Synthesis and Ligand Binding of η^6-(2β-Carbomethoxy-3β-phenyltropane) Transition Metal Complexes

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The transition metal complexes [η^6-(2β-carbomethoxy-3β-phenyltropane)]tricarbonylchromium (**3**) and [η^6-(2β-carbomethoxy-3β-phenyltropane)][η^5-(pentamethylcyclopentadienyl)]ruthenium(II) triflate (**4**) were synthesized from 2β-carbomethoxy-3β-phenyltropane (**2**, WIN 35,065) to further elucidate the influence of substituents on the 3β-aryl on the affinity of the ligand for cocaine-binding sites at the dopamine transporter. The compounds were tested for their ability to displace bound [³H]WIN 35,428 (**5**) from rat caudate putamen tissue and for their ability to inhibit [³H]dopamine uptake. The binding affinity for **3** was 2-fold greater than those observed for cocaine (**1**) and **2**, while the binding affinity for **4** was found to be 100-fold less than those of **1** and **2**. In addition, **3** was equipotent with **1** and **2** in [³H]dopamine uptake inhibition studies, while **4** was 10-fold less potent. The potencies of the complexes **3** and **4** correlated well with the structure–activity relationships of other 2β-carbomethoxy-3β-aryltropane derivatives. These data further support a pharmacophore model in which the region occupied by the aryl ring is a lipophilic pocket with electropositive character.

Introduction

Molecular characterization of the cocaine-binding site on the dopamine transporter from structure–activity relationship (SAR) studies of cocaine (**1**) and related analogs has been the subject of numerous recent investigations.[1–14] A variety of 2β-substituted-3β-substituted aryltropanes have been found to possess a high affinity for cocaine-binding sites on the dopamine transporter. From these SAR studies, the 3β-aryl group has been established as one of the vital substructures for molecular recognition and high-affinity binding at cocaine-binding sites. Moreover, these studies have demonstrated the profound effect of functional group substitution on the 3β-aryl ring upon ligand affinity and binding site selectivity.[1–9] However, the nature of the molecular interaction between the binding site and the 3β-aryl group of high-affinity compounds is still unclear.

η^6-Transition metal (Cr, Mo, Rh, Ru) arene complexes of steroids and amino acids have been found to be useful biological probes for molecular characterization of biological systems.[15–18] The η^6-coordinated transition metal moiety has been shown to dramatically alter the electronic character and reactivity of the arene unit of the ligand. In addition, selective η^6-coordination of the transition metal moiety to either the α- or the β-face of the arene has served to introduce an element of asymmetrical molecular volume to the otherwise planar arene unit. Moreover, coordination of a transition metal moiety to a pharmacologic substrate has proven to be useful for the introduction of spectrochemical labels (Cr(CO)$_3$)[15] and radiolabels (⁹⁷Ru) in biological systems.[18] Herein we wish to report the synthesis and ligand affinity of the first transition metal (Cr, Ru) complexes of high-affinity cocaine-binding site ligands.

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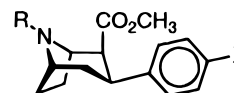† University of New Orleans.
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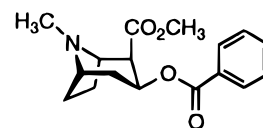
(-)-cocaine **1**
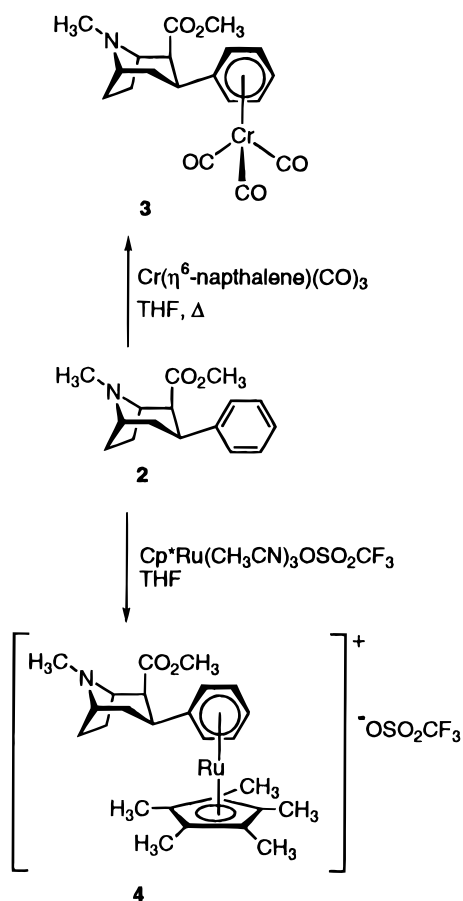

2 X = H; R = CH₃
5 X = F; R = C³H₃

Results and Discussion

Chemistry. A variety of tricarbonylchromium (Cr(CO)$_3$) and [η^5-(pentamethylcyclopentadienyl)]ruthenium(II) (Cp*Ru(II)) η^6-arene complexes have been readily prepared by direct substitution reactions of electrophilic transition metal complexes with corresponding arenes in the presence of a diverse number of functional groups.[19–22] For the preparation of an η^6-coordination complex of a potent cocaine analog, 2β-carbomethoxy-3β-phenyltropane (**2**, WIN 35,065) was envisaged to be better suited toward arene coordination than cocaine (**1**). It was believed that η^6-transition metal coordination to the electronically neutral 3β-phenyl ring of **2** would provide a more stable complex than coordination of the transition metal to the deactivated 3β-benzoyl group of **1**. The 2β-carbomethoxy-3β-phenyltropane (**2**) was prepared from **1** *via* the procedure developed by Carroll *et al.*[3]

As illustrated in Scheme 1, treatment of **2** with Cr-(η^6-naphthalene)(CO)$_3$[23] in refluxing tetrahydrofuran under an atmosphere of argon furnished the [η^6-(2β-carbomethoxy-3β-phenyltropane)]tricarbonylchromium (**3**) in 85% yield. The Cr(CO)$_3$ complex **3** was

Scheme 1

Table 1. K_i Values for Displacement of Receptor-Bound [^{3}H]WIN 35,428 (**5**) and IC$_{50}$ Values for Inhibition of [^{3}H]Dopamine Uptake[a]

analog	K_i (nM)[b]	IC$_{50}$ (nM)
1	32 ± 5	405
	388 ± 221	
2	33 ± 17	373
	314 ± 222	
3	17 ± 15^c	418
	224 ± 83	
4	2280 ± 183	3890

[a] All values are mean $\pm$ SEM of three experiments, each performed in triplicate under conditions indentical with those described in ref 26. [b] Both the high-affinity and low-affinity K_i values are reported for those drugs in which the binding data fit a two-site model better than a one-site model (ref 26). [c] The K_i value for the one-site model was 124 ± 10 nM.

unlabeled ligands. The linear portions of the [^{3}H]-dopamine uptake inhibition curves were analyzed using standard analysis of variance and linear regression techniques.

The Cr(CO)$_3$ derivative **3** was found to be 2-fold more potent than cocaine (**1**) and the free ligand **2** in the inhibition of **5** binding (Table 1). The complex **3** modeled better for two binding sites than for a one-site model. This type of differential binding has been observed for the 2β-carbomethoxy-3β-aryltropanes **2** and **5** as well as for cocaine (**1**).[26] Both high- and low-affinity K_i values for the two-site model are reported in Table 1. In addition, **3** was equipotent with **1** and **2** for inhibition of dopamine uptake (Table 1). By contrast, the Cp*Ru(II) complex **4** exhibited a 100-fold decrease in the inhibition of high-affinity binding relative to **1** and **2** and a 10-fold decrease in potency in dopamine uptake inhibition.

The high binding affinity observed for the Cr(CO)$_3$ complex **3** clearly demonstrates that the specific region of the cocaine receptor which is occupied by the aryl ring of the high-affinity ligand **2** can readily accommodate the increased volume of the lipophilic Cr(CO)$_3$ moiety, while the slightly larger Cp*Ru(II) moiety of **4** did not interact favorably with this region of the dopamine transporter. However, the large difference in binding affinities of **3** and **4** is not adequately described by the moderate steric differential of the transition metal moieties.[27] The electrostatic differences between **3** and **4** are thought to contribute significantly to the observed difference in activity. It has been shown in other receptor systems that comparison of the electronic effect of the Cp*Ru(II) moiety to the Cr(CO)$_3$ residue was of greater significance than the steric effect.[17] The electron-rich oxygen atoms of the Cr(CO)$_3$ tripod of **3** are believed to interact favorably with the aryl ring region of the cocaine recognition site. However, the charged electropositive character of the Cp*Ru(II) moiety of **4** interacts unfavorably with this region of the dopamine transporter which results in the diminished activity observed for the compound.

The potencies of **3** and **4** are consistent with the pharmacophore model recently proposed by Carroll *et al.*[9] Based on comparative molecular field analysis (CoMFA) of 25 2β-carbomethoxy-3β-aryltropane derivatives, the model demonstrated that increased electron density around the aryl ring correlated with high ligand potency. In addition, the model correlated excessive steric bulk and increased electropositive character around the aryl ring (electron-withdrawing substitu-

found to be an air stable yellow crystalline material. Treatment of **3** with an etheral solution of anhydrous hydrogen chloride provided the corresponding water soluble hydrochloride salt which was utilized for biological testing. The [η^5-(pentamethylcyclopentadienyl)][η^6-(2β-carbomethoxy-3β-phenyltropane)]ruthenium(II) triflate (**4**) was also easily prepared from **2** (Scheme 1). Treatment of **2** with Cp*Ru(CH$_3$CN)$_3$OTf[24] in dry tetrahydrofuran under an argon atmosphere at room temperature gave **4** in 80% yield. The complex **4** was found to be air stable and water soluble.

η^6-Coordination of the transition metal moieties Cr-(CO)$_3$ and Cp*Ru(II) to the phenyl ring of **2** was found to restrict rotation of the phenyl group and introduced chirality about the C(3)−C(1′) bond. This was evident from the ^{1}H and ^{13}C NMR spectra of **3** and **4** in which each atom of the phenyl ring exhibited an unique chemical shift which was not observed for the free ligand **2**.[25] In addition, the chemical shifts of the carbomethoxy and *N*-methyl groups of **3** and **4** were not affected relative to **2** by the coordination of the transition metal moiety.[25] From these spectral data, it was inferred that the transition metal moieties of **3** and **4** were coordinated to the less hindered external face of the phenyl ring to give a single diastereomer of each complex (Scheme 1).

Biological Activity. The transition metal complexes **3** and **4** were tested for their ability to displace bound [^{3}H]WIN 35,428 (**5**) from rat caudate putamen tissue.[26] In addition, the compounds **3** and **4** were tested for their ability to inhibit high-affinity uptake of [^{3}H]dopamine in rat caudate putamen tissue.[25] The K_i values reported in Table 1 are the dissociation constants derived for the

ents) with decreased ligand affinity.[9] The high affinity observed for the electron-rich $Cr(CO)_3$ complex **3** and low affinity observed for the electropositive Cp*Ru(II) complex **4** are in complete agreement with these features of the model. Additionally, on the basis of the high affinity of **3**, it is apparent that the region which is occupied by the aryl group of 2β-carbomethoxy-3β-aryltropanes is of sufficient volume to accommodate large bulky lipophilic substituents.

In summary, the potencies of complexes **3** and **4** correlate well with the SAR of other 2β-carbomethoxy-3β-aryltropane derivatives and further support a pharmacophore model which favors electron-rich 3β-aryl substituents for high-affinity ligands. In addition, the synthetic approach developed for the preparation of **3** and **4** will undoubtedly prove useful for the preparation of additional transition metal complexes to be used as biological probes and labels.

Experimental Section

All chemicals and reagents not otherwise noted were purchased from Aldrich Chemical Co. Tetrahydrofuran and ether were dried by distillation from Na/benzophenone. Dichloromethane (E. M. Science) was dried by distillation from P_2O_5. Flash silica gel (silica gel 60, E. M. Science, 230–400 mesh) and TLC plates (E. M. Science, kiesel gel 60, F_{254}, 0.2 mm layer glassback) were purchased from Curtin Matheson Scientific. NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. IR spectra were recorded on a Perkin–Elmer 2000 FTIR spectrometer. Optical rotations were measured on an Autopol III polarimeter. Melting points were recorded on a Mel–Temp apparatus and are uncorrected. Elemental analyses were obtained from Atlantic Microlab Inc., Norcross, GA. All reactions were performed under argon in an inert atmosphere glovebox and worked up routinely in air.

[η^6-(2β-Carbomethoxy-3β-phenyltropane)]Cr(CO)$_3$ (3). To a solution of **2** (100 mg, 0.38 mmol) in dry THF (5 mL) was added $Cr(\eta^6$-naphthalene)$(CO)_3$[23] (106 mg, 0.40 mmol), and the mixture was heated to reflux for 4 h in the dark under an atmosphere of argon. The solvent was removed under reduced pressure and the oil chromatographed (SiO$_2$, MeOH/CH$_2$Cl$_2$, 5:95) to give **3** (127 mg, 85%) as a yellow crystalline solid: mp 144–148 °C; ^{1}H NMR (CDCl$_3$) δ 5.51 (br s, 1H, *p-Ph*), 5.39 (br s, 2H, *m-Ph*), 5.19 (br s, 1H, *o-Ph*), 5.15 (br s, 1H, *o-Ph*), 3.57 (s, 3H, *OCH$_3$*), 3.50 (br s, 1H, *H1*), 3.31 (br s, 1H, *H5*), 2.70 (m, 2H, *H2, H3*), 2.33–1.95 (m, 4H), 2.22 (s, 3H, *NCH$_3$*), 1.68 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 233.4, 172.8, 94.0, 93.3, 93.0, 92.9, 92.8, 90.9, 65.2, 61.9, 53.2, 51.5, 41.9, 34.2, 32.7, 25.7, 25.1; IR (KBr) 2955, 1965, 1885, 1738 cm^{-1}; $[\alpha]^{20}_D = -45.5°$ (CH$_3$-OH, $c = 0.47$). Anal. (C$_{16}$H$_{21}$NO$_2$Cr(CO)$_3$) C, H, N.

The hydrochloride salt of **3** was prepared by addition of an etheral solution of anhydrous HCl at 0 °C to a solution of **3** (25 mg, 0.06 mmol) in ether (2 mL). The yellow precipitate (25 mg) was filtered and dried under vacuum: mp 122–125 °C dec. Anal. (C$_{19}$H$_{21}$NO$_5$Cr·HCl·H$_2$O) C, H, N.

Cp*Ru[η^6-(2β-carbomethoxy-3β-phenyltropane)]OTf (4). To a solution of **2** (52 mg, 0.20 mmol) in THF (5 mL) at room temperature under an argon atmosphere was added Cp*Ru-(CH$_3$CN)OTf[24] (91 mg, 0.18 mmol) in one portion. The solution was stirred for 2 h, and the solvent was removed under reduced pressure. The residue was triturated with ether and recrystallized from dichloromethane/ether to give **4** (93 mg, 80%) as a brown microcrystalline solid: mp 115–117 °C; ^{1}H NMR (CDCl$_3$) δ 6.29 (d, $J = 6.0$ Hz, 1H, *o-Ph*), 5.85 (t, $J = 5.9$ Hz, 1H, *m-Ph*), 5.75 (d, $J = 5.9$ Hz, 1H, *o-Ph*), 5.61 (t, $J = 6.0$ Hz, 1H, *m-Ph*), 5.56 (m, 1H, *p-Ph*), 3.73 (br s, 1H, *H1*), 3.64 (br s, 1H, *H5*), 3.50 (s, 3H, *OCH$_3$*), 3.40 (m, 1H, *H3*), 3.06 (m, 1H, *H2*), 2.26 (s, 3H, *NCH$_3$*), 2.19–2.07 (m, 3H), 1.96 (s, 15H, *Cp-CH$_3$*), 1.87–1.45 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 172.0, 122.5, 107.6, 95.8, 87.6, 87.2, 86.5, 85.8, 85.7, 65.2, 61.8, 52.44, 51.6, 41.6, 36.7, 32.6, 25.3, 24.7, 10.7; $[\alpha]^{20}_D = +21.8°$ (EtOH, $c = 0.055$). Anal. (C$_{27}$H$_{36}$NO$_5$F$_3$RuS) C, H, N.

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