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Synthesis and characterization of cyclopentadienylruthenium(II) complexes of aromatic amino acid derivatives

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Abstract

New cyclopentadienylruthenium(II) complexes of *N*-acetyltryptamine, *N*-acetyl-L-tryptophan ethyl ester, tryptophol, *N*-acetyl-L-tyrosine ethyl ester and *N*-acetyl-L-phenylalanine were synthesized by thermal ligand exchange reactions between cyclopentadienyl tris(acetonitrile)ruthenium(II) hexafluorophosphate and the corresponding substrate in 60–80% yields. The novel ruthenium(II) complexes were characterized by elemental analyses and spectroscopic methods (^{1}H and ^{13}C NMR spectroscopy).

Introduction

Recently, there has been an upsurge of interest in labeling biologically active compounds with organometallic groups [1–3]. These compounds can function as "reporters" on the location of the bound molecules distributed within various media such as tissue, membranes and organs. Other potential applications include metalloimmunoassay and as radiopharmaceuticals [3–5]. In spite of this enormous potential, there are still very few studies reported on such complexes [1–3].

We have succeeded in attaching a cyclopentadienylruthenium(II) ($CpRu^{+}$) unit [6] onto the aromatic nucleus of biologically active compounds, specifically, *N*-acetyltryptamine, *N*-acetyl-L-tryptophan ethyl ester, tryptophol, *N*-acetyl-L-tyrosine ethyl ester and *N*-acetyl-L-phenylalanine (Scheme 1). These novel complexes are of potential interest as radiopharmaceuticals (^{97}Ru, ^{103}Ru and ^{106}Ru) in metalloimmunoassay [3,5], and in the synthesis of neuropeptides containing terminal tyrosine and alanine (enkephalin [7], human-β-endorphin [8] and peptide T [9]). Details

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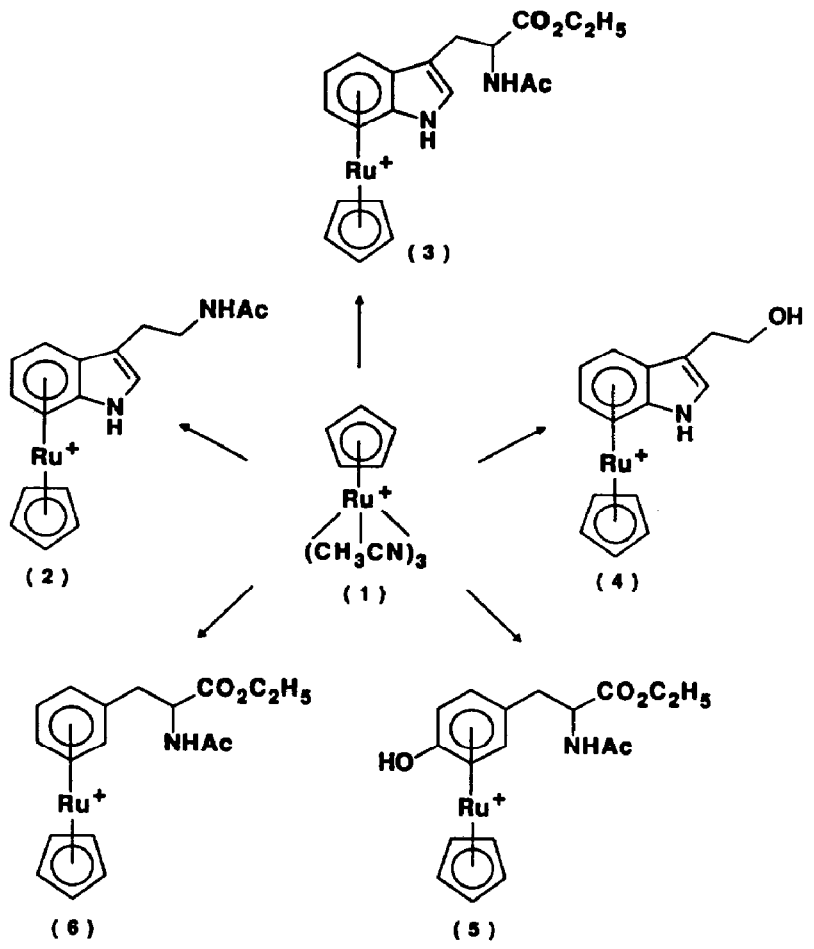
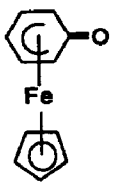


Scheme 1.

concerning the synthesis and characterization of these new ruthenium complexes are described herein.

Results and discussion

The new ruthenium sandwich complexes (**2–6**) were synthesized according to Scheme 1 in yields of 60–85%. In these reactions, the labile trisacetonitrile ligands of complex **1** were thermally exchanged with an aromatic ring of the corresponding indole and phenylalanine ligands. The analytical and NMR data for these new sandwich complexes are presented in Tables 1 and 2. These new complexes are thermally stable, crystalline solids except (η^5-cyclopentadienylruthenium(II)) (η^6-*N*-acetyl-L-tyrosine ethyl ester) hexafluorophosphate (**5**) which slowly decomposes to a gummy material after a few days at room temperature. This behavior can be rationalized in terms of adventitious deprotonation of the hydroxyl group to yield the neutral (air sensitive) complex. Similar behavior of phenolic complexes involving iron (**7**), manganese (**8**) as well as ruthenium (**9**) has been reported elsewhere [12a–c].



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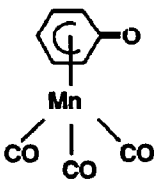

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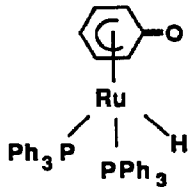

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The ^1H NMR indicated that the attachment of the ($CpRu^{II}$) occurs in a η^6-fashion to the aromatic ring of the free ligands, i.e. the ^1H NMR resonances for the ring protons of the complexes **2–6** are shifted upfield in the range usually of 0.4 to 0.6 ppm compared with the corresponding free ligands. This upfield shift is very similar to the upfield shifts of aromatic ring protons of simpler systems when attached to $CpRu^{II}$ unit [13a–d]. The cyclopentadienyl protons were observed at δ 5.0–5.3 ppm in all these cases. However, the proton decoupled ^{13}C NMR spectra of complexes **2–6** showed a greater upfield shift (30–40 ppm) of the six aromatic ring carbon atoms complexed to $CpRu^{II}$ unit. All the carbons for Cp ring appear at 79–81 ppm. ^1H and ^{13}C NMR data for all complexes (**2–6**) are given in Tables 1 and 2.

Table 1

Yields and ^1H NMR data for the new cyclopentadienylruthenium complexes

Complex	Yield (%)	Cp	^1H NMR δ (acetone-d_6), ppm from TMS	
			Complexed aromatics	Others
2	70	5.00 (s,5H)	7.08(d, *J* 6.0 Hz, 7-H), 7.01 (d, *J* 6.0 Hz, 4-H), 5.96 (t, *J* 5.6 Hz, 6-H), 5.92 (t, *J* 5.6 Hz, 5-H)	10.27 (s, NH), 7.67 (d, *J* 24. Hz, 2-H), 7.24 (s, N*H*COCH$_3$), 3.41–3.56 (m, C*H*$_2$CH$_2$NH), 2.93 (t, *J* 7.0 Hz, CH$_2$C*H*$_2$NH) and 1.88 (s, COC*H*$_3$)
3	72	5.09 (s,5H)	7.10 (d, *J* 6.0 Hz, 7-H), 7.01 (d, *J* 5.6 Hz, 4-H), 6.00 (t, *J* 5.6 Hz, 6-H), 5.95 (t, *J* 5.6 Hz, 5-H)	10.29 (s, NH), 7.75 (s, 2-H), 7.54 (d, *J* 8 Hz, NH), 4.69–4.75 (m, ABX further coupled to NH, CH$_2$C*H*NHCOCH$_3$), 4.16 (q, *J* 7 Hz, CO$_2$C*H*$_2$CH$_3$), 3.31, 3.14 (q, q, C*H*$_2$CHNH, J_{AB} 14.8 Hz), 1.98 (s, COC*H*$_3$) and 1.22 (t, *J* 7 Hz, CO$_2$CH$_2$C*H*$_3$)
4	60	5.03 (s,5H)	7.11 (d, *J* 6 Hz, 7-H), 7.03 (d, *J* 6 Hz, 4-H), 5.66 (t, *J* 5.5 Hz, 6-H), 5.93 (t, *H* 5.5 Hz, 5-H)	7.68 (s, 2-H), 3.86 (t, *J* 6 Hz, C*H*$_2$OH), 2.95 (t, *J* 6 Hz, C*H*$_2$CH$_2$)
5	62	5.39 (s,5H)	6.21 (d, 2H), 6.15 (d, 2H)	7.70 (d, *J* 7.6 Hz, NH), 4.68–4.73 (m, CH$_2$C*H*NH-, ABX further coupled with NH), 4.15 (q, *J* 7.0 Hz, CO$_2$C*H*$_2$CH$_3$), 3.02, 2.80 (1, 1, J_{AB} 14.8 Hz, C*H*$_2$CHNH-), 1.93 (s, COC*H*$_3$) and 1.22 (t, *J* 7 Hz, CO$_2$CH$_2$C*H*$_3$)
6	68	5.43 (s,5H)	6.30 (d, 1H), 6.26 (d, 1H), 6.18–6.21 (m, 3H)	7.67 (d, *J* 7 Hz, HN), 4.51–4.69 (m, CH$_2$C*H*NH, ABX further coupled with NH, 4.12 (q, *J* 7 Hz, CO$_2$C*H*$_2$CH$_3$), 3.08, 2.90 (q, q, C*H*$_2$CHNH-, J_{AB} 14.0 Hz), 1.91 (t, CO$_2$CH$_2$C*H*$_3$)

Table 2

Analytical and ^{13}C NMR data for the new cyclopentadienylruthenium(II) complexes

Complex	M.p. (°C)	Analysis (Found (Calcd.)(%))		^{13}C NMR δ (acetone-d_6), ppm from TMS		
		C	H	Cp	Complexed aromatics	Others
2	155–157	39.86 (39.77)	3.94 (3.73)	79.04	115.6 [a], 96.18 [a], 81.57, 81.37, 77.01 and 72.30	170.36 ($COCH_3$), 134.76 (C-2), 111.31 (C-3), 39.68, 25.43 (CH_2's) and 22.95 ($COCH_3$)
3	206–208	40.77 (41.03)	4.04 (3.93)	79.22	112.59 [a], 96.36 [a], 81.56, 81.46, 76.77 and 62.29	171.09 ($CO_2CH_2CH_3$), 170.99 ($COCH_3$), 136.08 (C-2), 110.84 (C-3), 62.13 ($CHCO_2CH_2CH_3$), 54.24 ($CO_2CH_2CH_3$), 36.76 (CH_2CH), 22.60 (CCH_3) and 14.37 ($CO_2CH_2CH_3$)
4	103–105	38.29 (38.14)	3.47 (3.41)	79.04	115.83 [a], 96.27 [a], 81.56, 81.37, 77.56 and 75.68	135.02 (C-2), 106.23 (C-3), 62.27 (CH_2CH_2OH) and 28.94 (CH_2CH_2OH)
5 [b]		–	–	81.19	133.88 [a], 98.66 [a], 86.58, 75.77 and 75.68	171.09 ($CO_2CH_2CH_3$), 170.99 ($COCH_3$), 62.13 ($CHCO_2$), 54.24 ($CO_2CH_2CH_3$), 36.76 (CH_2CH), 22.60 ($COCH_3$) and 14.37 ($CO_2CH_2CH_3$)
6	113–115	40.01 (39.57)	4.03 (4.06)	81.31	102.23 [a], 87.94, 86.13 and 85.81	170.99 ($CO_2CH_2CH_3$), 170.63 ($NHCOCH_3$), 61.98 (CH_2CH), 53.97 ($CO_2CH_2CH_3$), 36.97 (CH_2CH), 22.50 ($COCH_3$) and 14.18 ($CO_2CH_2CH_3$)

[a] Asterisks denote quaternary carbons. [b] Rapid decomposition precluded C + H analysis.

An important feature of the present methodology is the ease with which one can attach the cyclopentadienylruthenium(II) ($CpRu^{II}$) unit to an aryl ring of aromatic amino acids and other biologically important compounds. Thus stable $CpRu^{II}$ complexes of suitably protected aromatic amino acids of potential biological importance can be synthesized.

Experimental

All reactions were performed under a nitrogen atmosphere using standard techniques. Solvents such as 1,2-dichloroethane, acetonitrile were dried over molecular sieves (4 Å). ^1H and ^{13}C NMR spectra were taken using Bruker WP-400 MHz NMR spectrometer. Elemental analyses were performed by Microtech Labs Skokie, IL.

Ruthenium(III) chloride hydrate, 1,4-cyclohexadiene, cyclopentadienylthallium, ammonium hexafluorophosphate, *N*-acetyltryptamine, *N*-acetyl-L-tryptophan ethyl ester, tryptophol, *N*-acetyl-L-tyrosine ethyl ester and *N*-acetyl phenylalanine were purchased from Aldrich or Sigma.

Cyclopentadienyl tris(acetonitrile)ruthenium(II) hexafluorophosphate, $[CpRu(CH_3CN)_3]PF_6$ (**1**) was prepared by photolysis of η^6-benzene-η^5-cyclopentadienyl-

ruthenium(II) hexafluorophosphate [11] in acetonitrile as described in the literature [11.

Synthesis of η^6-N-acetyltryptamine-η^5-cyclopentadienylruthenium(II) hexafluorophosphate (2)

To a degassed solution of *N*-acetyl tryptamine (404 mg, 2.0 mmol) in 1,2-dichloroethane (20 ml) under a nitrogen atmosphere was added $[CpRu(CH_3CN)_3]PF_6$ (**1**) (668 mg, 1.5 mmol). The yellow reaction mixture was stirred for 12 h at 45–50 °C. Then the solvent was removed on a rotary evaporator and the remaining dark brown residue was washed with ether (4 × 15 ml) to remove unreacted *N*-acetyltryptamine. The brown residue was redissolved in acetone (40 ml), dried over Na_2SO_4 and decolorized with charcoal. After concentration of acetone solution to about 5–7 ml, ether was added to yield (539 mg, 70%) of η^6-*N*-acetyltryptamine-η^5-cyclopentadienylruthenium(II) hexafluorophosphate (**2**) as a greenish yellow crystalline solid. Analytical and spectroscopic data are given in Tables 1 and 2.

Complexes **3–6** were obtained using essentially the same procedure as above. Yields, melting points, analytical and spectroscopic data are given in Tables 1 and 2.

Acknowledgement

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