Metal Complexes of Biologically Important Ligands, CLV [1]. Some Derivatives of 4-Ethynylphenylalanine

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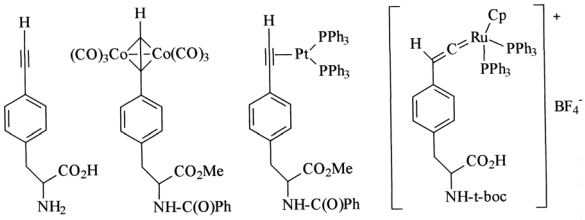
The benzoyl protected 4-ethynyl-L-phenylalanine methyl ester gives with octacarbonyldicobalt and ethylene-bis(triphenylphosphine)platinum(0) the complexes $Co_2(CO)_6(HC{\equiv}CR)$ and $(Ph_3P)_2Pt(HC{\equiv}CR)$ (R = p-$C_6H_4CH_2CH(CO_2Me)N(HCOPh)$.

The heterocumulene $[Cp(Ph_3P)_2Ru{=}C{=}C(H)R]^+BF_4^-$ (R = p-$C_6H_4CH_2C(H)N(H)$-Boc is formed from $[Cp(Ph_3P)_2Ru]^+BF_4^-$ and N-t-Boc-4-ethynylphenylalanine methyl ester. The alkynyl bridged tetraamino acid with a tetraphenylmethane backbone C[p-$C_6H_4C{\equiv}C$-p-C_6H_4-$CH_2CH(CO_2Me)$NH-t-Boc]$_4$ was synthesized from tetrakis(4-iodophenyl)methane and N-Boc-4-ethynylphenylalanine methyl ester by Sonogashira coupling.

Key words: 4-Ethynylphenylalanine, Cobalt, Platinum, Ruthenium, Tetraphenylmethane

4-Ethynyl-L-phenylalanine (**1**) is available by palladium catalyzed Sonogashira coupling [2] of trimethylsilylacetylene with 4-iodophenylalanine [3]. It is of interest as a potential drug and was proven to be a selective and potent inhibitor of tryptophan hydroxylase which is a regulator for the neurotransmitter serotonine [4]. 4-Iodophenylalanine was recently used by Kraatz *et al.* [5] for the synthesis of p-diphenylphosphino-phenylalanine, and alkynyl aminoacids were attached by Metzler-Nolte *et al.* [6] to ferrocene and may be useful for the organometallic labelling of peptides. In the following some novel derivatives of **1** are presented.



1 **2** **3** **4**

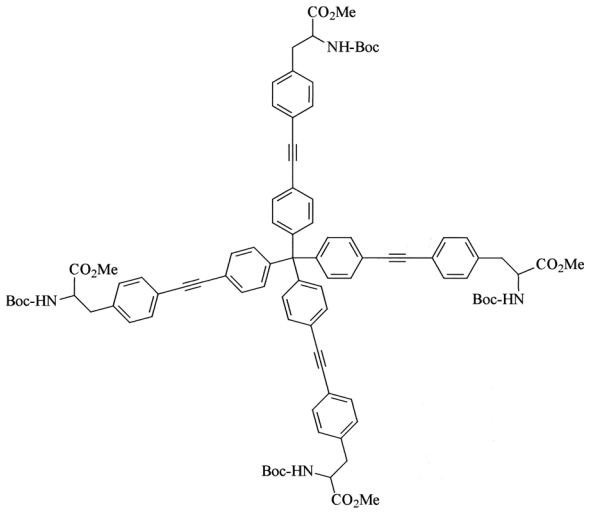
Results and Discussion

The N-benzoyl protected methyl ester of **1** gives with $Co_2(CO)_8$ the alkyne bridged $Co_2(CO)_6$ complex **2**, a dicobaltatetrahedrane.

Complexes of this type have been widely studied; they are of interest for the Pauson-Khand reaction [7] and $Co_2(CO)_6$ compounds of hormones modified with alkyne groups or with an activated pentyne carbocylic acid are useful for the labelling of hormones, peptides or drugs [8] using Jaouen's carbonyl metallo immuno assay (CMIA) with intensive CO IR absorptions [9 – 11]. Jaouen's [12] $Co_2(CO)_6(MeC{\equiv}CR)$ complexes with R = Boc(or Ac)NHCH$(CO_2R')CH_2^-$ and Boc-Phe-NHCH$(CO_2R')CH_2^-$ have to be mentioned. Metzler-Nolte *et al.* obtained a $Co_2(CO)_6(HC{\equiv}CR)$ complex with an alkynyl amino acid (R = Boc-NHCH(R')C(O)NHCH_2^-) [13]. Moreover $Co_2(CO)_6$ complexes with alkyne groups proved to be antitumor active *in vitro* [14, 15]. (Alkyne)$Co_2(CO)_6$ complexes are also of use for the protection of the C≡C bond [16].

The dark violet complex **2** which is readily soluble in organic solvents shows the characteristic IR *ν*CO absorptions of the $Co_2(CO)_6$ unit and a low field shift of the HC≡C ^{1}H NMR signal.

Another organometallic derivative of **1** was obtained by reaction of the N-benzoyl-4-ethinylphenylalanine methyl ester with $(Ph_3P)_2Pt(C_2H_4)$ to give **3**. Metzler-Nolte reported a comparable platinum(0) complex of a ferrocene containing alkynyl amino acid [13]. Com-



5

plex **3** shows the characteristic $^{31}P\{^1H\}$ NMR spectrum (see Experimental Section).

A further important reaction of terminal alkynes occurs upon treatment with the cation $[CpRu(PPh_3)_2]^+$ to give metalla cumulenes involving the tautomerization of the coordinated alkyne into the vinylidene [17]. Similarly, N-Boc-4-ethinylphenylalanine methyl ester affords with $[CpRu(PPh_3)_2]^+BF_4^-$ the brick red heterocumulene **4**.

Complex **4** exhibits in its ^1H NMR spectrum the expected triplet for the vinylidine protons at $\delta = 5.39$ pm.

In previous studies [3, 18] we have used **1** for the synthesis of structurally unique [19] and esthetic benzene bridged polyamino acids [3] and their complexes [20]. In continuation of these studies the tetraphenylmethane bridged tetraalkynylamino acid ester **5** was prepared by the Pd catalyzed Sonogashira coupling of tetrakis(4-iodophenyl)methane [21] with N-Boc-4-ethynylphenylalanine methyl ester.

The colorless stable compound with a star shaped structure **5** may be of use for the synthesis of dendrimers. It was purified by column chromatography and shows only one set of ^1H and ^{13}C NMR signals for the four (equivalent) amino acid residues. Tetrakis(4-iodophenyl)methane is an important starting material for the synthesis of various novel compounds [22,23] also of organometallic complexes [24] with interesting properties. The synthesis of tetrakis(4-ethynylphenyl)methane from $C(p\text{-}C_6H_4I)_4$ and TMS and the crystal structure of the product were reported [25]. Polyethynyl compounds are to be considered as carbon rich compounds [26] and may be very unstable [27] or even explosive [28].

Experimental Section

N-Benzoyl and N-Boc-4-ethynyl-L-phenylalanine methyl ester [3], tetrakis(4-iodophenyl)methane [21] and the starting complexes $(Ph_3P)_2Pt(C_2H_4)$ [29], $CpRu(PPh_3)_2Cl$ [30] were prepared according to literature procedures.

2: N-Benzoyl-4-ethynyl-L-phenylalanine methyl ester (120 mg, 0.40 mmol) and $Co_2(CO)_8$ (0.40 mmol) which contained 3 – 5% hexane were stirred in 25 ml of CH_2Cl_2 for 2 h at room temperature. From the dark red solution the solvent was removed *in vacuo* and the violet residue was washed several times with n-pentane and was recrystallized from diethylether/pentane. After drying *in vacuo* 197 mg of a violet powder were obtained (yield 83%). – ^1H NMR (270 MHz, 25 °C, $CDCl_3$): $\delta = 7.80 - 7.00$ (m, 9H, C_6H_4, C_6H_5), 6.59 (d, 1H, NH, $^3J_{H,H} = 7.3$ Hz), 6.43 (s, 1H, HC≡), 5.03 (m, 1H, NCH), 3.74 (s, 3H, OMe), 3.21 (m, 2H, CH_2). – IR (nujol, cm^{-1}): $\nu = 3391$ w, 2091 m, 2054 s, 2015 s, 1997 m, 1969 w, 1733 m, 1655 m. – MS (DEI+): 593 (M^+). – $C_{25}H_{17}Co_2NO_9$ (593.3): calcd. C 50.61, H 2.88, N 2.36; found C 50.28, H 2.97, N 2.32%.

3: N-Benzoyl-4-ethynyl-L-phenylalanine methyl ester (100 mg, 0.33 mmol) and $(Ph_3P)_2Pt(C_2H_4)$ (299 mg, 0.40 mmol) were stirred in 20 ml of benzene for 3 h at room temperature. From the yellow solution the solvent was removed and the yellow-brown residue was washed several times with diethylether. The colorless product was recrystallized from CH_2Cl_2/n-pentane. Yield 210 mg (86%). – ^1H NMR (270 MHz, 25 °C, CD_2Cl_2): $\delta = 7.80 - 6.60$ (m, 40H, PPh_3, C_6H_5, C_6H_4, C≡CH), 6.42 (d, 1H, NH, $^3J = 7.7$ Hz), 4.89 (m, 1H, NCH), 3.62 (s, 3H, OMe), 3.21 (m, 2H, CH_2). – $^{31}P\{^1H\}$ NMR (109 MHz, 25 °C, CD_2Cl_2): $\delta = 30.7$ (d, 1P, $^1J_{P,Pt} = 3552$ Hz, $^2J_{P,P} = 33$ Hz); 27.0 (d, $^1J_{P,Pt} = 3468.5$, $^2J_{P,P} = 33$ Hz). – IR (KBr, cm^{-1}): $\nu = 3436$ s, 3057 m, 1742 m, 1665 s, 1435 s. – MS (FAB+): 1027 ($M+H^+$). – $C_{55}H_{47}NO_3P_2Pt \cdot 0.75\ CH_2Cl_2$; $C_{55}H_{47}NO_3P_2Pt$ (1027.0): calcd. 61.39, H 4.48, N 1.28; found C 61.42, H 4.73, N 1.21%.

4: To a solution of $CpRu(PPh_3)_2Cl$ (167 mg, 0.23 mmol) in 10 ml of THF a solution of $AgBF_4$ (45 mg, 0.23 mmol) in 5 ml of THF was added at −78 °C. The mixture was allowed to warm up to room temperature and was stirred for 1 h. The colorless precipitate was centrifuged off, the red solution was cooled to −78 °C and N-*t*-Boc-4-ethynylphenylalanine methyl ester (70 mg, 0.23 mmol) was added to the solution. After removing the cooling bath the solution was stirred for 12 h at room temperature. Then, the solvent was removed and the residue was washed several times with diethylether and dried *in vacuo*. Orange powder; yield 206 mg (83%). –

^{1}H NMR (270 MHz, 25 °C, CD_2Cl_2): $\delta = 7.60 - 6.80$ (m, 34H, C_6H_4, PPh_3), 5.38 (t, 1H, RuCCH, $^4J_{P,H} = 2.5$ Hz), 5.26 (s, 5H, C_6H_5), 4.94 (m, 1H, NH), 4.47 (m, 1H, NCH), 3.60 (s, 3H, OMe), 3.04 (m, 2H, CH_2), 1.37 (s, 9H, *t*-Boc). – $^{31}P\{^1H\}$ NMR (109.4 Hz, 25 °C, CD_2Cl_2): $\delta = 43.7$(s). – IR (KBr, cm^{-1}): $\nu = 3057$ w, 2977 w, 1743 m, 1713 s, 1637 s, 1435 s. – $C_{58}H_{56}BF_4NO_4P_2Ru$ (1080.9): calcd. C 64.45, H 5.22, N 1.29; found C 63.54, H 5.14, N 1.27%.

5: Tetrakis(4-iodophenyl)methane (350 mg, 0.42 mmol), $(Ph_3P)_2PdCl_2$ (20 mg, 0.03 mmol), CuI (10 mg, 0.05 mmol) were stirred in a mixture of 30 ml of THF and 20 ml triethylamine under N_2 atmosphere and then N-*t*-Boc-4-ethynyl-L-phenylalanine methyl ester (600 mg, 1.98 mmol) was added. The mixture was stirred for 12 h at room temperature. The solvent was removed *in vacuo* and the yellow-brown residue was extracted several times with diethylether. The solution was purified by column chromatography on silica gel (30 cm, ethylacetate/n-hexane = 2/3). Colorless product; yield 639 mg (62%). – $[\alpha]D = 34.7°$ (c = 1.00 mol/l, $CHCl_3$). – ^{1}H NMR (270 MHz, 25 °C, $CDCl_3$): $\delta = 7.45$ (m, 16H, C_6H_4), 7.19 (m, 16H, C_6H_4), 4.98 (d, 4H, NH, $^3J = 6.7$ Hz), 4.59 (m, 4H, CH), 3.72 (s, 12H, OMe), 3.11 (m, 8H, CH_2), 1.42 (s, 36H, $C(CH_3)_3$). – ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): $\delta = 172.3$ (CO_2Me), 155.0 (CO_2NH), 146.0, 136.6, 131.8, 131.1, 131.0, 129.4, 122.0, 121.4 (C_6H_4), 89.3, 88.6 (C≡C), 80.0 ($C(CH_3)_3$), 65.1 ($C(C_6H_4)_4$), 54.2 (CH), 52.4 (OCH_3), 38.3 (CH_2), 28.2 ($C(CH_3)_3$). – IR (nujol, cm^{-1}): $\nu = 3272$ m, 1726 s. – $C_{93}H_{96}N_4O_{16}$ (1525.8): calcd. C 73.21, H 6.34, N 3.34; found C 72.77, H 6.42, N 3.60%.

Acknowledgments

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