is not well defined in alkane solvents and it may be shifted to lower temperatures. In certain other solvents[35] the a^H vs. T curve shows a more clearly defined maximum at ~200–220 K (see supplementary material).
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(25) The general form of this double-minimum potential function is

$$V(\theta) = A\theta^4 - B\theta^2 \ (A, B > 0)$$

Equation 1 is obtained by substituting $A = V_0/(\theta_{min})^4$, $B = 2V_0/(\theta_{min})^2$ and $\xi = \theta/\theta_{min}$. This transformation to the dimensionless coordinate, ξ, obviously leads to a significant simplification.
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Peptide Formation in the Presence of a Metal Ion Protecting Group. Pentaammine Cobalt(III)–Peptide Complexes

Sir:

The use of metal ions to activate and/or protect amino acid derivatives for peptide formation has been demonstrated in a number of studies using cobalt(III), copper(II), and platinum(II) complexes.[1-8] The work on cobalt(III) which showed the most promise centered around the use of cobalt(III) to *protect* the N terminal of an amino acid ester by coordination and to *activate* the ester carbonyl toward nucleophilic attack by coordination to the same tripositive cobalt(III) center This dual function of the metal ion (i.e., to protect and to activate) appeared promising at first, but has found little application in peptide synthesis presumably because the other methods used for the activation of amino acid derivatives (especially the C-terminal activation using carbodiimides and other active esters) are easier to carry out.

In this communication we present the first example of a synthetic scheme where a kinetically inert metal ion, $[(NH_3)_5Co^{III}-]$, functions as a carboxylate protecting group and directs peptide formation. The type of synthesis reported herein is an example where a designed peptide ligand is synthesized in a stepwise fashion in the vicinity of a metal center.

The kinetic inertness of the $[(NH_3)_5Co^{III}-]$ moiety and its resistance to hydrolysis in strong acids[9] makes it one of the few classes of coordination compounds that can remain in tact under the conditions used in peptide synthesis.[10] Furthermore, the $[(NH_3)_5Co^{III}-]$ moiety selectively binds to the C terminal of an amino acid (acting like an inorganic ester), thus allowing one to employ the known stepwise peptide synthetic techniques.[10] Herein we report our results on the aforementioned scheme for the synthesis of cobalt(III) dipeptide complexes and the progress of our work on the extension of the same methods for the synthesis of cobalt(III) complexes with longer peptide chains.

Cobalt(III) pentaammine-amino acid complexes have been synthesized by a number of investigators.[11-13] The synthesis of these complexes usually required heating $[(NH_3)_5Co(OH_2)]^{3+}$ with an amino acid at >60 °C for a number of hours. A dipeptide, under the conditions required to prepare the cobalt(III)-amino acid complexes, is prone to undergo hydrolysis and therefore cobalt(III)-peptide complexes could not be prepared by the above methods.

A versatile synthetic route for the preparation of cobalt(III) peptide complexes can only be achieved using mild conditions (ca. room temperature). We have succeeded in using two procedures for the synthesis of cobalt(III)-amino acid derivatives and -peptide complexes under ambient conditions. The first procedure involves the reaction of $[(NH_3)_5Co(OH)]^{2+}$[14] with a *tert*-butoxycarbonyl-(Boc-) amino acid (or Boc peptide) active ester. This procedure can be used to introduce cobalt(III) at the C terminal of a N-protected amino acid or peptide. In this work this method was used to prepare only the compound $[Boc\text{-}Gly\text{-}Co(NH_3)_5](ClO_4)_2$ (Table I).

The second method which involves peptide formation in the presence of cobalt(III) is the subject of the remaining part of this communication. This procedure involves stepwise peptide formation starting with the [amino acid-$Co^{III}(NH_3)_5$] com-

Table I

complex	IR, $\nu_{peptide\ C=O}$, cm^{-1}	UV-visible, λ_{max} (ϵ), nm ($M^{-1}\ cm^{-1}$)	anal., % C calcd	C found	H calcd	H found	N calcd	N found
$[Gly\text{-}Co(NH_3)_5](BF_4)_3$		502 (64) 350 (5)	5.01	5.47	4.20	4.21	17.52	17.68
$[Pro\text{-}Co(NH_3)_5](BF_4)_3$		499	11.56	12.03	4.66	4.64	16.17	15.34
$[(Boc\text{-}Gly)Co(NH_3)_5](BF_4)_2$	1740[a]	505	16.26	16.86	5.26	5.51	16.25	16.81
$[Gly\text{-}Gly\text{-}Co(NH_3)_5](BF_4)_3$	1698	503 (77) 348 (65)	8.95	9.30	4.32	4.25	16.27	18.10
$[Phe\text{-}Gly\text{-}Co(NH_3)_5](BF_4)_3$[b]	1685	503 (70) 348 (sh) (58)	21.08	20.17	4.66	4.74	15.64	14.84
$[Pro\text{-}Pro\text{-}Co(NH_3)_5](BF_4)_3\cdot 2H_2O$	1728	502 (77) 348 (70)	17.93	17.93	5.42	4.68	14.64	14.43

[a] $\nu_{C=O}$. [b] Reference 16.

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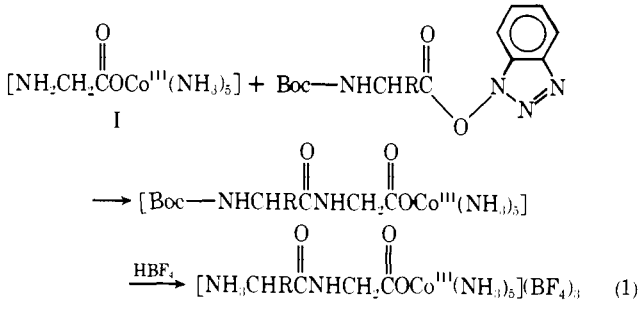
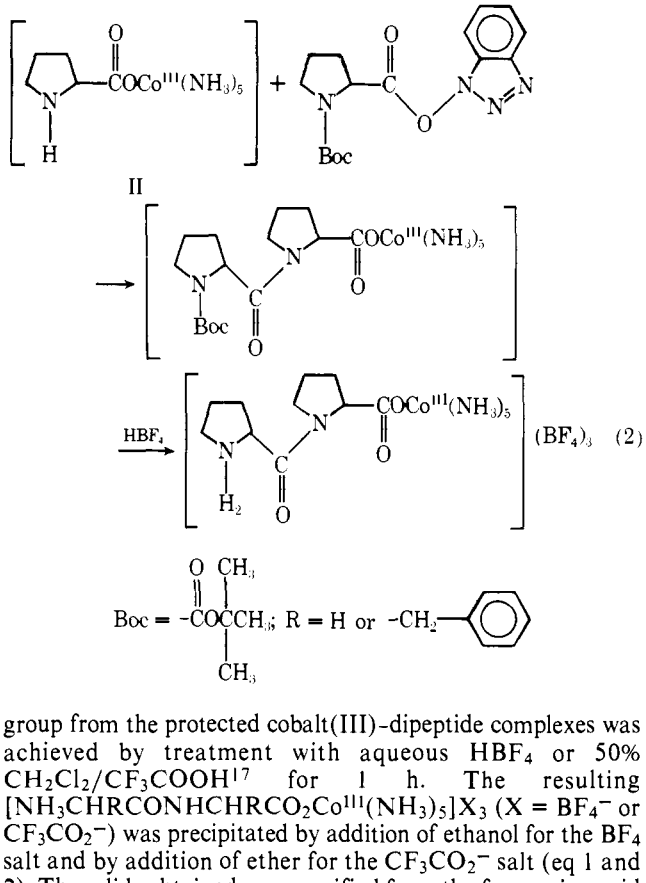
plex and a Boc-amino acid active ester. The versatility of this method is demonstrated in the following synthesis.

Starting with $[(NH_3)_5Co^{III}(OH_2)](ClO_4)_3$[15] and the amino acids glycine and proline, the ions, $[Gly\text{-}Co^{III}(NH_3)_5]^{3+}$ (I) and $[Pro\text{-}Co^{III}(NH_3)_5]^{3+}$ (II), have been prepared in good yields according to literature procedures.[11] The BF_4^- salts of these complexes were precipitated using 48% HBF_4 by the addition of ethanol. The purity of the solids obtained was established by elemental analysis (C, H, N, Co) (Table I).[16] The advantages of these BF_4^- salts over Cl^- or other salts is the high solubility of these amino acid complexes in organic media (e.g., DMF, or DMF/CH_2Cl_2 mixtures); in addition to this, the BF_4^- salts avoid the explosive hazards of the normally used perchlorate salts. The Boc-amino acid, to be added to the cobalt-amino acid complex, was activated by converting it to the hydroxybenzotriazole (HOBT) active ester with dicyclohexylcarbodiimide (DCC). When I or II was treated with the Boc-amino acid active ester in the presence of small amounts of triethylamine (for a period of 1 h at room temperature), peptide formation occurred (eq 1 and 2). Removal of the Boc



(1)



(2)

group from the protected cobalt(III)-dipeptide complexes was achieved by treatment with aqueous HBF_4 or 50% CH_2Cl_2/CF_3COOH[17] for 1 h. The resulting $[NH_3CHRCONHCHRCO_2Co^{III}(NH_3)_5]X_3$ (X = BF_4^- or $CF_3CO_2^-$) was precipitated by addition of ethanol for the BF_4 salt and by addition of ether for the $CF_3CO_2^-$ salt (eq 1 and 2). The solids obtained were purified from the free amino acid acid derivatives by gel filtration and the pink cobalt(III)-peptide complexes were evaporated to dryness by rotary evaporation at room temperature.[18] The solids were identified by UV-visible spectra, IR spectra, elemental analyses, and amino acid analyses. Table I lists some of the compounds that have been synthesized following this general procedure.

In the above reactions the $[(NH_3)_5Co^{III}\text{-}]$ moiety proved to be a useful protecting group for the C terminal of amino acids and peptides. One of its advantages over most organic ester protecting groups[19] lies in the ease of its removal by reduction under mild conditions. The $[(NH_3)_5Co^{III}\text{-}]$ protecting group was removed from the peptide by treatment with a solution of Na_2S in $NaHCO_3$ (~2 equiv of sulfide/cobalt) for 1 or 2 min at room temperature. The cobalt sulfide precipitate was filtered off and the colorless peptide solution was either directly analyzed for its peptide content on an amino acid analyzer or hydrolyzed and analyzed for its amino acid content. Using this procedure yields of >90% of the dipeptides, Gly-Gly and Phe-Gly, were obtained as compared with authentic samples. The amino acid content of these peptides after acid hydrolysis independently confirmed the peptide analysis. Analysis of the product solution after this mild removal of the cobalt protecting group can be used to detect small amounts of impurities. In the cases examined so far where the above reaction was carried out for pentaammine cobalt complexes of Gly-Gly, Gly-Phe, Phe-Gly, Pro-Pro, and $(Pro)_4$, no side products (i.e., due to incomplete coupling) were detected.[20]

The possible racemization of peptides in the vicinity of a $[(NH_3)_5Co^{III}\text{-}]$ center has not been investigated yet. Note that this work deals mainly with amino acids like glycine or proline directly attached to cobalt(III). For glycine no racemization is possible; and *l*-proline is not among the easily racemized amino acids. Work by Legg et al. on amino acid complexes chelated to cobalt(III) showed that in the cases studied racemization was very slow, ca. half-lives of the order of days.[21] We are currently investigating any racemization resulting from the $[(NH_3)_5Co^{III}\text{-}]$ protecting group.

We have extended this method to the synthesis of a tetrapeptide-cobalt complex, $[(Pro)_4Co(NH_3)_5](CF_3CO_2)_3$, by three stepwise additions of Boc-proline to $[ProCo(NH_3)_5]^{3+}$.[22]

The use of cobalt(III) to protect amino acid terminals and side chains during peptide synthesis is currently under more extensive investigation in our laboratories.

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Binuclear Bridging Imidazolate Complexes of Cobalt and Ruthenium

Sir:

The imidazole ring of histidyl peptide residues is known to form part of the coordination environment of a large number of metalloenzymes.[1] More recently, the imidazolate anion (i), the conjugate base of imidazole (ii), has been proposed as a bridging ligand in a number of cases. For example, crystal-


Im, i


ImH, ii

lographic evidence supports the presence of imidazolate between copper and zinc in bovine superoxide dismutase.[3] Palmer et al.[4] have also postulated the involvement of bridging imidazolate between iron and copper in cytochrome *c* oxidase. Such a model implies the participation of the histidyl imidazolate in the electron-transfer process of oxygen reduction. The above facts and speculation have intensified the interest in studying imidazole and imidazolate as ligands in simple metal complexes.

Although there are a number of known imidazolate bridged transition metal complexes, almost all of these examples are insoluble polymeric species.[5] Solution identification of imidazolate bridging species is limited to only a few examples.[6] Recently, the synthesis and characterization of a series of soluble copper(II) complexes with bridging imidazolate[7] have been reported (e.g., $[Cu(pip)]_2(imidazolate)(NO_3)_3$ where pip = 2-[2-(2-pyridyl)ethyliminomethyl]pyridine). These latter complexes are of structural value; however, their lability precludes any detailed studies on the nature of imidazolate as a ligand and more specifically on the electron-mediating properties of the imidazolate anion.

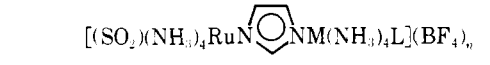
In contrast to these labile complexes, herein we report on the synthesis, characterization, and some of the properties of a class of binuclear complexes with imidazolate bridging groups in which the metal ions (ruthenium and cobalt) are relatively inert to substitution. These compounds allow for the first time the examination of the electron-mediating properties of the imidazolate anion when bridging between two metals of different oxidation states.

Table I. UV-Visible Spectra for Mononuclear and Binuclear Imidazole and Imidazolate Complexes

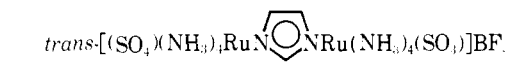
complex	λ_{max}, nm	ϵ, M^{-1} cm^{-1}
$[(NH_3)_5Ru(Im)Ru(NH_3)_4(SO_4)](BF_4)_3$	332	5.2×10^3
	420 (sh)	3.6×10^3
	460 (sh)	3.4×10^3
	296 (sh)	2.9×10^3
$[(NH_3)_5Co(Im)Ru(NH_3)_4(SO_4)](BF_4)_3$	339	4.3×10^3
	460 (sh)	4.5×10^2
	298 (sh)	2.2×10^3
$[(SO_4)(NH_3)_4Ru(Im)Ru(NH_3)_4(SO_4)]BF_4$	326	
	360 (sh)	
	500 (sh)	
$[(NH_3)_5Ru(ImH)](BF_4)_3$[a]	299	1.8×10^3
	430	1.9×10^2
$[(NH_3)_5Ru(Im)]^{2+}$[a]	362	2.4×10^3
	550	6.2×10^2
$[(SO_4)(NH_3)_4Ru(ImH)](BF_4)$	312	3.0×10^3
	390 (sh)	4.8×10^2
$[(OH_2)(NH_3)_4Ru(ImH)]^{3+}$[b]	297	2.8×10^3
	385	1.5×10^2
$[(SO_4)(NH_3)_4Ru(Im)]$	322	3.7×10^3
	440	1.7×10^2
$[(NH_3)_5Co(ImH)](ClO_4)_3$[c]	334	7.1×10^1
	472	6.2×10^1
$[(NH_3)_5Co(Im)]^{2+}$[c]	344	1.1×10^2
	478	7.0×10^1

[a] Reference 10. [b] Generated by sulfate aquation from $[(SO_4)(NH_3)_4Ru(ImH)](BF_4)$. [c] Reference 9.

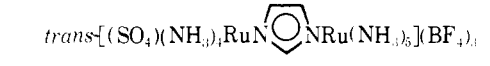
A brief description of the synthesis of these species is as follows. Addition of solutions of $[(O_3S)(NH_3)_4Ru^{II}(OH_2)]$[8] to concentrated solutions of $[(NH_3)_5Co(Im)]^{2+}$ [9] (ImH = imidazole and Im = imidazolate anion), $[(NH_3)_5Ru(Im)]^{2+}$,[10] or $[(SO_4)(NH_3)_4Ru(Im)]$[11] under an argon atmosphere in 0.1 M LiOH resulted in a very rapid reaction (~1 s). Acidification with 48% HBF_4 led to the precipitation of



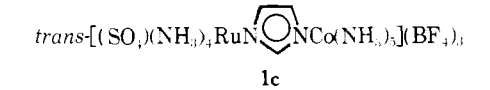
where for M = Ru^{III}, L = NH_3 (n = 4) or SO_4^{2-} (n = 2), and for M = Co^{III} L = NH_3 (n = 4). Oxidation of each of the above compounds with hydrogen peroxide[12] in aqueous 20% HBF_4, followed by addition of ethanol, resulted in the precipitation of **1a, 1b,** and **1c** salts. Compounds **1a, 1b,** and **1c**


trans-$[(SO_4)(NH_3)_4RuNRu(NH_3)_4(SO_4)]BF_4$

1a


trans-$[(SO_4)(NH_3)_4RuNRu(NH_3)_5](BF_4)_3$

1b


trans-$[(SO_4)(NH_3)_4RuNCo(NH_3)_5](BF_4)_3$

1c

were purified by gel chromatography. Elemental analyses of the complexes corresponded to the above formulations.[13]

The UV-visible spectra of the binuclear ions are sufficiently different from the corresponding mononuclear species to differentiate them. Table I lists the UV-visible characteristics, λ_{max} and extinction coefficients for the binuclear and the corresponding mononuclear complexes for comparison. Dilute aqueous solutions of compounds **1b** and **1c** showed no sign of decomposition for periods of hours.

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