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Peptide Bond Formation and Subsequent Hydrolysis at a Cobalt(III) Center

Sir:

We wish to report the rapid formation of a peptide bond in nonaqueous solutions at room temperature using the $Co(trien)^{3+}$ (trien = triethylenetetramine) moiety as a N-terminal protecting group and as an activating center. This discovery was made during a preparative study of cobalt(III) complexes containing monodentate amino acid amides and esters.

Treatment of α- or β-$[Co(trien)(TBP)_2]^{3+}$ [1] or β_2-$[Co(trien)Cl(glyOEt)](ClO_4)_2$ [2] with glycine ethyl ester in dry TBP, and sulfolane or dimethylformamide solutions, respectively, results in the rapid condensation of two glycine ester residues and the formation of the β_2-$[Co(trien)glyglyOEt]^{3+}$ ion. The reactions (eq 1–3) are complete within 2 min at 25°.

$$\alpha\text{-}[Co(trien)(TBP)_2]^{3+} + 2glyOEt \xrightarrow{TBP} \beta_2\text{-}[Co(trien)glyglyOEt]^{3+} + HOEt + 2TBP \quad (1)$$

$$\beta_2\text{-}[Co(trien)ClglyOEt](ClO_4)_2 + glyOEt \xrightarrow[(DMF)]{sulfolane} \beta_2\text{-}[Co(trien)glyglyOEt]^{3+} + HOEt + 2ClO_4^- + Cl^- \quad (2)$$

$$\beta\text{-}[Co(trien)(TBP)_2]^{3+} + 2glyOEt \xrightarrow{TBP} \beta_2\text{-}[Co(trien)glyglyOEt]^{3+} + HOEt + 2TBP \quad (3)$$

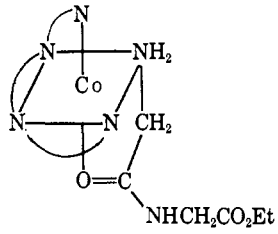
Chromatography on cation ion-exchange paper (Whatman cellulose phosphate P81) showed almost quantitative formation of the dipeptide ester complex, and analytically pure β_2-$[Co(trien)glyglyOEt](ClO_4)_3 \cdot H_2O$ was isolated in high yield (~80%) from each of the reactions. (*Anal.* Calcd: C, 21.17; H, 4.74; N, 12.35. Found: C, 20.86; H, 4.82; N, 12.16). An identical product was isolated following treatment of β-$[Co(trien)(H_2O)_2]^{3+}$ with glycylglycine ethyl ester in aqueous solution at pH 7.5–8.0 for 1 hr at 25° and addition of $NaClO_4$ (reaction 4).

$$\beta\text{-}[Co(trien)(H_2O)_2]^{3+} + glyglyOEt \cdot HCl \longrightarrow \beta_2\text{-}[Co(trien)glyglyOEt]^{3+} + 2H_2O + H^+ + Cl^- \quad (4)$$

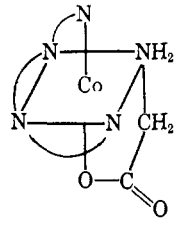
The equivalence of the products isolated from reactions 1–4 was established by comparisons of pmr (δ 1.3 (triplet), 4.36, 4.27, and 4.25 ppm (masked quartet); intensity ratio 3:2:2:2), infrared (1735 cm^{-1} ester carbonyl, 1630 cm^{-1} coordinated amide carbonyl), and visible (ϵ_{346} 153; ϵ_{478} 141) spectra, as well as by their chromatographic behavior and analytical data. The compound β_2-$[Co(trien)glyglyOEt](ClO_4)_3 \cdot H_2O$ is easily recrystallized without change from neutral or acidic solutions, but undergoes hydrolysis in basic solutions (pH $\geq$8) liberating 1 equiv of glycine ethyl ester (reaction 5). The resulting glycine chelate β_2-$[Co(trien)gly]^{2+}$ ion was isolated as its I^- and ClO_4^- salts (*Anal.* Calcd for $[CoC_8H_{22}O_2N_5](ClO_4)_2 \cdot 0.5H_2O$: C, 19.72; H, 4.75; N, 14.38. Found: C, 19.82; H, 4.53; N, 14.33) and is identical with that obtained in the reaction of β-$[Co(trien)(H_2O)_2]^{3+}$ with glycine (ϵ_{346} 145 ϵ_{478} 134).[3] In view of reactions 4 and 5 and structure I below, it is now proposed that the β_2-$[Co(trien)glyglyOEt]^{3+}$ ion is the intermediate in the hydrolysis of peptide esters and amides catalyzed by the β-$[Co(trien)OH(H_2O)]^{2+}$ ion.[4]

$$\beta_2\text{-}[Co(trien)glyglyOEt](ClO_4)_3 + OH^- \longrightarrow \beta_2\text{-}[Co(trien)gly]^{2+} + glyOEt + 3ClO_4^- \quad (5)$$

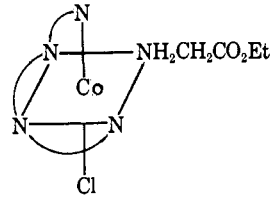
An X-ray structural study of β_2-$[Co(trien)glyglyOEt](ClO_4)_3 \cdot H_2O$ establishes its geometrical configuration as I[5] in which glycylglycine ethyl ester functions



I



II



III

as a bidentate ligand by attachment to cobalt through the terminal amino nitrogen and peptide carbonyl oxygen atoms. This, together with the experiments below, establishes the geometrical structure of the hydrolyzed product, β_2-$[Co(trien)gly]^{2+}$, and reactant, β_2-$[Co(trien)Cl(glyOEt)]^{2+}$, as II and III, respectively, in agreement with previous assignments.[3]

To establish that formation of the peptide bond does occur at the cobalt(III) center, β_2-$[Co(trien)Cl(glyOEt)](ClO_4)_2$ (1 g) (*Anal.* Calcd: C, 22.13; H, 5.02; N, 12.91. Found: C, 21.98; H, 5.12; N, 12.99) containing C^{14}-labeled glycine ethyl ester (4850 ± 17 cpm/mg of complex) was treated with 2 equiv of freshly prepared inactive glycine ethyl ester (0.4 g) in sulfolane (10 ml) and the reaction quenched after 2 min by addition of ethanol and ether. The β_2-$[Co(trien)glyglyOEt](ClO_4)_3 \cdot H_2O$ obtained after two recrystallizations from hot water (*Anal.* Calcd: C, 21.17; H, 4.74; N, 12.35. Found: C, 21.25; H, 4.42; N, 12.40) and unreacted glycine ethyl ester recovered by chromatography were analyzed for their C^{14} content, and

(1) α and β refer to the geometrical arrangement of triethylenetetramine about the metal atom: G. H. Searle and A. M. Sargeson, *Inorg. Chem.*, 4, 45 (1965). TBP = tri(*n*-butyl) phosphate.

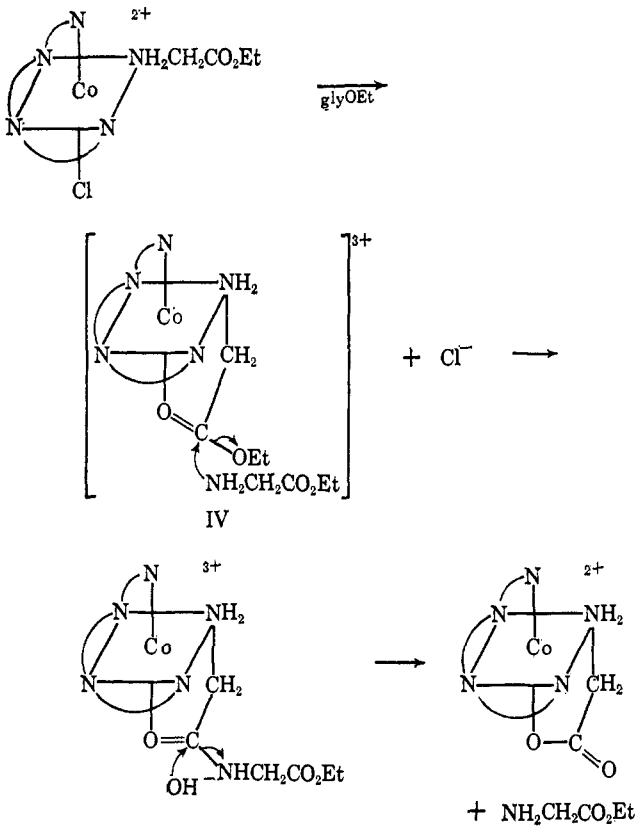
(2) Subscripts β_1 and β_2 are used to distinguish between the two nonequivalent positions in the β structure; see II and III below.

(3) L. G. Marzilli and D. A. Buckingham, *Inorg. Chem.*, 6, 1042 (1967).

(4) D. A. Buckingham, J. P. Collman, D. A. R. Happer, and L. G. Marzilli, *J. Am. Chem. Soc.*, 89, 1082 (1967).

(5) M. Fehlmann, H. Freeman, D. A. Buckingham, and A. M. Sargeson, to be published.

the results of 3890 ± 10 cpm/mg and approximately 200 ± 50 cpm/mg, respectively, establish that *no significant exchange of coordinated and free glycine ethyl ester has occurred during the reaction.* Thus formation of the peptide bond must involve condensation of the coordinated ester and must occur on the complex. Subsequent hydrolysis of the C^{14}-labeled β-[Co(trien)glyglyOEt]$(ClO_4)_3 \cdot H_2O$ at pH ≃10 and 25° and examination of the β_2-[Co(trien)gly]$(ClO_4)_2 \cdot 0.5H_2O$ isolated from the resulting solution (4930 ± 10 cpm/mg) shows 96% retention of activity in the chelated glycine residue, and indicates a similar retention in the N-terminal glycine of the β_2-[Co(trien)-glyglyOEt]$^{3+}$ ion. These results are consistent with, but do not unequivocally establish, the following mechanism for peptide formation and subsequent hydrolysis. Formation of the peptide bond prior to chelation is also allowed by the results, but prior coordination of the incoming ester followed by condensation is excluded.



Preliminary results indicate that the intermediate IV condenses with dipeptide esters to give a coordinated tripeptide ester, which leads to the possibility that this process may be useful as a general method for N-terminal addition of integral amino acid residues to peptide esters. Experiments to distinguish between the mechanistic possibilities are presently being conducted. Also the scope and versatility of this reaction are being investigated.

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Chlorosilyl Derivatives of Transition Metals and Evidence for a Conformational Effect on Metal Carbonyl Stretching Bands

Sir:

The chemistry of silicon–transition metal compounds has been developed to a much smaller extent than that of germanium, tin, and lead; this situation may result in part from a lack of suitable preparative methods. We reported recently[1] that triphenylsilane, known[2] to react readily with cobalt carbonyl, would react under more vigorous conditions with the carbonyls of manganese and rhenium, affording $(C_6H_5)_3SiM(CO)_5$ (M = Mn, Re). We now communicate further studies showing that the silane–metal carbonyl reaction is a rather general one, providing a convenient route to new compounds both expected and unexpected. The reactions of trichlorosilane are particularly interesting, and a number are summarized in Table I. Yields vary widely,

Table I. Trichlorosilane Reactions[a]

Reactant	Product[b]	Mp, °C[c]	CO stretching fundamentals, cm^{-1} [d]
$Mn_2(CO)_{10}$	$Cl_3SiMn(CO)_5$	130–131	2123, 2035
$Re_2(CO)_{10}$	$Cl_3SiRe(CO)_5$	169–169.5	2139, 2037, 2028
$Fe(CO)_5$	$[Cl_2SiFe(CO)_4]_2$	Dec >200	2094, 2053, 2048, 2038
$Fe_3(CO)_{12}$	$(Cl_3Si)_2Fe(CO)_4$	94–96	2125, 2078 2071, 2061
$[C_5H_5(CO)_3Mo]_2$	$Cl_3SiMo(CO)_3C_5H_5$	149–151	2041, 1976, 1959
$[C_5H_5(CO)_2Fe]_2$	$Cl_3SiFe(CO)_2C_5H_5$	128–130	2039, 1995
$[C_5H_5(CO)Ni]_2$	$Cl_3SiNi(CO)C_5H_5$	38–40	2062

[a] In sealed tubes in the 100–180° temperature range using excess Cl_3SiH. [b] Products characterized by elemental analysis and mass spectrum. In several cases other products are formed which have not yet been fully characterized. [c] Kofler hot-stage microscope. [d] In cyclohexane solution.

but the formation of $Cl_3SiMn(CO)_5$ is almost quantitative. On the basis of their infrared spectra, the products are structurally analogous to known derivatives of germanium, tin, and lead. It may be noted that silicon–molybdenum and silicon–nickel bonds have not been reported previously.

The trichlorosilyl derivatives of Table I are of interest in view of the numerous compounds of the trichlorostannyl ligand now known. The latter is regarded as a strong π acceptor and a weak σ donor.[3] Strong π-acceptor character for the Cl_3Sn ligand is also consistent with trends in CO stretching force constants in $Cl_3SnMn(CO)_5$ and related compounds, as we have pointed

(1) W. Jetz, P. B. Simons, J. A. J. Thompson, and W. A. G. Graham, *Inorg. Chem.*, **5**, 2217 (1966).
(2) A. J. Chalk and J. F. Harrod, *J. Am. Chem. Soc.*, **87**, 1133 (1965).
(3) R. V. Lindsay, Jr., G. W. Parshall, and V. G. Stolberg, *ibid.*, **87**, 658 (1965); G. W. Parshall, *ibid.*, **88**, 704 (1966).