Preparation, Reactivity and Peptide Labelling Properties of (η^6-Arene)ruthenium(II) Complexes with Pendant Carboxylate Groups

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(η^6-Arene)ruthenium(II) complexes of the type [{[η^6-$C_6H_5(CH_2)_nCOOH$]Ru(μ-Cl)Cl}$_2$] (**2a**, n = 1; **3**, n = 3) with tethered carboxylate groups can be obtained by dehydrogenation of the appropriate cyclohexadiene with $RuCl_3 \cdot 3H_2O$. Formation of a κ*O*-coordinated chelate in weakly acidic solution is observed by means of a ^{1}H NMR titration for both [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(aq)](OTf)$_2$ (**3a′**) and [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(phen)(aq)](OTf)$_2$ (**5′**). Sandwich complexes of the type [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(η^6-amino acid)](OTf)$_2$ [amino acid = AcpheOH (**6**), ActyrOEt (**7**), ActrpOH (**8**)] can be prepared by treating [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(acetone)$_3$](OTf)$_2$ with the appropriate aromatic bioligand in CF_3COOH (**6**/**8**) or CH_2Cl_2 (**7**). Chemospecific η^6-labelling of the *C*-terminal indole function is observed for the peptide HphetrpOH in the analogous complex **9**. Quantitative formation of **8** can also be achieved in aqueous solution in the presence of a 3:1 excess of the {η^6-$C_6H_5(CH_2)_3COOH$}Ru^{II} fragment. This can also be employed for the *N*-terminal labelling of amino acids and peptides in its sandwich complex [(η^6-C_6Me_6)Ru{η^6-$C_6H_5(CH_2)_3$-COOH}](OTf)$_2$ (**10**). Coupling reactions by the carbodiimide method with EDC afford water-stable complexes of the type [(η^6-C_6Me_6)Ru{η^6-$C_6H_5(CH_2)_3C(O)R$}](OTf)$_2$ [R = trpOMe (**11**), pheOMe (**12**), glyglyOEt (**13**)] in good yields. X-ray structures of [(η^6-$C_6H_5CH_2COOC_2H_5$)RuCl(phen)](OTf) (**4b′**) and **10** are reported.

Introduction

Current interest in (η^6-arene)ruthenium(II) complexes with heteroatom donors tethered to the η^6-arene moiety has primarily been motivated by their potential as homogeneous catalysts.[1,2] Examples of chelating side-chains have included amines,[1] alcohols,[1−3] thioethers,[4] and phosphanes.[1,5−9] Chloro-bridged complexes of the type [{(η^6-arene)Ru(μ-Cl)Cl}$_2$] with *N*-terminal protected derivatives of phenylglycine ethyl ester as the functionalised arene ligand have also been reported recently.[10] In comparison to the analogous dimeric ruthenium(II) compounds with η^6-coordinated benzene or cymene ligands,[11,12] these η^6-phenylglycine complexes exhibit a strongly enhanced solubility in polar solvents. Their ensuing decomposition in solution may well be due to participation of side-chain donor atoms in the metal coordination sphere[10] and apparently renders them unsuitable for possible further application, e.g. for the labelling of peptides or proteins as previously reported for the CpRu^{II}, Cp*Ru^{II} and (η^6-cymene)Ru^{II} fragments.[13−18]

Given that they have an adequate stability in polar solvents, (η^6-arene)ruthenium(II) complexes with pendant free carboxylate groups should be of interest not only for the chemospecific η^6-labelling of tryptophan, tyrosine or phenylalanine residues but also for the more general *N*-terminal labelling of peptides. Furthermore, the recent report that [{η^5-$C_5H_4(CH_2)_2NH_2$-κ*N*}Ru(CH_3CN)$_2$](PF_6) with its tethered amine side-chain can quantitatively label the phenylalanine side-chain of the hormone secretin[19] suggests that a hemilabile carboxylate coordination might also enhance the π-complexing ability of (η^6-arene)ruthenium(II) complexes in aqueous solution. We have, therefore, prepared compounds of the type [{[η^6-C_6H_5-$(CH_2)_n$COOH]Ru(μ-Cl)Cl}$_2$] (n = 1, 3) and studied their reactivity and peptide labelling properties.

Results and Discussion

(η^6-Arene)ruthenium(II) complexes with tethered carboxylate groups (n = 1, 3) can be obtained by dehydrogenation of the appropriate cyclohexadiene with $RuCl_3 \cdot 3H_2O$ in accordance with the general method of Bennett et al.[11,12] 2,5-Dihydrophenylacetic acid[20] and 2,5-dihydro-4-phenylbutyric acid (**1**) were prepared for this purpose by a Birch reduction of phenylacetic acid (paa) and 4-phenylbutyric acid (pba), respectively. Treatment of 3-phenylpropionic acid (ppa) with sodium in ammonia solution leads, in contrast, to reduction not only of the phenyl moiety but also of the carboxylate function. Employment of the ethyl ester of ppa affords 2,5-dihydro-3-phenylpropanol[21,22] in high yield (74%). As 3-phenylpropanol has already been studied as a functionalised η^6-arene ligand by Kurosawa et

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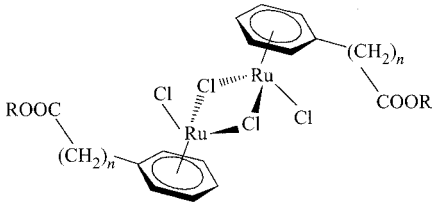
al.[1−3] our own investigations have concentrated on the coordination behaviour of the (η^6-ppa)Ru^{II} and (η^6-pba)Ru^{II} fragments.

Treatment of 2,5-dihydrophenylacetic acid or 2,5-dihydro-4-phenylbutyric acid with ruthenium(III) trichloride in an acetone/water solution at reflux leads to the formation of [{(η^6-paa)Ru(μ-Cl)Cl}$_2$] (**2a**) and [{(η^6-pba)Ru(μ-Cl)Cl}$_2$] (**3**), respectively, in high yields (Scheme 1). Use of ethanol as the solvent affords ethyl esters such as [{(η^6-$C_6H_5CH_2COOC_2H_5$)}Ru(μ-Cl)Cl}$_2$] (**2b**), which can subsequently be hydrolysed with NaOH at pH = 12 to provide the chloro-bridged η^6-complexes of the free carboxylic acids. Interestingly, the reaction of 2,5-dihydrophenylacetic acid with $RuCl_3 \cdot 3H_2O$ takes only 20 min to reach completion in refluxing ethanol in comparison to 4 h for 1,3-cyclohexadiene or α-phellandrene.[11,12] This suggests that initial rapid κ*O*-coordination by the tethered carboxylate function may facilitate subsequent η^4-coordination of the neighbouring cyclohexadiene ring. η^6-Coordination of the phenyl moieties in **2a**, **2b**, and **3** is confirmed by the pronounced upfield ^{1}H NMR shifts of their aromatic protons in comparison to the parent carboxylic acids. For instance complex **3** exhibits resonances at δ = 5.44 (d, 2 H), 5.68 (t, 2 H) and 5.61 ppm (t, 1 H) for its phenyl *ortho*, *meta*, and *para* protons in acetonitrile solution. The esterification of the carboxylate function in **2b** is indicated by the observation of a strong ν(CO) band at 1749 cm^{-1} in its IR spectrum. In contrast, **2a** and **3** display typical CO valence absorptions for free carboxylic acids at 1704 and 1711 cm^{-1}, respectively.



2a, n = 1, R = H; **2b**, n = 1, R = C_2H_5; **3**, n = 3, R = H

Scheme 1

Aqueous solutions of **2a**, **2b**, and **3** are stable for a period of several weeks over a wide pH range (2 ≤ pH ≤ 12). As a result of their free carboxylate groups, **2a** and **3** exhibit enhanced solubility in water or methanol in comparison to the ester complex **2b**. The extent of any participation of the tethered arm in the metal coordination sphere may be expected to be dependent both on the arm length and on the pH value of an aqueous solution of **2a** or **3**. In order to study the possibility of carboxylate κ*O*-coordination, aqueous solutions of [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(aq)](OTf)$_2$ (**2a′**) and [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(aq)](OTf)$_2$ (**3′**) were prepared by addition of 2 equiv. of Ag(OTf) to **2a** and **3**, respectively, followed by filtration of the resulting precipitated AgCl. A pH titration of **2a′** in the range of 1.53 ≤ pH* ≤ 12.12 (Figure 1a) provides no evidence for the presence of new species in comparison with those of the type [{(η^6-arene)Ru}$(H_2O)_3]^{2+}$, [{(η^6-arene)-Ru(μ-OH)(H_2O)}$_2]^{2+}$, and [{(η^6-arene)Ru}$_2$(μ-OH)$_3]^+$ observed for [(η^6-C_6H_6)Ru(aq)]$^{2+}$.[23,24] In Figure 1a MH refers to [(η^6-$C_6H_5CH_2COOH$)Ru$(H_2O)_3]^{2+}$, M to [(η^6-$C_6H_5CH_2COO$)Ru$(H_2O)_3]^+$, M_2H_{-2} to [{(η^6-$C_6H_5CH_2COO$)Ru(μ-OH)(H_2O)}$_2$], and M_2H_{-3} to [{(η^6-$C_6H_5CH_2COO$)Ru}$_2$(μ-OH)$_3]^-$. The formation of the dinuclear species M_2H_{-3} in weakly acidic and alkaline solutions is indicated by characteristic highfield shifts of ca. 0.6 ppm for the aromatic protons. Figure 1a suggests that the tethered carboxylate group of the short side-chain in **2a′** does not participate in intramolecular κ*O*-coordination to any significant degree. The presence of the intermediate hydroxy-bridged complex M_2/M_2H_{-2} leads to an additional set of ^{1}H NMR signals in the range 3.6 ≤ pH* ≤ 6.2.

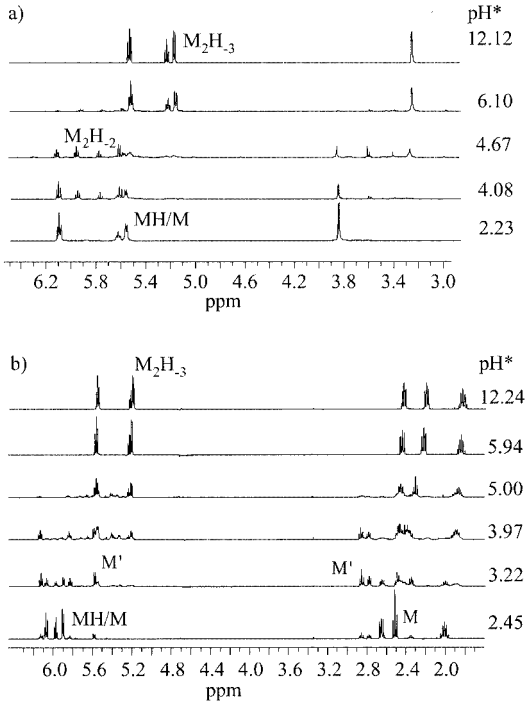
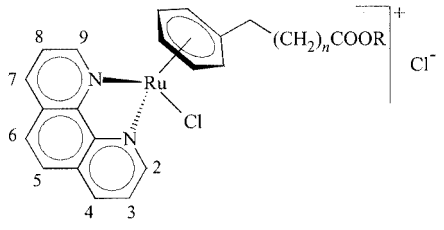


Figure 1. pH dependence of the ^{1}H NMR spectra of (a) [(η^6-$C_6H_5CH_2COOH$)Ru(aq)]$^{2+}$ (**2a′**) and (b) [{η^6-$C_6H_5(CH_2)_3$-COOH}Ru(aq)]$^{2+}$ (**3′**); the species nomenclature is based on the assignment of MH to [(η^6-$C_6H_5CH_2COOH$)Ru$(H_2O)_3]^{2+}$ in (a) and [(η^6-$C_6H_5(CH_2)_3COOH$) Ru$(H_2O)_3]^{2+}$ in (b)

A comparison of Figure 1a and b indicates that the lengthening of the side-chain in [{η^6-C_6H_5-$(CH_2)_3COOH$}Ru(aq)](OTf)$_2$ (**3′**) enables the formation of a new distinct species M′ (or possibly a dinuclear species M′$_2$ in the range 2.4 ≤ pH* ≤ 5.5). The pronounced low-field shifts of the side-chain α−γ-methylene protons and the opposite highfield shifts of the phenyl *ortho* and *meta* protons are characteristic of this complex. As deprotonation of the carboxylate group will be expected in the range 4 ≤ pH* ≤ 5, it is reasonable to postulate that the tethered arm must participate in the ruthenium(II) coordination sphere in this species, i.e. that M′ will probably be [{η^6-

$C_6H_5(CH_2)_3COO$-κ*O*} $Ru(H_2O)_2]^+$. Since intermolecular κ*O*-carboxylate coordination cannot be ruled out, the alternative dinuclear species [{[η⁶-$C_6H_5(CH_2)_3COO$-κ*O*]$Ru(H_2O)_2$}$_2$] (M′$_2$) must also be taken into consideration.

To simplify the analysis of the pH-titration data for (η⁶-arene)ruthenium(II) complexes with functionalised arene moieties, it is helpful to block two of the three potential κ*O*-coordination sites with the bidentate ligand 1,10-phenanthroline (1,10-phen). The light-brown mononuclear complexes **4a**, **4b**, and **5** of the type [(η⁶-arene)RuCl(1,10-phen)]$^+$ were prepared for this purpose by reaction of the chloro-bridged dinuclear compounds **2a**, **2b**, and **3** with 1,10-phen in ethanol at reflux (Scheme 2). Bidentate κ²*N*,*N*′-coordination of 1,10-phenanthroline leads to characteristically pronounced downfield shifts of the signals for the *ortho* and *meta* protons of the η⁶-arene moiety, e.g. 0.60 ppm for **4b** in CD_3OD solution in comparison to 0.49 ppm for **2b** in CD_3CN. In contrast, the signals of the *para* protons are only shifted by 0.16 ppm to the lower field for the **2b**/**4b** pair. The ^{1}H NMR signal for the benzyl protons of **4b** can be observed at δ = 3.67 ppm in acetonitrile (or CD_3OH) but disappears within 5 min in D_2O or CD_3OD. The responsible rapid H/D exchange in the latter solvents is clearly a consequence of the relatively high acidity of the methylene protons in **4b** as a result of both the η⁶-coordination of the phenyl group[25,26] and the presence of a neighbouring carboxylate group. A similar H/D exchange is also observed for **4a** in CD_3OD but not for the η⁶-phenylbutyric acid complex **5** with its longer side-chain. The formation of the neutral enol form of the acetic acid side-chain in **4a**/**4b**, following the loss of a methylene proton and concomitant addition of a deuteron to the carboxylate C=O double bond, is apparently of importance in rate determining for the H/D exchange.



4a, *n* = 1, R = H; **4b**, *n* = 1, R = C_2H_5; **5**, *n* = 3, R = H

Scheme 2

After addition of 1 equiv. of Ag(OTf) to **4b** and filtration of the precipitated AgCl, crystals of the resulting complex, [(η⁶-$C_6H_5CH_2COOC_2H_5$)RuCl(phen)](OTf) (**4b**′), were grown by gas diffusion of diethyl ether into a methanol solution of the complex. As depicted in Figure 2, the complex cation of **4b**′ displays an effectively eclipsed conformation for its substituent methylene carbon atom C17 relative to N21 of the bidentate 1,10-phen ligand. This is in accordance with the expectations for half-sandwich complexes of the general type [(η⁶-arene)]$ML_3]^{n+}$ with a +I substituent in the η⁶-arene moiety and electron donor ligands L.[27] Interestingly both of the relatively acidic methylene protons participate in the formation of C−H···O hydrogen bonds to the triflate oxygen atoms. Respective C···O/H···O distances of 3.448/2.480 and 3.440/2.472 Å are observed for these interactions.

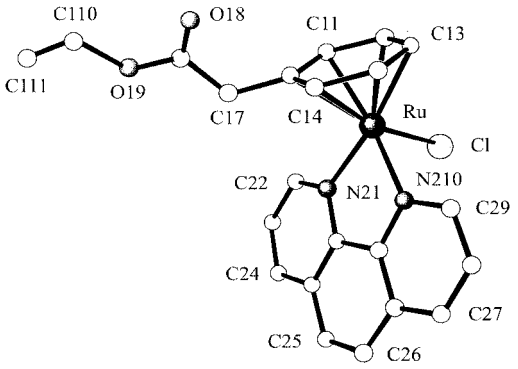


Figure 2. Molecular structure of the cation of [(η⁶-$C_6H_5CH_2COOC_2H_5$)RuCl(phen)](OTf) (**4b**′); selected bond lengths [Å] and angles [°]: Ru−N21 2.096(5), Ru−N210 2.097(5), Ru−Cl 2.398(9); N21−Ru−N210 77.7(2), N21−Ru−Cl 84.1(1), N210−Ru−Cl 85.4(9)

Aqueous solutions of [(η⁶-$C_6H_5CH_2COOH$)Ru(phen)(aq)](OTf)$_2$ (**4a**′) and [{η⁶-$C_6H_5(CH_2)_3COOH$}Ru(phen)(aq)](OTf)$_2$ (**5**′) were prepared by addition of 2 equiv. of Ag(OTf) to **4a** and **5** and subsequent filtration of the resulting precipitated AgCl. Selected ^{1}H NMR spectra in D_2O are depicted in Figure 3 for **5**′ in the range 3.40 ≤ pH* ≤ 11.46. The aqua complex [{η⁶-$C_6H_5(CH_2)_3COOH$}$Ru(OH_2)(phen)]^{2+}$ (MH) predominates at low pH* (2.48, Figure 4) and exhibits two deprotonation steps to afford [{η⁶-$C_6H_5(CH_2)_3COO$}Ru(OH$_2$)(phen)]$^+$ (M) and subsequently [{η⁶-$C_6H_5(CH_2)_3COO$}Ru(OH)(phen)] (MH_{-1}). The latter hydroxy complex predominates in alkaline solution at pH* = 11.46. Initial loss of the side-arm carboxylate protons leads to modest lowfield shifts for the 1,10-phen protons H2/H9 and the η⁶-pba aromatic protons in the approximate range 3.5 ≤ pH* ≤ 5.5, which are then followed by more pronounced upfield shifts on deprotonation of the aqua ligand between pH* values of ca. 6.5 and 8.5.

The presence of a second monocation M′ in acid or weakly alkaline solution (ca. 3 ≤ pH* ≤ 8) is indicated by the appearance of a second set of ^{1}H NMR signals for the protons of the η⁶-pba ligand at pH* = 3.40. The side chain resonances are recorded at a lower field to those of M, as was previously observed for the analogous protons in [{η⁶-$C_6H_5(CH_2)_3OH$-κ*O*}Ru(phen)](BF$_4$).[1] This suggests that the deprotonated carboxylate group of the tethered arm in **5**′ must also coordinate the ruthenium(II) atom in species M′ (Figure 4). A dimeric structure in which the phenylbutyric acid ligands adopt an η⁶:κ*O*-bridging mode cannot be

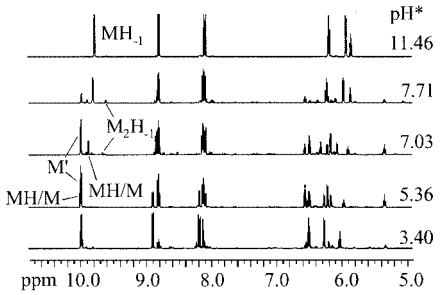


Figure 3. pH dependence of the ^{1}H NMR spectra of [{η-$C_6H_5(CH_2)_3COOH$}Ru(aq) (phen)](OTf)$_2$ (**5′**), where MH represents [(η^6-pba)Ru(H_2O)(phen)]$^{2+}$

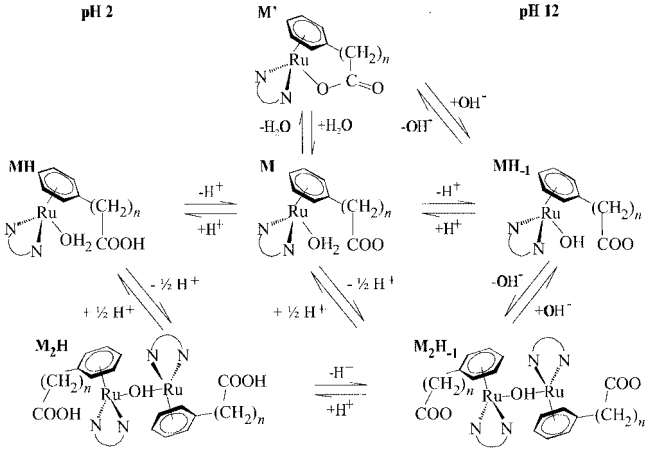


Figure 4. Proposed structures for the species MH/M/MH$_{-1}$, M′, and M_2H/M_2H_{-1} formed by **5′** in aqueous solutions

ruled out with certainty but would appear to be improbable. Neither M′ nor the minor hydroxy-bridged dinuclear species M_2H_{-1} can undergo deprotonation and their ^{1}H NMR signals therefore exhibit no significant shifts in the range $6.5 \leq pH^* \leq 8.5$.

Using the ^{1}H NMR integral values for the 1,10-phen H2/H9 signals it is possible to establish the pH dependence of the individual microspecies MH/M/MH$_{-1}$, M′ and M_2H/M_2H_{-1}. As depicted in Figure 5, the tethered arm chelate M′ clearly predominates in weakly acidic solutions and reaches a concentration maximum at $pH^* \approx 5.5$. The general pH dependence of the macrospecies MH, M/M′, M_2H_{-1}, and MH$_{-1}$ was confirmed by potentiometric pH titrations (Figure 6). Although signals for an analogous tethered arm chelate M′ could also be observed in the ^{1}H NMR spectra of **4b′** in the range $3 \leq pH^* \leq 8$, the concentration of this microspecies is much lower than for that of **5′**. The aqua complex [(η^6-$C_6H_5CH_2COO$)Ru(OH_2)(phen)]$^+$ (M) predominates for **4b′** in weakly acidic solution and even at its concentration maximum the microspecies M′ only accounts for ca 8% of the (η^6-arene)Ru^{II} complexes in solution.

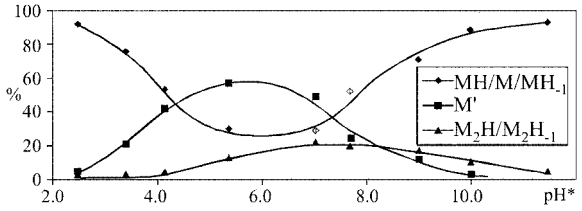


Figure 5. pH-dependent microspecies distribution for **5′** on the basis of the ^{1}H NMR titration data

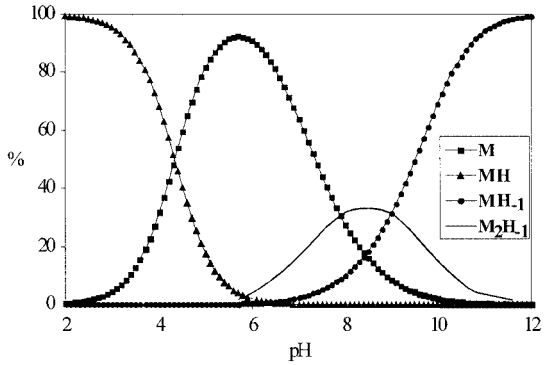
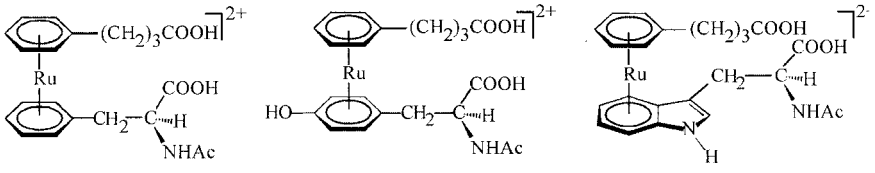


Figure 6. pH-dependent macrospecies distribution for **5′** as determined by potentiometric titration; the following stability constants were obtained from the least-squares refinement with HYPERQUAD:[27] logβ (MH) = 4.40(1), logβ (MH$_{-1}$) = −8.62(1), logβ (M_2H_{-1}) = −4.42(8) for a goodness-of-fit S = 4.6

Amino Acid and Peptide Labelling

We have previously reported the suitability of [(η^6-cymene)Ru(acetone)$_3$]$^{2+}$ for the labelling of aromatic amino acids and their residues in peptides.[17,18] In contrast to the tris(acetonitrile) complex cation [(η^5-C_5Me_5)Ru(CH_3CN)$_3$]$^+$, which delivers the entropically favoured sandwich complex as an insoluble product on treatment with the free aromatic acids phenylalanine (HpheOH), tyrosine (HtyrOH), and tryptophan (HtrpOH) in THF,[15,16] the analogous reaction of [(η^6-cymene)Ru(acetone)$_3$]$^{2+}$ leads predominantly to κ^2*N*,*O*-chelates in CH_2Cl_2 or H_2O. η^6-Coordination of the half-protected or free amino acids can, however, be achieved for the (η^6-cymene)Ru^{II} fragment by employing CF_3COOH as the reaction medium. The protonation of the amino and carboxylato groups under such strongly acidic conditions prevents their incorporation into the Ru^{II} coordination sphere. (η^6-paa)Ru^{II} and (η^6-pba)Ru^{II} sandwich complexes of aromatic amino acids can also be obtained in high yields under analogous reaction conditions and the complexes **6**−**9** are presented as typical examples for η^6-labelling.

The characteristic ^{1}H and ^{13}C NMR spectroscopic data for these sandwich complexes are similar to those of the analogous (*p*-cymene)Ru^{II} complexes.[17,18] For instance, the ^{1}H NMR signals for the aromatic protons of **6** (Scheme 3) all lie in the narrow range δ = 7.00−7.19 ppm. This means that, whereas the pba phenyl proton resonances are shifted downfield by up to ca. 1.2 ppm, the phenylalanine aromatic



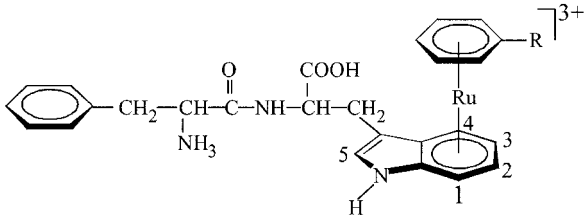
6 **7** **8**

Scheme 3

resonances experience only modest upfield shifts (ca. 0.2 ppm) relative to those of the uncoordinated ligands.[17] η^6-Labelling of tyrosine derivatives leads to a marked enhancement in the acidity of the *p*-hydroxy function, that is effectively fully deprotonated in polar solvents.[18] The associated increase in shielding for the *N*-acetyltyrosine ethyl ester aromatic protons in **7** causes their ^{1}H NMR resonances to move upfield to δ = 6.49/6.57 (*ortho*) and 6.00 (*meta*) in CD_3OD solution. Evidence for the stabilisation of the ketonic form of the η^6-coordinated tyrosine moiety of **7** in polar solvents is also provided by the upfield shift of ca 15 ppm observed for the ^{13}C NMR signal of the *para* carbon atom on going from a [D_3]nitromethane to a [D_4]methanol solution. The possibility of facial chirality leads to the formation of diastereomers of the η^6-ActrpOH sandwich complex **8** in a ca. 1:1 ratio. The pronounced lowfield ^{1}H NMR shifts, for the signals of the pyrrolic protons H5 to δ = 8.24 and 8.28 ppm, are characteristic for the η^6-coordination of the indole moieties in these isomers.

Koefod and Mann[29] demonstrated that kinetically controlled η^6-coordination of the Cp*Ru^{II} moiety leads to a preference for partially localised arene π-systems (e.g. indole) over highly delocalised arenes (e.g. phenyl). This kinetically derived chemospecificity was also observed by us for the reaction of [(η^6-cymene)Ru(acetone)$_3$]$^{2+}$ with the dipeptide HphetrpOH.[18] Exclusive η^6-indole coordination was confirmed during this work for [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(η^6_{ind}-HphetrpOH)]-$(OTf)_2$·CF_3COOH (**9**, Scheme 4), which was obtained in good yield by stirring a 1:1 mixture of [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(acetone)$_3$](OTf)$_2$ with the dipeptide in CF_3COOH solution for 4 h at room temperature. Formation of a mononuclear complex was confirmed by FAB MS and elemental analysis, which also indicated that **9** contains a third counter anion (CF_3COO^-), i.e. that its peptide amino function must be protonated. Both the characteristic lowfield shifts of the indole H5 protons to δ = 8.25 and 8.30 ppm in two diastereomers and the unchanged values of the five phenylalanine aromatic protons (δ = 7.37 ppm) are in accordance with chemospecific tryptophan labelling.

As a result of competitive coordination by amino and/or carboxylate functions and the stability of the predominant hydroxy-bridged dimer [{(η^6-arene)Ru}$_2$(μ-OH)$_3$]$^+$, yields of sandwich complexes of aromatic amino acids are relatively low for [(η^6-cymene)Ru(aq)]$^{2+}$ in weakly acid or alkaline aqueous solution. This state of affairs is illustrated in Figure 7 for the reaction of [(η^6-cymene)Ru(aq)]$^{2+}$ with *N*-



9, R = $(CH_2)_3COOH$

Scheme 4

acetyltryptophan (ActrpOH) in D_2O at pH* = 5.0 and T = 60 °C. Formation of the sandwich complex [(η^6-cymene)Ru(η^6-ActrpOH)]$^{2+}$ was monitored by ^{1}H NMR spectroscopy using the integral values of its characteristic lowfield indole H5 resonances. After 18 h, no further change was observed for the integral ratio of the combined η^6-coordinated indole signals at $\delta \approx$ 8.2 ppm to that at $\delta \approx$ 7.5 ppm for free ActrpOH. The final value corresponds to a 15% yield of the amino acid sandwich complex. Formation of the macrochelates [(η^6-pbaH$_{-1}$-κO)Ru(H_2O)$_2$]$^+$ and [(η^6-pbaH$_{-1}$-κO)Ru(OH)(H_2O)] in weakly acidic solution (see Figure 1b) significantly reduces the concentration of the bis(hydroxy)-bridged species M_2H_{-2} in comparison to the (η^6-cymene)Ru^{II} fragment. Furthermore, intramolecular charge neutralisation in these pendant-arm species should also disfavour competitive κO coordination by amino acid carboxylato functions. Taken together both factors would be expected to lead to an increased level of η^6-labelling as is indeed confirmed in Figure 7 for ActrpOH. A 37% yield of the sandwich complex [(η^6-pba)Ru(η^6-ActrpOH)]$^{2+}$ (**8**) was indicated by the ratio of the indole H5 integral values at ca. 8.2 and δ = 7.5 ppm after 18 h. Employment of a 3:1 excess of [(η^6-pba)Ru(aq)]$^{2+}$ leads to an effectively quantitative η^6-labelling of the aromatic amino acid. This observed water tolerance for direct derivatisation of ActrpOH is analogous to that reported for [{η^5-$C_5H_4(CH_2)_2NH_2$-κN}Ru($CH_3CN)_2$]$^+$ by Grotjahn.[19] The applicability of the (η^6-pba)Ru^{II} fragment to peptide labelling will be the subject of further studies.

Given the presence of suitable functional groups and an adequate stability for classical peptide synthetic conditions, organometallic fragments can be introduced at either the N or C terminus of the bioligand. A range of sandwich complexes have been prepared for this purpose in recent years including the ferrocenylmethyl[30,31] and [(η^5-Cp*)M{η^6-

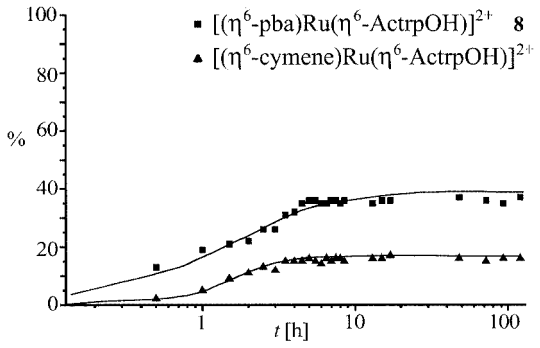


Figure 7. Time dependence for the η^6-labelling of *N*-acetyltryptophan with (a) (η^6-pba)Ru^{II} and (b) (η^6-cymene)Ru^{II} in D_2O solution at pH* = 5.0 and T = 60 °C

$CH_3OC_6H_4(CH_2)_2COOR\}]^{n+}$ (R = *N*-succinimide; M = Ir, n = 2; M = Ru, n = 1) fragments.[32,33] We, therefore, prepared both $[(\eta^6\text{-}C_6Me_6)Ru(\eta^6\text{-ppa})](OTf)_2$ and $[(\eta^6\text{-}C_6Me_6)Ru(\eta^6\text{-pba})](OTf)_2$ (**10**) as potential *N*-terminal labels for peptides. However, preliminary reactivity studies indicated that yields of coupling products for the former complex would be at best very low, as also observed for $[(\eta^5\text{-Cp*})Ir(\eta^6\text{-}CH_3OC_6H_4CH_2COOR)](BF_4)_2$ (R = *N*-succinimide)[32] which also only has one CH_2 group in its pendant arm. Further investigations were, therefore, restricted to the 4-phenylbutyric acid complex **10**, which was prepared by reaction of $[(\eta^6\text{-pba})Ru(acetone)_3](OTf)_2$ with C_6Me_6 in trifluoroacetic acid.

The X-ray structure of the dication of **10** is depicted in Figure 8. Its butyric acid side chain adopts an almost perpendicular position relative to the η^6-coordinated phenyl ring, as indicated by the torsion angle of −93.8(6)° for C11−C16−C17−C18. The asymmetric unit also contains a methanol molecule, whose oxygen atom O51 participates in O111−H···O51 and O51−H51···O hydrogen bonds of length 2.607(4) and 2.741(4) Å, respectively, to neighbouring sandwich cations and OTf^- anions.

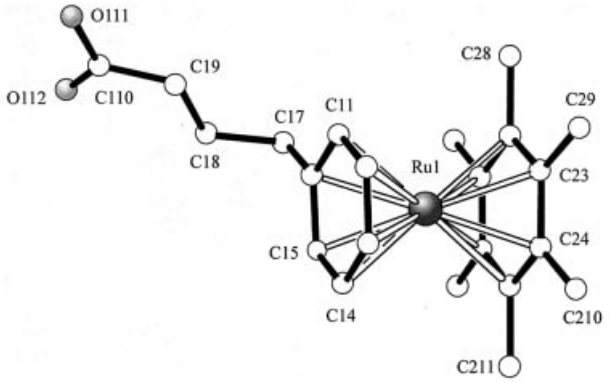
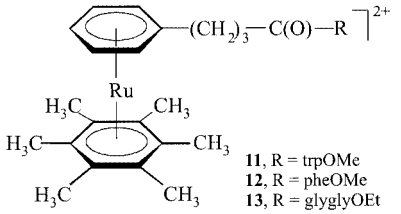


Figure 8. Molecular structure of the cation of $[\{\eta^6\text{-}C_6H_5(CH_2)_3COOH\}Ru(\eta^6\text{-}C_6Me_6)](OTf)_2{\cdot}CH_3OH$ (**10**)

N-Terminal coupling reactions were performed for **10** with HtrpOMe, HpheOMe, and HglyglyOEt by the carbodiimide method in the presence of *N*-[3-(dimethylamino)-propyl]-*N*′-ethylcarbodiimide EDC. The resulting labelled amino acids and peptides were separated in good yields (46−73%) from the reaction mixture by semi-preparative reversed-phase HPLC with pentafluoropropionic acid as an ion-pairing agent. $[(\eta^6\text{-}C_6Me_6)Ru\{\eta^6\text{-}C_6H_5(CH_2)_3C(O)trpOMe\}](OTf)_2$ (**11**), $[(\eta^6\text{-}C_6Me_6)Ru\{\eta^6\text{-}C_6H_5(CH_2)_3C(O)pheOMe\}](OTf)_2$ (**12**), and $[(\eta^6\text{-}C_6Me_6)Ru\{\eta^6\text{-}C_6H_5(CH_2)_3C(O)glyglyOEt\}](OTf)_2$ (**13**) were characterised by FAB MS and $^1H/^{13}C$ NMR spectroscopy (Scheme 5).



Scheme 5

As depicted for **12** and **13** in Figure 9 the resonances of the five aromatic pba protons at δ ≈ 6.7−6.8 ppm lie in the characteristic spectral window for amino acids and peptides (δ = 4.8−6.8 ppm) and should therefore allow for the adequate quantitative estimates of such labelled peptides in biological systems. Compounds **11**−**13** are soluble in a range of polar solvents and exhibit long-term stability in aqueous solution.

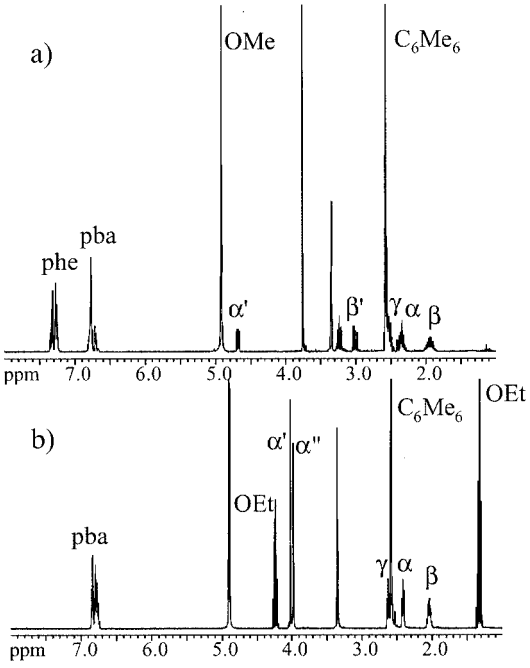


Figure 9. ^1H NMR spectra of (a) $[(\eta^6\text{-}C_6Me_6)Ru\{\eta^6\text{-}C_6H_5(CH_2)_3C(O)pheOMe\}](OTf)_2$ (**12**) and (b) $[(\eta^6\text{-}C_6Me_6)Ru\{\eta^6\text{-}C_6H_5(CH_2)_3C(O)glyglyOEt\}](OTf)_2$ (**13**)

In summary, our present work demonstrates that the pendant-arm fragment $\{\eta^6\text{-}C_6H_4(CH_2)_3COOH\}Ru^{II}$ is eminently suitable for both η^6- and *N*-terminal labelling of amino acids and peptides. The formation of κ*O*-coordinated

species involving the tethered carboxylate function may, as shown for ActrpOH, favour markedly higher yields of the former type of complex in aqueous solution in comparison with (η^6-cymene)Ru^{II}.

Experimental Section

General: All manipulations and reactions were performed under argon in carefully dried solvents using standard Schlenk techniques. FTIR: Perkin−Elmer 1760X as KBr discs. FAB MS: Fisons VG Autospec with 3-nitrobenzyl alcohol as the matrix. ^1H and ^{13}C NMR spectroscopy: Bruker DRX 400 with chemical shifts reported as δ values relative to the signal of the deuterated solvent. ^{13}C NMR signals for the $CF_3SO_3^-$ anions are observed in the range δ = 121.8−122.8 ppm (q) and are not given for individual complexes. Elemental analyses: Vario EL of Elementar Analysensysteme GmbH. 2,5-Dihydrophenylacetic acid[20] and 2,5-dihydro-3-phenylpropanol[21,22] were prepared as for 2,5-dihydro-4-phenylbutyric acid by Birch reduction of the appropriate phenyl-substituted acid. $RuCl_3·3H_2O$ was purchased from Chempur, amino acids and peptides from Bachem and carboxylic acids from Acros. Potentiometric titrations were performed with a fully automated microprocessor-controlled pH-titration unit (Metrohm 691 with Dosimat 665) in a thermostatted vessel at 25±1 °C under Ar with carbonate-free 0.1 mol·dm^{-3} NaOH. A constant background ionic strength of 0.1 mol·dm^{-3} KNO_3 (p.a.) was employed for all titrations. Further details of the experimental procedure are given in ref.[34] pH* values for ^1H NMR spectra in D_2O were not corrected for deuterium isotope effects. Semipreparative HPLC separations were carried out at an eluent flow rate of 15−25 mL·min^{-1} with a Knauer 64 pump, A0258 sample injector and Merck L-4000A UV detector using columns (25 × 2 cm i.d.) packed with Nucleosil 100-C_{18} (d_p = 10 μm).

2,5-Dihydro-4-phenylbutyric Acid (1): A solution of 4-phenylbutyric acid (9.85 g, 0.06 mol) in diethyl ether (100 mL) was added to a solution of sodium (14.80 g, 0.6 mol) in ammonia (400 mL) at −78 °C. Ethanol (112 mL, 1.80 mol) was added dropwise over 90 min and the solution was stirred until its original blue colour disappeared. After removal of NH_3 and addition of water (200 mL), the product was extracted with diethyl ether following an adjustment to pH = 2 with hydrochloric acid. The diethyl ether phase was then washed with water and dried with $MgSO_4$ before removal of the solvent in vacuo to afford **1**. Yield 8.57 g (86%). $C_{10}H_{14}O_2$ (166.2): calcd. C 72.3, H 8.5; found C 71.7, H 8.2. FAB MS: *m/z* (%) = 166 (38) $[M]^+$, 106 (38) $[M - C_2H_4O_2]^+$, 79 (100) $[M - C_4H_8O_2]^+$. ^1H NMR (CD_3Cl): δ = 1.70 (m, $^3J_{H,H}$ = 7.5 Hz, 2 H, β-CH_2), 2.28 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, α-CH_2), 2.56 (m, 4 H, CH_2 dihydrophenyl), 5.37 (m, 1 H, CH), 5.63 (m, 2 H, CH), 10.90 (br., 1 H, COOH) ppm. ^{13}C NMR (CD_3Cl): δ = 22.2, 26.7, 28.7, 34.4, 36.6, 119.4, 124.2, 124.2, 133.7, 180.1 ppm.

[{(η^6-$C_6H_5CH_2COOH$)Ru(μ-Cl)Cl}$_2$ (2a): 2,5-Dihydrophenylacetic acid (2.24 g, 16.20 mmol) was added to a solution of $RuCl_3·3H_2O$ (1.06 g, 4.05 mmol) in acetone/water (5:1, 48 mL) and the reaction mixture heated at reflux with stirring for 6 h. After removal of acetone, the deep-red aqueous solution was left to stand at 4 °C to afford a red precipitate of **2a** within 12 h, which was washed with diethyl ether and dried in vacuo. Yield 1.08 g (86%). $C_{16}H_{16}Cl_4O_4Ru_2$ (616.3): calcd. C 31.2, H 2.6, O 10.4; found C 31.0, H 2.6, O 10.7. FAB MS: *m/z* (%) = 580 (16) $[M - Cl]^+$, 546 (10) $[M - 2\ Cl]^+$, 458 (100) $[M - 2\ Cl, - 2\ CO_2]^+$. ^1H NMR (CD_3CN): δ = 3.59 (s, 4 H, α-CH_2), 5.54 (d, $^3J_{H,H}$ = 5.5 Hz, 4 H, *ortho*-H), 5.67 (t, $^3J_{H,H}$ = 5.5 Hz, 2 H, *para*-H), 5.74 (t, $^3J_{H,H}$ = 5.5 Hz, 4 H, *meta*-H) ppm. ^{13}C NMR (CD_3CN): δ = 39.0, 83.0, 84.5, 86.6, 97.3, 175.1 ppm. IR: $\tilde{\nu}$ = 1704 vs. (CO) cm^{-1}. **2a** can also be prepared by alkaline hydrolysis of **2b** at pH = 12.

[{(η^6-$C_6H_5CH_2COOC_2H_5$)Ru(μ-Cl)Cl}$_2$] (2b): 2,5-Dihydrophenylacetic acid (1.68 g, 12.15 mmol) was added to a solution of $RuCl_3·3H_2O$ (1.00 g, 4.05 mmol) in ethanol (60 mL) and the reaction mixture heated at reflux while stirring for 20 min. The resulting red precipitate was filtered, washed with ethanol, and dried in vacuo. Yield 1.34 g (98%). $C_{20}H_{24}Cl_4O_4Ru_2$ (672.4): calcd. C 35.7, H 3.6, O 9.5; found C 35.3, H 3.5, O 9.7. FAB MS: *m/z* (%) = 637 (100) $[M - Cl]^+$. ^1H NMR (CD_3CN): δ = 1.22 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, OEt), 3.59 (s, 4 H, α-CH_2), 4.14 (dd, $^3J_{H,H}$ = 7.0 Hz, 4 H, OEt), 5.55 (d, $^3J_{H,H}$ = 5.0 Hz, 4 H, *ortho*-H), 5.69 (t, $^3J_{H,H}$ = 5.5 Hz, 2 H, *para*-H), 5.74 (t, $^3J_{H,H}$ = 5.0, 5.5 Hz, 4 H, *meta*-H) ppm. ^{13}C NMR (CD_3CN): δ = 14.4, 39.3, 62.1, 83.2, 84.6, 86.4, 95.6, 170.5 ppm. IR: $\tilde{\nu}$ = 1749 vs. (CO) cm^{-1}.

[{(η^6-$C_6H_5(CH_2)_3COOH$)Ru(μ-Cl)Cl}$_2$] (3): 2,5-Dihydrophenylbutyric acid (2.02 g, 12.15 mmol) was added to a solution of $RuCl_3·3H_2O$ (1.06 g, 4.05 mmol) in acetone/water (5:1, 48 mL) and the reaction mixture heated at reflux while stirring for 6 h. After removal of acetone, the deep-red aqueous solution was left to stand at 4 °C to afford a red precipitate of **3** within 12 h, that was washed with diethyl ether and dried in vacuo. Yield 1.20 g (88%). $C_{20}H_{24}Cl_4O_4Ru$ (672.4): calcd. C 35.7, H 3.6, O 9.5; found C 35.7, H 3.6, O 9.6. FAB MS: *m/z* (%) = 637 (100) $[M - Cl]^+$ 602 (65) $[M - 2\ Cl]^+$. ^1H NMR (CD_3CN): δ = 1.90 (m, $^3J_{H,H}$ = 7.4, 7.0 Hz, 4 H, β-CH_2), 2.38 (t, $^3J_{H,H}$ = 7.4 Hz, 4 H, α-CH_2), 2.56 (t, $^3J_{H,H}$ = 7.0 Hz, 4 H, γ-CH_2), 5.44 (d, 4 H, *ortho*-H), 5.61 (t, 2 H, *para*-H), 5.68 (t, 4 H, *meta*-H) ppm. ^{13}C NMR (CD_3CN): δ = 25.4, 33.3, 33.6, 82.5, 83.1, 84.1, 86.6, 174.5 ppm. IR: $\tilde{\nu}$ = 1711 vs. (CO) cm^{-1}.

[(η^6-$C_6H_5CH_2COOH$)RuCl(1,10-phen)]Cl (4a): 1,10-Phenanthroline (0.441 g, 1.575 mmol) and **2a** (0.462 g, 0.75 mmol) were stirred in ethanol (75 mL) at reflux for 1 h. After cooling, the light-brown product was precipitated by addition of diethyl ether (40 mL) washed with ethanol and diethyl ether and dried in vacuo. Yield 0.610 g (83%). $C_{20}H_{16}Cl_2N_2O_2Ru$ (488.3): calcd. C 49.2, H 3.3, N 5.7, O 6.6; found C 47.6, H 3.2, N 5.4, O 6.7. FAB MS: *m/z* (%) = 453 (100) $[M - Cl]^+$. ^1H NMR (CD_3OD): δ = 5.83 (t, $^3J_{H,H}$ = 6.5 Hz, 1 H, *para*-H), 6.04 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H, *ortho*-H), 6.37 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, *meta*-H), 8.11 (dd, 2 H, phen H3/8), 8.22 (s, 2 H, phen H5/6), 8.85 (dd, 2 H, phen H4/7), 9.88 (dd, 2 H, phen, H2/9) ppm. ^{13}C NMR (CD_3OD): δ = 39.4, 85.0, 91.3, 107.5, 127.8, 129.0, 132.4, 140.3, 147.7, 157.2, 179.1 ppm. IR: $\tilde{\nu}$ = 1702 vs. (CO) cm^{-1}.

[(η^6-$C_6H_5CH_2COOC_2H_5$)RuCl(1,10-phen)]Cl (4b): Preparation as for **4a** with **2b** (0.504 g, 0.75 mmol) and a reaction time of 2.5 h. Yield of light-brown **4b** 0.651 g (84%). $C_{22}H_{20}Cl_2N_2O_2Ru$ (516.4): calcd. C 51.2, H 3.9, N 5.4, O 6.2; found C 50.5, H 4.0, N 5.4, O 6.9. FAB MS: *m/z* (%) = 481 (100) $[M - Cl]^+$. ^1H NMR (CD_3OD): δ = 1.25 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, Et), 4.13 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, Et), 5.99 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H, *para*-H), 6.31 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, *ortho*-H), 6.38 (t, $^3J_{H,H}$ = 6.0 Hz, 2 H, *meta*-H), 8.12 (dd, 2 H, phen H3/8), 8.22 (s, 2 H, phen H5/6), 8.86 (dd, 2 H, phen H4/7), 9.90 (dd, 2 H, phen H2/9) ppm. ^{13}C NMR (CD_3OD): δ = 14.7, 39.2, 62.9, 85.0, 87.8, 89.5, 100.0, 127.8, 129.0, 132.4, 140.4, 147.6, 157.3, 171.0 ppm. IR: $\tilde{\nu}$ = 1752 vs. (CO) cm^{-1}.

[(η^6-$C_6H_5(CH_2)_3COOH$)RuCl(1,10-phen)]Cl (5): Preparation as for **4a** with **3** (0.504 g, 0.75 mmol) and a reaction time of 1 h. Yield of light-brown **5** 0.712 g (92%). $C_{22}H_{20}Cl_2N_2O_2Ru$ (516.4): calcd. C 51.2, H 3.9, N 5.4, O 6.2; found C 50.4, H 3.8, N 5.2, O 6.4. FAB MS: *m/z* (%) = 481 (100) $[M - Cl]^+$. ^1H NMR (CD_3OD): δ =

2.01 (m, $^3J_{H,H}$ = 7.1, 7.5 Hz, 2 H, β-CH_2), 2.45 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H, α-CH_2), 2.71 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, γ-CH_2), 5.91 (t, 1 H, *para*-H), 6.13 (d, 2 H, *ortho*-H), 6.36 (t, 2 H, *meta*-H), 8.13 (dd, 2 H, phen H3/8), 8.23 (s, 2 H, phen H5/6), 8.86 (dd, 2 H, phen H4/7), 9.88 (dd, 2 H, phen H2/9) ppm. ^{13}C NMR (CD_3OD): δ = 26.3, 34.1, 34.4, 83.5, 85.4, 90.5, 99.7, 127.8, 129.0, 132.5, 140.3, 147.6, 157.2, 175.8 ppm. IR: $\tilde{\nu}$ = 1707 vs. (CO) cm^{-1}.

[{η^6-$C_6H_5(CH_2)_3COOH$}Ru(η^6-AcpheOH)]$(CF_3SO_3)_2$ (6): Ag(OTf) (103 mg, 0.4 mmol) was added to a solution of **3** (67.2 g, 0.1 mmol) in acetone (5 mL) and the solution stirred for 20 min. After centrifugation of the precipitated AgCl and removal of acetone, CF_3COOH (5 mL) was added to the resulting [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(acetone)$_3$](OTf)$_2$ and the solution stirred with *N*-acetylphenylalanine (41.4 mg, 0.2 mmol) in CF_3COOH (5 mL) at 50 °C for 5 h. The solution was reduced in volume to 3 mL and the yellow product precipitated with diethyl ether (10 mL), washed with methanol/diethyl ether and dried in vacuo. Yield 140.1 mg (91%). $C_{23}H_{25}F_6NO_{11}RuS_2$ (770.6): calcd. C 35.7, H 3.3, N 1.8, S 8.3; found C 35.5, H 3.0, N 1.5, S 8.2. FAB MS: *m*/*z* (%) = 621 (3) [M − OTf]$^+$, 472 (100) [M − 2 OTf]$^+$. ^{1}H NMR (CD_3OD): δ = 2.01 (s, 3 H, Ac), 2.03 (m, 2 H, β-CH_2 pba), 2.53 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, α-CH_2 pba), 2.84 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, γ-CH_2 pba), 3.11, 3.36 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 7.3 Hz, 2 H, β-CH_2 AcpheOH), 4.81 (dd, $^3J_{H,H}$ = 7.3 Hz, 1 H, α-CH AcpheOH), 7.00−7.15 (mm, 9 H, phenyl), 7.19 (m, 1 H, phenyl) ppm. ^{13}C NMR (CD_3OD): δ = 22.7, 26.4, 33.6, 34.1, 37.6, 54.0, 95.3, 95.6, 96.0, 96.3, 96.4, 96.9, 97.3, 114.8, 119.0, 172.5, 173.7, 176.4 ppm. IR: $\tilde{\nu}$ = 1657, 1701, 1739 vs. (CO) cm^{-1}.

[(η^6-$C_6H_5(CH_2)_3COOH$)Ru(η^6-ActyrOEt)]$(CF_3SO_3)_2$ (7): Preparation as for **6** with *N*-acetyltyrosine ethyl ester (50.3 mg, 0.2 mmol) and 3 h of refluxing in CH_2Cl_2 (10 mL) instead of CF_3COOH. The resulting solid was dissolved in methanol and the product precipitated by addition of diethyl ether. Drying in vacuo afforded the yellow complex **7**. Yield 148.9 mg (91%). $C_{25}H_{29}F_6NO_{12}RuS_2$ (814.7): calcd. C 36.9, H 3.6, N 1.7, S 7.8; found C 36.4, H 3.2, N 1.5, S 8.0. FAB MS: *m*/*z* (%) = 664 (5) [M − OTf]$^+$, 516 (100) [M − 2 OTf]$^+$. ^{1}H NMR (CD_3OD): δ = 1.32 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, OEt), 2.02 (s, 3 H, Ac), 2.00 (m, 2 H, β-CH_2 pba), 2.53 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, α-CH_2 pba), 2.68 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, γ-CH_2 pba), 2.94, 3.14 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 7.5 Hz, 2 H, β-CH_2 ActyrOEt), 4.26 (q, $^3J_{H,H}$ = 7.3 Hz, 2 H, OEt), 4.77 (dd, $^3J_{H,H}$ = 7.5 Hz, 1 H, α-CH ActyrOEt), 6.00 (m, 2 H, *meta*-H tyr), 6.49, 6.57 (m, 2 H, *ortho*-H tyr), 6.62 (t, 1 H, pba), 6.67 (t, 2 H, pba), 6.76 (d, 2 H, pba) ppm. ^{13}C NMR (CD_3OD): δ = 14.7, 22.7, 26.5, 33.6, 33.8, 36.7, 54.4, 63.5, 81.5, 93.0, 93.4, 94.1, 96.7, 96.9, 103.6, 114.3, 156.8, 171.5, 173.7, 175.2 ppm. IR: $\tilde{\nu}$ = 1629, 1708, 1756 vs. (CO) cm^{-1}.

[{η^6-$C_6H_5(CH_2)_3COOH$}Ru(η^6-ActrpOH)]$(CF_3SO_3)_2$ (8): Preparation as for **6** with *N*-acetyltryptophan (49.26 mg, 0.2 mmol) and 3 h of stirring at 50 °C. Yield 136.0 mg (84%). $C_{25}H_{26}F_6N_2O_{11}RuS_2$ (809.7): calcd. C 37.1, H 3.2, N 3.5, S 7.9; found C 37.5, H 3.5, N 3.2, S 8.1. FAB MS: *m*/*z* (%) = 660 (9) [M − OTf]$^+$, 511 (100) [M − 2 OTf]$^+$. ^{1}H NMR (CD_3OD): δ = 1.90 (m, 2 H, β-CH_2 pba), 2.02, 2.05 (2 s, 3 H, Ac), 2.32 (m, 2 H, α-CH_2 pba), 2.47 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, γ-CH_2 pba), 3.23 (2 d, 1 H, β-CH_2 ActrpOH), 3.43 (2 dd, 1 H, β-CH_2 ActrpOH), 4.81 (m, 1 H, α-CH ActrpOH), 6.53 (t, 1 H, pba), 6.60−6.70 (m, 5 H, pba/trp), 6.75 (dd, 1 H, trp), 7.74−7.82 (mm, 2 H, trp), 8.24, 8.28 (2 s, 1 H, trp) ppm. ^{13}C NMR (CD_3OD): δ = 22.7, 22.9, 26.1, 27.7, 28.1, 32.5, 33.7, 53.6, 53.7, 82.0, 82.1, 87.4, 87.5, 88.4, 88.5, 88.9, 91.8, 93.0, 93.4, 93.8, 94.7, 104.1, 107.4, 114.0, 114.1, 115.4, 115.5, 144.4, 173.6, 174.0, 176.5 ppm. IR: $\tilde{\nu}$ = 1668, 1748 vs. (CO) cm^{-1}.

[{η^6-$C_6H_5(CH_2)_3COOH$}Ru(η$^6_{ind}$-HphetrpOH)]$(CF_3SO_3)_2$·CF_3COOH (9): Preparation as for **6** with HphetrpOH (70.8 mg, 0.2 mmol) and 4 h of stirring at room temperature. Yield 160.6 mg (78%). $C_{32}H_{33}F_6N_3O_{11}RuS_2$·$CF_3COOH$ (1028.8): calcd. C 39.7, H 3.3, N 4.1, S 6.2; found C 39.4, H 3.7, N 4.0, S 6.4. FAB MS: *m*/*z* (%) = 766 (4) [M − OTf, − CF_3COOH]$^+$, 616 (100) [M − 2 OTf, − CF_3COOH]$^+$. ^{1}H NMR (CD_3OD): δ = 1.98 (m, 2 H, β-CH_2 pba), 2.36 (2 t, 2 H, α-CH_2 pba), 2.47 (2 t, 2 H, γ-CH_2 pba), 3.12 (2 dd, 1 H, β-CH_2 HphetrpOH), 3.44 (2 dd, 1 H, β′-CH_2 HphetrpOH), 4.28 (2 dd, 1 H, α-CH_2 HphetrpOH), 4.81 (m, 1 H, α′-CH_2 HphetrpOH), 6.50−6.78 (mm, 7 H), 7.37 (m, 5 H, phenyl), 7.77 (2 d, 1 H, trp), 7.82 (2 d, 1 H, trp), 8.25, 8.30 (2 s, 1 H, trp) ppm. ^{13}C NMR (CD_3OD): δ = 26.2, 27.7, 27.9, 32.6, 32.7, 33.7, 38.7, 38.8, 53.8, 54.0, 55.8, 55.9, 82.0, 82.1, 87.5, 87.6, 88.4, 88.5, 88.9, 92.0, 93.0, 93.5, 93.8, 94.0, 94.7, 104.0, 104.1, 112.7, 114.0, 114.1, 115.0, 115.1, 129.2, 130.4, 130.9, 135.6, 144.6, 144.7, 170.1, 173.4, 176.6 ppm.

[(η^6-C_6Me_6)Ru{η^6-$C_6H_5(CH_2)_3COOH$}]$(CF_3SO_3)_2$ (10): Preparation as for **6** by stirring [{η^6-$C_6H_5(CH_2)_3COOH$}Ru(acetone)$_3$](OTf)$_2$ (1 mmol) with C_6Me_6 (162 mg, 1 mmol) in CF_3COOH (50 mL) at reflux for 2 h. Yield 701 mg (97%). $C_{24}H_{30}F_6O_8RuS_2$ (725.7): calcd. C 39.7, H 4.2, S 8.8; found C 39.6, H 3.7, S 8.6. FAB MS: (*m*/*z*) (%) = 427 (100) [M − 2 OTf]$^+$. ^{1}H NMR (CD_3OD): δ = 2.00 (m, $^3J_{H,H}$ = 7.0, 8.3 Hz, 2 H, β-CH_2 pba) 2.51(t, $^3J_{H,H}$ = 7.0 Hz, 2 H, α-CH_2 pba), 2.59(s, 18 H, CH_3 C_6Me_6), 2.62 (t, $^3J_{H,H}$ = 8.3 Hz, 2 H, δ-CH_2 pba), 6.72−6.81 (m, 5 H, pba) ppm. ^{13}C NMR (CD_3OD): δ = 17.8, 27.8, 32.1, 33.5, 95.7, 96.3, 96.9, 111.1, 115.2 ppm.

[(η^6-C_6Me_6)Ru{η^6-$C_6H_5(CH_2)_3C(O)trpOMe$}]$(CF_3SO_3)_2$ (11): Compound **10** (108 mg, 0.15 mmol) was added to a solution of HtrpOMe·HCl (42 mg, 0.165 mmol) in CH_2Cl_2 (8 mL). After cooling to −15 °C, EDC (33 mg, 0.165 mmol) and triethylamine (30.7 mg, 0.30 mmol) were added to the suspension which was stirred at this temperature for 12 h and then at room temp. for 4 h. After removal of the solvent, the resulting solid was dissolved in CH_3OH (15 mL) and the product **11** separated by ion-pairing reversed-phase semi-preparative HPLC (Nucleosil 100-C18, d_p = 10 μm; eluent 45% CH_3OH/55% H_2O, 0.1% PFP, 20 mL/min; t_R = 16.9 min). Recrystallisation from CH_3OH afforded 93.0 mg (67%) of **11**. $C_{36}H_{42}F_6N_2O_9S_2Ru$ (925.2): calcd. C 46.7, H 4.6, N 3.0, S 6.9; found C 46.9, H 4.6, N 2.9, S 6.7. FAB MS: (*m*/*z*) (%) = 777 (3) [M − OTf]$^+$, 627 (100) [M − 2 OTf]$^+$. ^{1}H NMR (CD_3OD): δ = 1.91 (m, 2 H, β-CH_2 pba), 2.35 (m, 2 H, α-CH_2 pba), 2.44 (m, 2 H, γ-CH_2 pba), 2.52 (s, 18 H, CH_3 C_6Me_6), 3.22 (dd, 1 H, β′-CH_2 trp), 3.37 (dd, 1 H, β′-CH_2 trp), 3.77 (s, 3 H, OMe), 4.73 (dd, 1 H, α′-CH_2 trp), 6.61 (m, 3 H, pba), 6.72 (2 t, 2 H, bpa), 7.08 (t, 1 H, trp), 7.16 (t, 1 H, trp), 7.19 (s, 1 H, trp), 7.40 (dd, 1 H, trp), 7.58 (dd, 1 H, trp) ppm. ^{13}C NMR (CD_3OD): δ = 17.7, 27.7, 28.5, 32.3, 34.9, 53.2, 55.4, 95.9, 96.0, 96.9, 97.1, 111.2, 111.3, 112.8, 115.0, 119.5, 120.3, 122.9, 125.0, 129.0, 138.4, 174.6, 174.9 ppm.

[(η^6-C_6Me_6)Ru{η^6-$C_6H_5(CH_2)_3C(O)pheOMe$}]$(CF_3SO_3)_2$ (12): Preparation as for **11** with HpheOMe·HCl (33 mg, 0.17 mmol) and **10** (108 mg, 0.15 mmol) as starting compounds. HPLC separation was performed with a 50% CH_3OH/50% H_2O, 0.1% PFP eluent mixture (t_R = 13.1 min). Yield 61.1 mg (46%). $C_{34}H_{41}F_6NO_9S_2Ru$ (886.9): calcd. C 46.0, H 4.7, N 1.6, S 7.2; found C 45.9, H 4.8, N 1.4, S 7.2. FAB MS: (*m*/*z*) (%) = 588 (100) [M − 2 OTf]$^+$. ^{1}H NMR (CD_3OD): δ = 1.94 (m, 2 H, β-CH_2 pba), 2.23 (m, 2 H, α-CH_2 pba), 2.54 (m, 2 H, γ-CH_2 pba), 2.57 (s, 18 H, CH_3 C_6Me_6), 3.00 (dd, 1 H, β′-CH_2 phe), 3.22 (dd, 1 H, β′-CH_2 phe), 3.76 (s, 3 H, OMe), 4.68 (dd, 1 H, α′-CH_2 phe), 6.70 (t, 1 H, pba), 6.77 (m, 4 H, pba), 7.29 (m, 5 H, phe) ppm. ^{13}C NMR (CD_3OD): δ = 17.8,

27.9, 32.5, 34.9, 38.4, 53.1, 55.8, 96.0, 96.1, 96.2, 97.1, 111.4, 115.0, 128.3, 129.9, 130.5, 138.6, 168.6, 175.0 ppm.

[(η⁶-C_6Me_6)Ru{η⁶-$C_6H_5(CH_2)_3C(O)glyglyOEt$}]$(CF_3SO_3)_2$ (13): Preparation as for **11** with HglyglyOEt·HCl (46.1 mg, 0.165 mmol) and **10** (108 mg, 0.15 mmol) as starting materials. HPLC separation was performed with a 15% CH_3OH/85% H_2O, 0.1% PFP eluent mixture (t_R =20.1 min). Yield 93.4 mg (73%). $C_{30}H_{40}F_6N_2O_{10}S_2Ru$ (867.8): calcd. C 39.9, H 4.8, N 3.3, S 7.6; found C 39.9, H 4.7, N 3.1, S 7.5. FAB MS: (*m*/*z*) (%) = 546 (100) $[M - 2\ OTf]^+$, 379 (29) $[M - 2\ OTf, - glyglyOEt]^+$, 263(26) $[M - 2\ OTf, - C_6H_5(CH_2)_3C(O)glyglyOEt]^+$. ^1H NMR (CD_3OD): δ = 1.32 (t, $^3J_{H,H}$ = 7.6 Hz, 3 H, OEt), 2.04 (2 t, 2 H, β-CH_2 pba), 2.42 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, α-CH_2 pba), 2.59 (s, 18 H, CH_3 C_6Me_6), 2.62 (t, $^3J_{H,H}$ = 7.9 Hz, 2 H, γ-CH_2 pba), 3.98, 4.01 (2 s, 4 H, α′-,α"-CH_2 gly), 4.24 (q, 2 H, OEt), 6.78 (m, 3 H, pba), 6.84 (m, 2 H, pba) ppm. ^{13}C NMR (CD_3OD): δ = 14.8, 17.8, 27.9, 32.3, 35.0, 42.5, 45.3, 62.7, 96.0, 96.2, 97.1, 111.4, 115.2, 171.7, 172.3, 175.4 ppm.

X-ray Structural Analyses of 4b′ and 10: Crystal and refinement data are summarised in Table 1. Unit cell constants were obtained from least-squares fits to the settings of 25 reflections centred with a Siemens P4 diffractometer. Intensities were collected with the diffractometer at varied speeds using the ω-scan mode for Mo-K_α radiation. Monitored control reflections exhibited no significant alterations in intensity during data collection. Semi-empirical absorption corrections were performed for **4b′** on the basis of ψ scans and the structures solved by direct methods. Refinement against F^2 was performed by SHELX-97[35] with anisotropic temperature factors for non-hydrogen atoms and protons at geometrically calculated positions. Compound **10** contains a methanol molecule in its asymmetric unit. CCDC-195945 and -195946 (**4b′** and **10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; Email: deposit@ccdc.cam.ac.uk].

Table 1. Crystal and refinement data for **4b′** and **10**

	4b′	**10**·CH_3OH
Empirical formula	$C_{23}H_{20}ClF_3N_2O_5RuS$	$C_{25}H_{34}F_6O_9RuS_2$
M	630.0	757.7
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
a [Å]	8.134(5)	13.006(2)
b [Å]	18.878(4)	14.891(2)
c [Å]	15.953(3)	16.091(2)
β [°]	90.00(3)	94.81(6)
V [$Å^3$]	2449.8(8)	3105.4(8)
Z	4	4
F(000)	1264	1544
$P_{calcd.}$ [g/cm^3]	1.708	1.621
Crystal size [mm]	0.39·0.15·0.14	0.60·0.38·0.28
Radiation	Mo-K_α	Mo-K_α
μ [mm^{-1}]	0.895	0.723
$2\theta_{max}$ [°]	25	25
h, *k*, *l* range	9/−0, 0/22, −18/18	−1/14, −1/17, −19/19
Collected reflections	4808	6659
Unique reflections	4313	5388
No. of variables	326	403
R_1 [$I > 2\sigma(I)$]	0.059	0.038
wR_2 (all data)	0.115	0.098
S (goodness-of-fit)	1.005	1.025
max./min. Δρ [e·$Å^3$]	0.38/−0.38	0.40/−0.49

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