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# Reactivity and reaction pathways of electrochemically generated 17-electron tricarbonyl steroid chromium cations

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**Electrochemical oxidation of α- and β-diastereomers of a range of steroid hormone receptor marker chromium tricarbonyl complexes, (steroid)$Cr(CO)_3$, have been examined at platinum electrodes in dichloromethane. Data confirm the general nature of previously published conclusions on the oxidation of (arene)$Cr(CO)_3$ complexes (arene = benzene or steroid). That is, with 0.1 M $Bu_4NPF_6$ as the electrolyte, and in the absence of nucleophiles, a reversible one-electron process, (steroid)$Cr(CO)_3 \rightleftharpoons$[(steroid)$Cr(CO)_3$]$^+ + e^-$, is observed, followed by an irreversible one-electron process at considerably more positive potentials. The reversible half-wave potentials (approximately $E^\circ$-values) calculated for the [(steroid)$Cr(CO)_3$)]$^+$/(steroid)$Cr(CO)_3$ redox couple are shown to be dependent on whether the α- or β-diastereomer is oxidized. Similarly the rate of nucleophilic attack on the 17-electron cation [(steroid)$Cr(CO)_3$]$^+$ by nucleophiles such as $ClO_4^-$, $PPh_3$ and bis(diphenylphosphine)methane confirms a previous observation that the stereochemistry of this class of compound is important with respect to redox, kinetic and hormone receptor properties. The nature of the electrochemical data obtained on the (arene)$Cr(CO)_3$ complexes in the presence of nucleophiles suggests that reactions associated with the nucleophilic attack on the 17-electron cations are complex and that a range of reaction pathways occur simultaneously. Electrochemical studies on the oxidation of (benzene)$Cr(CO)_2PPh_3$ and (oestradiol)$Cr(CO)_2PPh_3$ confirm some aspects of the proposed mechanisms, although it is clear that a great deal still has to be learned concerning mechanistic aspects of nucleophilic attack on these 17-electron complexes.**

**Keywords: Electrochemistry, oxidation, carbonyl steroid chromium complexes**

## INTRODUCTION

The chemistry of the —$M(CO)_3$ fragment [M = Cr, Mo, W] is one of the most widely studied in the field of organometallic chemistry.[1] In the particular case when the —$M(CO)_3$ moiety is coordinated to an arene, then generally a highly stable 18-electron organometallic compound, (arene)$M(CO)_3$, is formed. Thermodynamic and kinetic studies of the reactions of (arene)$M(CO)_3$ compounds have been widespread and data have been used to explore factors influencing metal–ligand bond strengths. For example, calorimetric studies have been undertaken on a series of (arene)$MoCO_3$ complexes to measure the relative stability in solution of the various arene complexes (arene = *o*-xylene, *m*-xylene, *p*-xylene, etc.) and heats of reaction of (toluene)$Mo(CO)_3$ with nitriles, isocyanides and other ligands have been described[2] and provide fundamental thermodynamic information on exchange reactions.

The majority of reactions of 18-electron (arene)$M(CO)_3$ complexes involving ligand exchange or redistribution reactions are extremely slow. However, electrochemical oxidation of (arene)$M(CO)_3$ may lead to the formation of a 17-electron cation, [(arene)$M(CO)_3$]$^+$, which is

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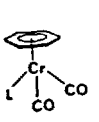
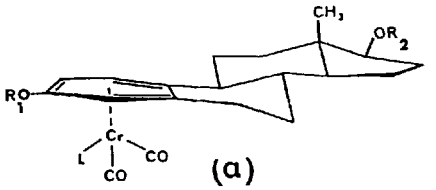
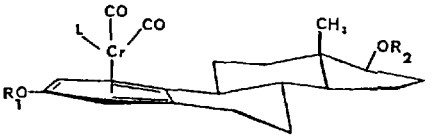




(α)



(β)

1 L = CO

2 L = $P\phi_3$

3 $R_1$ = $\phi$-$CH_2$—; $R_2$ = H—; L = CO

4 $R_1$ = $\phi$-$CH_2$—; $R_2$ = t-$BuMe_2Si$—; L = CO

5 $R_1$ = $\phi$-$CH_2$—; $R_2$ = $\phi$-$CH_2$—; L = CO

6 $R_1$ = t-$BuMe_2Si$—; $R_2$ = H—; L = CO

7 $R_1$ = H—; $R_2$ = H—; L = CO

8 $R_1$ = H—; $R_2$ = H—; L = $P\phi_3$

**Scheme 1**

highly activated with respect to its 18-electron counterpart. For example, electrochemical oxidation of (arene)$Cr(CO)_3$ in acetonitrile at ambient temperatures produces evidence for the formation of $[(CH_3CN)_3Cr(CO)_3]^+$ as an intermediate on the voltammetric (seconds) time scale via the reaction sequence

$$(\text{arene})Cr(CO)_3 \rightleftharpoons [(\text{arene})Cr(CO)_3]^+ + e^- \quad [1a]$$

$$[(\text{arene})Cr(CO)_3]^+ + 3CH_3CN \rightarrow$$

$$[(CH_3CN)_3Cr(CO)_3]^+ + \text{arene} \quad [1b]$$

In contrast, the 18-electron (arene)$Cr(CO)_3$ complex is stable in acetonitrile for many hours at ambient temperatures.

Whilst it would generally be expected on the basis of charge effects that nucleophilic attack on the cationic 17-electron $[(\text{arene})M(CO)_3]^+$ species would occur at an enhanced rate, relative to the neutral 18-electron analogue (e.g. $[(\text{benzene})Cr(CO)_3]^+$ is even attacked rapidly by the weak $ClO_4^-$ ligand on the voltammetric time scale[4]), Basolo and co-workers[5] have reported some novel aspects concerning rates and mechanisms of CO substitution reactions of similar 17- and 18-electron metal carbonyl complexes. These workers concluded that considerable differences in rate may occur, depending on whether an associative of dissociative mechanism is involved in the substitution reaction.

Recently, it has been shown that (steroid)$M(CO)_3$ complexes can be electrochemically oxidized, as is the case with other arenes.[6,7] Additionally, chromium tricarbonyl derivatives of suitable hormones can act as analytical markers for receptor and chemical immunological studies,[8–11] with the ability of the hormones to recognize their specific receptor site being significantly dependent on their stereochemistry ($\alpha$- or $\beta$-forms). In our earlier study,[7] the electrochemistry of the steroid hormone receptor marker [3-(benzyloxy)-17$\beta$-hydroxyoestra-1,3,5(10)-triene) tricarbonylchromium] was examined as a function of electrolyte and both thermodynamic and kinetic dependencies of the stereochemistry were observed, as is the case with the biological activity. In the present paper we have extended our electrochemical studies to encompass the oxidation of a range of hormone receptor markers and related (arene)$Cr(CO)_3$ complexes in the presence and absence of nucleophiles, in order to establish a more systematic understanding of the chemistry of activated 17-electron steroid complexes. The structures of the compounds studied are given in Scheme 1.

## EXPERIMENTAL

### General

NMR ($^{1}H$, $^{13}C$, $^{31}P$) spectra were obtained in dichloromethane on a JEOL 270 instrument at 270 MHz using the internal references tetramethylsilane (TMS), $CDCl_3$ and 90% $H_3PO_4$ respectively. Fourier transform infrared (FTIR) spectra were obtained using a Biorad FTS-7 instrument calibrated with carbon monoxide gas and polystyrene film (accuracy $\pm 2\,cm^{-1}$). Electron impact mass spectra were obtained on a JEOL JMS DX 300 instrument at 70 eV; data were acquired via a JMA-3100 data system and polyfluorokerosene (PKF) was used as the calibration standard.

All operations with the organometallic complexes were carried out under a dry argon or nitrogen atmosphere. Benzene (Mallinckrodt) was purified by distillation from sodium benzophenone ketyl immediately before use. Triphenylphosphine, bis(diphenylphosphino)-methane (dpm) and other chemicals were used as supplied by the manufacturer.

Photochemistry experiments to synthesize (benzene)$Cr(CO)_2P(C_6H_5)_3$ were performed with an ACE photochemical reactor using a Hanovia 450 W medium-pressure mercury lamp. The benzene solvent was sparged with dry argon prior to the addition of the chemicals to be photolysed, and dry argon sparging was continued during photolysis.

A standard chromatography/filtration compound work-up procedure with several useful modifications given below proved to be an effective way of eliminating organic residues, traces of oils and any unreacted ligands. In a 60 mm × 240 mm flash chromatography column, 80 g of alumina (Machcray Nagel) was mixed with hexane. A Whatman No. 1 filter paper was placed on top of the alumina to collect any insoluble material present in the reaction mixture. The desired coloured reaction products are absorbed at the top of the alumina. The other reaction products were eluted with hexane (0.5–1.0 litre) until the washings did not contain any oils or unreacted ligands as monitored by standard thin-layer chromatographic or spectroscopic procedures. The desired product can be eluted from the column by passing a non-polar solvent such as dichloromethane, diethyl ether or benzene through the column/filter. The solvent was removed using a Buchi rotary evaporator in an argon or nitrogen atmopsphere. The procedure used enables reaction products to be isolated conveniently in an inert atmosphere.

### Electrochemical

The electrolytes, tetrabutylammonium perchlorate ($Bu_4NClO_4$, G. F. Smith Chemical Co.) and tetrabutylammonium hexafluorophosphate ($Bu_4NPF_6$, Southwestern Analytical Chemicals), were dried over phosphorus pentoxide for 48 h before use.

The electrochemical solvent dichloromethane (Mallinckrodt) was passed through a neutral alumina column of activity 1 prior to use in electrochemical experiments.

Before use, solutions for electrochemistry were degassed with dry argon or nitrogen for at least 10 min to remove oxygen. All electrochemical experiments were done at (20 ± 1)°C under a blanket of nitrogen or argon that was saturated in dichloromethane. Alumina (preheated to 600 °C and allowed to cool) was included in the electrochemical cell to ensure that water was kept to a minimum during the electrochemical experiments. Glassware was cleaned and stored in a drying oven prior to use. The working electrode used in voltammetric experiments was a platinum disc electrode. A platinum wire counter-electrode was used and the reference electrode was a Ag/AgCl electrode filled with $CH_2Cl_2$ (0.1 M $Bu_4NClO_4$) and saturated with LiCl and separated from the test solution by a salt bridge containing $CH_2Cl_2$ and the electrolyte in use.

Oxidation of $5 \times 10^{-4}$ M solutions of ferrocene (Merck) at a platinum electrode was used to calibrate the Ag/AgCl reference electrode. The reversible half-wave potential of the ferrocene oxidation process was 0.520 ± 0.010 V vs Ag/AgCl at 20 °C in dichloromethane.

Voltammetric experiments were recorded using a Bioanalytical Systems CV 27 Voltammograph and a Houston Instruments Model 100 *X–Y* recorder. A PAR Model 173 Potentiostat/Galvanostat was used for controlled potential electrolysis experiments with a platinum gauze basket working electrode, a platinum gauze auxiliary electrode separated from the test solution by a salt bridge and the same Ag/AgCl reference electrode used for voltammetry.

## Syntheses

**$\eta^6$-Benzenetricarbonylchromium, (benzene)$Cr(CO)_3$ (compound 1)**

2-Picoline (100 ml), benzene (100 ml) and chromiumhexacarbonyl (8.80 g; 0.04 mol) were added to a two-necked 500-ml flask fitted with a double-surface condenser and a nitrogen gas tube. Nitrogen was bubbled continuously and the reaction mixture was refluxed for 96 h, during which time the reaction solution turned dark red. The reaction mixture was transferred to the rotary evaporator under nitrogen and the solvents and excess reagents partly removed. The yellow–green residue was transferred to a flash chromatography column, as described earlier, and eluted with diethyl ether. Extracts were concentrated and the product filtered. On the second recrystallization from diethyl ether, 7.56 g (90%) of yellow crystals of benzenetricarbonylchromium were obtained, m.p. 161–162 °C (lit. mp. 162–165 °C[12]). The $M^+$ ion obtained from mass spectrometry had *m/z* 214, which corresponds to the theoretically expected formula weight. NMR in $CH_2Cl_2$: $^1H$ 5.32 ppm, single resonance, $^{13}C$ 232.8 ppm (CO) and 92.8 ppm (benzene). Infrared (KBr disc) 1965 (s) $cm^{-1}$, 1857(s) [$\nu$(CO)] which is in agreement with the literature.[12,13]

**($\eta^6$-Benzene)dicarbonyl(triphenylphosphine)chromium, (benzene)$Cr(CO)_2P(C_6H_5)_3$ (compound 2)**

Benzenetricarbonylchromium (900 mg, 4.2 mmol) was added to a 300-ml solution of triphenylphosphine (2.15 g, 8.1 mmol) in benzene under argon in a quartz water-jacketed photochemical reactor. The solution was irradiated with a mercury lamp, keeping the benzene solution mixture below 30 °C and continuously degassed with dry argon. The reaction was monitored by FTIR spectroscopy.[12] The solvent was removed by rotary evaporation. Chromatography and work-up procedures described earlier yielded 1.70 g of products (88% yield). Formula weight = 448.2 for $C_{26}H_{21}CrO_2P$; microanalysis requires C, 69.62; H, 4.70. Found: C, 69.85; H, 4.60%. The $M^+$ ion obtained from mass spectrometry had *m/z* 448. NMR in $CH_2Cl_2$: $^{31}P$, 91.6 ppm; $^{13}C$ 241.0. 240.7 (C of CO); 139.8, 132.9, 132.8 [C of $P(C_6H_6)_3$], 128.9, 127.9, 127.7; 89.9 ppm (C of $C_6H_5Cr$). Infrared (KBr disc) 1891 $cm^{-1}$ (s), 1837(s) [$\nu$(CO)].

**($\eta^6$-Oestradiol)$Cr(CO)_2P(C_6H_5)_3$ (compound 8)**

1,3,5(10)Oestratriene-3,17$\beta$-diol (oestradiol) (0.55 g, 2.0 mmol) was dissolved in di-n-butyl ether (250 ml). The solution was purged with dry oxygen-free argon for 20 min and heated to 50 °C. To the solution was added hexacarbonylchromium (0.44 g, 2.0 mmol) and triphenylphosphine (1.57 g, 6.0 mmol). This reaction mixture was refluxed for 60 h under an argon atmosphere. The unreacted $Cr(CO)_6$ was sublimed, the solution filtered and the filtrate evaporated to dryness *in vacuo*. The remaining orange–yellow solid residue was taken up in a minimum quantity of diethyl ether and filtered, and the procedure was repeated until the clear orange solution afforded orange–yellow crystals of ($\eta^6$-oestradiol)$Cr(CO)_2P(C_6H_5)_3$. Yield 0.4 g (31%); m.p. 169–170 °C; infrared in $CH_2Cl_2$ 1895(s), 1840(s) $cm^{-1}$ [$\nu$(CO)]. This compound is relatively unstable and could not be as well characterized as the (benzene)$Cr(CO)_2P(C_6H_5)_3$ analogue.

**($\eta^6$-Oestradiol)$Cr(CO)(\eta^2$-dpm)**

A procedure similar to the preparation of ($\eta^6$-oestradiol)$Cr(CO)_2P(C_6H_5)_3$ was followed except that bis(diphenylphosphino)methane (2.31 g, 6.0 mmol) replaced triphenylphosphine. Creamy yellow crystals of ($\eta^6$-oestradiol)$Cr(CO)(\eta^2$-dpm) were obtained. Yield 0.7 g (31%); m.p. 114–115 °C; infrared 1815 (s) $cm^{-1}$ [$\nu$(CO)]. This compound is also relatively unstasble and has not been completely characterized (see Results and discussion section for further details).

**$\beta$-(3,17$\beta$-bis (benzyloxy)oestra-1,3,5(10)-triene) tricarbonylchromium (compound 5$\beta$)**

To a solution of $\beta$-3-(benzyloxy)-17$\beta$-hydroxyoestra-1,3,5(10)-triene tricarbonylchromium (0.22 g, 0.6 mmol) in THF (30 ml) was added 50% NaOH (0.24 g, 6 mmol). The mixture was heated under reflux for 6 h. $C_6H_5CH_2Br$ (1.03 g, 6 mmol) was added to the solution and the reflux was maintained overnight. After hydrolysis with ice–water, ether extraction and solvent removal, the residue was chromatographed on silica gel plates using ether/pentane (1:2). The yellow solid was identified as the desired complex (0.145 g, 53%), m.p. 153 °C. $^1H$ NMR ($CD_3COCD_3$): $\delta$ 7.40 and 7.31 (m, $C_6H_5$), 5.92 (d, $H_1$), 5.40 (d, $H_4$), 5.32 (dd, $H_2$), 5.03 and 4.53 (s, $CH_2$), 3.51 (t, $H_{17}$), 2.85 (m, $H_6$), 0.87 ppm (s, Me-13). IR ($CH_2Cl_2$) 1955 (s),

1872 $cm^{-1}$ (s) [$\nu$(CO)]. Mass spectrum: $m/z$ 588 $[M]^+$, 504 $[M-3CO]^+$, 412 $[M-Cr(CO)_3]^+$.

The $\alpha$-[3,17$\beta$-bis(benzyloxy)oestra-1,3,5(10)-triene] tricarbonylchromium was obtained by the same procedure, m.p. 150 °C. $^1H$ NMR ($CD_3COCD_3$): $\delta$ 7.39 and 7.30 (m, $C_6H_5$), 6.10 (d, $H_1$), 5.42 (d, $H_4$), 5.47 (dd, $H_2$), 4.99 and 4.53 (s, $CH_2$), 3.53 (t, $H_{17}$), 2.87 (m, $H_6$), 0.83 ppm (s, Me-13). IR ($CH_2Cl_2$) 1955 (s), 1872 $cm^{-1}$ (s). Mass spectrum: $m/z$ 588 $[M]^+$, 504 $[M-3CO]^+$, 412 $[M-Cr(CO)_3]^+$.

**Other compounds**

Other compounds were synthesized as described in Refs 6 and 9.

## RESULTS AND DISCUSSION

Figure 1(a) and (b) shows cyclic voltammograms obtained at a platinum electrode in dichloromethane for oxidation of the $\alpha$-diastereomer of ($R_1R_2$ steroid)$Cr(CO)_3$ ($R_1 = C_6H_5CH_2$–, $R_2$ = t-$BuMe_2Si$—; (Structure **4α** in Scheme 1) at a scan rate of 400 mV $s^{-1}$ in dichloromethane with $Bu_4NPF_6$ or $Bu_4NClO_4$ as the electrolyte. Electrochemical data for this and other complexes in both electrolytes are summarized in Tables 1 and 2. As can be seen from Fig. 1, the one-electron oxidation process

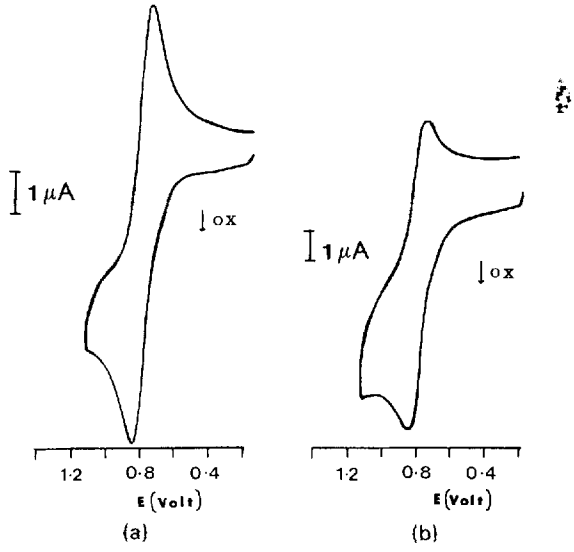



**Figure 1** Cyclic voltammograms (scan rate = 400 mV $s^{-1}$) at 20 °C for oxidation (first process) of $5 \times 10^{-4}$ M $\alpha$-($R_1R_2$ steroid)$Cr(CO)_3$ ($R_1 = C_6H_5CH_2$—, $R_2$ = t-$BuMe_2Si$—, compound **4α** in Scheme 1) at a platinum disc electrode in dichloromethane which contains (a) 0.1 M $Bu_4NPF_6$ and (b) 0.1 M $Bu_4NClO_4$ as the electrolyte.

$$(\text{steroid})Cr(CO)_3 \rightleftharpoons [(\text{steroid})Cr(CO)_3]^+ + e^- \quad [2]$$

is reversible with $Bu_4NPF_6$ as the electrolyte, and close to reversible with $BuNClO_4$ as the electrolyte on the time scale of cyclic voltammetry (scan rate = 50–800 mV $s^{-1}$). A second, irreversible, one-electron process is also observed at more positive potentials.[6,7] this process corresponds to the overall reaction in Eqn [3], but is not discussed further.

$$[(\text{steroid})Cr(CO)_3]^+ \rightarrow Cr^{2+} + \text{steroid} + 3CO \uparrow + e^- \quad [3]$$

The reversible half-wave potential ($E'_{1/2}$) for the $[(\text{steroid})Cr(CO)_3]^+/(\text{steroid})Cr(CO)_3$ process in Eqn [2] is more positive for the $\beta$-isomer than the $\alpha$-isomer by 10–30 mV. Data suggest that the presence of the R = t-$BuMe_2Si$— substituent leads to considerable stability of the $[(\text{steroid})Cr(CO)_3]^+$ complex. For example, a chemically irreversible rather than a reversible process is frequently observed with perchlorate as the electrolyte for oxidation of (arene)$Cr(CO)_3$ complexes at ambient temperatures under conditions of cyclic voltammetry using a scan rate in the 50 mV $s^{-1}$ range.[4,6,7,14]

Figure 2 shows an example where a non-reversible process is observed when the $\alpha$-($R_1R_2$ steroid)$Cr(CO)_3$ ($R_1 = C_6H_5CH_2$—, $R_2 = C_6H_5CH_2$—, (Structure **5α** in Scheme 1) complex is oxidized in dichloromethane with perchlorate as the electrolyte and slow scan rates are used under conditions of cyclic voltammetry. In the presence of $ClO_4^-$, the first oxidation process changes from a chemically irreversible two-electron process towards a reversible one-electron process (Eqn [2]) as the scan-rate increases. That is, the apparent number of electrons being transferred, $n_{app}$, in the first step varies between 1 and 2, the exact value depending on the scan rate and perchlorate concentration. Concomitantly, as $n_{app}$ increases, the height of the second oxidation process decreases and is completely absent when $n_{app} = 2$. A mechanism consistent with the experimental observations[7] is given in Eqn [4].

**Table 1** Reversible half-wave potentials, $E^r_{1/2}$, for the $[(\text{steroid})\text{Cr}(\text{CO})_3]^+/(\text{steroid})\text{Cr}(\text{CO})_3$ and related redox couples in dichloromethane[a]

| Compound | $E^r_{1/2}$ vs Ag/AgCl (v) | | | |
|---|---|---|---|---|
| | 0.1 M $Bu_4NClO_4$ | | 0.1 M $Bu_4NPF_6$ | |
| Ferrocene | 0.520 | | 0.520 | |
| $(\text{benzene})\text{Cr}(\text{CO})_3$ | 0.925 | | 0.945 | |
| $(\text{oestradiol})\text{Cr}(\text{CO})_3$ (structure **7**) | 0.705 | | 0.725 | |
| | $\alpha$-isomer | $\beta$-isomer | $\alpha$-isomer | $\beta$-isomer |
| $(R_1R_2\text{steroid})\text{Cr}(\text{CO})_3$ | | | | |
| $R_1 = C_6H_5CH_2$—, $R_2$ = H— (structure **3**) | 0.750 | 0.770 | 0.730 | 0.760 |
| $R_1 = C_6H_5CH_2$—, $R_2$ = t-$BuMe_2Si$— (structure **4**) | 0.780 | 0.795 | 0.810 | 0.820 |
| $R_1 = R_2 = C_6H_5CH_2$— (structure **5**) | 0.765 | 0.790 | 0.790 | 0.810 |
| $R_1$ = t-$BuMe_2Si$—, $R_2$ = H— (structure **6**) | 0.760 | 0.785 | 0.770 | 0.805 |

[a]Values of $E^r_{1/2}$ calculated at 20 °C from cyclic voltammograms (average of oxidation and reduction peak potentials) obtained over scan rate range of 100–800 mV $s^{-1}$ under conditions where process is chemically reversible. Concentration of compounds = $5 \times 10^{-4}$ M. Errors are ±0.005 mV, based on five determinations. Second irreversible oxidation process observed as in Eqn [3] for all $(\text{steroid})\text{Cr}(\text{CO})_3$ complexes.[6,7,14]

**Table 2** Second-order rate constant, $k$, obtained for the reaction $[(R_1R_2\text{steroid}(\text{Cr}(\text{CO})_3]^+ + ClO_4^- \xrightarrow{k}$ product(s), from cyclic voltammograms for the first oxidation process for $5 \times 10^{-4}$ M $(R_1R_2\text{steroid})\text{Cr}(\text{CO})_3$ in dichloromethane[a]

| Compound | $k$($M^{-1}s^{-1}$ | |
|---|---|---|
| | $\alpha$-isomer | $\beta$-isomer |
| $(R_1R_2$ Steroid$)(\text{Cr}(\text{CO})_3$ | | |
| $R_1 = C_6H_5CH_2$—, $R_2$ = H— (structure **3**) | $44 \pm 9$[b] | $85 \pm 7$[b] |
| $R_1 = C_6H_5CH_2$—, $R_2$ = t-$BuMe_2Si$— (structure **4**) | —[c] | —[c] |
| $R_1 = R_2 = C_6H_5CH_2$— (structure **5**) | $10 \pm 3$ | $19 \pm 5$ |
| $R_1$ = t-$BuMe_2Si$—, $R_2$ = H— (structure **6**) | $44 \pm 15$ | $53 \pm 15$ |

[a]Ionic strength maintained at 0.1 M by using $Bu_4NPF_6$–$Bu_4NClO_4$ mixtures and assuming $Bu_4NPF_6$ is an inert electrolyte. Rate constant calculated using a diffusion coefficient of $10^{-5}$ $cm^2$ $s^{-1}$ for all species, applying the theory of Nicholson and Shain[15,16] over the scan rate range 100–800 mV $s^{-1}$, and assuming pseudo-first-order conditions apply for an ECE mechanism. Further details are available in Ref. 7. [b]Value taken from Ref. 7. [c]Too slow to detect. That is, a chemically reversible or close to reversible one-electron oxidation process over scan rate range 100–800 mV $s^{-1}$ in both 0.1 M $Bu_4NPF_6$ and 0.1 M $Bu_4NClO_4$.

$$\begin{array}{ccccc} (\text{steroid})\text{Cr}(\text{CO})_3 & \overset{-e}{\underset{+e}{\rightleftharpoons}} & [(\text{steroid})\text{Cr}(\text{CO})_3]^+ & \overset{-e^-}{\underset{+e^-}{\rightleftharpoons}} & [(\text{steroid})\text{Cr}(\text{CO})_3]^{2+} \\ & & \downarrow +\text{ClO}_4^-,\ k_1 & & \downarrow +\text{ClO}_4^-,\ k_2 \\ & & (\text{steroid})\text{Cr}(\text{CO})_3(\text{ClO}_4) & \overset{-e^-}{\underset{+e^-}{\rightleftharpoons}} & [(\text{steroid})\text{Cr}(\text{CO})_3(\text{ClO}_4)]^+ \\ & & & & \downarrow \text{fast},\ k_3 \\ & & & & \text{Cr}^{2+} + \text{steroid} + \text{ClO}_4^- \end{array} \quad [4]$$

Although the step involving perchlorate attack is written in Eqn [4] as an associative step involving formation of a 19-electron intermediate $(\text{steroid})\text{Cr}(\text{CO})_3(\text{ClO}_4)$, this intermediate has not been detected, nor has the postulated 18-electron complex $[(\text{steroid})\text{Cr}(\text{CO})_3(\text{ClO}_4)]^+$. Finally, a change in $n_{app}$ from 1 to 2 may occur by a wide range of mechanisms, of which Eqn [4] is only one possible pathway. Assuming the mechanism for the first oxidation process involves an ECE mechanism,[15,16] then the method of Nicholson and Shain[15,16] can be applied to calculate $k_1$ (via assumed pseudo-first order conditions) for the rate constant associated with the step

$$[(\text{steroid})\text{Cr}(\text{CO})_3]^+ + \text{ClO}_4^- \xrightarrow{k_1} (\text{steroid})\text{Cr}(\text{CO})_3(\text{ClO}_4) \quad [5]$$

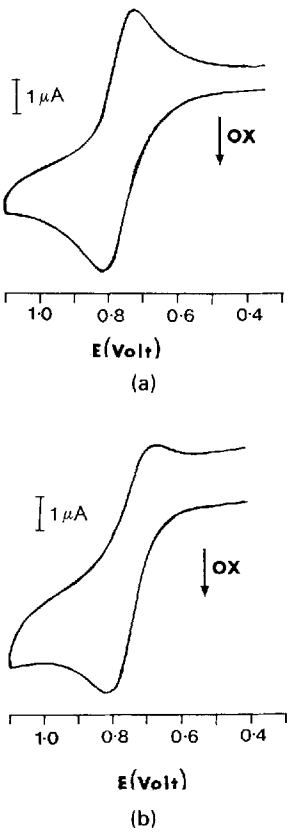



**Figure 2** Cyclic voltammograms (scan rate = 400 mV $s^{-1}$) at 20 °C for oxidation (first process) of $2 \times 10^{-4}$ M $\alpha$-($R_1R_2$ steroid)$Cr(CO)_3$ ($R_1 = R_2 = C_6H_5CH_2$—, compound **5α** in Scheme 1) at a platinum disc electrode in dichloromethane which contains (a) 0.1 M $Bu_4NPF_6$ and (b) 0.1 M $Bu_4NClO_4$ as the electrolyte.

Results obtained over the cyclic voltammetric scan rate of 100–800 mV $s^{-1}$ and with variable concentration of $Bu_4NClO_4$ give the values of $k_1$ contained in Table 2. It is evident that the rate of attack on the $\beta$-isomer is faster than that for the $\alpha$-isomer for all complexes studied. The original observation[7] of thermodynamic and kinetic dependence is the isomeric form for the particular case ($R_1R_2$ steroid)$Cr(CO)_3$ ($R_1 = C_6H_5CH_2$—, $R_2$ = H—; structure **3** in Scheme 1) would appear to be generally true for all the steroid hormone marker compounds. Interestingly, with lamb uterine receptor sites, the binding affinity to $\alpha$- and $\beta$-diastereomers of the tricarbonylchromium derivatives is also significantly dependent on the isomeric form,[10] so that the stereochemistry appears to play a significant role in a number of aspects of the chemical and biological reactions of this class of compound.

The perchlorate anion generally is inert or operates as a weak ligand, although in dichloromethane it may in some circumstances form quite stable complexes with some metal ions. However,

very few carbonyl perchlorate complexes are known.[17-19] Phosphines, on the other hand, form complexes with almost all carbonyl compounds and a range of (arene)$Cr(CO)_{(3-x)}P_x$ (P = phosphine, $x = 1, 2, 3$) or related species are known in their 18-electron configuration.[20-25] They are usually prepared by reaction of (arene)$M(CO)_3$ with the ligand under energetically vigorous conditions of refluxing, high temperatures and/or UV irradiation.

In order to understand further the nuances of the nucleophilic attack on the 17-electron complexes $[(arene)Cr(CO)_3]^+$, cyclic voltammetric experiments have been conducted in dichloromethane (0.1 M $Bu_4NPF_6$) on a range of (arene)$Cr(CO)_3$ complexes in the presence of triphenylphosphine and the results compared with those obtained in the presence of $ClO_4^-$ and other phosphines.[14] The system studied in most detail is the (benzene)$Cr(CO)_3$ system after addition of $P(C_6H_5)_3$, since pure and stable authentic samples of (benzene)$Cr(CO)_2P(C_6H_5)_3$ are readily prepared and used as a reference material. Phosphine derivatives of the steroid complexes are not as readily accessible and are far more reactive.

Figure 3 contains cyclic voltammograms for the first oxidation step of (benzene)$Cr(CO)_3$ in dichloromethane (0.1 M $Bu_4NPF_6$) in the absence and presence of small concentrations of $P(C_6H_5)_3$. In the absence of $P(C_6H_5)_3$, the first process is a chemically reversible one-electron process[4,14] and corresponds to the one-electron oxidation step

$$(benzene)Cr(CO)_3 \rightleftharpoons [(benzene)Cr(CO)_3]^+ + e^- \quad [6]$$

A second oxidation step at more positive potentials[14] is not discussed. On addition of $P(C_6H_5)_3$ concentrations up to approximately equimolar with (benzene)$Cr(CO)_3$, the first oxidation wave-height increases and, as on addition of perchlorate, approaches the height expected for a two-electron process ($n_{app} = 2$). The process also becomes chemically irreversible under these conditions. However, on addition of a considerable concentration excess of $P(C_6H_5)_3$, (Fig. 4) the wave-height decreases from $n_{app} = 2$ and approaches the value $n_{app} = 1$, expected for an irreversible, rather than reversible, one-electron oxidation process. Concomitantly with the change from $n_{app} = 2$ back to the original value of $n_{app} = 1$, but only in the presence of a considerable concentration excess of $P(C_6H_5)_3$ and the attainment of complete irreversibility, a new reversible one-electron process is observed on the reverse or reduction scan direction and on subsequent scans of cyclic voltgammograms (Fig. 5).

Figure 5 also includes a cyclic voltammogram for the first oxidation process of the compound (benzene)$Cr(CO)_2P(C_6H_5)_3$. For this compound, two one-electron oxidation processes are observed in $CH_2Cl_2$ (0.1 M $Bu_4NPF_6$), the first of which is described by Eqn [7] and is coincident with the new wave which appears in cyclic voltammograms for oxidation of (benzene)$Cr(CO)_3$ in the presence of a large concentration excess of $P(C_6H_5)_3$.

$$(benzene)Cr(CO)_2P(C_6H_5)_3 \rightleftharpoons [(benzene)Cr(CO)_2P(C_6H_5)_3]^+ + e^- \quad [7]$$

The above data imply that there are (at least) two distinctly different mechanisms for nucleophilic attack on 17-electron $[(arene)Cr(CO)_3]^+$ complexes.

In the pioneering work of Brown and co-workers[26,27] it was elegantly demonstrated that 17-electron metal carbonyl radicals are substitution-labile. In the majority of cases studied since this initial report, substitution reactions

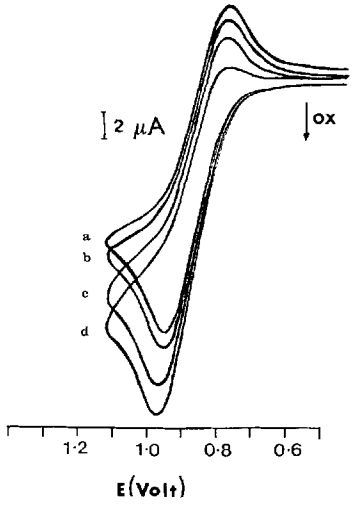



**Figure 3** Cyclic voltammogram (scan rate = 500 mV $s^{-1}$) at 20 °C for oxidation (first process) of $5 \times 10^{-4}$ M (benzene)$Cr(CO)_3$ (compound **1**, in Scheme 1) in dichloromethane (0.1 M $Bu_4NPF_6$) at a platinum disc electrode after addition of (a) 0, (b) $1 \times 10^{-4}$ M, (c) $2 \times 10^{-4}$ M, and (d) $3 \times 10^{-4}$ M triphenylphosphine.

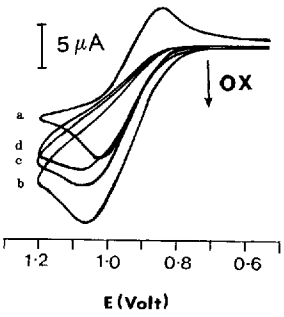



**Figure 4** As for Fig. 3, but after addition of (a) 0, (b) $5\times10^{-4}$ M, (c) $1\times10^{-3}$ M, and (d) $2\times10^{-3}$ M triphenylphosphine.

of 17-electron carbonyl complexes proceed via an associative pathway involving a 19-electron transition state or reactive intermediate.[28] Recently, some slower substitution reactions involving 17-electron carbonyl complexes have been reported[29] and the work of Basolo and colleagues[5] clearly demonstrates how both associative and dissociative pathways may arise. At present, no complete kinetic description is available to explain the complex concentration dependence of the cyclic voltammetry of (benzene)$Cr(CO)_3$ in the presence of $P(C_6H_5)_3$.

Electrochemical oxidation of (oestradiol)-$Cr(CO)_3$ in dichloromethane (0.1 M $Bu_4NPF_6$) occurs via two processs,[6] as is the case with most (arene)$Cr(CO)_3$ complexes.[4,14,30] The first process with either 0.1 M $Bu_4NClO_4$ or 0.1 M $Bu_4NPF_6$ as the electrolyte is

$$\text{(oestradiol)}Cr(CO)_3 \rightleftharpoons [\text{(oestradiol)}Cr(CO)_3]^+ + e^- \qquad [8]$$

and the second

$$\text{(oestradiol)}Cr(CO)_3^+ \rightarrow Cr^{2+} + \text{oestradiol} + 3CO\uparrow + e^- \qquad [9]$$

Figure 6(a) shows the influence of $P(C_6H_5)_3$ addition on the first process. The oxidation peak current is almost unaltered, any apparent increase

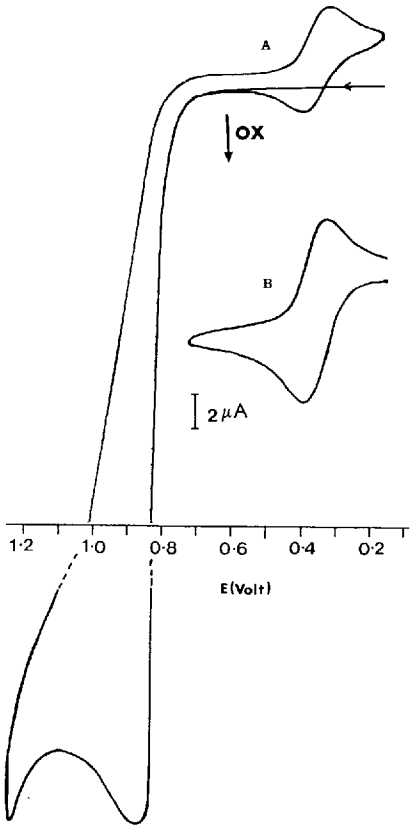
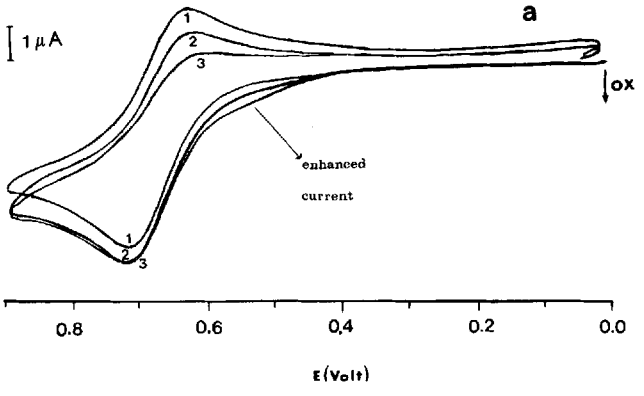
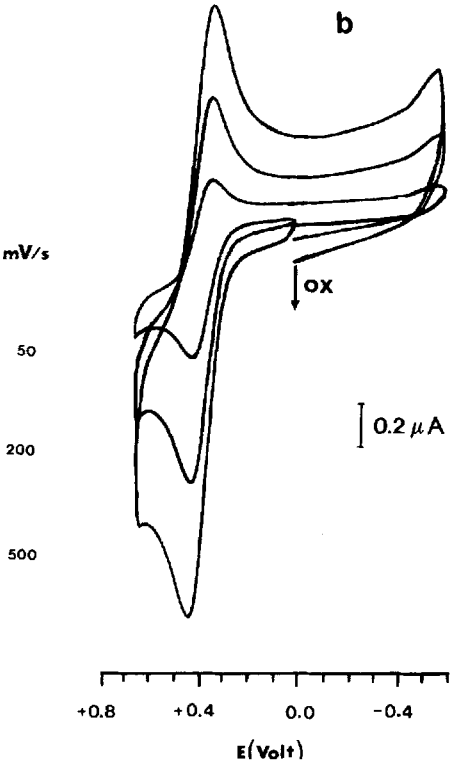


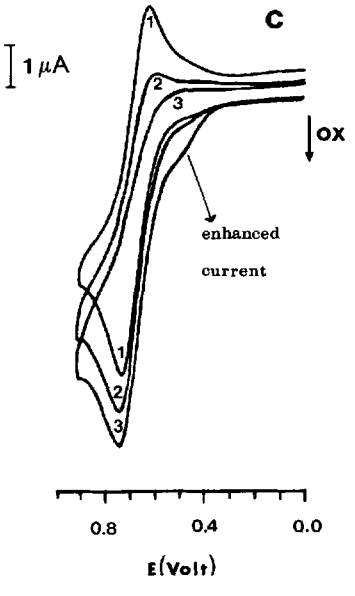

**Figure 5** Cyclic voltammogram (scan rate = 500 mV $s^{-1}$) at 20 °C for oxidation (first process) of (A) $1+10^{-3}$ M (benzene)$Cr(CO)_3$ (compound **1** in scheme 1) in the presence of $10^{-2}$ M triphenylphosphine and (B) $1\times10^{-3}$ M (benzene)$Cr(CO)_2P(C_6H_5)_3$ (compound **2** in Scheme 1) at a platinum disc electrode in dichloromethane (0.1 M $Bu_4NPF_6$).

being explained by a small enhancement of current which occurs at less positive potentials. There is a slight decrease in the reverse scan direction reduction current and a potential shift occurs towards less positive potentials. Finally, the second process, which is attributable to oxidation of $[\text{(oestradiol)}Cr(CO)_3]^+$ decreases in height on addition of $P(C_6H_5)_3$. The observations are consistent with the much greater lability of (oestradiol)$Cr(CO)_3$ than (benzene)$Cr(CO)_3$ and a mechanism of the kind given in Eqn [10].

$$\begin{array}{ccc} \text{(oestradiol)}Cr(CO)_3 + P(C_6H_5)_3 & \rightleftharpoons & \text{(oestradiol)}Cr(CO)_2P(C_6H_5)_3 + CO \\ +e^- \downarrow\uparrow -e^- & & +e^- \downarrow\uparrow -e^- \\ [\text{(oestradiol)}Cr(CO)_3]^+ + P(C_6H_5)_3 & \rightleftharpoons & [\text{(oestradiol)}Cr(CO)_2P(C_6H_5)_3]^+ + CO \end{array} \qquad [10]$$



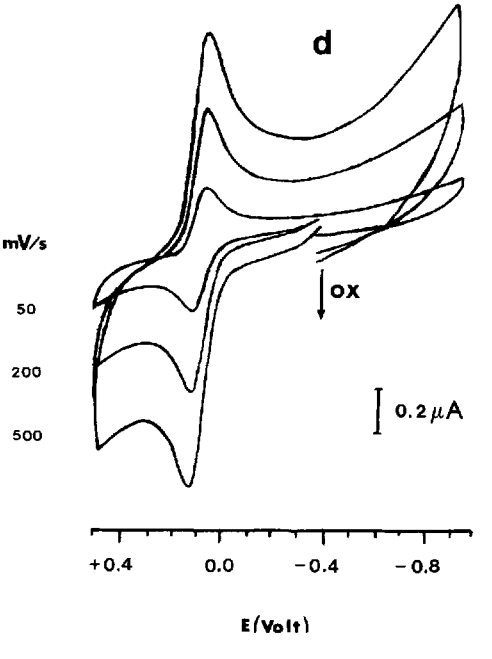




**Figure 6** Cyclic voltammograms (scan rate = 200 mV $s^{-1}$) at a platinum disc electrode in dichloromethane (0.1 M $Bu_4NClO_4$) at 20 °C for the first oxidation process of (a) $1 \times 10^{-3}$ M (oestradiol)$Cr(CO)_3$ (compound **7** in Scheme 1) in the presence of (1) 0, (2) $1 + 10^{-3}$ M, (3) $5 \times 10^{-3}$ M triphenylphosphine; (b) $2 \times 10^{-4}$ M (oestradiol)$Cr(CO)_2P(C_6H_5)_3$ (compound **8**); (c) $1 \times 10^{-3}$ M (oestradiol)$Cr(CO)_3$ in the presence of (1) 0, (2) $1 \times 10^{-3}$ M and (3) $1 \times 10^{-2}$ M dpm, (d) $2 \times 10^{-4}$ M (oestradiol)$Cr(CO)(\eta^2$-dpm).

with the cross-redox reaction given in Eqn [11] also contributing to the response.

$$[(\text{oestradiol})Cr(CO)_2P(C_6H_5)_3]^+ + (\text{oestradiol})Cr(CO)_3 \rightleftharpoons (\text{oestradiol})Cr(CO)_2P(C_6H_5)_3 + [(\text{oestradiol})Cr(CO)_3]^+ \quad [11]$$

This kind of mechanism and related nuances have been reviewed by Evans and O'Connell.[31]

Figure 6(b) verifies that the oxidation of $(\text{oestradiol})Cr(CO)_2P(C_6H_5)_3$ occurs at a less positive potential than that of $(\text{oestradiol})Cr(CO)_3$ and that the enhanced current is observed in Fig. 6(a) at the potential region expected if the redox couple $[(\text{oestradiol})Cr(CO)_2P(C_6H_5)_3]^+/(\text{oestradiol})Cr(CO)_2P(C_6H_5)_3$ is involved.

Addition of the potentially bidentate ligand, dpm, to $(\text{oestradiol})Cr(CO)_3$ produces cyclic voltammograms shown in Fig. 6(c). In this case, the reverse peak attributable to reduction of $[(\text{oestradiol})Cr(CO)_3]^+$ decreases and an enhanced current region is observed on the forward scan which has a counterpart on the reverse scan. Additionally the peak height for oxidation of $(\text{oestradiol})Cr(CO)_3$ increases and the second oxidation process decreases, indicating a change in $n_{app}$ from 1.0 to greater than 1.0. The new process is consistent with the formation of $(\text{oestradiol})Cr(CO)_2(\eta^1\text{-dpm})$. That is, the mechanism is a combination of Eqn [12], relevant cross-redox reactions and other reactions giving $n_{app} = 2$.

To date we have been unable to synthesize $(\text{oestradiol})Cr(CO)_2(\eta^1\text{-dpm})$ containing a monodentate dpm ligand. Rather, we have isolated what we believe to be $(\text{oestradiol})Cr(CO)(\eta^2\text{-dpm})$ which contains a bidentate ligand. However, since the reaction of 1,2-bis(diphenylphosphino)ethane (dpe) with $(\text{benzene})Cr(CO)_3$ gives a mixture of $(\text{benzene})Cr(CO)_2(\eta^1\text{-dpe})$ and the phosphine bridged complex[32] rather than $(\text{benzene})Cr(CO)(\eta^2\text{-dpe})$, some uncertainty exists in this assignment. Figure 6(d) shows that electrochemical oxidation of what is believed to be $(\text{oestradiol})Cr(CO)(\eta^2\text{-dpm})$ occurs at a considerably less positive potential than for $(\text{oestradiol})Cr(CO)_3$[6] or $(\text{oestradiol})Cr(CO)_2P(C_6H_5)_3$ or assumed oestradiol $Cr(CO)_2(\eta^1\text{-dpm})$. This shift in potential to less positive values is predicted on the basis of normal substituent effects observed when carbon monoxide is replaced by a phosphine ligand.

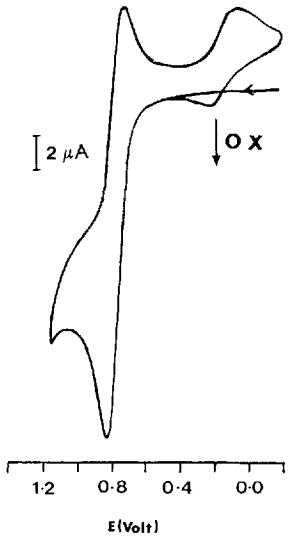



**Figure 7** Cyclic voltammmogram (scan rate = 400 mV $s^{-1}$) for the first oxidation process of $5 \times 10^{-4}$ M $\alpha$-($R_1R_2$ steroid)$Cr(CO)_3$ ($R_1$ = t-$BuMe_2Si$–, $R_2$ = H–, structure **6α** in Scheme 1) at a platinum disc electrode in dichloromethane (0.1 M $Bu_4NPF_6$) at 20 °C in the presence of $5 \times 10^{-4}$ M dpm.

Voltammograms for oxidation of $\alpha$- and $\beta$-diastereomers of ($R_1R_2$steroid)$Cr(CO)_3$ in the presence of $P(C_6H_5)_3$ and dpm show the formation of what can be assumed to be $[(R_1R_2\text{steroid})Cr(CO)_2L]^+$ ($L = P(C_6H_5)_3$) or $[(R_1R_2$ steroid)$Cr(CO)(\eta^2\text{-dpm})]^+$ or $[(R_1R_2$ steroid)$Cr(CO)_2(\eta'\text{-dpm})]^+$ (Fig. 7). Distinct differences in the rate of formation of the 17-electron cations are observed for the diastereomers. Apparently, for these complexes the

$$\begin{array}{ccc} (\text{oestradiol})Cr(CO)_3 + \text{dpm} & \rightleftharpoons & (\text{ocstradiol})Cr(CO)_2(\eta^1_1 - \text{dpm}) + CO \\ {\scriptstyle +e^-}\ 1\!\downarrow\ {\scriptstyle -e^-} & & {\scriptstyle +e^-}\ 1\!\downarrow\ {\scriptstyle -e} \\ \{(\text{oestradiol})Cr(CO)_3]^+ + \text{dpm} & \rightleftharpoons & [(\text{oestradiol})Cr(CO)_2(\eta^1 - \text{dpm})]^+ + CO \end{array} \quad [12]$$

$n_{app} = 1$ pathway corresponding to formation of substituted $[(R_1R_2$ steroid$)Cr(CO)_3]^+$ is more favoured over the pathway which leads to $n_{app} = 2$, relative to the situation which prevails when (benzene)$Cr(CO)_3$ is oxidized in the presence of the $P(C_6H_5)_3$ ligand.

On the longer time scale experiments using controlled potential electrolysis, a two-electron process (Eqn [13]) is observed for all complexes, irrespective of whether the applied potential is held at values more positive than either the first or second oxidation processes.

$$(\text{arene})Cr(CO)_{(3-x)}P_x \rightarrow Cr^{2+} + \text{arene} + xP + (3-x)CO + 2e^- \quad [13]$$

(arene = benzene, oestradiol, hormone steroid; P = phosphine.) Thus whilst $[(\text{arene})Cr(CO)_{(3-x)}P_x]^+$ and $[(\text{arene})Cr(CO)_3]^+$ species are stable on the voltammetric time scale, they are not on the synthetic time scale, which is consistent with the occurrence of a change in $n_{app} = 1$ to $n_{app} = 2$ as the time scale of the voltammetry increases. Clearly, the high reactivity of the 17-electron systems $[(\text{arene})Cr(CO)_3]^+$ makes them rather difficult to study and a great deal more work is required to understand the complete mechanistic details. Since 18-electron (arene)$Cr(CO)_3$ complexes can also undergo nucleophilic addition to the arene ring[33,34] and ring substitution by phosphites and phosphines[35] in addition to carbonyl replacement, these pathways may also be available with the 17-electron counterparts. It is therefore not surprising that electrocatalytic ligand substitution in 17-electron $[(\text{arene})Cr(CO)_3]^+$ cations is potentially a very complex subject where numerous reaction pathways may exist and be dependent on all three of the arene, the solvent and the nucleophile.[14,36]

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