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# Regulated Dioxygen Affinities by Steric Restrictions on Axial Bases in "Jellyfish" Type Cobalt(II) Porphyrins[1]

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The title compounds were prepared to examine the effect of axial base orientation on the dioxygen affinities of (porphyrinato)-cobalt(II) complexes. These porphyrins were derived from *meso*-tetrakis(2-aminophenyl)porphyrin, with valeramido or pivalamido groups appended on one side of the porphyrin plane as fences in order to control the orientation of the axial base plane, while a nonanediamido or dodecanediamido group is bridged over the other side of the porphyrin plane to inhibit the binding of axial bases. Equilibrium constants in toluene solution are reported for bindings of imidazoles, pyridine, and $O_2$ to the cobalt(II) complexes of these porphyrins. As the steric bulk of the fences increases, the bindings of axial bases are enhanced, while the dioxygen affinities are decreased. These changes in dioxygen affinities are interpreted in terms of the orientation of the axial base plane, which changes the strength of $\pi$-electron donation from the axial base to the (porphyrinato)cobalt(II).

Hemoglobin (Hb) and myoglobin (Mb) bind $O_2$ reversibly, and the factors regulating dioxygen affinities of them can be divided into two classes: distal histidine (E7) and proximal histidine (F8). The latter, the proximal histidine, is one of the amino acids in globin, and its imidazole group (axial base) is considered to be bound to the iron with some steric restriction by the globin. Such restrictions might affect both the bond length and the bond angle between the iron and the imidazole and also the rotational orientation of the imidazole plane.[2] Indeed, it has been suggested that the dioxygen affinity of the T-structure in the subunits of Hb is lowered mostly by the rotational orientation and by the tilt of the imidazole, which opposes its movement toward the porphyrin plane.[3,4] Furthermore, Scheidt et al.[5] have been suggested that the spin state of (porphyrinato)iron(III) complexes can be controlled by the axial base orientation.

Many studies[6-11] using model porphyrinato complexes have dealt with the role of cavity, and reports[12-14] on the effects of axial base on dioxygen affinities have also appeared. These works have confirmed that the dioxygen affinities of both cobalt and iron porphyrinato complexes are increased with increases in $\sigma$- and $\pi$-basicities of axial bases. Since $\pi$-electron donation from the axial base to the metal can be varied with the rotational orientation of the axial base plane,[15] it is possible that the dioxygen affinities of hemoproteins are controlled by changes in the rotational orientation of the axial base plane. In order to examine the effect of axial base orientation on the dioxygen affinities, we report here on the so called "jellyfish" type (porphyrinato)cobalt(II) complexes. In the "jellyfish" type (porphyrinato)cobalt(II) complexes (Figures 1 and 2), valeramido or pivalamido groups are appended on one side of an porphyrin plane as a "fence" in order to control the orientation of an axial base plane, and the other side of the porphyrin plane has a "basket-handle" type[9] cavity to inhibit the binding of the axial bases. This paper reports the effects of the steric changes in fences both on the binding of the axial bases and on the dioxygen affinities for these "jellyfish" porphyrins.

## Experimental Section

**General Information.** Proton NMR spectra were recorded on a JEOL-FX-100 and a JEOL-MH-100 spectrometer. Mass spectra were obtained on a JEOL JMX-DX300 instrument. Electronic spectra were recorded on a Hitachi 340 spectrophotometer. Oxygenation equilibria were determined by spectrophotometric titration as reported earlier.[16] Toluene solutions containing the complex and an axial base were exposed to various partial pressures of $O_2$ in a cell mounted with a rubber septum equipped with gas inlet and gas outlet tubes. Various partial pressures of $O_2$ were obtained by a Gas Mixture instrument (Kofloc Model GM-3A). Temperatures were maintained to a precision of ±0.1 °C by the use of a constant-temperature circulation pump (Neslab Model RTE-8) passing through a variable-temperature cell holder. Base concentrations were chosen to give >99% of the five-coordinate complex. The spectra were recorded in the 600–460 nm range. $P_{1/2}$ values (half-saturation oxygen pressures of $O_2$ binding) were calculated by the method of Beugelsdijk and Drago.[17] Equilibrium constants for the axial base bindings to the (porphyrinato)cobalt(II) complexes were determined by spectrophotometric titration. Aliquots of axial base, either neat or diluted with toluene, were added from a calibrated syringe through a rubber septum to a toluene solution of the (porphyrinato)cobalt(II) complex ($5 \times 10^{-5}$ M) under $N_2$ in a cell used for the oxygenation equilibria. The spectra were recorded in the 600–460-nm range.

**Materials.** Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Pyridine (py), 1-methylimidazole (1-MeIm), and 1,2-dimethylimidazole (1,2-$Me_2$Im) were vacuum distilled from KOH just before use. Purifications of 2-methylimidazole (2-MeIm) and 2-ethylimidazole (2-EtIm) were carried out by alumina column chromatography. Toluene were

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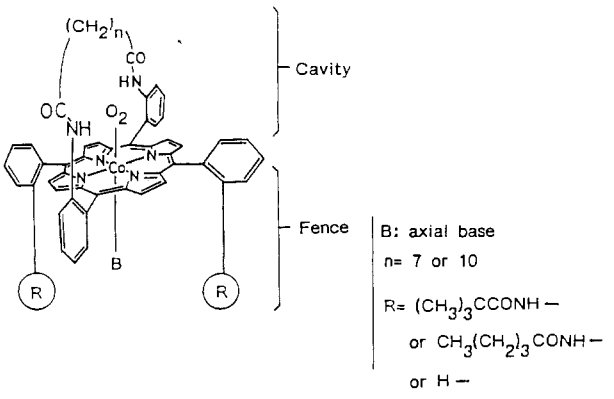


**Figure 1.** Schematic representation of cavity and fence in "jellyfish" (porphyrinato)cobalt(II) complexes.

stirred with concentrated $H_2SO_4$ and then washed with $H_2O$, 5%-NaOH, and $H_2O$ in turn, dried over $CaCl_2$, and distilled.

**Synthesis.** 5β,15β-Bis(2-aminophenyl)-10α,20α-(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az-amββ), 5β,15β:10α,20α-bis(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az2), 5β,15β-bis(2-pentanamidophenyl)-10α,20α-(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az-valββ), and cobalt(II) complexes of $H_2$-Az2 and $H_2$-Az-valββ were prepared by the method described before.[16b] 5β,15β-Bis(2-pentanamidophenyl)-10α,20α-(dodecanediamidodi-*o*-phenylene)porphyrin ($H_2$-De-amββ) and 5β,15β:10α,20α-bis(dodecanediamidodi-*o*-phenylene)porphyrin ($H_2$-De2) were prepared by the literature method.[9]

**5α,15β-Bis(2-aminophenyl)-10α,20α-(nonanediamidodi-*o*-phenylene)-porphyrin ($H_2$-Az-amαβ) and 5α,15α-Bis(2-aminophenyl)-10α,20α-(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az-amαα).** $H_2$-Az-amββ (1 g) was dissolved in 500 mL of benzene containing silica gel (70–230 mesh, 300 g), and the mixture was heated at reflux for 8 h with stirring. After the mixture was cooled, the porphyrins adsorbed on silica gel were extracted with acetone and the extract evaporated to dryness. The residue was dissolved in $CHCl_3$ and then chromatographed on silica gel ($CHCl_3$, 4 × 30 cm). Elution with 3:2 $CHCl_3$/ether afforded $H_2$-Az-amαβ and then elution with 5:4:1 $CHCl_3$/ether/acetone afforded $H_2$-Az-amββ. Each band was collected, evaporated to dryness, and then crystallized from benzene. The yield of $H_2$-Az-amαβ was 30% and that of $H_2$-Az-amαα was 30%. $^1$H NMR data are shown in Table I.

**5β,15β-Bis[2-(2,2-dimethylpropanamido)phenyl]-10α,20α-(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az-pivββ).** A $CH_2Cl_2$ solution (250 mL) of $H_2$-Az-amββ (0.3 g, 0.36 mmol) was treated with pyridine (0.5 mL) and pivaloyl chloride (1.68 mL, 12.6 mmol) at room temperature. The solution was stirred for 0.5 h, then 10% aqueous ammonia (100 mL) was added, and the solution was stirred for 0.5 h. The organic layer was separated and stripped to dryness. The resultant solid was dissolved in $CHCl_3$ and chromatographed on a silica gel column ($CHCl_3$, 4 × 30 cm). The column was eluted with 3:2 $CHCl_3$/ether. The product was crystallized from benzene. Yield was 0.28 g (78 %). Anal. Calcd for $C_{63}H_{62}N_8O_4$: C, 76.03; H, 6.28; N, 11.26. Found: C, 76.20; H, 6.27; N, 10.85. FAB-MS: *m/e* 995 ($M^+ + 1$). $^1$H NMR data are shown in Table I.

**5,15-Diphenyl-10α,20α-(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az-P).** $H_2$-Az-amββ (0.1 g, 0.12 mmol) was suspended in 0.6 M HCl (10 mL), and to the mixture was added 0.024 M $NaNO_2$ (10 mL) dropwise in an ice bath. The resulting mixture was stirred for 1 h in an ice bath, and then 50% $H_3PO_2$ solution (50 mL) was added. The mixture was placed in a refrigerator for 8 h, then neutralized with 10% aqueous ammonia, and extracted with $CHCl_3$. The extract was chromatographed on a silica gel column ($CHCl_3$, 3 × 20 cm) using 9:1 $CHCl_3$/ether as eluent. The product was crystallized from benzene. Yield was 0.06 g

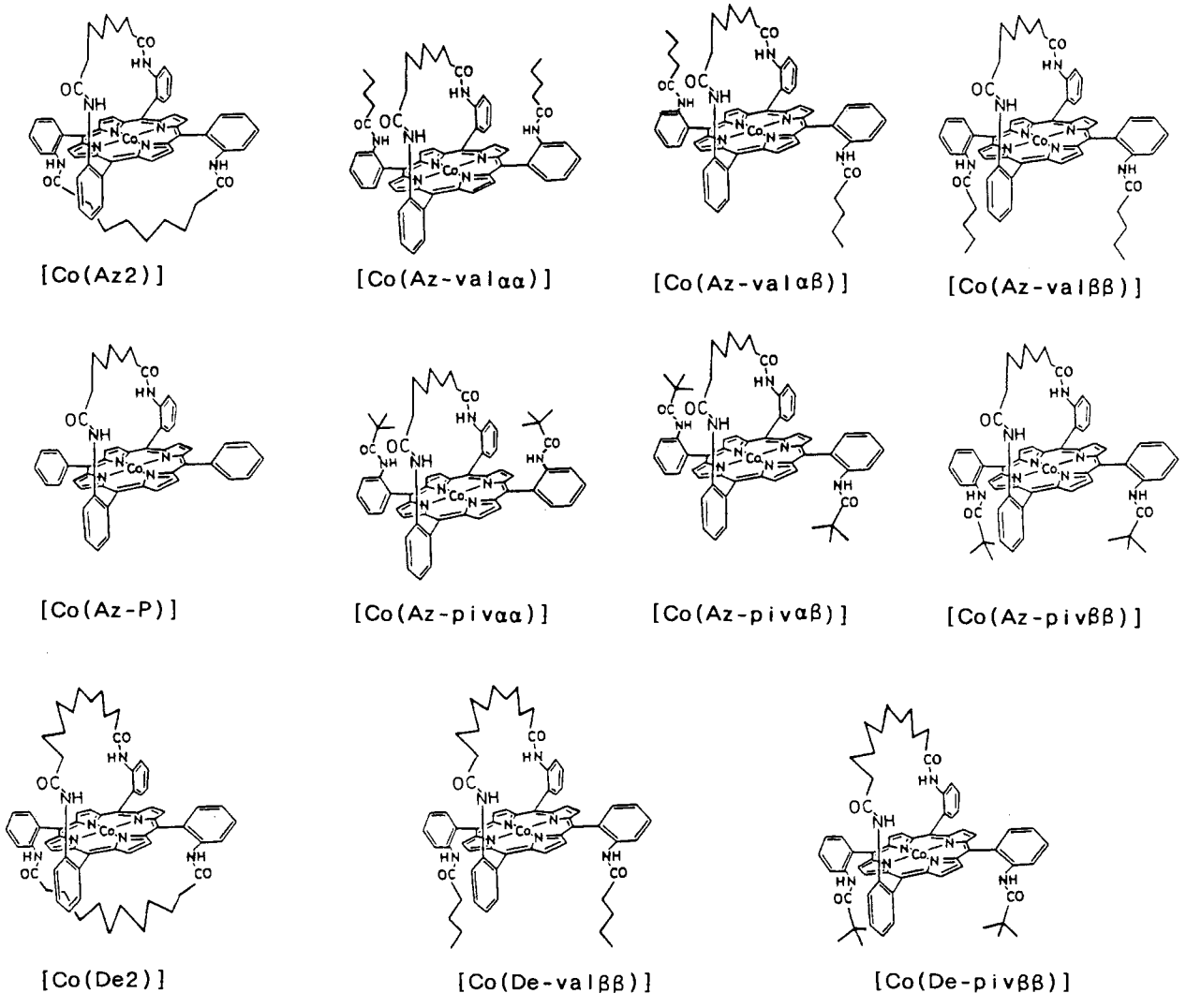


**Figure 2.** "Jellyfish" (porphyrinato)cobalt(II) complexes.

**Table I.** $^1$H NMR Data[a]

| porphyrins | aliphatic protons[b] | methyl protons[c] | amino protons[d] | amido (fence) protons[e] | amido(strap) protons[f] |
|---|---|---|---|---|---|
| $H_2$-Az-am$\beta\beta$ | −2.61, −1.32, −0.60, 0.94 | | 3.50 | | 5.86 |
| $H_2$-Az-am$\alpha\beta$ | −2.81, −2.28, −1.43, −1.03, −0.55, 1.14 | | 3.73,3.27 | | 6.02 |
| $H_2$-Az-am$\alpha\alpha$ | −2.51, −1.18, −0.59, 1.21 | | 3.76 | | 6.02 |
| $H_2$-Az-piv$\beta\beta$ | −2.49, −1.26, −0.56, 1.17 | 0.14 | | 7.01 | 5.95 |
| $H_2$-Az-piv$\alpha\beta$ | −3.49, −2.58, −1.83, −1.03, −0.63, 0.96 | 0.13,0.06 | | 7.35,7.07 | 6.07 |
| $H_2$-Az-piv$\alpha\alpha$ | −3.31, −1.46, −0.90, 1.24 | 0.44 | | 7.44 | 6.33 |
| $H_2$-Az-val$\beta\beta$ | −2.51, −1.25, −0.54, *g* | | | 6.52 | 5.95 |
| $H_2$-Az-val$\alpha\beta$ | −2.99, −2.43, −1.60, −1.08, −0.53, *g* | | | 7.17,6.42 | 6.12 |
| $H_2$-Az-val$\alpha\alpha$ | −3.17, −1.47, −1.06, *g* | | | 7.12 | 6.29 |
| $H_2$-Az-P | −2.51, −1.24, −0.51, 1.16 | | | | 5.99 |
| $H_2$-Az2 | −2.28, −1.08, −0.48, 0.94 | | | | 5.95 |
| $H_2$-De-am$\beta\beta$ | −0.42, 0.40 | | 3.47 | | 6.87 |
| $H_2$-De-piv$\beta\beta$ | −0.57, 0.39 | 0.20 | | 7.12 | 6.82 |
| $H_2$-De-val$\beta\beta$ | −0.56, *g* | | | 6.60 | 6.84 |
| $H_2$-De2 | −0.48, 0.33 | | | | 6.77 |

[a] Chemical shifts (ppm) from TMS in $CDCl_3$. [b] Protons in strapped chains. [c] Methyl protons in pivaloyl groups. [d] Amino protons in phenylamino groups. [e] Amido protons in pivalamido groups and valeramido groups. [f] Amido protons in strapped chains. [g] Resonance was not assigned.

(62 %). Anal. Calcd for $C_{53}H_{44}N_6O_2$: C, 79.87; H, 5.57; N, 10.55. Found: C, 79.48; H, 5.50; N, 10.89. FAB-MS: *m/e* 797 ($M^+ + 1$). $^1$H NMR data are shown in Table I.

The following six porphyrins were prepared from the coupling of the corresponding porphyrin and acid chloride in $CH_2Cl_2$ containing pyridine, following the general procedure described for $H_2$-Az-piv$\beta\beta$.

**5$\alpha$,15$\beta$-Bis(2-pentanamidophenyl)-10$\alpha$,20$\alpha$-(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az-val$\alpha\beta$).** Anal. Calcd for $C_{63}H_{62}N_8O_4$: C, 76.03; H, 6.28; N, 11.26. Found: C, 75.40; H, 6.28; N, 11.15. $^1$H NMR data are shown in Table I.

**5$\alpha$,15$\alpha$-Bis(2-pentanamidophenyl)-10$\alpha$,20$\alpha$-(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az-val$\alpha\alpha$).** Anal. Calcd for $C_{63}H_{62}N_8O_4$: C, 76.03; H, 6.28; N, 11.26. Found: C, 75.43; H, 6.15; N, 11.24. $^1$H NMR data are shown in Table I.

**5$\alpha$,15$\beta$-Bis[2-(2,2-dimethylpropanamido)phenyl]-10$\alpha$,20$\alpha$-(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az-piv$\alpha\beta$).** Anal. Calcd for $C_{63}H_{62}N_8O_4$: C, 76.03; H, 6.28; N, 11.26. Found: C, 75.83; H, 6.11; N, 10.80. $^1$H NMR data are shown in Table I.

**5$\alpha$,15$\alpha$-Bis[2-(2,2-dimethylpropanamido)phenyl]-10$\alpha$,20$\alpha$-(nonanediamidodi-*o*-phenylene)porphyrin ($H_2$-Az-piv$\alpha\alpha$).** Anal. Calcd for $C_{63}H_{62}N_8O_4$: C, 76.03; H, 6.28; N, 11.26. Found: C, 75.67; H, 5.90; N, 11.59. $^1$H NMR data are shown in Table I.

**5$\beta$,15$\beta$-Bis(2-pentanamidophenyl)-10$\alpha$,20$\alpha$-(dodecanediamidodi-*o*-phenylene)porphyrin ($H_2$-De-val$\beta\beta$).** Anal. Calcd for $C_{66}H_{68}N_8O_4$: C, 76.42; H, 6.61; N, 10.80. Found: C, 75.79; H, 6.45; N, 11.00. $^1$H NMR data are shown in Table I.

**5$\beta$,15$\beta$-Bis[2-(2,2-dimethylpropanamido)phenyl]-10$\alpha$,20$\alpha$-(dodecanediamidodi-*o*-phenylene)porphyrin ($H_2$-De-piv$\beta\beta$).** Anal. Calcd for $C_{66}H_{68}N_8O_4$: C, 76.42; H, 6.61; N, 10.80. Found: C, 76.33; H, 6.55; N, 11.16. $^1$H NMR data are shown in Table I.

**Cobalt(II) Insertion.** Cobalt(II) complexes of **$H_2$-Az-piv$\alpha\alpha$**, $H_2$-Az-piv$\alpha\beta$, $H_2$-Az-piv$\beta\beta$, $H_2$-Az-val$\alpha\alpha$, $H_2$-Az-val$\alpha\beta$, and $H_2$-Az-P were synthesized in THF by using $CoCl_2$, those of $H_2$-Az2, $H_2$-De-piv$\beta\beta$, $H_2$-De-val$\beta\beta$, and $H_2$-De2 were synthesized in acetic acid by using Co$(CH_3COO)_2$·$4H_2O$, and purification was carried out by alumina column chromatography as described previously.[16]

## Results and Discussion

The porphyrin $H_2$-Az-P can be also prepared from 5,15-diphenyl-10$\alpha$,20$\alpha$-bis(2-aminophenyl)porphyrin,[18] but the preparation method of the latter porphyrin was tedious and proceeded in low yield. $H_2$-Az-P was therefore prepared by diazotization[19] of $H_2$-Az-am$\beta\beta$ followed by replacement of the diazonium group with hydrogen. The isomerization of $H_2$-Az-am$\beta\beta$ was carried out by refluxing benzene solution of $H_2$-Az-am$\beta\beta$ for 8 h in the presence of silica gel.[20] By this method, the $\alpha\beta$ and $\alpha\alpha$ isomers were isolated in 30% yield.

Three isomers of $H_2$-Az-am were characterized by $^1$H NMR (Table I). The signals of amino groups of $H_2$-Az-am$\alpha\alpha$ and $H_2$-Az-am$\beta\beta$ are appeared at 3.76 and 3.50 ppm, respectively. On the other hand, these signals of $H_2$-Az-am$\alpha\beta$ are split with a ratio of 1:1 at 3.73 and 3.27 ppm. These $^1$H NMR data imply that two amino groups of $H_2$-Az-am$\alpha\alpha$ or $H_2$-Az-am$\beta\beta$ are equivalent and two amino groups of $H_2$-Az-am$\beta\beta$ are on the other side of the porphyrin plane from that bridged by the aliphatic chain.[16b] The two amino groups in $H_2$-Az-am$\alpha\alpha$ are therefore concluded to be on the same side of the porphyrin plane. In $H_2$-Az-am$\alpha\beta$, the two amino groups are not equivalent, and thus the two amino groups are concluded to be on opposite sides of the porphyrin plane.

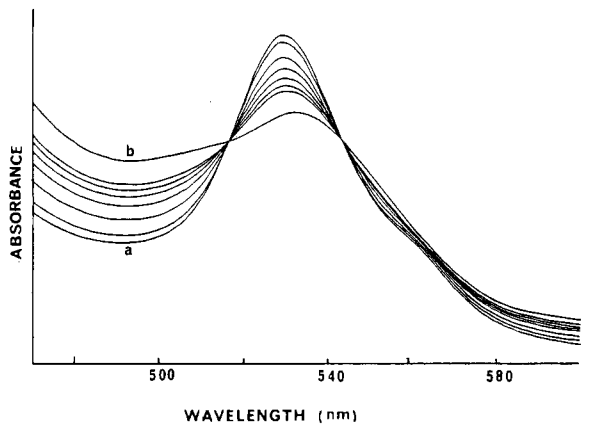


**Figure 3.** Spectral changes occurring upon titration of a $6 \times 10^{-5}$ M toluene solution of [Co(Az-piv$\alpha\beta$)] with 1-MeIm in toluene at 25 °C: (a) [1-MeIm] = 0 M; (b) [1-MeIm] = $8.2 \times 10^{-3}$ M. The following intermediate concentrations of 1-MeIm were used: $0.8 \times 10^{-5}$, $2.4 \times 10^{-5}$, $3.9 \times 10^{-5}$, $5.5 \times 10^{-5}$, $7.0 \times 10^{-5}$, and $8.5 \times 10^{-5}$ M.

The lack of isomerization during the introduction of valeramido or pivalamido groups was confirmed by $^1$H NMR measurements. That is, the signals of amide group in valeramido or pivalamido groups are split in two in $H_2$-Az-piv$\alpha\beta$ and $H_2$-Az-val$\alpha\beta$ and are singlets in $\alpha\alpha$ and $\beta\beta$ isomers of $H_2$-Az-piv and $H_2$-Az-val, similar to the pattern observed for the signals of amino groups in the three isomers of $H_2$-Az-am. Thus, the amido signals may also be used as a marker to characterize these isomers. The lack of isomerization during cobalt insertion was confirmed by TLC (thin-layer chromatography) or $^1$H NMR of the demetalated products[16b] of (porphyrinato)cobalt(II) complexes.

The upfield shifts of methylene protons in nonanediamido and dodecanediamido groups are due to the ring current shift of the porphyrins.[21] These groups are thus confirmed to be bridging over the porphyrin plane. In $H_2$-Az-P, $H_2$-Az-piv$\beta\beta$, and $H_2$-

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**Table II.** Base and $O_2$ Binding to "Jellyfish" Type Cobalt(II) Porphyrins[a]

| | base = py | | base = 1-MeIm | |
|---|---|---|---|---|
| complexes | $K_B$, $M^{-1}$ | $P_{1/2}$, Torr | $K_B$, $M^{-1}$ | $P_{1/2}$, Torr |
| [Co(Az-piv$\alpha\alpha$)] | $3.5 \times 10^3$ | 80 | $2.9 \times 10^4$ | 9 |
| [Co(Az-piv$\alpha\beta$)] | $8.5 \times 10^3$ | 452 | $6.8 \times 10^4$ | 104 |
| [Co(Az-piv$\beta\beta$)] | $1.5 \times 10^4$ | 12000[b] | $2.1 \times 10^5$ | 1460[b] |
| [Co(Az-val$\alpha\alpha$)] | $4.4 \times 10^3$ | 404 | $3.2 \times 10^4$ | 93 |
| [Co(Az-val$\alpha\beta$)] | $8.6 \times 10^3$ | 1000 | $6.9 \times 10^4$ | 240 |
| [Co(Az-val$\beta\beta$)] | $1.0 \times 10^4$ | 3200[b] | $9.5 \times 10^4$ | 396 |
| [Co(Az-P)] | $1.7 \times 10^3$ | 671 | $1.2 \times 10^4$ | 146 |
| [Co(Az2)] | <10 | | $1.1 \times 10^2$ | 382 |
| [Co(De-piv$\beta\beta$)] | | | $1.6 \times 10^5$ | 8000[b] |
| [Co(De-val$\beta\beta$)] | | | $5.5 \times 10^4$ | 2200[b] |
| [Co(De2)] | | | $3.4 \times 10^4$ | 3000[b] |

[a] At 25 °C in toluene. Error limits <10% in $P_{1/2}$ and <20% in $K_B$. [b] Extrapolated from the van't Hoff plots.

Az-val$\beta\beta$, methylene protons of nonanediamido group exhibit identical chemical shifts, so it is evident that these three porphyrins have the same size of cavity. Similarly it is concluded that $H_2$-De-piv$\beta\beta$ and $H_2$-De-val$\beta\beta$ have the same sized cavity as judged by chemical shifts of dodecanediamido group.

**Axial Base Binding.** The equilibrium constant ($K_B$) for an axial base (B) binding to a (porphyrinato)cobalt(II) complex (CoP) is represented in (1). The $K_B$ values were measured in toluene

$$[CoP] + B \overset{K_B}{\rightleftharpoons} [CoPB] \quad (1)$$

at 25 °C. Upon addition of an axial base, clear isosbestic points for the formation of the five-coordinate complex were observed (Figure 3). The formation of a six-coordinated base adduct was not observed under these experimental conditions.[13b] The results are listed in Table II.

The $K_B$ value for the binding of pyridine (py) or 1-methylimidazole (1-MeIm) to [Co(Az2)] is ca. 100-fold less than those of other complexes having the "cavity" constructed by a nonanediamido group. Thus, it is clear that the axial base bindings to the cavity constructed by a nonanediamido group can be negligible in the discussion on the changes in the $K_B$ values. The $K_B$ value for the binding of 1-MeIm to [Co(De2)] is, however, comparable to that of [Co(Azpiv$\alpha\alpha$)]. It is evident that the cavity constructed by a dodecanediamido group cannot inhibit the binding of 1-MeIm. Therefore, we can discuss the changes in $K_B$ values of the complexes having the cavity constructed by nonanediamido group.

The electronic effect[22] of substituents on phenyl rings may be responsible for observed changes in the $K_B$ values between [Co(Az-val$\alpha\alpha$)] and [Co(Az-piv$\alpha\alpha$)], which have the same geometrical location of the amido groups. Since the valeramido group is a more electron-withdrawing substituent than the pivalamido group,[23] the larger $K_B$ valle of [Co(Az-val$\alpha\alpha$)] as compared with that of [Co(Az-piv$\alpha\alpha$)] is consistent with the observation of Walker et al.[22]

The $K_B$ values for the binding of py or 1-MeIm to each three isomers of [Co(Az-val)] and of [Co(Az-piv)] are increased in the order of $\alpha\alpha$, $\alpha\beta$, and $\beta\beta$ isomers. Because this is the same order of the increase in the number of "fences", this result can be explained by that axial base bindings affinities are enhanced by increasing the number of amido groups around the binding site. An analogous explanation has been given by Lexa et al.[24] in the study on "basket-handle" (porphyrinato)iron(II) complexes. They have been found that the axial base bindings of these complexes are affected by the geometrical location of amido groups. They have concluded, however, that the $\alpha\alpha$ isomer gives a more favorable geometrical location of the amido groups for axial base bindings than does the $\beta\beta$ isomer.

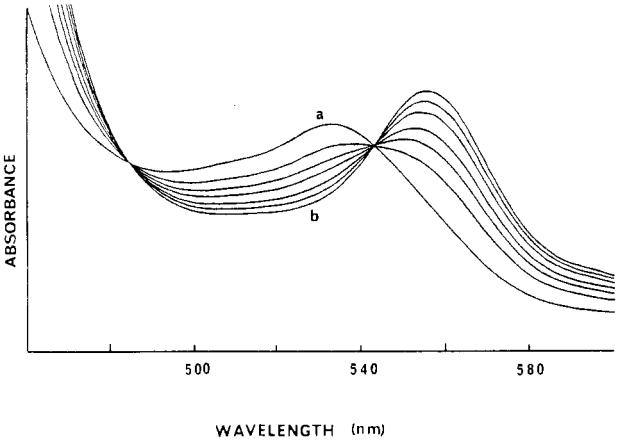


**Figure 4.** Spectroscopic determination of $P_{1/2}$ values for [Co(Az-piv$\alpha\beta$)(1-MeIm)] in toluene at 25 °C: (a) under $N_2$; (b) under 755 Torr of $O_2$. The following partial pressures of $O_2$ were used: 76, 151, 227, 378, and 529 Torr.

The changes in the $K_B$ values of [Co(Az-val$\beta\beta$)] and [Co(Az-piv$\beta\beta$)], however, cannot be explained by the argument described above. That is, these two complexes have the same geometrical location of the amido groups. Nevertheless, the $K_B$ value of [Co(Az-piv$\beta\beta$)] is ca. 10-fold larger than that of [Co(Az-val$\beta\beta$)]. Also, this observation cannot be explained by an electronic effect. Therefore, in the $\beta\beta$ isomers, it is suggested that other factors such as the steric interaction between the axial base and fence may be responsible for this observation. A possible explanation is that the fences may act as a cavity for the binding of the axial base as the pivalamido groups in picket-fence complexes do for the binding of $O_2$.[25] Because of limited data, further discussion on the details of this kind of interaction cannot be given.

**Dioxygen Binding.** The dioxygen binding to five-coordinate (porphyrinato)cobalt(II) complexes (CoPB) is illustrated by (2),

$$[CoPB] + O_2 \overset{K_{O_2}}{\rightleftharpoons} [CoPB(O_2)] \quad (2)$$

where $P_{1/2} = 1/(K_{O_2})$. The complexes prepared in this work bind $O_2$ reversibly in toluene at 25 °C in the presence of an excess axial base (ca. 100-fold excess) as shown in Figure 4. The $P_{1/2}$ values obtained are listed in Table II. As stated in the section on axial base binding, the axial base bindings to the cavity side of the complexes having a strapping nonanediamido group are negligible. Thus, the dioxygen binding site is concluded to be on the cavity side in these complexes.

In [Co(Az-piv$\alpha\alpha$)(B)] and [Co(Az-val$\alpha\alpha$)(B)], pivalamido and valeramido groups are attached on the same side of the porphyrin plane to which $O_2$ binding occurs, so it is expected that these groups function as a cavity stabilizing the Co–$O_2$ bond. Indeed, the $P_{1/2}$ value of [Co(Az-piv$\alpha\alpha$)(1-MeIm)] is smaller (higher dioxygen affinity) than that of [Co(Az-val$\alpha\alpha$)(1-MeIm)] and is about 16-fold smaller than that of [Co(TpivPP)].[7b] This observation is in accord with our previous results[11] that the pivalamido group functions as a cavity more effectively than the valeramido group in the derivatives of picket-fence (porphyrinato)cobalt(II) complexes.

Since there is one valeramido group that can act as a cavity, the dioxygen affinity of [Co(Az-val$\alpha\beta$)(B)] must be higher than that of [Co(Az-P)(B)]. The $P_{1/2}$ value of [Co(Az-val$\alpha\beta$)(B)] is, nevertheless, larger than that of [Co(Az-P)(B)] as shown in Table II. These results can be explained by assuming that there is a valeramido group which acts as a cavity in [Co(Az-val$\alpha\beta$)(B)]; however, there is another valeramido group as a fence. Therefore the presence of fences may be responsible for the decreased dioxygen affinity of [Co(Az-val$\alpha\beta$)(B)].

While the cavities are identical in structure in the series [Co(Az-P)(B)], [Co(Az-val$\beta\beta$)(B)], and [Co(Az-piv$\beta\beta$)(B)], their

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**Table III.** Base and $O_2$ Binding to "Jellyfish" Type Cobalt(II) Porphyrins[a]

| complexes | base = 1-MeIm | | base = 1,2-$Me_2$Im | | base = 2-MeIm | | base = 2-EtIm | |
|---|---|---|---|---|---|---|---|---|
| | $K_B$, $M^{-1}$ | $P_{1/2}$, Torr | $K_B$, $M^{-1}$ | $P_{1/2}$, Torr | $K_B$, $M^{-1}$ | $P_{1/2}$, Torr | $K_B$, $M^{-1}$ | $P_{1/2}$, Torr |
| [Co(Az-P)] | $1.2 \times 10^4$ | 13 | $5.7 \times 10^{13}$ | 44 | $4.6 \times 10^3$ | 13 | $1.3 \times 10^3$ | 13 |
| [Co(Az-val$\beta\beta$)] | $9.5 \times 10^4$ | 51 | $5.6 \times 10^4$ | 115 | $5.1 \times 10^4$ | 49 | $1.7 \times 10^4$ | 68 |
| [Co(Az-piv$\beta\beta$)] | $2.1 \times 10^5$ | 268 | $6.8 \times 10^4$ | 1220 | $8.6 \times 10^4$ | 566 | $3.1 \times 10^4$ | 1090 |

[a] $K_B$ at 25 °C in toluene; $P_{1/2}$ at 0 °C in toluene. Error limits <10% in $P_{1/2}$ and <20% in $K_B$.

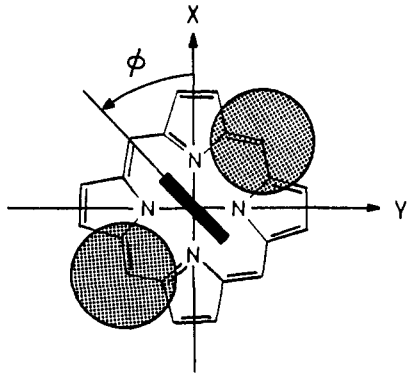


**Figure 5.** Schematic representation of the dihedral angle ($\phi$) and the coordinate axis system in [Co(Az-piv$\beta\beta$)(1-MeIm)]. The large, dotted circles indicate pival groups, and a solid rectangle indicates the 1-MeIm.

$P_{1/2}$ values increased in the order [Co(Az-P)(B)] < [Co(Az-val$\beta\beta$)(B)] < [Co(Az-piv$\beta\beta$)(B)]. Furthermore, the $P_{1/2}$ values increase in the order [Co(De2)(1-MeIm)] < [Co(De-piv$\beta\beta$)(1-MeIm)], although some fraction of $O_2$ binding to the fence side of [Co(De-piv$\beta\beta$)] might occur as judged from the argument on the axial base bindings.

To explain these observations, the electronic effect of the porphyrin is considered first. It has been reported[22] that electron-withdrawing groups located at the para position of benzene ring in (*meso*-tetraphenylporphyrinato)cobalt(II) complexes lead to increases in both the $K_B$ and $P_{1/2}$ values. The $K_B$ value of [Co(Az-val$\alpha\alpha$)] is larger than that of [Co(Az-piv$\alpha\alpha$)], so it might be expected that the $P_{1/2}$ values of the $\beta\beta$ isomers would increase in the same order. Our observation, however, is just the opposite. Thus the electronic effect of porphyrin induced by the pivalamido or the valeramido group is not responsible for the observed changes in dioxygen affinities.

Because the order of decrease in the dioxygen affinity ([Co(Az-P)(B)] > [Co(Az-val$\beta\beta$)(B)] > [Co(Az-piv$\beta\beta$)(B)]) is the same as that of the increase in fence bulk, it is reasonable to expect that these changes in the dioxygen affinity are due to the changes in stereochemical environment at the binding site of axial bases. To examine that the dioxygen affinity can be controlled by changes in both the bulk of fence and the axial base, the $P_{1/2}$ values of the complexes having the same cavities ([Co(Az-P)], [Co(Az-val$\beta\beta$)] and [Co(Az-piv$\beta\beta$)]) were determined in the presence of a series of substituted imidazoles. The results are listed in Table III. As shown in each column in Table III, the $P_{1/2}$ values increase in the order [Co(Az-P)(B)], [Co(Az-val$\beta\beta$)(B)], and [Co(Az-piv$\beta\beta$)(B)], regardless of the bases employed. The ratio of the $P_{1/2}$ value of [Co(Az-piv$\beta\beta$)(B)] to that of [Co(Az-val$\beta\beta$)(B)] is larger for the case where 1,2-$Me_2$Im (ca. 11) was used as the axial base than for that where 1-MeIm was used (ca. 5). The $P_{1/2}$ values of [Co(Az-P)(B)] and [Co(Az-val$\beta\beta$)(B)] are similar for both the 1-MeIm and 2-MeIm complexes. That of [Co(Az-piv$\beta\beta$)(B)], however, becomes larger in the case using 2-MeIm as an axial base. Thus, we suggest that the methyl group at the 2-position of imidazoles interacts with pivalamido groups in the fences. Furthermore, the introduction of the bulky ethyl group, instead of the methyl group, results in a greater increase in the dioxygen affinity of [Co(Az-piv$\beta\beta$)(B)] as compared with the case of 2-MeIm. From these results, it may be concluded that (i) the dioxygen affinities of the series of complexes ([Co(Az-P)(B)], [Co(Az-val$\beta\beta$)(B)], and [Co(Az-piv$\beta\beta$)(B)] are increased with fence bulk and (ii) the dioxygen affinities of [Co(Az-piv$\beta\beta$)(B)] are decreased by introducing a bulky substituent at the 2-position of imidazole.

Analysis of a CPK molecular model suggests that the rotation of axial bases is restricted by *tert*-butyl groups in the fence of [Co(Az-piv$\beta\beta$)], and the locations of axial bases are enforced to the position in which the dihedral angle ($\phi$) is equal to 45° as shown in Figure 5. In accord with our model experiment, Walker et al.[26] have reported that the rotation of 1-MeIm in [Fe($\alpha^2$-trans-TpivPP)(1-MeIm)$_2$]Cl is restricted by pivalamido groups, and the dihedral angle of the bound 1-MeIm is, on the average, equal to 45°. Thus the dihedral angle of bound 1-MeIm of [Co(Az-piv$\beta\beta$)](1-MeIm)] might be equal to 45°, because the binding site of 1-MeIm to [Co(Az-piv$\beta\beta$)] is in structure identical with that of [Fe($\alpha^2$-*trans*-TpivPP)]Cl. At this orientation, the overlap between the $\pi$ orbital (d$\pi$ or p$\pi$) of Co and the p$\pi$ orbital of N on the axial base becomes a minimum.[15]

Here, we propose one possible explanation for our results. If the orientation of the axial base is held upon the dioxygen bindings by the steric repulsion with the fences, the $\pi$-electron donation from the axial base to dioxygen via Co–porphyrin will be reduced and the dioxygen affinity will be correspondingly decreased. Since this charge transfer is an essential part of metal-$O_2$ bonding,[8a] the increased electron density on the metal will enhance its dioxygen affinity. On the other hand, the axial base will be able to rotate freely in [Co(Az-P)(B)], because of the lack of fences. Upon $O_2$ binding, the axial base will be able to reduce its dihedral angle to 0°, so that the $\pi$-electron donation from the axial base will be maximized, and the dioxygen affinity of [Co(Az-P)] should increase.

Our explanation for the changes in the dioxygen affinities of "jellyfish" porphyrins with various type of fences may be applied to the structure–activity relationship in hemoproteins. Indeed, some investigators of X-ray structural studies on hemoproteins have been postulated that the selected orientation of the imidazole group of histidine (F8) can operate as a control on dioxygen affinity of both Mb and $\alpha$ subunit of Hb.[27,28]

**Acknowledgment.** This work was partially supported by a grant supplied by the Japan Private School Promotion to which our thanks are due.

**Registry No.** $H_2$-Az-am$\beta\beta$, 104544-26-5; $H_2$-Az-am$\alpha\beta$, 111956-17-3; $H_2$-Az-am$\alpha\alpha$, 107911-17-1; $H_2$-Az-piv$\beta\beta$, 111956-16-2; $H_2$-Az-piv$\alpha\beta$, 111956-18-4; $H_2$-Az-piv$\alpha\alpha$, 107830-32-0; $H_2$-Az-val$\beta\beta$, 104544-28-7; $H_2$-Az-val$\alpha\beta$, 111956-19-5; $H_2$-Az-val$\alpha\alpha$, 111956-20-8; $H_2$-Az-P, 111870-40-7; $H_2$-Az2, 104544-27-6; $H_2$-De-am$\beta\beta$, 105120-30-7; $H_2$-De-piv$\beta\beta$, 112018-14-1; $H_2$-De-val$\beta\beta$, 111870-41-8; $H_2$-De2, 98360-58-8; [Co(Az-piv$\alpha\alpha$)], 111957-09-6; [Co(Az-piv$\alpha\beta$)], 111957-13-2; [Co(Az-piv$\beta\beta$)], 107374-49-2; [Co(Az-val$\alpha\alpha$)], 111957-10-9; [Co(Az-val$\alpha\beta$)], 111957-14-3; [Co(Az-val$\beta\beta$)], 105007-85-0; [Co(Az-P)], 107374-48-1; [Co(Az2)], 111902-94-4; [Co(De-piv$\beta\beta$)], 111902-95-5; [Co(De-val$\beta\beta$)], 111902-96-6; [Co(De2)], 111902-97-7; [Co(Az-piv$\alpha\alpha$)(py)], 111902-98-8; [Co(Az-piv$\alpha\beta$)(py)], 111957-15-4; [Co(Az-piv$\beta\beta$)(py)], 111957-16-5; [Co(Az-val$\alpha\alpha$)(py)], 111957-11-0; [Co(Az-val$\alpha\beta$)(py)], 111957-17-6; [Co(Az-val$\beta\beta$)(py)], 111957-18-7; [Co(Az-P)(py)], 111902-99-9; [Co(Az2)(py)], 111903-00-5; [Co(Az-piv$\alpha\alpha$)(1-MeIm)], 111957-12-1; [Co(Az-piv$\alpha\beta$)(1-MeIm)], 111957-19-8; [Co(Az-piv$\beta\beta$)(1-MeIm)], 107374-53-8; [Co(Az-val$\alpha\alpha$)(1-MeIm)], 111903-01-6; [Co(Az-val$\alpha\beta$)(1-MeIm)], 111903-01-6; [Co(Az-val$\beta\beta$)(1-MeIm)], 111903-11-8; [Co(Az-P)(1-MeIm)], 107374-51-6; [Co(Az2)(1-MeIm)], 107374-50-5; [Co(De-piv$\beta\beta$)(1-MeIm)], 111903-02-7; [Co(De-val$\beta\beta$)(1-MeIm)],

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111903-03-8; [Co(De2)(1-MeIm)], 111903-04-9; [Co(Az-P)(1,2-$Me_2$Im)], 111903-05-0; [Co(Az-val$\beta\beta$)(1,2-$Me_2$Im)], 111933-38-1; [Co(Az-piv$\beta\beta$)(1,2-$Me_2$Im)], 111933-39-2; [Co(Az-P)(2-MeIm)], 111933-40-5; [Co(Az-val$\beta\beta$)(2-MeIm)], 111903-06-1; [Co(Az-piv$\beta\beta$)(2-MeIm)], 111903-07-2; [Co(Az-P)(2-EtIm)], 111903-08-3; [Co(Az-val$\beta\beta$)(2-EtIm)], 111903-09-4; [Co(Az-piv$\beta\beta$)(2-EtIm)], 111903-10-7; pivaloyl chloride, 3282-30-2; pentanoyl chloride, 638-29-9; oxygen, 7782-44-7.

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# Bulky Ligand Substituent Effect on the Reaction of 5'-GMP with Pt(1,3-diamine). Rotation of 5'-GMP about the Pt-N Bond and Kinetic Effects

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Substituent effects in the reaction of 5'-GMP with [Pt(1,3-diamine)$(OH_2)_2$] have been investigated. The 1,3-diamines used are 1,3-propanediamine (dap), 1,3-cyclohexanediamine (1,3-dach), 2,2,*N*,*N*-tetramethyl-1,3-propanediamine (tmdap), *N*-methyl-1,3-propanediamine (mdap), and *N*-ethyl-1,3-propanediamine (edap). The bulky substituents have a large influence on the rotation of 5'-GMP about the Pt-N7 bond and also on the rate constants for the formation of [Pt(1,3-diamine)(5'-GMP-*N7*)$(OH_2)$] and [Pt(1,3-diamine)(5'-GMP-*N7*)$_2$] products. In the 1:1 and 2:1 products containing tmdap, the rotation of 5'-GMP cis to the $N(CH_3)_2$ group is slow on the NMR time scale. On the other hand, the presence of only one methyl group on the coordinated nitrogen atom (i.e. $N(H)(CH_3)$) seems not to retard the rotation of 5'-GMP. The kinetics of the reaction of 5'-GMP with [Pt(1,3-diamine)$(OH_2)_2$] are sensitive to the presence of the bulky substituents. The 1:1 and 2:1 compounds containing 1,3-dach show fast rotation of 5'-GMP about the Pt-N7 bond, but the binding rate is somewhat reduced by the steric hindrance originating from the cyclohexane ring. The presence of the N-substituted group slows down the rate for binding 5'-GMP at the coordination side cis to the N-substituted group. There is almost no difference between the binding rates of 5'-GMP at the coordination side cis to the $NH_2$ group, except for the case of Pt(1,3-dach), where the rate is slightly decreased.

## Introduction

In the antitumor properties of cis-platinum compounds (general formula *cis*-Pt(amine)$_2X_2$, X = leaving group), the nature of nonleaving ligands, i.e. the amine ligands, plays an important role. The early observation of a structure-activity relationship indicated that the activity of Pt(amine)$_2Cl_2$ decreases along the series $NH_3 \approx RNH_2 > R_2NH > R_3N$.[1] The degree of antitumor activity may depend on various kinds of factors such as solubility, stability, toxic side reactions and cell permeability of platinum compounds, and so on. Principally it might be possible to improve these properties by modification of the leaving ligand, but more likely the nonleaving ligands present an essential factor for the actual antitumor activity.

It has been generally accepted that DNA is a primary target of antitumor platinum drugs[2] and that N7 of the guanine base is a preferential platinum binding site. The interaction between the platinum compound and the guanine base, such as the intrastrand cross-link between two adjacent guanine bases,[3-8] appears to play an important role in cell killing.[9,10] Differences in the nature of the nonleaving ligands are expected to affect the reactivity between the platinum compound and the ultimate target DNA, especially when the platinum compounds have different substituents, which may result in steric effects and H-bonding differences. A bulky amine substituent in the platinum compound may induce a conformational change of the DNA after platinum modification and may lead to decrease and/or disappearance in hydrogen-bonding ability between the coordinated amino group and nucleic acid constituents (bases, phosphates). Such effects are likely to appear in a series of ligands that have only small differences.

In the present study, the reaction of guanosine 5'-monophosphate (5'-GMP) with a series of Pt(1,3-diamine) compounds containing sterically bulky substituents will be described.[11] Structures and abbreviations of the used Pt(1,3-diamine) compounds are shown in Figure 1. In the platinum complex containing 1,3-dach, the cyclohexane ring lies roughly perpendicular to the platinum coordination plane,[12] and it is likely to influence the approach of the incoming ligand, 5'-GMP. The ligand tmdap has a tertiary and a primary amino group. The two methyl groups on the coordinated nitrogen atom occupy an axial and equatorial position, with rapid interconversion of the Pt-NN chelate ring. Steric effects of the $N(CH_3)_2$ group are therefore expected to be effective below and above the Pt coordination plane. The ligands mdap and edap both have a secondary and a primary amino group. The methyl and ethyl groups may generate different steric effects because of their difference in size.

A major aim of the present study is to evaluate how the reactions between 5'-GMP and the Pt(1,3-diamine) compounds are influenced by the substituents in the ligands. The presence of the substituents may lead to restricted rotation of 5'-GMP about the Pt-N7 bond and retardation of the reaction rate between 5'-GMP and Pt(1,3-diamine). The reaction between 5'-GMP and bifunctional platinum compounds occurs via a two-step mechanism.[13,14] The first step corresponds to formation of the 1:1

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