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(η^5-Cyclopentadienyl)Fe(CO)$_2$-Complex of Maleimide Anion: An Organometallic Carbonyl Probe for Biomolecules Containing HS Groups

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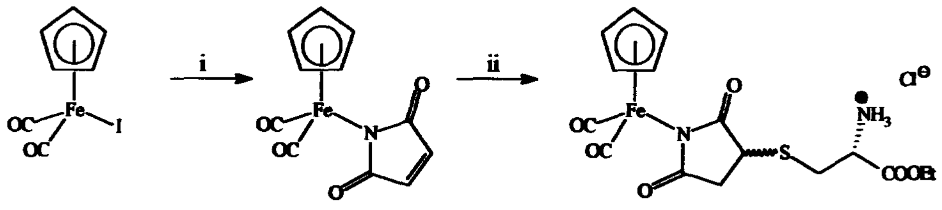
Abstract: Synthesis of (η^5-cyclopentadienyl)Fe(CO)$_2$(η^1-N-maleimidato) complex and its reaction with L-cysteine ethyl ester hydrochloride and glutathione are reported. This reaction enables introduction of a metal carbonyl probe into biomolecules containing HS groups.

Carbonylmetalloimmunoassay (CMIA) method, recently introduced by Jaouen et al.[1] is based on the fact that transition metal carbonyl complexes show very strong IR absorption at ~2200-1900 cm^{-1} i.e. in the region which is practically devoid of absorption of molecules of biological interest (peptides, nucleic acids etc.). Consequently, compounds labelled with organometallic carbonyl probes can be easily detected in subpicomol quantities by FT IR spectroscopy. It has been demonstrated that detection of bound carbonyl probe in the presence of unbound probe molecules is also feasible.[2] Obviously, the future development of CMIA will critically depend on the elaboration of efficient and highly selective methods for attachement of organometallic carbonyl probes to biomolecules.

We have previously reported an efficient photochemical synthesis of (η^5-C_5H_5)Fe(CO)$_2$(η^1-N-imidato) complexes.[3] In this communication we describe synthesis of (η^5-C_5H_5)Fe(CO)$_2$(η^1-N-maleimidato) complex 1 and its reaction with L-cysteine ethyl ester hydrochloride and glutathione, which may by regarded as a model of the attachement of a metal carbonyl probe to cysteine-containing peptides.



1 2

(i) maleimide-diisopropylamine - hv; (ii) L-cysteine ethyl ester hydrochloride

Complex 1 was obtained in 79% yield by illumination with visible light of (η^5-C_5H_5)Fe(CO)$_2$I, maleimide and diisopropylamine in benzene.[4] The low frequency of ν (CO imide) and relatively high ν (C≡O) stretching frequencies observed in the IR spectrum of 1 suggest strongly polar character of the iron-nitrogen bond

($Fe^{\delta+}$-$N^{\delta-}$).[5] The increase of the electron density at maleimidato ligand is expected to reduce its reactivity towards nucleophiles. Nevertheless, we have found that **1** reacts slowly (3 days at 35°C) with L-cysteine ethyl ester hydrochloride to afford **2** in 80% isolated yield.[6] The complexity of the 200 MHz ^{1}H NMR spectrum of **2** suggests formation of a mixture of diastereoisomers (resulting from creation of a chirality center at the succinimide ring). In the same way **1** reacts with glutathione in water. The resulting organometallic tripeptide was characterized by FAB-MS, IR and ^{1}H NMR.

Substituted maleimides have found numerous applications as spin-labels[7] and luminescent labels.[8,9] Similarly, **1** may be regarded as a metal carbonyl label for biomolecules containing HS groups. This label and the labelled cysteine and glutathione are quite stable in aerated aqueous solutions (no decomposition within 24h at r.t.). A detailed study of the chemical reactivity of **1** towards thiols (including cysteine-containing peptides) is currently under way in our laboratory.

References and Notes

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4. A solution of (η^5-C_5H_5)$Fe(CO)_2I$ (0.67 g, 2.2 mmol), maleimide (0.19 g, 2.0 mmol) and, diisopropylamine (1.7 ml) in benzene (25 ml) was illuminated (4 x 150 W tungsten lamps) under argon at 0-5°C for 2h. The solid formed (diisopropylamine hydroiodide) was filtered off and the filtrate was evaporated to dryness. Column chromatography of the residue (silica gel Merck 60, 230-400 mesh; eluent $CHCl_3$) afforded **1** as yellow crystalline solid. Yield 0.43 g (79%). ^{1}H NMR (200 MHz, $CDCl_3$): 6.63 (s, 2H, olefinic H's) 5.06 (s, 5H, Cp). IR ($CHCl_3$, ν [cm^{-1}]): 2050, 2010 (FeCO), 1655 (CO imide). Elemental analysis: Calcd. (Found): C 48.38 (48.43); H 2.59 (2.48); N 5.13 (5.07).
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6. L-Cysteine ethyl ester hydrochloride (0.185 g, 1.0 mmol) and **1** (0.272 g, 1 mmol) in 5 ml of 95% ethanol were reacted for 3 days at 35°C. Ether (4.5 ml) was then added and the reaction mixture was cooled to -10°C to give **2** as an yellow solid. Yield 0.345 g (80%). IR ($CHCl_3$, ν [cm^{-1}]): 2050, 2010 (FeCO), 1749 (CO ester) 1645 (CO imide) ^{1}H NMR 200 MHz, DMSO-d_6): 5.05 (s, 5H, Cp), 4.16 (q, 2H,$COO\underline{CH_2}CH_3$), 3.66 (m, 1H, $\underline{CH}$-S), 3.1 [m, 6H, NH_3^+ +$\underline{CH_2}$-$\underline{CH}$(cysteine)], 2.5 [m, 2H, -CH_2-(succinimide)], 1.20 (t, 3H, $COOCH_2\underline{CH_3}$). Elemental analysis: Calcd. (Found): C 41.86 (41.66); H 4.17 (4.38); N 6.10 (5.96); S 6.98 (6.85); Cl 7.74 (7.60).
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