV. Since no common interaction is possible to both Cl^- and NH_3 as a fourth ligand, we interpret the results as due to a favorable interaction of the phenylalanyl side chain with the metal ion which is possible only in rotamer h.

We describe coordination of unidentate amine to the tridentate (Gly-Phe)Pd complex, MP, by designating the phenylalanyl rotamer in the complex with subscripts and, as above, the conformation of the coordinating unidentate amine as open, A, or closed, C. We then write

$$MP_t + A \rightleftarrows AMP_t \rightleftarrows CMP_t$$

$$K_{AP_t} = [AMP_t]/[MP_t][A]$$

$$K_{CP_t} = [CMP_t]/[MP_t][A]$$

$$MP_g + A \rightleftarrows AMP_g \rightleftarrows CMP_g$$

$$K_{AP_g} = [AMP_g]/[MP_g][A]$$

$$K_{CP_g} = [CMP_g]/[MP_g][A]$$

$$MP_h + A \rightleftarrows AMP_h \rightleftarrows CMP_h \text{ and } AMP_h \rightleftarrows CMP_h'$$

$$K_{AP_h} = [AMP_h]/[MP_h][A]$$

$$K_{CP_h} = [CMP_h]/[MP_h][A]$$

$$K_{CP_h}' = [CMP_h']/[MP_h][A]$$

There are two possible closed or interacting forms of the complexing amine when the phenylalanine side chain adopts rotamer h. We employ CMP_h' to designate the form in which there is a

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Table V. Rotameric Mole Percentages in (Gly-Phe)Pd Complexes with Amines

amine	AMP_h	AMP_g	AMP_t	CMP_h	CMP_g	CMP_t	CMP_h'	$\log(1 + E_{LL})$
H_2NH	61	31	8	0	0	0	0	0
H_2NCH_3	45	23	6	0	0	0	26	0.20
$H_2NCH_2CH_3$	37	19	5	0	0	0	40	0.32
$H_2N(CH_2)_2CH_3$	31	16	4	0	0	0	50	0.42
$H_2N(CH_2)_3CH_3$	31	16	4	0	0	0	50	0.42
$H_2N(CH_2)_4CH_3$	33	17	4	0	0	0	46	0.38
$H_2N(CH_2)_5CH_3$	33	17	4	0	0	0	46	0.38
$H_2NC_7H_{13}$	32	16	4	0	0	0	48	0.40
H_2NCH_2Ph	22	11	3	10	10	2	42	0.46
$H_2N(CH_2)_2Ph$	14	7	2	11	12	3	51	0.67
$H_2N(CH_2)_3Ph$	23	12	3	3	3	1	55	0.54
$H_2N(CH_2)_4Ph$	24	12	3	5	5	1	49	0.49

ligand–ligand interaction between the phenylalanyl side chain and the complexing amine and CMP_h to indicate the form in which there is a metal–ligand interaction with the complexing amine on the opposite side of the chelate plane from the phenylalanyl side chain. The latter interaction is similar to that occurring in the (Gly-Gly)Pd complex. For this reason we set $K_{CP_h} = K_{CG}/2$, as the metal–ligand interaction occurring in the Gly-Gly complex takes place only on the side of the Gly-L-Phe complex that is opposite the phenylalanyl side chain.

It is useful to define the two equilibrium constants between rotamers in the (Gly-Phe)Pd complex.

$$K_{ht} = [MP_t]/[MP_h] = 0.13$$

$$K_{hg} = [MP_g]/[MP_h] = 0.51$$

The values are obtained from the rotamer mole percentages for the Cl^- and NH_3 complexes in Table IV. The total concentration of tridentate complex in all three rotameric forms is given by

$$C_{MP} = [MP_t] + [MP_g] + [MP_h] = [MP_h](1 + K_{ht} + K_{hg}) = [MP_h]S \quad (4)$$

where the term in parentheses is $S = 1.64$ for the tridentate (Gly-Phe)Pd complex.

The observed stability constant of a unidentate amine, A, with the tridentate (Gly-Phe)Pd complex is given by

$$K_p = N/([A]C_{MP})$$

where C_{MP} is given in eq 4 and N is the sum of the seven complex concentration terms elaborated above and appearing across Table V. The three equilibrium constants for coordination of the open form of the amine to the tridentate (Gly-Phe)Pd complex with the phenylalanyl side chain in each of the three rotamers is taken as the same base-line constant as for the (Gly-Gly)Pd complex, K_G for aliphatic amines and K_o for aromatic amines.

$$K_{APt} = K_{APg} = K_{APh} = K_o$$

For coordination of the closed form of the amine to the complex with side chain rotamers t and g, where the phenylalanyl side chain orients away from the metal ion, the two equilibrium constants are taken as the corresponding constant in the (Gly-Gly)Pd case, K_{CG}.

$$K_{CP_t} = K_{CP_g} = K_{CG}$$

Since we have previously set $K_{CPh} = K_{CG}/2$, the only one of seven equilibrium constants that remains to be determined is K_{CPh}', the stability constant for the conformer with interaction between amine and phenylalanyl side chain. Manipulation of the previous equations leads to the result

$$K_{CPh}' = S(K_p - K_G) + K_{CG}/2$$

where K_G is the observed stability constant for the amine with the tridentate (Gly-Gly)Pd complex (eq 3).

The significance of the stability constant values may be more fully appreciated by calculating the mole percentages of each of the seven complex species present when a unidentate amine coordinates to tridentate (Gly–Phe)Pd. In the following list each complex species is followed by the combination of equilibrium constants to which its concentration is proportional: AMP_t, K_oK_{ht}; AMP_g, K_oK_{hg}; AMP_h, K_o; CMP_t, $K_{CG}K_{ht}$; CMP_g, $K_{CG}K_{hg}$; CMP_h, $K_{CG}/2$; and CMP_h', K_{CPh}. The resulting mole percentages for all seven complex species for each amine studied are tabulated in Table V. The last column of Table V is discussed in the next section.

The mole percentage sum for each of the rotamers for several complexes in Table V are tabulated in Table IV under the heading stabilities. Thus the rotamer mole percentages estimated from a primarily stability constant analysis may be compared with those determined by a wholly NMR method and listed under the heading NMR in Table IV.

When the Phe side chain is transferred to the amino-terminal residue of the dipeptide to give the tridentate (Phe-Gly)Pd complex, the aliphatic and aromatic unidentate amine stability constants are closely similar to those of (Gly-Gly)Pd. This lack of stability enhancement for an amino-terminal Phe side chain is insufficiently accounted for by a reduced mole percentage of rotamer h to about 34% from 61% in (Gly-Phe)Pd.[3] Instead, the lack of stability enhancement must be ascribed to the greater flexibility of a side chain attached to an amino terminal tetrahedral nitrogen over a stiff amide trigonal nitrogen[13,14] and to a less satisfactory interaction between the Phe side chain and hydrocarbon portions of coordinated amines in (Phe-Gly)Pd. In the latter complex there is a more nearly cis relation between amine hydrocarbon and Phe side chain. Molecular models show that the two hydrocarbons interact less favorably than when in the nearly trans relationship occurring in (Gly-Phe)Pd.

Substitution of the phenylalanyl by an isoleucyl side chain to give the tridentate (Gly-Ile)Pd complex yields stability constants, when compared to (Gly-Gly)Pd, that show little or no increase for aliphatic amines and small increases for aromatic amines. For the four aromatic amines with one to four methylene groups, the stability constant logarithms for coordination to (Gly–Ile)Pd(H_2O) are 6.95, 7.27, 7.18, and 7.36, respectively.

The isoleucyl side chain contains a secondary butyl group so that in two rotamers g and h a methyl or ethyl group is directed toward the Pd in tridentate (Gly-Ile)Pd. Only the total of rotamer g and h mole percentages is available from the vicinal coupling constant analysis of the two protons, one on the α and one on the β carbon. In the (Gly-Ile)Pd complex 96% of the molecules possess rotamers g and h and only about 4% rotamer t, where the β hydrogen is directed toward the Pd.[3] The stability constant results for coordination of aromatic amines to (Gly-Ile)Pd were analyzed in a way parallel to that already presented for aromatic amine binding to (Gly-Phe)Pd. For each of the four aromatic amines the favored complex conformers all involve the mole percentage sum of rotamers g and h and decrease in the order open-chain amine > Ile–aromatic interaction > aromatic–Pd interaction.

Discussion

The Figure 1 plot of stability constant logarithm for association of (Gly-Gly)Pd(H_2O) with aliphatic amine vs. amine basicity

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yields an excellent straight line over 1.4 pK_a units. The straight line shown in Figure 1 is used as the base line from which the stability constant of a noninteracting amine, K_o, may be predicted from its pK_a.

The least-squares straight line in Figure 1 is based on 10 points. The points for NH_3 and CH_3NH_2 fall 0.03 log unit below the line. If a straight line is drawn through the two points for NH_3 and CH_3NH_2, a small side chain–Pd interaction is suggested for the other aliphatic amines. There would be 11% or less closed form (15% for ethanolamine). Because of the small deviation of the NH_3 and CH_3NH_2 points from the least-squares line in Figure 1, we have chosen it as the base line for further calculations. However, the small deviations might be real. The isoleucyl and valyl side chains in (dipeptide)Pd(II) complexes favor occupying space over the metal ion.[3] The aliphatic dipeptide side chains joined to a chelated ligand possess fewer noninteracting conformers than the unidentate amines of this study.

The original rotamer distribution of the phenylalanyl side chain in (Gly-Phe)Pd is unaffected by binding of the unidentate amines in the open form. As shown in Table IV, when the bound amine interacts with the phenylalanyl side chain, it increases the rotamer *h* mole percentage from its original value of 61% found in the Cl^- and NH_3 complexes to 65–71% according to the wholly independent NMR analysis and to 71–80% according to the primarily stability constant analysis. The reasons for the small difference between the last two sets of percentages are not understood; no single reason appears able to account for it. Both the NMR coupling constant analysis and the stability constant analysis rest on sets of approximations and assumptions. Deviations from normal dihedral angles upon ligand–ligand interaction may contribute to the difference. The important point, however, is that both analyses show an increase in rotamer *h* population in the presence of a phenylalanyl side chain–amine hydrocarbon interaction in the complex.

The results obtained in this research permit a comparison of the energies involved in interactions of the unidentate amine hydrocarbons with both the metal ion in tridentate (dipeptide)Pd complexes and with the phenylalanyl side chain in (Gly-Phe)Pd. Following an approach suggested for assessing the amount of macrochelate formation in metal ion complexes of nucleotides[15] and also applied to ligand–ligand interactions in complexes,[1] we provide a formulation for enhanced stability due to interactions not present in a base line complex. In terms of eq 1–3, we define the stability *enhancement E* by

$$E_{ML} = (K_G - K_o)/K_o = K_{CG}/K_o = [CMG]/[AMG] \quad (5)$$

The subscript ML signifies that this specific enhancement results from a metal–ligand (hydrocarbon) interaction present in closed species CMG but absent in species AMG. The amount by which the enhancement contributes to an increase in stability constant is found by rearrangement of eq 5 to give

$$K_G = K_o(1 + E_{ML}) \quad (6)$$

We label the quantity in parentheses, $1 + E$, the *enhancement factor*. It is the factor by which the base-line stability constant, K_o, need be multiplied to give the observed stability constant, K_G. Provided K_o may be estimated, enhancements, E, and enhancement factors, $1 + E$, are easily calculated from eq 6 from the expression

$$1 + E = 10^{\log(K_G/K_o)}$$

The contribution of the enhancement factor to the free energy change for complex formation is given by $-\Delta G° = RT \ln (1 + E)$.

By the definition of eq 5 the stability enhancements due to the metal–aromatic ring interaction for coordination to (Gly–Gly)-Pd(H_2O) by the four aromatic amines in Table II are $E_{ML} = 0.87$, 1.62, 0.29, and 0.45, respectively. The corresponding log $(1 + E_{ML})$ values are 0.27, 0.42, 0.11, and 0.16. Since the coordinated amine can interact with Pd on either side of the coordination plane, there is a statistical factor of 2 included in E_{ML}.

For later comparative purposes we are interested in the intrinsic enhancement that refers to the enhanced stability due to interaction on only one side of the coordination plane of (dipeptide)Pd. To allow for the statistical bias of two receptor sides for an amine hydrocarbon interaction, we remove the inherent statistical factor of 2 from eq 5 by defining a new enhancement E_{LM} (with reversed subscripts).

$$E_{LM} = K_{CG}/(2K_o) = E_{ML}/2$$

Values of the enhancement factor log, log $(1 + E_{LM})$, appear in the last column of Table II. These values correspond to an intrinsic enhanced stability due to an aromatic ring–Pd interaction from 0.3 to 1.5 kJ/mol in $-\Delta G°$. The associated lack of enhanced stability with aliphatic amines suggests that there is a favorable aromatic ring–Pd interaction and not merely a more passive aromatic ring preference for space near the metal ion over out in solution.

Analogous to the metal–ligand enhancement defined in eq 5, we define an enhancement due to a ligand–ligand interaction appropriate for the interaction between the dipeptide phenyl ring and the amine hydrocarbon as

$$E_{LL} = [CMP_h']/[AMP_h] = K_{CPh'}/K_{APh} = K_{CPh'}/K_o$$

The enhancement factor due to a ligand–ligand interaction is given by $1 + E_{LL}$. Values of log $(1 + E_{LL})$ appear in the last column of Table V.

Three different measurements lead to the identical conclusion that the maximum interaction of the linear unidentate amines with the phenylalanyl side chain in (Gly-Phe)Pd occurs with a three-carbon length as in propylamine and that additional length does not strengthen the interaction further. The chemical shift differences in Table III fade to near insignificance after the third carbon. The primarily stability constant analysis summarized in Table V shows a leveling off near 50% at propylamine of the mole percentage of species CMP_h', the species with a ligand–ligand interaction. Finally, the conclusion is strengthened by results of the NMR coupling constant analysis reported in Table IV where the rotamer *h* mole percentage increases and levels off at propylamine.

The conclusions summarized in the previous paragraph receive clear, quantitative expression in the enhancement factor logs for the ligand–ligand interaction tabulated in the last column of Table V. For the (Gly-Phe)Pd complex the log $(1 + E_{LL})$ values increase from 0 for NH_3 to 0.20 for CH_3NH_2 to 0.32 for $CH_3CH_2NH_3$ and level off at about 0.40 log unit for propyl and higher aliphatic amines. The 0.40 value corresponds to 2.3 kJ/mol in $-\Delta G°$. The dipeptide phenyl ring–aromatic amine ring interactions show, from the last four entries in Table V, enhancement factor logs from 0.46 to 0.67 log unit, corresponding to 2.6 to 3.8 kJ/mol in $-\Delta G°$.

For the isoleucyl side chain in (Gly-Ile)Pd, the enhancement factor $(1 + E_{LL})$ logarithms due to the isoleucyl–aromatic interaction for the four aromatic amines with one to four methylene groups are given by 0.27, 0.27, 0.15, and 0.17 log unit, respectively. Interestingly, the 0.27 log unit values for benzylamine and phenethylamine with the isoleucyl side chain, containing a methyl and ethyl group, is between the enhancement factor logs for the side chain phenyl group with methyl- and ethylamines listed in the last column of Table V.

This paper compares the stabilities and conformations of a series of aliphatic and aromatic unidentate amines coordinated to the fourth position of tridentate (dipeptide)Pd complexes. The rotamer mole percentages of the side chains in (Gly-Phe)Pd and (Gly-Ile)Pd are included in the analysis. The order of decreasing interaction energies as determined by optimal enhancement factor logarithms listed in the last columns of Tables II and V and the previous paragraph is given by phenyl–aromatic > phenyl–(propyl or larger) > phenyl–ethyl > isoleucyl–aromatic > Pd–aromatic > phenyl–methyl >> Pd–aliphatic ~ isoleucyl–aliphatic ~ 0.

Estimates have been attempted for association of amino acid side chains into hydrophobic bonds. As adjustable parameters in a theory have been scaled to conform to experimental results,

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the values quoted should be reasonable. For association of two phenylalanyl side chains the free energy change is estimated to be −1.4 kcal/mol,[16] which yields the equilibrium constant K_{NS} = 11 M^{-1}. Neither the free energy change nor K_{NS} may be compared directly to quantities in the paper because the enhancement factor given by $1 + E_{LL}$ is unitless. However the ratio $(1 + E_{LL})/K_{NS}$ = [B] may be taken as the effective molar concentration of the second intramolecular reactant within our complexes. From Table V the optimum $1 + E_{LL} = 10^{0.67} = 4.7$ for the interaction between the phenylalanyl side chain and coordinated phenethylamine. The corresponding concentration [B] = 0.44 M corresponds to the effective concentration of the second intramolecular reactant. This concentration is greater than that of the complex which is in the mM range in our experiments. For the phenylalanyl–isoleucyl association, the estimated free energy change is −0.8 kcal/mol,[16] which corresponds to the equilibrium constant K_{NS} = 3.9 M^{-1}. For the enhancement factor between the isoleucyl side chain and phenethylamine $(1 + E_{LL}) = 10^{0.27} = 1.9$, from which [B] = 0.48 M, similar to the concentration found above. Though approximate, these higher than experimental values for [B] are, like the chelate effect, a result of a high effective amine hydrocarbon concentration due to prior nitrogen coordination to Pd.

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Single Electron Transfer Reaction of Aluminum Hydride with N-Heterocycles. ESR Characterization of the Radical Products

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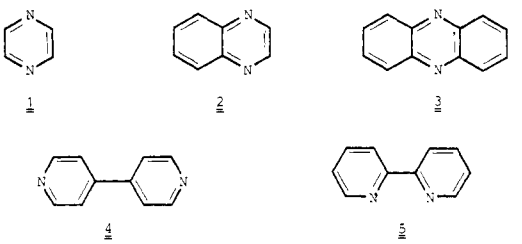
Abstract: The single electron transfer (SET) reactions AlH_3 and AlD_3 in THF with pyrazine (**1**), quinoxaline (**2**), phenazine (**3**), 4,4′-bipyridine (**4**), and 2,2′-bipyridine (**5**) have been studied by electron spin resonance (ESR) spectroscopy. Besides the conventional diamagnetic reduction products, persistent radical complexes are formed as escape products that could be fully characterized by ESR. The paramagnetic species obtained from the bridging systems **1**–**4** are binuclear radical anion complexes $[\mathbf{1}(AlH_3)_2]^{-\bullet}$–$[\mathbf{4}(AlH_3)_2]^{-\bullet}$, whereas the chelating 2,2′-bipyridine radical anion coordinates with one $^{+}AlH_2$ ion from the aluminum hydride dissociation equilibrium. A hyperconjugative model (π_N/σ_{Al-H}) is used to relate the aluminum hydride coupling constants with the coordination geometry in the radical complexes.

There is rapidly accumulating evidence that the reductions of organic compounds, S, by metal alkyls and hydrides may proceed via single electron transfer (SET) mechanisms (eq 1).[1]

$$S + MX \xrightarrow{SET} [S^{-\bullet}, M^{+\bullet}] \begin{cases} \xrightarrow{\text{escape}} [S^{-\bullet}, M^{+}] + X^{\bullet} \\ \xrightarrow{\text{cage}} XSM \xrightarrow{\text{hydrolysis}} \text{products} \end{cases} \quad (1)$$

The frequent observation of relatively persistent radicals as "escape" products by electron spin resonance (ESR) has added evidence to substantiate this mechanism,[2-6] even though the identity of the radical products was not always clearly established (e.g., ref 3a).

In the course of studies on organometallic radical complexes we have found that the radical anions of aromatic N-heterocycles such as various 1,4-diazines[7] pyrazine (**1**), quinoxaline (**2**), and phenazine (**3**) as well as those from bipyridines **4**[8a] and **5**[8b] are very suitable ligands for organoaluminum species.[9] Presented



here is evidence that paramagnetic (open shell) complexes are also produced in SET reactions of aluminum hydrides with the neutral heterocycles,[4c-f] i.e., from diamagnetic (closed shell) precursors. The spectroscopic results obtained previously[9] have thus become very valuable for the analysis and identifications of these new radical complexes.

In this paper, the results of detailed ESR studies on the radical complexes formed from the simple hydride AlH_3 (or AlD_3) and substrates **1**–**5** will be presented. These new radical complexes offer the advantage that all relevant nuclei, ^1H, ^2D, ^{14}N, and ^{27}Al, have nonzero nuclear spins and exhibit ESR coupling constants large enough to be detected under conventional high-resolution

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