regions of the molecule; around the benzo moiety and the phenyl group at C5. Separation of the disordered structures was not straightforward since several of the related disordered atoms were located within 0.5 Å of each other. Nonetheless, smooth convergence was eventually realized by constraining corresponding bond lengths to be equal within $\sigma = 0.005$ Å. The phenyl groups were treated as rigid planar groups with C–C bond lengths 1.395 Å and internal angle 120°. Only the hydrogen atoms around the nondisordered phenyl group at C1, which could be readily located on a difference Fourier map, were included in the refinement with fixed coordinates and temperature factors. The occupancy factors of the disordered structures, constrained to add to 1.0, refined to 50% in each region. This value was fixed in the final stages of structural refinement. A unit weighting scheme was found to be adequate.

When all the non-hydrogen atoms in the disordered structure were refined with individual temperature factors, the conventional R factor converged to 0.105. Further structural refinement with anisotropic temperature factors for the atoms of the ozonide ring and the phenyl group at C1, which were not evidently disordered, produced an R factor of 0.092. The final difference Fourier map contained no feature greater than ± 0.36 e$^-$ Å^{-3}.

In addition to the tabulated material already mentioned in the main text, tables of thermal vibrational parameters, calculated least-square planes, and observed and calculated structure factor amplitudes for each determination are available as supplementary material.

Acknowledgment. We thank Dr. M. B. Hursthouse (QMC, London) for X-ray intensity data collection, Drs. R. A. Howie (Aberdeen University) and M. D. Walkinshaw (Edinburgh University) for use of computer programs, and the University of Aberdeen Computer Centre for computer time.

Registry No. **1a**, 22360-62-9; **1b**, 51310-25-9; **1c**, 58310-20-6; **1d**, 2177-48-2; **2a**, 84810-14-0; **2b**, 84810-15-1; **2c**, 84810-16-2; **2d**, 84810-17-3; **2e**, 73258-06-7; **3a**, 84847-60-9; **3b**, 84847-61-0; **3c**, 84847-62-1; **3d**, 84847-63-2; **4a**, 84810-18-4; **4a** tosylhydrazone, 84810-19-5; **4b**, 84810-20-8; **4c**, 84810-21-9; **5a**, 84810-22-0; **5b**, 84810-23-1; **6a**, 73721-00-3; **6d**, 84810-24-2; **7a**, 84810-25-3; **7b**, 75519-83-4; **15a**, 84810-26-4; **15d**, 84810-27-5; **16a**, 84810-28-6; **17a**, 84810-29-7; **19b**, 84810-30-0; **19c**, 84810-31-1; **19d**, 84810-32-2; **20b**, 84810-33-3; **20c**, 84810-34-4; **20d**, 84810-35-5; **21b**, 84810-36-6; **21c**, 84810-37-7; **21d**, 84810-38-8; **22d**, 84810-39-9; **31**, 77196-47-5; **32a**, 84810-40-2; **32d**, 84810-41-3; **33a**, 84847-64-3; **33d**, 84847-65-4; $ClSO_3H$, 7790-94-5; $SbCl_5$, 7647-18-9; *cis*-1-methyl-3-phenylindanone, 84810-42-4; *trans*-1-methyl-3-phenylindanone, 84810-43-5; 2-(2-hydroxyphenyl)propionaldehyde, 84810-44-6; 1-(2-hydroxyphenyl)ethyl phenyl ketone, 84810-45-7; 1-phenyl-4-methyl-1*H*-2-benzopyran, 50431-53-3; *trans*-3,4-dihydro-1-phenyl-4-methyl-1*H*-2-benzopyran, 84810-46-8; *cis*-3,4-dihydro-1-phenyl-4-methyl-1*H*-2-benzopyran, 84810-47-9; *cis*-3,4-dihydro-1,4-dimethyl-1*H*-2-benzopyran, 84810-48-0; *trans*-3,4-dihydro-1,4-dimethyl-1*H*-2-benzopyran, 84810-49-1.

Supplementary Material Available: The listing of thermal vibrational parameters, calculated least-squares mean planes, and the observed and calculated structure factors for **3a** and **2b** (19 pages). Ordering information is given on any current masthead page.

Synthesis, Molecular Structure, and Chemistry of (p)-[(Tris(2-aminoethyl)amine)(2-(dihydroxymethyl)-glycinate)]cobalt(III)–Zinc Tetrachloride–Water[1]

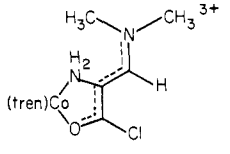
W. G. Jackson,* G. M. McLaughlin, A. M. Sargeson,*† and A. D. Watson

Contribution from the Chemistry Department, Faculty of Military Studies, University of New South Wales, Royal Military College, Duntroon A.C.T., 2600 Australia, and the Research School of Chemistry, The Australian National University, Canberra A.C.T., 2600 Australia.
Received July 19, 1982

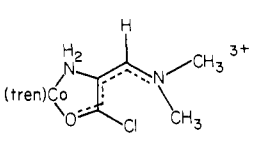
Abstract: The synthesis of chelated *C*-formylglycinate ion is described using the Vilsmeier–Haack adduct derived from the (p)-[Co(tren)glycinato]$^{2+}$ ion (tren = tris(2-aminoethyl)amine). The aldehyde hydrates readily in water, and an X-ray crystallographic study has established the structure of the hydrated formyl glycine residue and determined the overall stereochemistry of the complex. The aldehyde also equilibrates rapidly with the hydrate in water and tautomerizes to the enamine and to the imine. The last leads to proton exchange on the formyl group. The aldehyde is reduced readily with BH_4^- to the serinato complex and adds alcohols to give the hemiacetal.

Introduction

Recently[2] we described the reaction between the Vilsmeier reagent $POCl_3$/dimethylformamide and the activated methylene group of chelated glycine in (p)-[Co(tren)($NH_2CH_2CO_2$)]$^{2+}$. The remarkably stable iminium deriative (p)-[Co(tren)$NH_2C(CH{\cdot}N(CH_3)_2)CO(Cl)]ZnCl_4{\cdot}Cl{\cdot}2H_2O$ (*Z* isomer) was obtained in ≥80% yield. Evidence was presented for the existence of a small amount of the unstable *E* isomer, which appeared to hydrolyze rapidly to the aldehyde complex (p)-[Co(tren)$NH_2CH(CHO)CO_2$]$^{2+}$. We now report an efficient synthesis of chelated formylglycine from the major Vilsmeier product (*Z*) and some reactions of this aldehyde.[1] The protected formylglycine is a key intermediate in the laboratory synthesis of penicillin,[3] and the tetraaminecobalt(III)-protected molecules (particularly the chiral derivatives) are useful precursors to these and other natural products that we will report upon later.



Z



E

† To whom correspondence should be addressed at The Australian National University.

(1) tren = tris(2-aminoethyl)amine; p and t refer to the geometric isomers where the oxygen of the substituted glycine ligand is trans to a primary (p) nitrogen or the tertiary (t) nitrogen of the tren ligand.

(2) Jackson, W. G.; Sargeson, A. M.; Tucker, P. A.; Watson, A. D. *J. Am. Chem. Soc.* **1981**, *103*, 533-540.

(3) Busing, W. R.; Levy, H. A. *J. Chem. Phys.* **1957**, *26*, 563.

0002-7863/83/1505-2426$01.50/0

Experimental Section

Instrumentation and Materials. ^1H NMR spectra were measured by using a JEOL Minimar 100 MHz spectrometer on external lock with an internal reference sodium 3-(trimethylsilyl)propanesulfonate (NaTPS). Fourier transform ^{13}C NMR spectra were measured by using a JEOL JNM-FX60 spectrometer on internal lock (D_2O) and with the internal reference dioxane. Chemical shifts (ppm) are reported as positive downfield from the internal references. Visible spectra were recorded with a Cary Model 118C spectrophotometer, and rotary dispersion (RD) spectra were measured on a Perkin-Elmer P22 spectropolarimeter. The cation-exchange resin used was Dowex 50WX2 (200–400 mesh, H^+ or Na^+ form). All solvent evaporations were performed on a Büchi rotary evaporation device at reduced pressure (~20 mmHg) and so that the solution temperature did not exceed 25 °C.

(p)-[Co(tren)(2-(dihydroxymethyl)glycinate)]$ZnCl_4 \cdot 2H_2O$: Method 1. To (p)-[Co(tren)(3-(dimethylamino)-2-aminoacrylyl chloride)]$ZnCl_4 \cdot Cl \cdot H_2O$ (4.0 g)[2] in water (100 mL, 0 °C) was added excess H_2SO_4 (18 M, 1 L), slowly with stirring. After 5 h at 25 °C, the deep golden orange solution was poured into ice water (15 L) and then sorbed on a large column (1200 × 100 mm) of Dowex H^+ resin. After washing (H_2O), elution with 2 M HCl yielded a single orange band (2+ ion). This was collected and reduced to dryness; addition of excess $ZnCl_2$ in 3 M HCl to the residue in a small volume of water yielded golden orange needles of (p)-[Co(tren)((dihydroxymethyl)glycinate)]$ZnCl_4 \cdot 2H_2O$ (4.2 g, 91%). Attempts to carry out the reaction in $HClO_4$ (12 M) and in HCl (12 M) resulted in the recovery of mainly starting material from the Dowex column (^1H NMR spectrum). Anal. Calcd for $CoZnCl_4C_9H_{28}N_5O_6$: C, 19.01; H, 4.97; N, 12.32; Co, 10.37; Cl, 25.00. Found: C, 19.1; H, 5.1; N, 12.2; Co, 10.2; Cl, 25.1. ϵ_{max}^{470} 116 M^{-1} cm^{-1} (H_2O); ^1H NMR (D_2O) δ 2.8–3.55 (m, 12 H, tren CH_2), 5.44 (s, 0.85 H, $CH(OH)_2$), 7.5 (s, 0.15 H, CHO); ^{13}C NMR (D_2O) δ 116.1 (COO), 88.2 (0.15C, CHO, J_{CH} = 184 Hz), 21.6 (0.85 C, $CH(OH)_2$, J_{CH} = 170 Hz), −4.7, −7.3, −21.0, −21.8 (4 C, tren CH_2).

Method 2. To (p)-[Co(tren)(3-(dimethylamino)-2-aminoacrylyl chloride)]$ZnCl_4 \cdot Cl \cdot H_2O$ (2.0 g)[2] in H_2O (50 mL) was added aqueous Na_2CO_3 (0.5 M, 50 mL). The color changed instantly to a burgundy and then green-black. It was then quenched immediately with excess 1 M HCl and after dilution it was sorbed on Dowex H^+ resin. Elution with 2 M HCl yielded two orange bands; much brown decomposition product adhered to the top of the column. The first orange band (2+ ion, ~15%) was crystallized with excess $ZnCl_2$ in 3 M HCl to yield (p)-[Co(tren)-((dihydroxymethyl)glycinate)]$ZnCl_4 \cdot 2H_2O$ while the second orange band (3+ ion, ~50%) was characterized as staring material (^1H NMR spectrum).

Reactions of the Aldehyde Complex. (1) BH_4^- Reduction. The complex (2 g) was dissolved in phosphate buffer (0.01 M, pH 6.86, 30 mL), and $NaBH_4$ (1 g) was added slowly with stirring with the evolution of H_2. The solution was degassed with N_2, diluted with H_2O (100 mL) and sorbed on a column of Dowex Na^+ resin. After washing with H_2O, the column was eluted with 2 M HCl, and one yellow orange band was recovered (2+ ion). This was reduced to dryness and crystallized from H_2O by using $Li_2S_2O_6$ and ethanol to afford (p)-[Co(tren)(ser)]$S_2O_6 \cdot H_2O$ (96%) as orange needles, which were filtered, washed with ethanol and ether, and dried in air. Anal. Calcd for $CoC_9H_{24}H_5O_9S_2 \cdot H_2O$: C, 22.17; H, 5.38; N, 14.37; Co, 12.09. Found: C, 22.5; H, 5.3; N, 13.9; Co, 12.2. ϵ_{max}^{470} 109, ϵ_{max}^{341} 101 (H_2O); ^1H NMR (10^{-2} M DCl) δ 117.3 (COO), −4.9 (CH_2OH), −7.2 (CH), −4.9, −7.3, −21.0, −12.8 (tren CH_2).

(2) Conversion to (p)-[Co(tren)((hydroxyethoxymethyl)glycinate)]-$ZnCl_4$. (p)-[Co(tren)((dihydroxymethyl)glycinate)]$ZnCl_4 \cdot 2H_2O$ (5 g) was dissolved in H_2O (25 mL) with stirring. Ethanol (50 mL) was added and the solution cooled (4 °C, 24 h). The addition of excess $ZnCl_2$ in 3 M HCl yielded orange plates of (p)-[Co(tren)((hydroxyethoxymethyl)glycinato)]$ZnCl_4$ (3.2 g), which were filtered, washed with ethanol and ether, and dried in air (the hydroxymethoxy adduct can be prepared in a similar fashion by using methanol in lieu of ethanol). Anal. Calcd for $CoC_{11}H_{28}N_5O_4ZnCl_4$: C, 23.57; H, 5.04; N, 12.50; Co, 10.52; Cl, 25.36. Found C, 23.6; H, 5.3; N, 12.2; Co, 11.0; Cl, 26.5. ^1H NMR (D_2O) δ 1.18 (t, 3 H, CH_3, J = 8 Hz), 2.8–3.7 (m, 12 H, tren CHz), 3.80 (q, 1 H, OCH_2CH_3, J = 8 Hz), 3.84 (q, 1 H, OCH_2CH_3, J = 8 Hz), 5.13 (s, 0.5 H, $CH(OH)(OCH_2CH_3)$), 5.16 (s, 0.5 H, $CH(OH)(OCH_2CH_3)$). After several minutes, the signals due to the aldehyde complex (δ 5.44 (s, $CH(OH)_2$), 7.56 (s, CHO)) and free ethanol (δ 1.15 (q, CH_3, J = 8 Hz), 3.60 (q, CH_2, J = 8 Hz)) became apparent. The complex hydrolyzed to the (dihydroxymethyl)glycinate species and free ethanol during the time required for data accumulation for a reasonable ^{13}C NMR spectrum.

X-ray Structure Determination. Crystal Data. $C_9H_{24}CoN_5O_4 \cdot ZnCl_4 \cdot 2H_2O$, formula weight 568.5, monoclinic, space group Cc(C_s^4-No. 9), a = 9.217 (2) Å, b = 16.926 (3) Å, c = 13.315 (2) Å, β 92.92°, cell volume 2057.4 Å^3, density 1.83 (measured by flotation in C_6H_5Cl/CBr_4), 1.84 g cm^{-3} (calculated), Z = 4, $F(000)$ 1160, μ(Mo Kα) 25.88 cm^{-1}, graphite monochromator, λ 0.7107 Å, temperature 21 (1) °C.

Data Collection. Crystals suitable for data collection were obtained by slow recrystallization from an aqueous solution of the title compound with excess $ZnCl_2$ in 3 M HCl. The diffraction symmetry ($2/m$) and systematic absences (hkl, $h + k \neq 2n$; $h0l$, $l \neq 2n$) define the space group as either Cc or $C2/c$. The measured density indicated only four formula units per cell, and as the molecule does not possess a center of symmetry or a 2-fold axis the space group Cc was confirmed. Precise values for the unit cell dimensions were determined by least-squares analysis of the setting angles of 25 reflections ($35 < 2\theta < 40°$) measured on a Philips PW1100/20 diffractometer (Mo Kδ_1, λ 0.7093 Å, graphite monochromator). Dimensions of the specimen crystal were 0.22 by 0.13 by 0.14 mm between bounding faces {100}, {021}, and {0$\bar{2}$1} respectively. Reflection intensities were measured in the θ–2θ scan mode with scan velocity 2° min^{-1} (2θ) from 2θ − 0.8 to 2θ + 0.8 + Δ°, where Δ is the 2θ separation of the Kα_1 and Kα_2 peaks of the reflection concerned. Backgrounds were recorded in the stationary crystal–stationary counter mode (10-s duration) at each extreme of the scan range. Intensities of three standard reflections (400, 060, 008) were monitored regularly during data collection. No significant variations in their intensities were observed throughout the course of the experiment. Reflections were measured in the range $3 < 2\theta < 50°$ for each of the Bivoet nonequivalent quadrants $hk\pm l$ and $-h-k\pm l$. Of the 4014 reflections measured only 3624 were unique, and of these only 3071 (85%) for which $I > 2\sigma(I)$ were used in subsequent calculations. R_s for this data set (defined as $R_s = \sum\sigma/\sum|F_o|$ where σ is the error contribution to $|F_o|$ from counting statistics alone) is 0.04. In the calculation of σ_2 values,[3,4] an experimental uncertainty factor ρ = 0.04 was assumed. Data were not corrected at any stage for absorption or extinction effects.

Structure Analysis. The structure was solved by using conventional heavy-atom methods[5] and refined by full-matrix least-squares procedures minimizing the function $\sum w(|F_o| - |F_c|)^2$ where $w = \sigma_2^{-1}$. Atomic scattering factors and anomolous dispersion corrections were taken from ref 6. Atomic positions were calculated for the 22 hydrogens not bonded to oxygen by assuming bond lengths of 0.95 Å and normal trigonal or tetrahedral geometry. Positions for the hydroxyl and water hydrogens were obtained from a subsequent difference map. The hydrogen atoms were subsequently included in the refinement as fixed atom contributors with isotropic thermal parameters 10% greater than the atoms to which they are attached. In the final scattering model all nonhydrogen atoms were assigned anisotropic thermal parameters and refinement converged at R = 0.043 and R_w = 0.038 (where $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$ for 3071 data and 233 variables with a standard error of fit of 1.614. There were no significant features in the corresponding difference map above the general background level of ±0.5 e Å^{-3}. Final atomic coordinates (Table I), bond lengths and angles (Table II), hydrogen bonding parameters in Table (III), an ORTEP drawing of the complex ion (Figure 1), a table of thermal parameters, and tables of observed and calculated structure factor amplitudes are available as supplementary material.

Discussion

Hydrolysis of the Vilsmeier Adduct. The hydrolysis of the Vilsmeier adduct to produce the aldehyde is well-known in organic chemistry. The stability of the Vilsmeier moiety, engenderged by chelation to the metal ion, is remarable, however.[2] The reaction appears to be acid catalyzed, requiring relatively extreme conditions (>16 M H_2SO_4, 5 h, 25 °C) to effect a reasonable rate of hydrolysis. One plausible mechanism is given in Scheme I.

The driving force would appear to be protonation of the exo amine center, which diminishes the extensive π-electron delocalization over the entire ligand skeleton, present in the starting Vilsmeier structure,[2] and which is implied by the two reasonance structures **1** and **2** (Scheme I). Understandably, therefore, it is difficult to protonate this nitrogen center in the stable Z isomer.

(4) Corfield, P. W. R.; Doedens, R. J.; Ibers, J. A. *Inorg. Chem.* **1967**, *6*, 197.

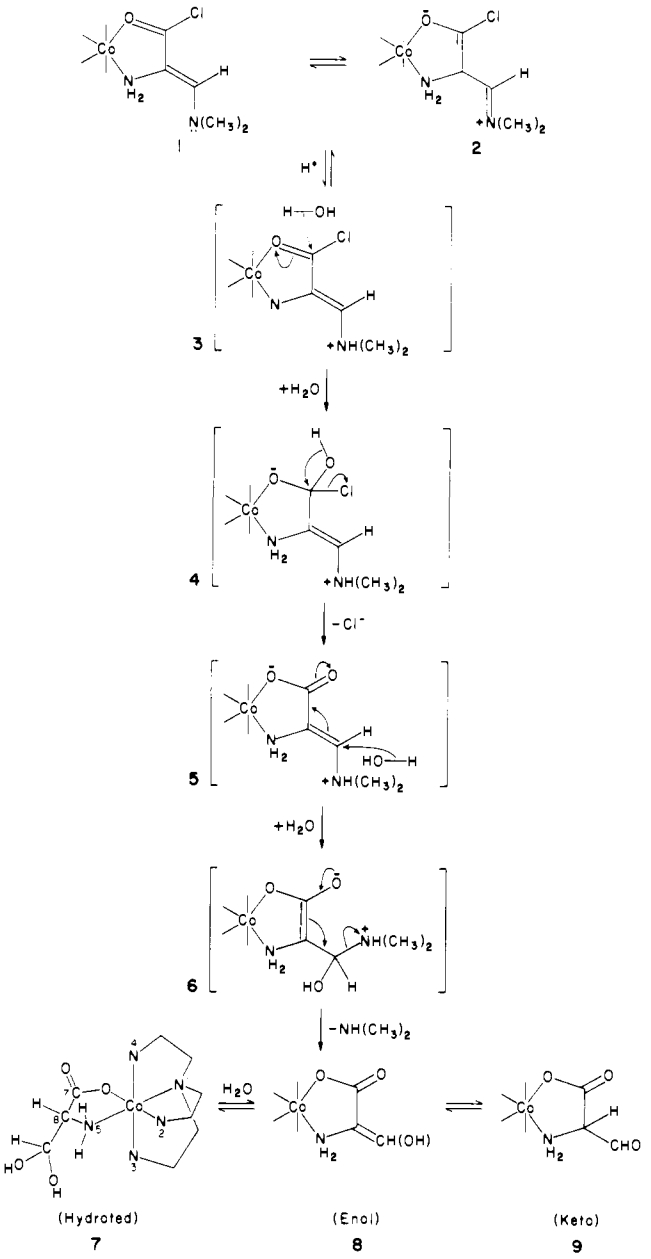
(5) Computer programs used for this structure analysis are part of the ANUCRYS structure determination package, devised and assembled by G. M. McLaughlin, D. Taylor, and P. O. Whimp., Research School of Chemistry, Australian National University, Canberra, A. C. T. 2600, Australia.

(6) "International Tables for X-ray Crystallography"; Ibers, J. A., Hamilton, W. C., Eds.; Kynock Press: Birmingham, AL, 1974; Vol. 4.

(7) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1957**, *79*, 1262–1263.

(8) "International Tables for X-Ray Crystallography"; Ibers, J. A., Hamilton, W. G., Eds.; Kynock Press: Birmingham, AL, 1974; Vol. IV, pp 99–102, 149–150.

Scheme I



7 8 9

The unstable *E* Vilsmeier isomer, which lacks the stabilization through this extensive π-electron delocalization because of severe steric restriction,[2] has also been found to hydrolyze to the aldehyde complex reported here. However, the hydrolysis is so rapid under the acidic conditions of the quenched reaction mixture that is has precluded its isolation (although it has been observed clearly in the ^1H and ^{13}C NMR spectra).[2]

The species **3–6** in Scheme I were not observed at any stage of the hydrolysis, consistent with the expected reactivity for such structures. Both Cl^- and $NHMe_2$ are eliminated in the course of complete hydrolysis, but the sequence is not known. (In Scheme I, Cl^- loss from the reactive coordinated acid chloride functionality is arbitrarily shown as the first step.)

Aspects of the Structure. The crystallographic asymmetric unit consists of an octahedral cobalt(III) complex cation (Scheme I (**7**)), a tetrahedral tetrachlorozincate anion, and two waters of crystallization, all of which are involved in hydrogen bonding (Table III). The tren ligand adopts the p configuration, and the identification of bidentate (dihydroxymethyl)glucinate chelate confirms the presence of the aldehyde functional group as a hydrate. The bond lengths and angles of the tren quadridentate do not differ significantly from those found in (p)-[Co(tren)-(*Z*)-(3-(dimethylamino)-2-aminoacrylyl chloride)]$ZnCl_4$·Cl·H_2O[2] or (p)- and (t)-$[Co(tren)(gly)]^{2+}$ complexes.[1,9] The Co–N(1) bond length (1.94 (1) Å), is shorter than the Co–N(2–4) primary amine bond lengths (1.95–1.98 Å), as expected. The Co–O(1) bond length of 1.91 (1) Å falls in the usual range (1.88–1.92 Å)[9,10] for coordination in these structures, and the conformation of the five-membered N,O-bound chelate ring does not significantly differ from that of similar complexes;[9,10] the N(5)–C(8), C(8)–C(7), and C(7)–O(1) bond lengths and angles are all within reported ranges.

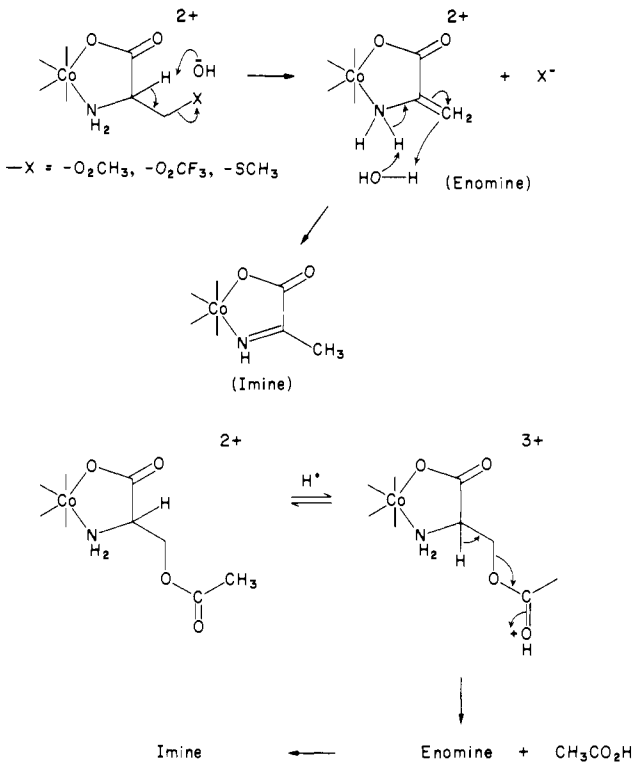
The $[Co(tren)(2\text{-}(dihydroxymethyl)glycinate)]^{2+}$ cation contains a chiral C center on the substituted glycine ligand, and each of the three five-membered chelates of the tren moiety can adopt either of the enantiomorphic λ or δ ring conformations.[2] Thus in principle 16 diastereoisomers can exist, 8 energetically distinct racemic pairs. The present structure belongs to the noncentrosymmetric but achiral space group *Cc* (No. 9-C_s^4), and it is clear that single crystals are racemic. The relative configurations of the contributions to the molecular chirality are obviously of importance here. The unit cell comprises four molecules, involving pairs of enantiomers ((*R*)-$\delta\lambda\delta$, (*S*)-$\delta\lambda\lambda$). Figure 1 shows one of these ((*R*)-$\delta\lambda\delta$). The interesting stereochemical feature of the result is the recurrence of the $\delta\lambda\delta$ form (or its enantiomer $\delta\lambda\lambda$).[2] This has been observed also in (p)-[Co(tren)(3-(dimethylamino)-2-aminoacrylyl chloride)]$ZnCl_4$·Cl·H_2O,[2] (p)- and (t)-[Co(tren)(gly)],[9] and $[Co(tren)(NCS)_2]NCS$.[11] Some significance may therefore be attached to the strain-energy minimization calculations,[2] which indicate that the $\delta\lambda\delta$ or $\delta\lambda\lambda$ ring conformation set is more stable than the next highest energy set by ~2.7 kcal mol^{-1}. The present structural result reinforces the stability relationship and indicates that the remote chiral carbon center of the glycine ligand is not sufficiently interacting with the tren conformers to alter them.

Characterization and Solution Structure. The aldehyde complex, which is formed essentially quantitatively, can exist in keto **9** or enol **8** forms, as well as a hydrated form, **7**. Elemental analysis of the isolated solid indicated the composition $[Co(tren)(NH_2CH(CH(OH)_2)CO_2)]ZnCl_4\cdot 2H_2O$. In solution, however, some free aldehyde complex exists in rapid equilibrium with the hydrate. The process is slow on the NMR time scale. Characteristic signals were observed at δ 5.44 (85%, C*H*$(OH)_2$) and δ 7.56 (15%, C*H*O) in the ^1H NMR spectrum in D_2O. ^{13}C signals also with the same 85:15 intensity ratio at δ 88.2 and 21.6, respectively, were recorded in the same solvent. This is an important consideration in the reactions of the aldehyde function since the free aldehyde, not its hydrated form, is the reactive entity. In basic solutions, oxygen exchange on the *gem*-diol may inhibit condensations at this center.

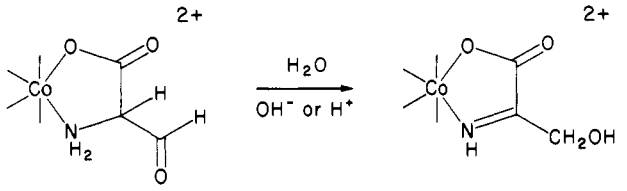
There was not evidence for any significant proportion of the enol form **8** in D_2O solution, although it is the obvious and likely intermediate for the hydration–dehydration reaction. Reaction via the enol form requires CH exchange at the "inner" methine C center. This was observed in D_2O and even in strong acid (1 M DCl) where H exchange is suppressed. Also, the inner carbon center was not observed in the ^{13}C NMR spectrum. Methine carbons of this type are commonly identified by exchanging H for D, which results in a significant reduction in the intensity in the H-decoupled ^{13}C NMR spectrum through the loss of the nuclear Overhauser intensity enhancement. These results suggest a rather acidic methine carbon proton ($pK_a < 12$). The yellow aldehyde complex is substantially deprotonated in 0.1 M $[OH^-]$ to give a deep red-maroon complex (unstable), indicating $pK_a \lesssim 13$; addition of acid regenerated the starting aldehyde complex. Qualitative work using several other bases whose conjugate acids lie in the pK_a range 9–13 indicated a $pK_a \sim 11$. The acidity is attributed to the chelation of the glycine aledehyde ligand to Co(III) through the NH_2 and CO_2^- groups; substantially enhanced

(9) Mitsui, Y.; Wantanabe, J.; Harada, Y.; Sakamaki, Titaka, Y.; Kushi, Y.; Kimura, E. *J. Chem. Soc., Dalton Trans.* **1976**, 2095–2102.
(10) "Molecular Structure by Diffraction Methods"; Specialist Periodical Reports; Chemical Society: London, 1975; Vol. 3.
(11) Kundell, F. A.; Hazell, R. G.; Razmussen, S. E. *Acta Crystallogr., Sect. B* **1975**, *B31*, 2879.

Scheme II

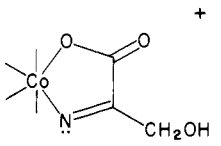


Scheme III



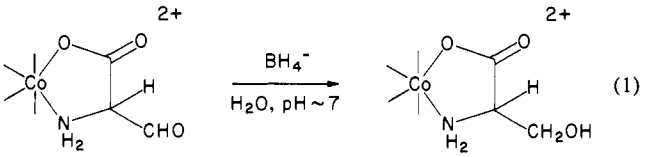
C–H acidity has been observed for a variety of Co(III)-chelated organic moieties of this kind, and the phenomenon is discussed in detail elsewhere.[12]

Although there is precedence for a rapid hydration–dehydration of the aldehyde via the enol form **8**, an additional process merits consideration. Recent work has demonstrated a propensity for chelated ligands of this type to rearrange (or eliminate) to give an especially stable chelated imine complex.[13] An enamine is implicated in this rearrangement (Scheme II). The thermodynamic drive for this rearrangement to the chelated imine is especially apparent from the reaction where X = CH_3S.[14] Methanethiolate is not normally considered a good leaving group, yet the thioether complex rearranges readily in base to the imine, with elimination of CH_3S^-. This reaction is based catalyzed, and for X substitutents that can protonate it is also acid catalyzed (Scheme II). These results suggest that the aldehyde might rearrange to the imine tautomer in base (Scheme III). However, the aldehyde is recovered unchanged from OH^- solution after acid quenching. Even so, the deep red-maroon of the complex



in OH^- is consistent with a deprotonated imine by analogy with the known chemistry[13] of chelated imines of this kind ($pK_a \sim 11$), provided that on reprotonation the imine rearranges rapidly back to the aldehyde. The results also require that the keto form of the complex is more thermodynamically stable than the imine in neutral and acidic conditions. Further evidence for the existence of the imine–enamine(enol) aldehyde equilibrium comes from H–D-exchange experiments. The aldehyde complex was recovered from 0.1 M NaOD (~2 s) by quenching with DCl (at ~25 °C), and both the inner and outer methine protons were found to be totally exchanged (^1H NMR) with deuterons.

Reactions of the Aldehyde Complex. The aldehyde functional group is reduced readily by BH_4^- (eq 1) in neutral to weakly basic



(1)

solution to give the alcohol. The reaction is essentially quantitive (95% yield). Overall this affords a convenient high-yield synthesis of serine from glycine, since the yields for the first two steps, glycine to Vilsmeier adduct (80%) and its hydrolysis to the aldehyde (~95%), are both high. The product, isolated as (p)-$[Co(tren)(ser)]S_2O_6 \cdot H_2O$, was characterized by elemental analysis, by ^1H and ^{13}C NMR spectroscopy, and by comparison with an authentic sample prepared directly[14] from the free L-serine ligand. In this synthesis, $[Co(tren)(OH)OH_2](ClO_4)_2$ and L-serine ethyl ester produced (p)- and (t)-$[Co(tren)(ser)]^{2+}$ together, and the isomeric products were separated by ion-exchange chromatography. Both isomers have been fully characterized.[14]

The aldehyde complex reacts rapidly (minutes, 25 °C) and reversibly in neutral or acidic aqueous solution with alcohols (CH_3OH and CH_3CH_2OH) to give hemiacetals. These have been isolated as $ZnCl_4^{2-}$ salts in good yield and free of both starting material and the corresponding acetal. Presumably the full acetals could have been obtained by using neat rather than aqueous alcohols, with the appropriate dehydrating agent, but these reactions were not pursued. The outer methine carbon of the hemiacetals is chiral, and this coupled with the chiral inner methine center gives rise to the two diastereoisomers that were observed in the ^1H NMR spectrum. As with the aldehyde complex, the inner methine proton is rapidly exchanged in D_2O or dilute D^+, via the enamine, which leads to racemization at this center and hence mutarotation of the two diastereoisomers. The process was slow on the NMR time scale, and a ~50:50 equilibrium distribution was observed. For the ethyl complex the doublet centered at δ 5.145 in the ^1H NMR spectrum (D_2O) comprises a peak for each diastereoisomer. It does not arise from H–H coupling. (This was confirmed by comparing the 60- and 100-MHz spectra and noting the doublet even after the inner methine proton was exhanged in D_2O.) The signals in the CH_2 (δ ~3.8) and CH_3 (δ ~1.18) regions integrate for one CH_3CH_2 group. There is some fine structure here that is complicated by the presence of two isomers and the existence of diastereotopic methylene protons for each. The ethyl hemiacetal was observed to hydrolyze quickly (minutes) in D_2O, reverting quantitatively to the aldehyde complex in ~1 h at the probe temperature (35 °C).

Conclusions

The racemic glycine aldehyde complex is produced in high yield by hydrolysis of the stable formylated glycine Vilsmeir intermediate reported previously.[2] In the solid state the aldehyde is fully hydrated, but in H_2O solution it is in rapid equilibrium with the free aldehyde (CHO, 15%; $CH(OH)_2$, 85%). It shows reactions characteristic of normal aldehydes, and these reactions probably proceed by the more reactive free-aldehyde form. The rapid H–D exchange at the inner methine and base-catalyzed exchange at the outer methine centers of the complex are properties consistent with the known chemistry of N,O-chelated substituted amino acids and imine complexes derived from them.[12-14]

The complex reported here is analogous to the protected glycine aldehyde used by Sheehan et al.[15] as a key intermediate in the

(12) Buckingham, D. A.; Marzilli, L. G.; Sargeson, A. M. *J. Am. Chem. Soc.* **1967**, *89*, 5133–5138.
(13) Harrowfield, J. M.; Sargeson, A. M. *J. Am. Chem. Soc.* **1979**, *101*, 1514–1520 and references therein.
(14) (a) Chong, C. K.; Jackson, W. G.; Sargeson, A. M.; unpublished data. (b) Chong, C. K. Ph.D Thesis, ANU, 1979.

total synthesis of penicillins. The substitutionally inert Co(III) center protects both the amine and carboxylato functional groups through chelation and is a useful single substitute for the more conventional phthalamido and ester protecting groups used in the organic chemistry.

Apart from the reactions reported herein, the aldehyde complex has obvious synthetic potential, particularly in penicillin chemistry. We will be reporting on this later but note here that the metal center, in addition of functioning as a protecting group, can be modified by using the appropriate ligands (e.g., the chiral Λ or Δ $Co(en)_2$ in lieu of (p)- or (t)-Co(tren)) to impart a specificity in asymmetric synthesis involving the aldehyde center. Also, as this work has shown, the inner chiral methine center of the substituted glycine is readily mutarotated.

A useful property of the glycine aldehyde complex, from a synthetic viewpoint, is its relative stability in dilute base. It does not self-condense as readily as normal aldehydes (aldol condensation), presumably because this involves two positively charged (2+) cations, nor does it readily undergo intramolecular cyclization with the coordinated amine centers, e.g., cyclic imine formation. This is probably a steric constraint, although the similar complex $[Co(en)_2NH_2{\cdot}CN(C{\equiv}N)CO_2]^{2+}$ condenses intramolecularly in base to give a cyclic (albeit strained) amidine.[16]

Acknowledgment. We thank the Microanalytical Section (A.N.U.) for elemental analyses and Dr. N.J. Curtis for checking some of the results.

Registry No. 1, 76024-02-7; **7**, 84809-81-4; $[Co(tren)(ser)]S_2O_6$, 84847-59-6; $[Co(tren)B]ZnCl_4$ (B = (hydroxyethoxymethyl)glycinate), 84809-83-6.

Supplementary Material Available: Tables of final atomic coordinates, bond lengths and angles, hydrogen bonding parameters, an ORTEP drawing of the complex ion, thermal parameters, and observed and calculated structure factor amplitudes (15 pages). Ordering information is given on any current masthead page.

(15) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 3089.

(16) Springborg, J.; Geue, R. J.; Sargeson, A. M.; Taylor, D.; Snow, M. R. *J. Chem. Soc., Chem. Commun.* **1978**, 647-649.

A Mild and General Method for the Synthesis of *O*-Glycosides

K. C. Nicolaou,*† S. P. Seitz, and D. P. Papahatjis

Contribution from the Department of Chemistry, University of Pennsylvania, Philadephia, Pennsylvania 19104. *Received April 22, 1982*

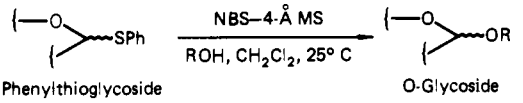
Abstract: A mild and general procedure for the synthesis of *O*-glycosides from phenyl thioglycosides (Scheme I) is described. The method involves treatment of the readily available phenyl thioglycosides with *N*-bromosuccinimide in the presence of various hydroxy components in organic solvents under anhydrous conditions at 25 °C to produce a series of *O*-glycosides in a few minutes. Applications to complex systems and intramolecular cases are included.

The widespread occurrence of the *O*-glycoside bond in nature and the importance of biomolecules containing this bond are becoming increasingly evident.[1] Methodology[2] for the construction of the *O*-glycoside linkage is, therefore, of paramount interest due to the central role of such reactions in organic synthesis and in assembling complex frameworks containing carbohydrate residues. Despite the great deal of work in this area, however, severe limitations and deficiencies still exist in the present technology.[3] One of the most widely used methods, for example, the utilization of 1-halo derivatives of carbohydrates, often suffers from the instability of the intermediates, the relative drastic conditions for their preparation, and the requirement of precious or other related heavy metal reagents as further activators.[2] In connection with our work in the total synthesis of complex and sensitive, carbohydrate-containing natural products from the macrolide area[4] we were faced with the problem of coupling carbohydrate units and of attaching them onto suitable aglycones efficiently and under extremely mild conditions. In this article we wish to report a mild and facile procedure that constitutes a convenient and general method for the construction of the *O*-glycoside bond and, furthermore, fulfills the above requirements.

Results and Discussion

Scheme I profiles this general method that employs the stable and readily available phenyl thioglycosides (*vide infra*) as starting materials. The phenyl thioglycoside is activated with *N*-bromosuccinimide (NBS, 1.1 equiv) in the presence of the hydroxy component (stoichiometric or near stoichiometric amounts) and 4-Å molecular sieves (to ensure strict anhydrous and neutral conditions) in methylene chloride (CH_2Cl_2) at 25 °C leading to *O*-glycosides (α- and β-anomers) in good to excellent yields, the reaction being complete usually in less than 15 min.[5] Table I includes some of the examples of *O*-glycosides synthesized according to the above prescription and helps to illustrate the ef-

Scheme I



† Fellow of the A. P. Sloan Foundation, 1979-1983; recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980-1985.

(1) For some recent reviews see: (a) Hanessian, S.; Dixit, D. M.; Liak, T. J. *Pure Appl. Chem.* **1981**, *53*, 129 and references cited therein. (b) *Chem. Eng. News* **1981**, *59* (13) 21.

(2) For some recent reviews see: (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Tsutsumi, H.; Ishido, Y. *Yuki Gosei Kagaku Kyokaiski* **1980**, *38*, 473. (c) Bochkov, A. F.; Zaikov, G. E. "Chemistry of the *O*-Glycosidic Bond: Formation and Cleavage"; Pergamon Press: Oxford, 1979. (d) Sinai, P. *Pure Appl. Chem.* **1978**, *50*, 1437. (e) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243. (f) Hanessian, S.; Banoub, J. *Adv. Chem. Ser.* **1976**, *No. 39*, 36. (g) Iley, D. E.; Frazer-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 2563. (h) Wulff, G., Rohl, G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 157.

(3) These deficiencies include both low yields and low stereoselectivities. See, for example: (a) Tatsuta, K.; Tanaka, A.; Fujimoto, K.; Kinoshita, M.; Umezawa, S. *J. Am. Chem. Soc.* **1977**, *99*, 5826. (b) *Ibid.*, ref 6c.

(4) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027. (b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *Ibid.* **1982**, *104*, 2030. (c) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *Ibid.* **1981**, *103*, 1222. (d) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Ibid.* **1981**, *103*, 1224.

0002-7863/83/1505-2430$01.50/0