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(Tetramethylcyclobutadiene)cobalt complexes of protected aromatic amino acids[†]

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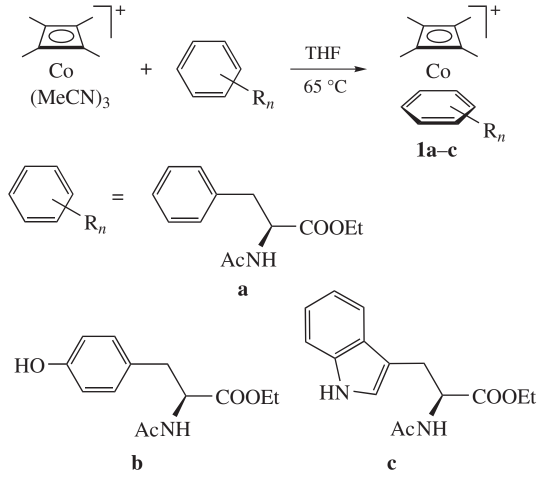
Reactions of $[(C_4Me_4)Co(MeCN)_3]PF_6$ with aromatic amino acid derivatives give the arene complexes $[(C_4Me_4)Co(\text{amino acid})]PF_6$ (amino acid = ethyl ester of *N*-acetylphenylalanine, *N*-acetyltyrosine or *N*-acetyltryptophan) in 75–85% yields; the structure of the tyrosine complex was determined by X-ray diffraction.

Organometallic derivatives of amino acids attract a considerable attention due to their applications in peptide synthesis, asymmetric catalysis and medicinal chemistry.[1] Complexes of 4*d* and 5*d* metals are widely studied while only a few compounds containing 3*d* metals are known.[2] The π-complexes of aromatic amino acids with 3*d* metals are described only for chromium.[3] The absence of cobalt π-complexes is a significant drawback considering the application of ^{57}Co and ^{60}Co derivatives in radiopharmacology.[4]

We have previously reported that the cobalt complexes $[Cb^*Co(\text{arene})]^+$ ($Cb^* = \eta^4\text{-}C_4Me_4$) can be conveniently prepared by heating $[Cb^*Co(MeCN)_3]^+$ with arene ligands.[5] Using this method, we synthesized the first cobalt π-complexes with aromatic amino acids. In particular, the reaction of $[Cb^*Co(MeCN)_3]^+$ with ethyl ester of *N*-acetylphenylalanine in THF gives complex **1a** in 85% yield (Scheme 1).[‡] The formation of **1a** is slow at room temperature (about four days) but fast at 65 °C (~1 h) as indicated by a color change of the reaction mixture from red to yellow. Similar reactions of $[Cb^*Co(MeCN)_3]^+$ with ethyl esters of *N*-acetyltyrosine and *N*-acetyltryptophan give complexes **1b**,**c** in 84 and 76% yields, respectively. Complex **1a** was also obtained in 91% yield by a photochemical reaction,[5(*d*),6] between $[Cb^*Co(C_6H_6)]^+$ and a phenylalanine derivative; however, a threefold excess of the ligand is required in this case in order to shift the equilibrium of the arene exchange. According to an NMR experiment, the irradiation of **1a** with benzene (50 equiv.) quantitatively converted it back into the free ethyl ester of *N*-acetylphenylalanine and $[Cb^*Co(C_6H_6)]^+$.



Scheme 1

Unfortunately, the reactions of $[Cb^*Co(MeCN)_3]^+$ or $[Cb^*Co(C_6H_6)]^+$ with non-protected phenylalanine give only decomposition products presumably due to the initial coordination of a cobalt atom with NH_2 and COOH groups. In contrast, the related ruthenium complexes $[Cp^*Ru(MeCN)_3]^+$ and $[CpRu(C_{10}H_8)]^+$ cleanly react with phenylalanine yielding $[(C_5R_5)Ru(\text{phenylalanine})]^+$ (R = H, Me).[7] The difference in the behaviors of cobalt and ruthenium congeners can be speculatively explained using the hard and soft acid and base principle developed by Pearson.[8] Accordingly, the 'hard' cobalt atom prefers coordination with the 'hard' NH_2 and COOH groups of the free amino acid while the 'soft' ruthenium atom coordinates with the 'soft' aromatic ring.[9]

[†] (Tetramethylcyclobutadiene)cobalt complexes, part 9. For part 8, see ref. 6.

[‡] Under an argon atmosphere, a yellow solution of $[Cb^*Co(C_6H_6)]PF_6$ (39 mg, 0.1 mmol) in MeCN (4 ml) was refluxed for 2 h. The reaction mixture turned from yellow to bright red indicating the formation of $[Cb^*Co(MeCN)_3]^+$ (alternatively, $[Cb^*Co(MeCN)_3]^+$ can be generated by 4 h irradiation using a 400 W high-pressure mercury lamp with a phosphor-coated bulb). The solution of $[Cb^*Co(MeCN)_3]^+$ was evaporated, the ethyl ester of *N*-acetylamino acid (0.12 mmol) and THF (4 ml) were added, and the mixture was refluxed for 3 h. The Schlenk tube was opened to air and the solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and eluted through a silica gel column (7×1 cm). The elution was carried out first with pure CH_2Cl_2 (to elute an excess of the unreacted amino acid) and then with a $CH_2Cl_2/MeNO_2$ (1:1) mixture (to elute the product). The yellow band was collected and evaporated *in vacuo*, and the solid was reprecipitated by Et_2O from Me_2CO to give pure [**1a**]PF_6 or [**1b**]PF_6. Complex [**1c**]PF_6 was additionally triturated with Et_2O to remove oily impurities. It solidifies completely only upon prolonged drying *in vacuo*.

[**1a**]PF_6: 47 mg (85%). ^{1}H NMR (acetone-d_6) δ: 1.20 (t, 3H, OCH_2*Me*, *J* 8 Hz), 1.67 (s, 12H, C_4Me_4), 1.85 (br. s, 3H, Ac), 3.08–3.26 (m, 2H, CH_2) 4.15 (q, 2H, OCH_2Me, *J* 8 Hz), 4.77 (m, 1H, CH), 6.66 (m, 5H, Ph), 7.80 (br. s, 1H, NH). Found (%): C, 46.28; H, 5.40. Calc. for $C_{21}H_{29}CoF_6NO_3P$ (%): C, 46.08; H, 5.34.

[**1b**]PF_6: 46 mg (84%). ^{1}H NMR (acetone-d_6) δ: 1.26 (t, 3H, OCH_2*Me*, *J* 8 Hz), 1.66 (s, 12H, C_4Me_4), 1.95 (s, 3H, Ac), 3.01–3.22 (m, 2H, CH_2), 4.20 (q, 2H, OCH_2Me, *J* 8 Hz), 4.79 (q, 1H, CH, *J* 8 Hz), 6.32 (m, 2H, C_6H_4), 6.49 (m, 2H, C_6H_4), 7.58 (br. s, 1H, NH), 10.04 (br. s, 1H, OH). Found (%): C, 44.73; H, 5.41. Calc. for $C_{21}H_{29}CoF_6NO_4P$ (%): C, 44.77; H, 5.19.

[**1c**]PF_6: 45 mg (76%). ^{1}H NMR (CD_2Cl_2) δ: 1.17 (m, 3H, OCH_2*Me*), 1.29 (s, 12H, C_4Me_4), 1.88 (s, 3H, Ac), 3.36, 3.46 (m, 2H, CH_2), 4.10, 4.20 (m, 2H, OCH_2Me), 5.16 (m, 1H, CH), 6.02 (br. s, 2H, C_6H_4), 6.73, 6.87, 6.94 (m, 2H, C_6H_4), 7.60, 7.66 (m, 1H, H^2 of the indole ring), 9.53 (br. s, 1H, NH of the indole ring), some signals are doubled due to the presence of two diastereoisomers. Found (%): C, 47.20; H, 5.32. Calc. for $C_{23}H_{30}CoF_6N_2O_3P$ (%): C, 47.11; H, 5.16.

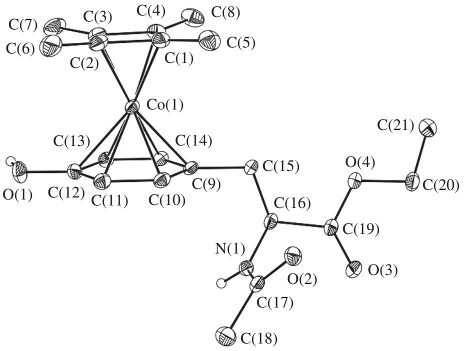


Figure 1 Structure of cation **1b** with ellipsoids at a 50% probability level. All hydrogen atoms except of OH and NH are omitted for clarity. Selected interatomic distances (Å): Co(1)–C(1) 1.9882(16), Co(1)–C(2) 1.9901(16), Co(1)–C(3) 1.9988(15), Co(1)–C(4) 1.9986(16), Co(1)–C(9) 2.1040(14), Co(1)–C(10) 2.0956(15), Co(1)–C(11) 2.1125(16), Co(1)–C(12) 2.1535(16), Co(1)–C(13) 2.1172(16), Co(1)–C(14) 2.0971(15), O(1)–C(12) 1.3364(17).

An attempt to prepare a cobalt complex of the ethyl ester of *N*-acetyl-*p*-fluorophenylalanine also failed presumably because of the insufficient donor ability of this arene.

Cations **1a–c** were isolated as PF_6^- salts. They are air-stable both in a solid and in solution in the dark; however, they notably decompose within several days on bright sunlight. The complexes were characterized by ^{1}H NMR spectra and elemental analysis. Signals of aromatic protons in the ^{1}H NMR spectra are shifted upfield by ~0.7 ppm upon coordination with the cobalt atom. Noteworthy, the signals of **1c** are doubled due to the presence of two diastereomers in an ~1:1 ratio. The structure of [**1b**]PF_6 was established by X-ray diffraction (Figure 1).[§] The distances from the metal to the ligand planes Co···C_4 (1.708 Å) and Co···C_6 (1.569 Å) are very close to those in $[Cb^*Co(C_6H_6)]^+$ (1.707 and 1.560 Å, respectively).[5(*d*)] The Co···C(12) bond is about 0.05 Å longer that other Co–C_{arene} bonds (av. 2.105 Å) due to C(12)–O(1) conjugation resulting in the bending of the C_6 ring along the C(11)···C(13) line by 1.7°.[¶] In a crystal, the cations of **1b** are arranged into double chains by the intermolecular hydrogen bonds N(1)–H···O(3) [N(1)···O(3) 2.871(2) Å; ∠NHO 148(1)°] and O(1)–H···O(2) [O(1)···O(2) 2.6039(18) Å; ∠OHO 174(1)°].

Thus, we developed a convenient method for the synthesis of stable cobalt π-complexes with protected aromatic amino acids, which can be used for labeling studies.

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[§] *Crystallographic data*. Crystals of [**1b**]PF_6 ($C_{21}H_{29}CoF_6NO_4P$, M = 563.35) are orthorhombic, space group $P2_12_12_1$, at 100 K: a = 8.950(4), b = 13.607(6) and c = 19.873(9) Å, V = 2420.2(18) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.546 g cm^{-3}, μ(MoKα) = 8.49 cm^{-1}, F(000) = 1160. Intensities of 58090 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 58°$], and 6428 independent reflections [R_{int} = 0.0305] were used in a further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atoms of NH and OH groups were located from the Fourier density synthesis. The H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation within a riding model. The refinement converged to wR_2 = 0.0642 and GOF = 1.006 for all the independent reflections [R_1 = 0.0237 was calculated against F for 6161 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

CCDC 848111 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.

[¶] The elongation of M–C bond in phenol complexes is generally attributed to partial contribution of η^5-oxocyclohexadienyl structure (see ref. 10).