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Improved Synthesis and Isolation of a Flexible Linear NSNN Tetradentate Ligand and the Crystal Structure of Its Stereospecific Dinitrocobalt(III) Complex

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This contribution reports upon the convenient synthesis and isolation of the tetradentate ligand *N*-((2-pyridyl)methyl)-2-((2-aminoethyl)thio)acetamide (pygeH) as its dihydrobromide salt. When deprotonated, this compound stereospecifically binds to Co(III) ion in the cis-β coordination geometry, as confirmed by X-ray diffraction analysis of $[Co(pyge)(NO_2)_2]\cdot H_2O$. The complex crystallized in the monoclinic space group $P2_1/n$ with $a = 7.935$ (3) Å, $b = 26.079$ (11) Å, $c = 7.698$ (4) Å, $\beta = 110.69$ (3)°, and $Z = 4$. The structure was refined by full-matrix methods to $R(|F|) = 0.046$. In addition to the tetradentate ligand, the coordination sphere is completed by two nitro ligands.

The synthetic design of flexible, linear tetradentate ligands that form octahedral complexes with very high stereoselectivity approaching de facto stereospecificity has been an area of intense research.[2-5] These complexes, especially those of Co(III), have proven of interest for the activation of carbonyl functions of coordinated amino acid derivatives,[2,6] thiolates,[7] and related small, functionalized molecules.[2,8,9]

We have continued and extended investigations involving Co(III) complexes of linear, tetradentate ligands with an NSNN donor set containing internal thioether and amido groups[2] with the intent of improving synthetic entry into these types of complexes. Among the most useful and accessible species in this class of ligands are pygeH (see Scheme I, compound **4** for the chemical structure) and geeH ($H_2NCH_2C(O)NH(CH_2)_2S(CH_2)_2NH_2$), both of which coordinate to Co(III) with concomitant deprotonation of the amide function. It has been previously demonstrated, via combined ^1H and ^{13}C NMR spectroscopies, that each of these two ligands forms an independent series of chemically interconvertible complexes of type $[Co(L)(X)_2]$ (where L is either pyge or gee, and $(X)_2$ is a pair of unidentate ligands or a symmetrical bidentate ligand). In each series of complexes, only one of three possible geometrical isomers was isolated for each $[Co(L)(X)_2]$ complex.[2] The unsymmetrical nature of the tetradentate ligands precluded the assignment of their stereochemistries as cis-α, cis-β, or trans (see Figure 1) by spectroscopic methods. In the case of L being gee, a single-crystal X-ray diffraction study of $[Co(gee)(NO_2)_2]\cdot H_2O$ established its coordination geometry as being cis-β.[2] This result, in conjunction with the chemical interconversion studies, strongly suggests that the other $[Co(gee)(X)_2]$ derivatives also are cis-β.

In this contribution, we report upon an improved synthesis of pygeH, in which the protonated ligand is conveniently isolated as its dihydrobromide salt. Since difficulties similar to those mentioned above for $[Co(gee)(X)_2]$ obtain in the stereochemical assignment regarding $[Co(pyge)(X)_2]$ (vida supra), we have determined the crystal structure of $[Co(pyge)(NO_2)_2]\cdot H_2O$ in order to establish unequivocally the stereochemistry for this series of Co(III) complexes.

Experimental Section

Materials and Methods. ^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer at 299.943 and 75.429 MHz, respectively. Spectra obtained in $CDCl_3$ or Me_2SO-d_6 solution were referenced to tetramethylsilane, while spectra obtained in D_2O solution were referenced to the sodium salt of 3-(trimethylsilyl)propionic acid (^1H) or dioxane (^{13}C). A Varian DMS-80 spectrophotometer was utilized for visible spectra at ambient temperature. All melting points are uncorrected. Elemental analyses were determined by Atlantic Microlabs, Inc. (Atlanta, GA).

Preparation of Compounds. Unless otherwise noted, all starting materials and solvents were obtained from standard sources and used without further purification.

***N*-((2-Pyridyl)methyl)-2-((2-(((benzyloxy)carbonyl)amino)ethyl)thio)acetamide (3).** *N*-((2-Pyridyl)methyl)-2-chloroacetamide hydrochloride (**1**)[2] (4.0 g, 18.1 mmol) and 2-[((benzyloxy)carbonyl)amino]ethanethiol (**2**)[10] (3.82 g, 18.1 mmol) were added to a solution of NaOH (1.45 g, 36.2 mmol) in methanol/water (20 mL/5 mL). The mixture was heated at reflux for 2 h and then cooled. The precipitated NaCl was filtered and the solvent removed on a rotary evaporator to give a yellow oil in essentially quantitative yield. This crude material was of sufficient purity for use in the subsequent reaction, below. The oil could be crystallized with some difficulty by cooling a concentrated methanol solution to give an off-white solid that was washed with water and dried to give analytically pure protected pygeH (**3**), mp 63–65 °C (lit.[11] mp 65 °C). Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.15; H, 5.89. Found: C, 60.08; H, 5.89. ^1H NMR ($CDCl_3$): δ 8.51 (d, 1 H, H-6 py), 7.99 (br, 1 H, NH), 7.66 (t, 1 H, H-4 py), 7.35 (broadened s, 5 H, aryl), 7.24 (d, 1 H, H-3 py), 7.12 (t, 1 H, H-5 py), 6.41 (br, 1 H, NH), 5.10 (s, 2 H, OCH_2), 4.58 (d, 2 H, $pyCH_2$), 3.37 (m, 2 H, SCH_2CH_2N), 3.29 (s, 2 H, SCH_2CO), 2.78 (t, 2 H, SCH_2CH_2N). ^{13}C NMR ($CDCl_3$): δ 169.26, 156.55, 155.90, 149.11, 137.04, 136.52, 128.50, 128.14, 128.10, 122.53, 122.20, 66.74, 44.50, 39.76, 36.32, 34.13.

***N*-((2-Pyridyl)methyl)-2-((2-aminoethyl)thio)acetamide Dihydrobromide (pygeH·2HBr) (4).** The yellow oil from the above preparation was stirred in 32% HBr/acetic acid (25 mL) for 1 h. Diethyl ether (100 mL) was then added to the reaction mixture, resulting in the formation of a light orange gum. The mother liquor was decanted, absolute ethanol (60 mL) was added to the gum, the suspension was stirred and heated (50–60 °C) overnight. The white solid (4.91 g) was collected, washed with a little diethyl ether, and dried. The yield was 70% based upon the alkyl halide (**1**) or thiol (**2**) from the above synthesis of protected pygeH (**3**). An analytical sample was obtained by recrystallization from hot absolute ethanol; mp 152–153 °C (lit.[11] mp 155 °C). ^1H NMR (D_2O): δ 8.71 (d, 1 H, H-6 py), 8.59 (t, 1 H, H-4 py), 7.99 (m, 2 H, H-3,5 py), 4.83 (s, 2 H, $pyCH_2$), 3.51 (s, 2 H, SCH_2CO), 3.26 (t, 2 H, SCH_2CH_2N), 2.94 (t, 2 H, SCH_2CH_2N). ^{13}C NMR (D_2O): δ 174.16, 153.22, 148.22, 141.86, 126.80, 126.54, 41.86, 38.98, 35.04, 30.10.

$[Co(pyge)(NO_2)_2]\cdot H_2O$ (5). PygeH·2HBr (**4**) (0.50 g, 1.30 mmol) was added to a solution of NaOH (0.104 g, 2.60 mmol) in methanol/water (6 mL/3 mL). A solution of $NaNO_2$ (0.180 g, 2.60 mmol) in water (3 mL) was added, followed by $CoCl_2\cdot 6H_2O$ (0.309 g, 1.30 mmol). Air was

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Scheme I

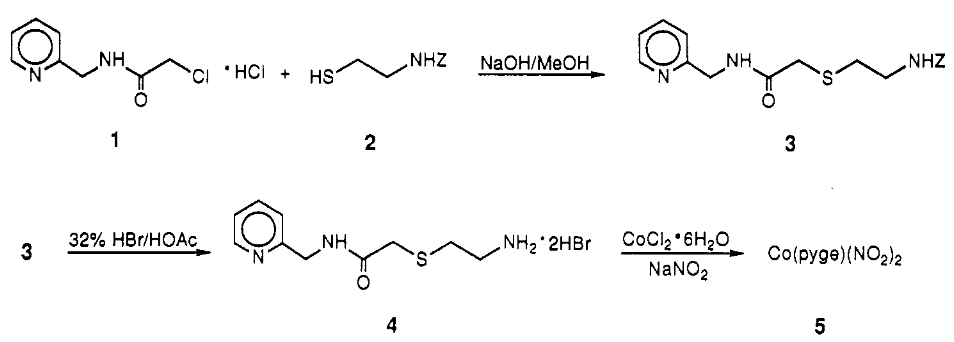
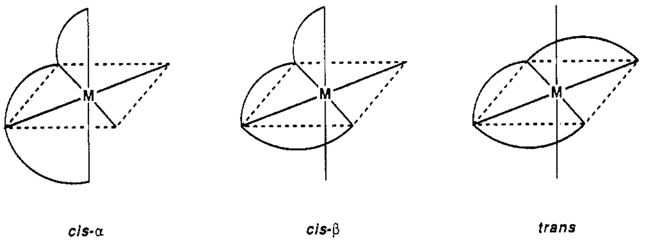


Table I. Crystal/Refinement Data for $[Co(pyge)(NO_2)_2]\cdot H_2O$ (**5**)

formula	$C_{10}H_{16}CoN_5O_6S$	V, Å^3	1490 (1)
M_r	393.2	D_c, g cm^{-3}	1.75 ($Z = 4$)
cryst syst	monoclinic	N_{unique}	4355
space group	$P2_1/n$; No. 14	N_{obs} ($2\theta_{max}$, deg)	2841 (60)
a, Å	7.935 (3)	$R(\|F\|)$	0.046
b, Å	26.079 (11)	$R_w(\|F\|)$	0.058
c, Å	7.698 (4)	μ_{Mo}, cm^{-1}	13.7
β, deg	110.69 (3)		



cis-α *cis*-β *trans*

Figure 1. The three possible coordination geometries for a flexible, linear tetradentate ligand in an octahedral metal complex.

bubbled through the reaction mixture for 4 h, and the red-orange crystalline product was collected and air-dried. Yield: 0.31 g (64%). Visible (H_2O) and ^{13}C NMR (Me_2SO-d_6) spectral data of **5** were essentially identical with literature values[2] for $[Co(pyge)(NO_2)_2]\cdot H_2O$. Dark orange blocklike crystals of **5**, suitable for single-crystal X-ray diffraction analysis, were obtained by slow evaporation of a saturated aqueous solution. ^1H NMR (Me_2SO-d_6): δ 8.72 (d, 1 H, H-6 py), 8.04 (t, 1 H, H-4 py), 7.62 (m, 2 H, H-3,5 py), 4.60 (AB m, 2 H, $pyCH_2$), 4.01 (br s, 1 H, NH), 3.76 (d, 1 H, SCH_2CO), 3.42 (d, 1 H, SCH_2CO), 2.88 (br s, 1 H, NH), 2.61 (m, 4 H, SCH_2CH_2N).

Structure Determination. A unique data set ($h,k,\pm l$) was measured at ~295 K by using a Syntex $P2_1$ four-circle diffractometer (graphite monochromated Mo Kα radiation, $\lambda = 0.71069$ Å; $2\theta/\theta$ scan mode), yielding N independent reflections, N_{obs}, with $I > 3\sigma(I)$ being considered "observed" and used in the full-matrix least-squares refinement after analytical absorption correction. Anisotropic thermal parameters were refined for the non-hydrogen atoms; for hydrogen atoms, all of $(x, y, z, U_{iso})_H$ were constrained at estimated values. Residuals at convergence are quoted on $|F|$; statistical weights derivative of $\sigma^2(I) = \sigma^2(I_{diff}) + 0.0005\sigma^4(I_{diff})$ were used. Refinement of extinction was not necessary. Neutral-atom complex scattering factors were employed;[12] computation used the X-RAY 76 program system[13] implemented by S. R. Hall. Crystallographic data are compiled in Table I, and the atomic coordinates are presented in Table II. Abnormal features: Difference map artifacts about 1 Å apart were modeled as solvent water oxygen atoms, since the visible spectral analysis indicated that the crystals of **5** were essentially identical in composition with the known monohydrate;[2] populations refined to 0.5 within experimental error and were constrained at that value, assuming a monohydrate model. Associated hydrogen atoms were not located.

Results and Discussion

New Synthesis of the Protonated Ligand PygeH. The preparation of the unsymmetrical pygeH·2HBr (**4**) follows a stepwise procedure from readily available starting materials as outlined in Scheme I, where Z is the (benzyloxy)carbonyl protecting group, $C_6H_5CH_2OC(O)$. Alkyl chloride (**1**) and protected thiol (**2**) were smoothly condensed under basic conditions to provide the protected ligand (**3**). The dihydrobromide salt of the protonated ligand, pygeH·2HBr (**4**), was obtained in ca. 50–60% overall yield (based upon 2-aminoethanethiol, used to prepare **2**) by deprotecting **3** with 32% HBr/acetic acid. Air oxidation of an aqueous solution of cobalt(II) chloride and **4** in the presence of sodium nitrite resulted in the deposition of deep red-orange crystals of $Co(pyge)(NO_2)_2$ (**5**).

Table II. Non-Hydrogen Atom Coordinates for **5**

atom	x	y	z
Co	0.23719 (5)	0.65241 (2)	0.48707 (6)
		Ligand	
N(1)	0.1580 (3)	0.5998 (1)	0.6230 (4)
C(11)	0.0538 (4)	0.6064 (2)	0.7286 (5)
C(12)	0.0070 (7)	0.5668 (2)	0.8170 (6)
C(13)	0.0679 (9)	0.5180 (2)	0.8019 (9)
C(14)	0.1743 (9)	0.5108 (2)	0.6951 (9)
C(2)	0.2156 (6)	0.5522 (2)	0.6070 (6)
C(3)	0.3315 (7)	0.5469 (2)	0.4894 (7)
N(4)	0.3347 (4)	0.5955 (1)	0.4010 (4)
C(5)	0.4089 (4)	0.5972 (2)	0.2730 (4)
O(5)	0.4686 (4)	0.5591 (1)	0.2141 (4)
C(6)	0.4208 (5)	0.6496 (2)	0.1959 (5)
S(7)	0.36041 (11)	0.70020 (4)	0.32425 (14)
C(8)	0.5730 (5)	0.7136 (2)	0.5081 (7)
C(9)	0.6233 (4)	0.6711 (2)	0.6489 (5)
N(10)	0.4665 (4)	0.6591 (1)	0.7021 (4)
		Nitrite Ligands	
N(2)	0.0130 (4)	0.6473 (1)	0.2800 (5)
O(21)	0.0068 (4)	0.6555 (1)	0.1218 (4)
O(22)	−0.1254 (4)	0.6363 (2)	0.3088 (5)
N(3)	0.1441 (4)	0.7121 (1)	0.5702 (6)
O(31)	0.0655 (7)	0.7455 (2)	0.4699 (7)
O(32)	0.1697 (6)	0.7167 (2)	0.7404 (7)
		Water Molecule[a]	
O	0.1331 (8)	0.9129 (3)	0.4628 (8)
O′	0.0892 (8)	0.9460 (2)	0.4070 (8)

[a] Population of components: 0.5 each.

The compound pygeH·2HBr (**4**) has been prepared and isolated previously in a five-step synthesis (overall yield of 14%, based upon starting materials).[11] However, this procedure includes a step that requires 15 days.

The free ligand, pygeH, has also been synthesized in solution in two steps in excellent, unisolated yields.[2] Although good yields of relatively pure cobalt complex (**5**) can be obtained in situ from the latter procedure, preparations of coordination complexes with metal ions other than cobalt(III) (e.g., Cu(II)) are hindered by the relatively impure ligand.[14]

In summary, the new method of synthesis (Scheme I) allows for the convenient isolation of gram quantities of **4** from easily prepared starting materials. Since cobalt(III) complexes of this

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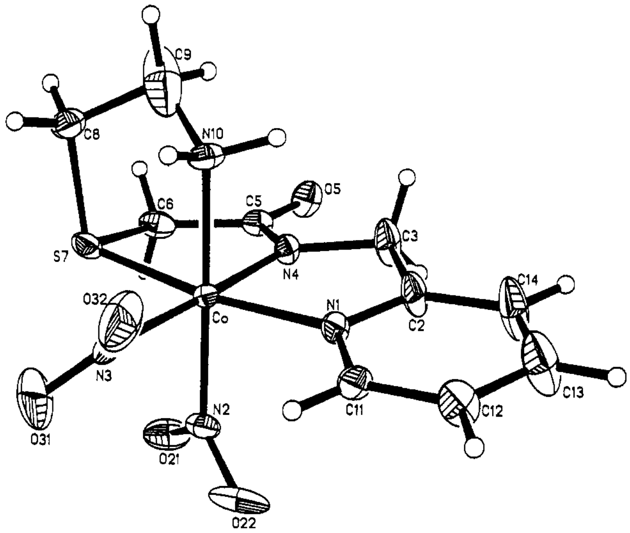

Figure 2. Molecular structure and atom-numbering scheme for [Co-(pyge)$(NO_2)_2$].

Table III. Cobalt Coordination Environment for **5**

	r^a	$N(4)^b$	S(7)	N(10)	N(2)	N(3)
N(1)	1.960 (3)	83.4 (1)	168.9 (1)	89.4 (1)	90.9 (1)	99.0 (1)
N(4)	1.899 (3)		85.8 (1)	89.6 (1)	91.6 (1)	177.6 (2)
S(7)	2.224 (1)			88.0 (1)	92.0 (1)	91.8 (1)
N(10)	1.988 (3)				178.8 (9)	89.9 (1)
N(2)	1.929 (3)					88.9 (1)
N(3)	1.926 (4)					

[a] Metal–Ligand distance (Å). [b] Other entries are the angles (deg) subtended at the metal by the relevant atoms at the head of the row and column.

ligand tend to be nicely crystalline compounds that are easy to isolate and purify,[2,14] this represents a significant improvement in the entry to this series of compounds.

Structural Results

The ligand pyge⁻ is designed to coordinate only in the cis-β fashion in octahedral coordination complexes. This anticipated stereochemical control derives from the nature of the internal donor atoms of the tetradentate ligand. Thus, the pronounced tendency of S for pyramidal coordination when it is at the junction of two five-membered chelate rings, coupled with the planar disposition of the atoms in the vicinity of the deprotonated amide donor atom, should lead to a predicted cis-β geometry for Co(III) complexes of this NSNN ligand, much as in the gee⁻ case.[2]

The molecular structure of **5** is depicted in Figure 2 and relevant bond distances and angles around the Co(III) ion are collected in Table III. The asymmetric unit of the centrosymmetric unit cell is comprised of one [Co(pyge)$(NO_2)_2$]·H_2O formula unit. Most importantly, the diffraction analysis reveals that the stereochemistry of the tetradentate ligand is, indeed, the predicted cis-β geometry, rather than the previously implied trans geometry.[11]

Bond lengths and angles in the complex are generally within expected values and are very similar to those found for [Co-(gee)$(NO_2)_2$]·H_2O (**6**).[2] Thus, considerable strain is again evident in the bond angles in the vicinity of S(7): Co–S(7)–C(6,8) = 98.8 (1) and 98.1 (2)°, respectively; C(6)–S(7)–C(8) = 102.3 (2)°. We note that small Co–S–C angles are observed only when the carbon atom is part of a five-membered chelate ring; values closer to the expected tetrahedral ones are found if the carbon atom is contained in a six-membered chelate (e.g., 114.6 (2), 109.5 (2)° in Co(ete)(NO_2)Cl,[15] where ete = $H_2N(CH_2)_2S(CH_2)_3S(CH_2)_2NH_2$). The most notable difference between the structures of **5** and **6** is the abnormally large N(1)–Co–N(3) angle in **5**, 99.0 (1), vs that in **6**, 92.83 (9)°.[2] This result is presumably a consequence of an unfavorable steric interaction between the hydrogen atom on C(11) of the pyridyl ring and O(32) and is reflected in a twist of the N(3) nitro ligand out of the major coordination plane of the pyge ligand. The Co–NO_2 bond lengths in **5** are virtually identical and are within the usual range found in similar Co(III) complexes.[16]

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Supplementary Material Available: Tables of crystal data and details of the intensity collection, anisotropic thermal parameters, hydrogen atom parameters, and complete bond lengths and bond angles for complex **5** (5 pages); a listing of observed and calculated structure factors for complex **5** (11 pages). Ordering information is given on any current masthead page.

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