Incorporation of the Tricarbonylchromium Ligand in Aqueous Media on the Side Chain of Aromatic Amino-acids

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Reaction of phenylalanine derivatives and phenylalanine-containing cyclic dipeptides with $Cr(CO)_6$ in aqueous solvents (water–tetrahydrofuran mixtures) allows the synthesis of stable $Cr(CO)_3$ complexes.

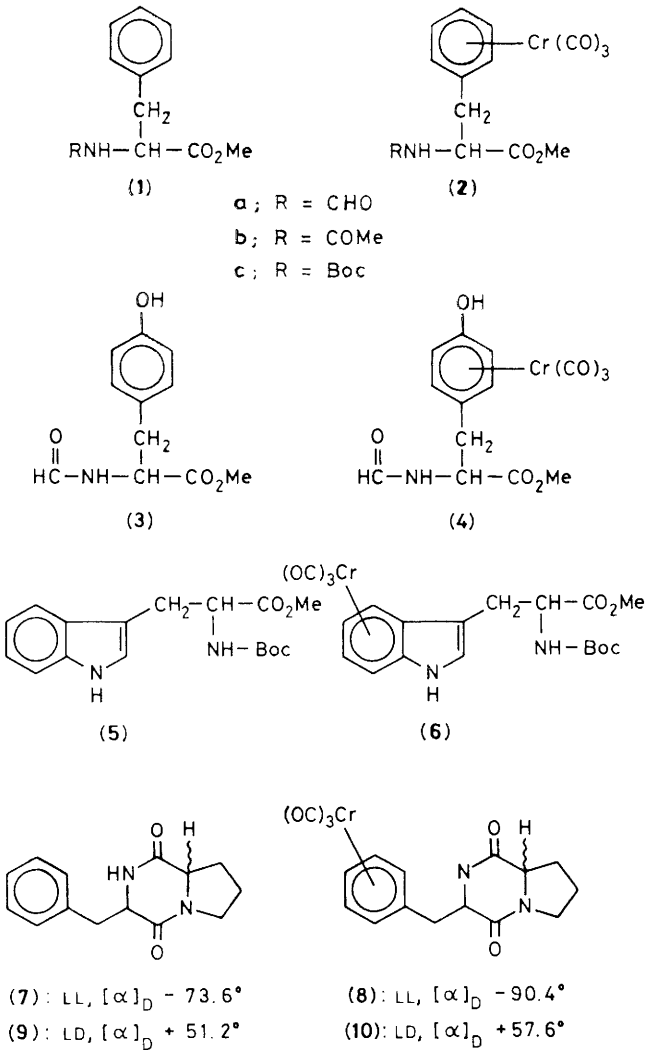
Incorporation of metallocenes into biological molecules has attracted the attention of several groups. Steroids,[1] penicillins,[2] and monosaccharides[3] have thus been investigated, either to take advantage of the increased lipophilicity of the metallocene structure or to use it as a covalently bound metal label. Among the different approaches for incorporating metallocenes into a peptide molecule, we first investigated the use of (η^5-arene)-type metallocene analogues of phenylalanine (ferrocenylalanine and cymantrenylalanine[4]) during the synthesis of the peptide. Another promising possibility was to incorporate *a posteriori* the organometallic ligand on a preformed peptide molecule. This approach was only possible for (η^6-arene)-type metallocenes; the aromatic side chain of phenylalanine, tyrosine, and tryptophan were thus likely candidates. We first checked this reaction with hexacarbonylchromium but hexacarbonyl-molybdenum or -tungsten are alternative possibilities.

A major problem was the choice of solvent. Mahaffy and Pauson[5] proposed the use of a mixture of n-butyl ether and tetrahydrofuran (THF) (90 : 10 v/v); the n-butyl ether allows a reasonably high temperature to be used while the better donor solvent THF leads to faster reactions. Unfortunately, unprotected amino-acids and most peptides are insoluble in such aprotic solvents, and we were thus limited to partially or fully protected molecules.

In order to determine which side chain was most suitable, the protected amino-acids (**1**), (**3**), and (**5**) were first studied, under the following conditions. Under nitrogen, the starting material (7.5 mmol) and $Cr(CO)_6$ (15 mmol) were stirred in refluxing n-butyl ether (32 ml)–THF (8 ml) during 24 h. Starting material and η-arene $Cr(CO)_3$ derivatives were separated by fractional crystallization, silica gel column chromatography, or reversed phase h.p.l.c. ($MeOH–H_2O$ as eluant).

Stable $Cr(CO)_3$ derivatives (**2a–c**) of phenylalanine were obtained in 40—50% yield. Moreover, photolytic elimination of the $Cr(CO)_3$ moiety regenerated the starting molecule with full optical activity indicating that no racemisation had occurred. The tyrosine derivative (**3**) led to an unstable adduct (**4**) which could not be isolated. The adduct (**6**) of the tryptophan derivative (**5**) could be isolated in 50% yield and characterized but it proved to be less stable than (**2a–c**).

The reaction was extended to the diastereoisomeric cyclic peptides (**7**) and (**9**) containing a phenylalanine unit, and under similar conditions the diastereoisomeric $Cr(CO)_3$ adducts (**8**) and (**10**) were obtained in 65% yield. These compounds were stable, remaining unchanged when stored at 4 °C



Optical rotations refer to solutions in dimethylformamide.

in the dark. All derivatives showed a shift of 2 p.p.m. for the aromatic ^{1}H n.m.r. resonances between starting material and π-arene $Cr(CO)_3$-complex (Table 1).

Table 1. Properties of the $Cr(CO)_3$ complexes.[a]

$Cr(CO)_3$ complex	M.p., t/°C	^{1}H N.m.r., δ(ArH)
(2a)	90	5.20[b]
(2b)	99	5.25[b]
(2c)	130	5.20[b]
(6)	155	5.5, 4.9, 4.1[c]
(8)	228	5.4[d]
(10)	218	5.4[d]

[a] All complexes showed ν_{max} (KBr) 1950 and 1850 cm^{-1} (C≡O). [b] In $CDCl_3$. [c] In CD_3SOCD_3. [d] In CD_3COCD_3.

In order to extend this work, it was necessary to use solvent mixtures which were more suitable for peptides. Although the use of carefully dehydrated solvents is generally recommended, we studied mixtures containing increasing quantities of water. The best results were obtained in refluxing water–THF (80:20); reactions proceeded reasonably quickly (although slower than in the organic medium) and yields were similar. Thus (**2c**) was isolated in 45% yield, and (**8**) and (**10**) were prepared in 60% yield, the products being identical with those obtained in the organic solvent. This shows that stable $Cr(CO)_3$ adducts of aromatic amino-acids can be isolated in solutions containing water and this is clearly potentially of biological importance. Preliminary work has shown that when an unprotected α-carboxy-group is present, the $Cr(CO)_3$ adduct is formed but reverts much more easily to the starting amino-acid, independently of the solvent.[7]

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