

Influence of the metal complex-to-peptide linker on the synthesis and properties of bioactive CpMn(CO)₃ peptide conjugates

Katrin Splith,^a Ines Neundorf,^{*a} Wanning Hu,^b Harmel W. Peindy N'Dongo,^b
Vera Vasylyeva,^b Klaus Merz,^b and Ulrich Schatzschneider^{*b}

^a Institut für Biochemie, Universität Leipzig, Brüderstr. 34, D-04103 Leipzig, Germany. Fax: (+)49 341 97-36909; E-mail: neundorf@uni-leipzig.de

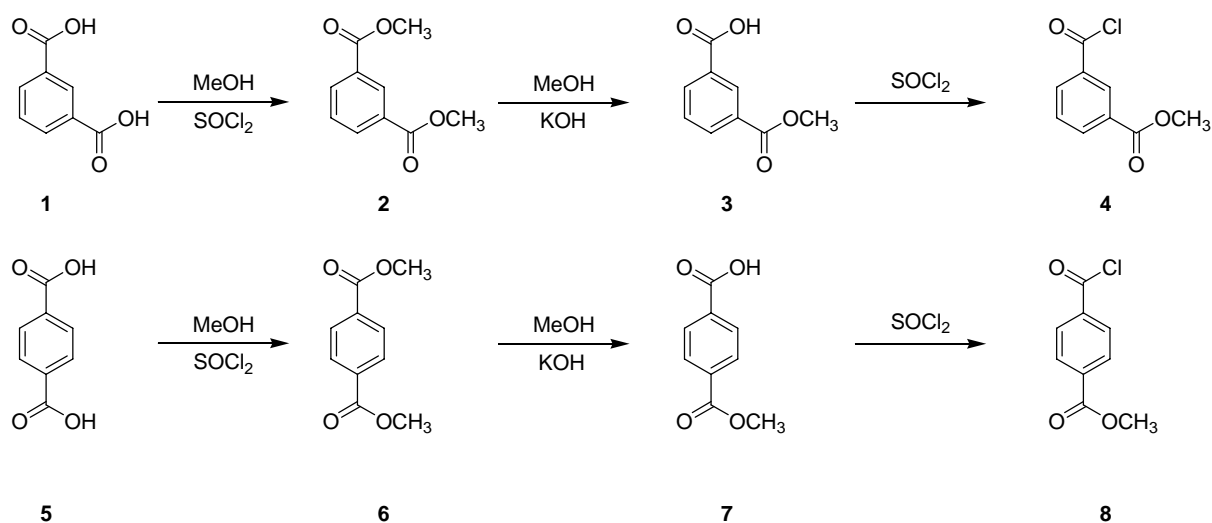
^b Lehrstuhl für Anorganische Chemie I - Bioanorganische Chemie, Ruhr-Universität Bochum NC 3/74, Universitätsstr. 150, D-44801 Bochum, Germany. Fax: (+)49 234 32-14378; E-mail: ulrich.schatzschneider@rub.de

Supporting information

Experimental

General procedures

Reactions were carried out in oven-dried Schlenk glassware under an atmosphere of pure dinitrogen when necessary. Solvents were dried over molecular sieves and degassed prior to use. All chemicals were obtained from commercial sources and used without further purification. NMR spectra were recorded on a Bruker DPX 200 spectrometer (^1H at 200.13 and ^{13}C at 50.33 MHz). Chemical shifts δ in ppm indicate a downfield shift relative to tetramethylsilane (TMS) and were referenced relative to the signal of the solvent.¹ Coupling constants J are given in Hz. Individual peaks are marked as singlet (s), doublet (d), triplet (t) quartet (q), or multiplet (m). EI mass spectra were measured on a VG Autospec instrument, only characteristic fragments are given for the most abundant isotope peak. IR spectra were recorded on pure solid samples with a Bruker Tensor 27 IR spectrometer equipped with a Pike MIRacle Micro ATR accessory. The elemental composition of the compounds was determined with a VarioEL analyzer from Elementar Analysensysteme GmbH.



Scheme S1. Synthesis of isophthalic and terephthalic acid monomethyl ester chlorides **4** and **8**.^{2, 3}

Synthesis of isophthalic and terephthalic acid dimethyl esters **2** and **6**

Terephthalic (**1**) or isophthalic acid (**2**) (each 10.0 g, 60.19 mmol) were dissolved in methanol (200 ml) by heating to reflux for 30 min. Then, thionyl chloride (20 ml) was added dropwise and the suspension maintained at reflux overnight. The solvent was distilled off and the mixture extracted with diethyl ether (3×200 ml) and washed with potassium hydroxide solution. The combined organic layers were dried over magnesium sulfate. After removal of the solvent, the diesters were obtained as pure colourless solids. Yield: 68% for **2** and 56% for **6**.

Isophthalic acid dimethyl ester (**2**): $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ_{ppm}): 8.69 (s, 1H, H_{Ar}), 8.20 (d, 2H, $^3J = 3.9$ Hz, H_{Ar}), 7.52 (t, H, $^3J = 3.9$ Hz, H_{Ar}), 3.94 (s, 6 H, $-\text{OCH}_3$); $^{13}\text{C-NMR}$ (50.33 MHz, CDCl_3 , δ_{ppm}): 166.37 (C=O), 133.93 (C_{Ar}), 130.84 (C_{Ar}), 130.72 (C_{Ar}), 128.75 (C_{Ar}), 52.49 ($-\text{OCH}_3$); EI-MS: $m/z = 194.1$ [M] $^+$; IR (ATR, cm^{-1}): 2961, 1719, 1428, 1312, 1286, 1238, 1192, 1128, 1092, 1076, 981, 865, 722; Elemental analysis (%): calc. for $\text{C}_{10}\text{H}_{10}\text{O}_4$: C 61.86, H 5.15, found: C 62.05, H 5.06.

Terephthalic acid dimethyl ester (**6**): $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ_{ppm}): 8.08 (s, 4H, H_{Ar}), 3.93 (s, 6H, $-\text{OCH}_3$); $^{13}\text{C-NMR}$ (50.33 MHz, CDCl_3 , δ_{ppm}): 166.23 (C=O), 134.07 (C_{Ar}), 129.82 (CH_{Ar}), 52.52 ($-\text{OCH}_3$); EI-MS: $m/z = 194.0$ [M] $^+$; IR (ATR, cm^{-1}): 2958, 1715, 1504, 1432, 1259, 1104, 950, 818, 731; Elemental analysis (%): calc. for $\text{C}_{10}\text{H}_{10}\text{O}_4$: C 61.86, H 5.15, found: C 61.68, H 5.25.

Synthesis of isophthalic and terephthalic acid monomethyl esters **3** and **7**

An equimolar amount of solid potassium hydroxide (1.89 g, 0.034 mmol) was added to a solution of dimethyl ester **2** or **6** (6.55 g, 0.034 mmol) in methanol (100 ml). The reaction mixture was heated to reflux overnight. After removal of the solvent, the mixture was redissolved in water, washed with dichloromethane, and acidified with concentrated hydrochloric acid to pH = 1 upon which a white solid precipitated. The precipitate was then dissolved in diethyl ether and dried over magnesium sulfate. Upon removal of the solvent, monoesters **3** and **7** were obtained as white solids. Yield: 75% for **3** and 82% for **7**.

Isophthalic acid monomethyl ester (**3**): $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ_{ppm}): 8.47 (s, 1H, H_{Ar}), 8.17 (m, 2H, H_{Ar}), 7.65 (t, 1H, $^3J = 7.7$ Hz, H_{Ar}), 3.88 (s, 3 H, $-\text{OCH}_3$); $^{13}\text{C-NMR}$ (50.33 MHz, $(\text{CD}_3)_2\text{SO}$, δ_{ppm}): 166.48 (C=O), 165.56 (C=O), 133.78 (C_{Ar}), 133.22 (C_{Ar}), 131.39 (CH_{Ar}), 130.06 (CH_{Ar}), 129.79 (CH_{Ar}), 129.37 (CH_{Ar}), 52.42 ($-\text{OCH}_3$); EI-MS: $m/z = 179.9$ [M] $^+$; IR (ATR, cm^{-1}): 2964, 2546, 1728, 1677, 1434, 1295, 1265, 1190, 1142, 1094, 1076, 961, 927; Elemental analysis (%): calc. for $\text{C}_9\text{H}_8\text{O}_4$: C 60.00, H 4.48, found: C 59.65, H 4.01.

Terephthalic acid monomethyl ester (**7**): $^1\text{H-NMR}$ (200 MHz, $(\text{CD}_3)_2\text{SO}$, δ_{ppm}): 8.06 (s, 4H, H_{Ar}), 3.89 (s, 3H, $-\text{O-CH}_3$); $^{13}\text{C-NMR}$ (50.33 MHz, $(\text{CD}_3)_2\text{SO}$, δ_{ppm}): 166.58 (C=O), 165.63 (C=O), 134.85 (C_{Ar}), 133.16 (C_{Ar}), 129.61 (CH_{Ar}), 129.36 (CH_{Ar}), 52.48 ($-\text{O-CH}_3$); EI-MS: $m/z = 180.1$ [M] $^+$; IR (ATR, cm^{-1}): 2955, 2540, 1688, 1421, 1277, 1106, 940, 726; Elemental analysis (%): calc. for $\text{C}_9\text{H}_8\text{O}_4$: C 60.00, H 4.48, found: C 59.73, H 4.44.

Synthesis of acid monomethyl ester chlorides **4** and **8**

Monomethyl ester **3** or **7** (1.0 g, 5.56 mmol) was heated to reflux in thionyl chloride overnight. Then, the thionyl chloride was distilled off and the white solid dried under vacuum. Yield: 90% for **4**; 91% for **8**.

Isophthalic acid monomethyl ester chloride (**4**): $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ_{ppm}): 8.76 (s, 1H, H_{Ar}), 8.32 (m, 2H, H_{Ar}), 7.62 (t, 1H, $^3J = 7.9$ Hz, H_{Ar}), 3.97 (s, 3 H, $-\text{O-CH}_3$); $^{13}\text{C-NMR}$ (50.33 MHz, $(\text{CD}_3)_2\text{SO}$, δ_{ppm}): 167.94 (C=O), 165.62 (C=O), 136.12 (C_{Ar}), 135.20 (C_{Ar}), 133.86 (CH_{Ar}), 132.56 (CH_{Ar}), 131.46 (CH_{Ar}), 129.40 (CH_{Ar}), 52.78 ($-\text{O-CH}_3$); EI-MS: $m/z = 197.9$ [M] $^+$; IR (ATR, cm^{-1}): 2955, 1760, 1724, 1602, 1443, 1430, 1301, 1279, 1196, 1179, 1107, 1086, 913, 823, 760; Elemental analysis (%): calc. for $\text{C}_9\text{H}_7\text{O}_3\text{Cl}$: C 54.43, H 3.55, found: C 54.41, H 3.29.

Terephthalic acid monomethyl ester chloride (**8**): $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ_{ppm}): 8.17 (s, 4H, H_{Ar}), 3.97 (s, 3H, $-\text{O}-\text{CH}_3$), $^{13}\text{C-NMR}$ (50.33 MHz, CDCl_3 , δ_{ppm}): 165.76 (C=O), 136.74 (C_{Ar}), 136.02 (C_{Ar}), 131.33 (CH_{Ar}), 130.13 (CH_{Ar}), 52.87 ($-\text{O}-\text{CH}_3$); EI-MS: $m/z = 197.9$ [M] $^+$; IR (ATR, cm^{-1}): 2957, 1788, 1719, 1432, 1406, 1275, 1192, 1103, 1062, 860, 817, 776, 692; Elemental analysis (%): calc. for $\text{C}_9\text{H}_7\text{O}_3\text{Cl}$: C 54.41, H 3.53, found: C 54.67, H 3.38.

References

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