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Transition metal complexes as electrochemical markers for steroids

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Abstract

The electrochemical behaviour of few $Co_2(CO)_6$(alkyne-estradiol) and $Mo_2Cp_2(CO)_4$(alkyne-estradiol) complexes is described. For purposes of comparison the electrochemical responses of free estradiols and of the model compound $Co_2(CO)_6(HC_2H)$ have also been investigated. From the cyclic voltammetric responses of the estradiol-organometallic derivatives, it is clear that the two constituent units, i.e. $Co_2(CO)_6''C{\equiv}C''$ and the estradiol frame, undergo relatively independent electrochemical processes. Significantly the labelling of steroids by means of bimetallic fragments (having an accessible LUMO) increases their electrochemical activity by adding a well-defined reduction process which makes the molecules cathodically detectable at stationary electrodes. This approach suffers from adsorption and filming problems, but these can be overcome by careful pretreatment of the solid electrodes. A method of evaluating the molecular mobility of such complexes from the ^{13}C-NMR line-width analysis is described.

Introduction

The complexation of a natural bioligand by an artificial organometallic graft may be of biochemical interest providing that some degree of recognition between this new bioorganometallic molecule and its natural accepting biomacromolecule (e.g. its specific receptor) can be maintained. This prerequisite established, the potential benefit of the introduction of an organometallic moiety can be investigated in several ways for therapeutic and diagnostic purpose [1]. For example, by taking advantage of the particular reactivity of organometallic complexes in order to identify the binding sites at molecular level or by using the metallic frame as a label

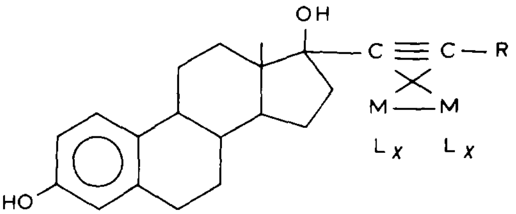

Fig. 1. Sketch of structures of metal-labelled estradiol complex; R=H, $(L)_xM = Co(CO)_3$, 1; R=CH_3, $(L)_xM = Co(CO)_3$, 2; R=H, $(L)_xM = MoCp(CO)_2$, 3.

in an analytical probe [2]. These different aspects can be exemplified in organometallic steroidal hormone series. It has been reported that the presence of a dicobalt fragment at the 17-α position of estradiol (complex 1 in Fig. 1) is compatible with a fair molecular recognition of estradiol receptors since the apparent relative binding affinity (R.B.A.) value is 12%. Complex 1 may be useful in estradiol receptor assay, which is an important assay in investigation of breast cancer. The detection is usually carried out by using FT-IR spectroscopy since such complex exhibits strong ν_{CO} bands in the range 2100–1850 cm^{-1}, a region in which absorption due to proteins is minimal [2].

An alternative method of detection of such metal-labelled steroidal hormones may be afforded by electrochemistry. Free steroids such as progestogens have been determined polarographically (i.e. in oral contraceptives) provided they have an easily electroreducible conjugated carbonyl group in the "A" ring [3]. On the other hand, most estrogens exhibit only ill-defined, multi-electron oxidation processes [4], probably involving their OH groups. In spite of some fouling problems, these oxidation waves have been used for the determination of growth-promoting hormones in meat by means of high-performance liquid-chromatography (HPLC) coupled with electrochemical detection (Ed) [5]. The labelling of estrogens with $M(CO)_3$ (M = Cr, Mo, W) fragments through the coordination of the aromatic ring modifies their electrochemical response simply by adding a couple of metal-centered oxidation processes [4]. No reduction processes could be observed in the usually accessible electrochemical range. While this tailoring with monometallic fragments has proved to be very useful for an electrochemical differentiation of the α- and β-diastereoisomers of 3-(benzyloxy)-17β-hydroxyestra-1,3,5(10)-trienetricarbonylchromium [6], it is obviously inadeguate in rendering these hormones cathodically detectable. In principle, bimetallic complexes can be easily reduced since there is an accessible LUMO (usually metal–metal antibonding in character) [7]. Thus, the coordination of bimetallic fragments [i.e. $Co_2(CO)_6$ or $Mo_2Cp_2(CO)_4$] to synthetic alkyne-estradiols should make these molecules electroreducible. This view is supported by a previous study on the electrochemical behaviour of $Co_2(CO)_6(RC_2R)$ (R = Ph, CF_3, t-Bu) derivatives in which well-defined reduction processes were found at potentials ranging from -0.5 to -1.1 V vs. Ag/AgCl [8]. That study was mainly focused on the electrochemistry at dropping mercury electrode (DME) or hanging mercury drop electrode (HMDE). We are interested at the electrochemistry at stationary solid electrodes such as Pt or mercury-plated Au electrodes, which are adaptable for continuous analyses in flowing systems and can constitute the electrochemical detector (ED) in HPLC technique, the only one sensitive enough for this kind of assay. Thus, in this paper we discuss the electrochemistry at stationary electrodes of few alkyne-estradiols complexes in view of their possible use as electrochemical markers in estradiol assay. A brief comparison of the electrochemical behaviour of the model complex $Co_2(CO)_6(HC_2H)$ and free estradiols is also reported.

Results and discussion

(17α-Ethynyl-1,3,5-estratriene-3,17β-diol)dicobalthexacarbonyl (**1**), (17α-propynyl-1,3,5-estratriene-3, 17β-diol)dicobalthexacarbonyl (**2**), (17α-ethynyl-1,3,5-estratriene-3,17β-diol)dimolybdenumtetracarbonyl, di-η^5-cyclopentadienyl) (**3**), hereafter Co_2-$(CO)_6$(EE) (**1**), $Co_2(CO)_6$(PE) (**2**), and $Mo_2Cp_2(CO)_4$(EE) (**3**), respectively, (Fig. 1), were synthesized as previously described [9]. We also prepared the simplest complex of the $Co_2(CO)_6$(alkyne) series [10], i.e. $Co_2(CO)_6(HC_2H)$ (**4**), for purposes of comparison.

Electrochemical behaviour of model compound

The cyclic voltammetric (CV) response of a CH_2Cl_2 solution of **4** recorded at a Pt electrode exhibits in the first cathodic scan (0 to -1.6 V) a reduction wave A at $E_p = -1.05$ V vs. SCE (Fig. 2). No associated reoxidation wave is found in the reverse scan even at scan rates as high as 5.0 V s^{-1}. Linear sweep voltammetric (LSV) analysis of wave A indicates a $[E_p - E_{p/2}]$ value of 60 mV, in accord with an electrochemically reversible one-electron reduction followed by a fast chemical reaction [11], as stated previously for other $Co_2(CO)_6$(alkyne) complexes [8]. The electrogenerated radical anion $Co_2(CO)_6(HCH)^{\cdot -}$ rapidly decomposes to a fragment

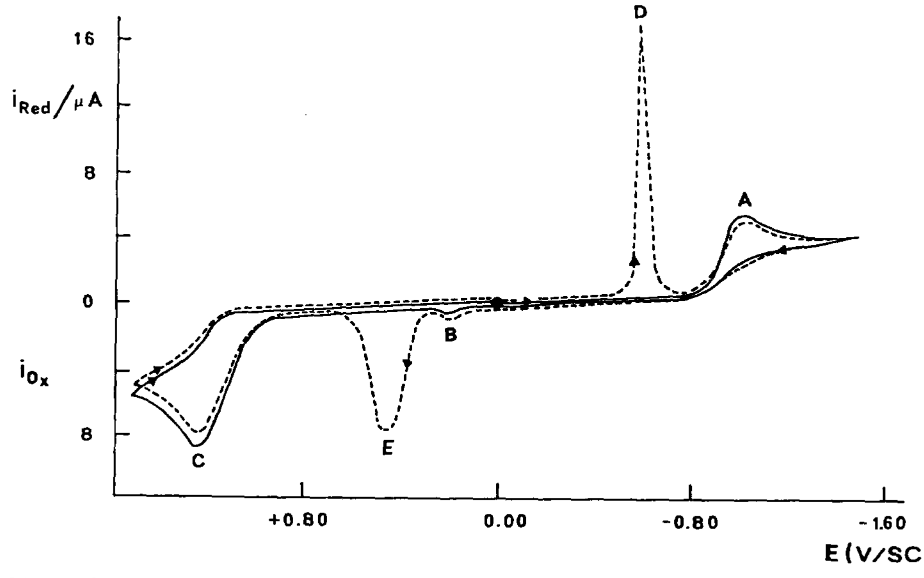

Fig. 2. CV response of a dichloromethane solution of $Co_2(CO)_6(HC_2H)$ (4) (0.8 mM) containing $[NBu_4][BF_4]$ (0.1 *M*) at a Pt electrode. Scan rate 200 mV s^{-1}, temperature 20 ° C (———) first cycle; (— — —) second cycle; (○) starting potential.

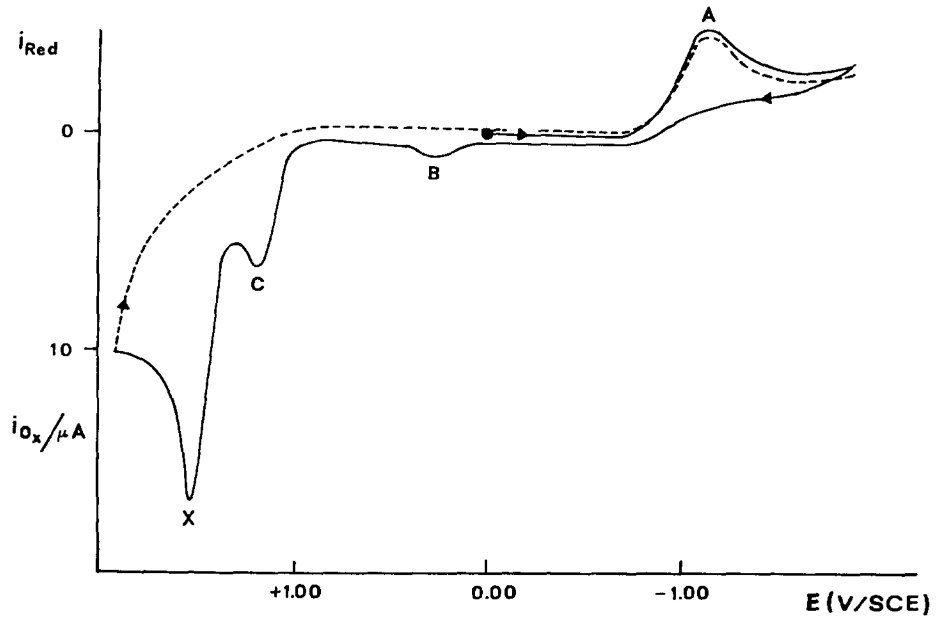

Fig. 3. CV response of an acetone solution of **4** (0.9 mM) containing $[NBu_4][BF_4]$ (0.1 *M*) at a Pt electrode. Scan rate 200 mV s^{-1}.

responsible for the oxidation wave (B) at $E_p = +0.2$ V. This peak is assigned to the oxidation of $Co(CO)_4^-$ to $Co(CO)_4$ and, accordingly, it increases in intensity when the solution is saturated with CO instead of N_2 [8]. When the anodic scan is continued to +1.6 V a broad peak (C), completely irreversible, is observed at $E_p = +1.3$ V. As a consequence of this oxidation, in the reverse cathodic scan a large spike (D) is observed at $E_p = -0.6$ V, typical of adsorbed or insoluble product attaching itself to the electrode surface. Finally, in the second anodic scan a new, broad peak (E) appears at ca. +0.5 V; which can be assigned to the anodic stripping in organic solvent of metallic cobalt deposited onto the Pt electrode [12] likely as consequence of process D. The peak system C–D–E is similar ot that reported for the oxidation of $Co_4(CO)_{12}$ [12], and $Co_3(CO)_9CX$ (X = halogen, alkyl, aryl) [13] complexes. Therefore, the D–E peak system, induced by the oxidation process C, is associated with the decomposition of **4** to binary carbonyl fragments.

Interestingly, when acetone is used as solvent in place of CH_2Cl_2 the CV response is somewhat different (Fig. 3). The reduction peak A ($E_p = -1.13$ V), and the oxidation peaks B ($E_p = +0.20$ V) and C ($E_p = +1.18$ V) are almost unchanged, apart from some potential shifts. A new, large oxidation wave (X) at ca. 1.5 V is found, while on the reverse scans peaks D–E are no longer detectable. It is probable that the binary carbonyl fragments, produced by process C, react with acetone giving rise to species, further oxidizable at peak X, which in the reverse scans are neither electroactive nor adsorbed at the electrode. The same electrochemical features can be observed even if acetone is added to the dichloromethane solution of **4** in a 1 : 20 v/v ratio.

As noted in the Introduction, most estrogens exhibit a multi-electron oxidation process. We recorded the CV responses of free estradiol, ethynylestradiol (EE) and

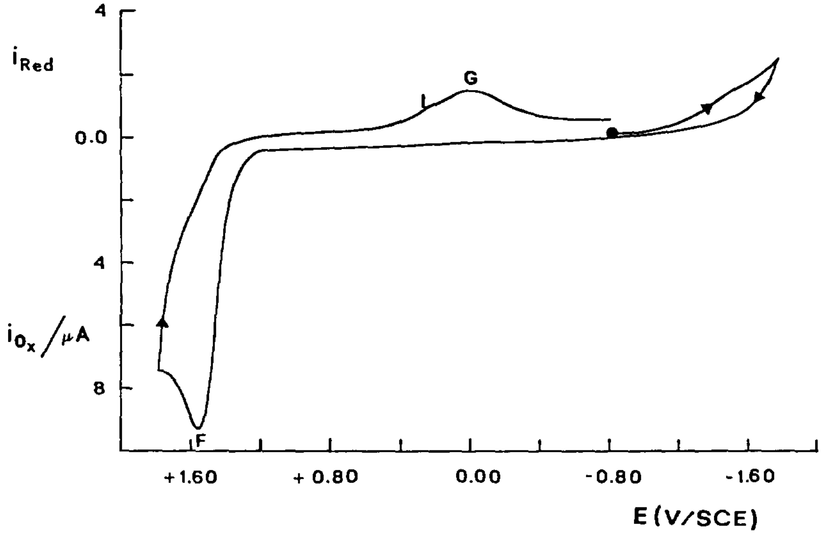

Fig. 4. CV response of free ethynylestradiol (EE) in the same experimental conditions reported for Fig. 2.

propynylestradiol (PE) in CH_2Cl_2 and found that they do indeed show an ill-defined oxidation peak (F) at +1.47, +1.55, and +1.57 V, respectively, near the region of solvent discharge (Fig. 4). In the reverse scan a broad peak (G) around 0.0 V is observed for each complex, consistent with product adsorption or stripping of insoluble material [4].

The overall CV response of $Co_2(CO)_6(EE)$ (1) in CH_2Cl_2 is reported in Fig. 5. From a comparison of voltammograms of the model complex $Co_2(CO)_6(HC_2H)$ (1) and free EE (see the relevant labelling), it is clear that in 1 the two constituent units,

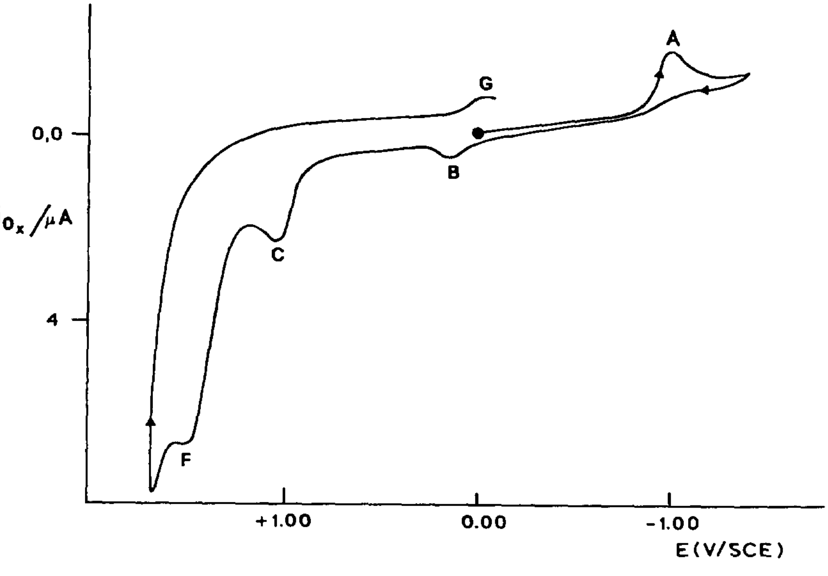

Fig. 5. CV response of $Co_2(CO)_6(EE)$ (1) in the same experimental conditions reported for Figs. 2 and 4.

i.e. the $Co_2(CO)_6$"C≡C" and the estradiol frame, undergo almost independent electrochemical processes.

Electrochemical behaviour of alkyne-estradiol complexes

Since only the wave A seems appropriate for quantitative determination of the above-mentioned metal-labelled steroids and the electrode suffers from rapid fouling when the overall electrochemical window is explored, in order to minimize electrode-surface effects we carried out the electrochemical analysis of **1**–**3** compounds in the cathodic range (0 ÷ − 1.5 V) in acetone by cyclic voltammetry (CV) or linear sweep voltammetry (LSV). LSV, in this context, refers to the forward (negative going) scan of the CV sweep. In the case of $Co_2(CO)_6$(EE) (**1**) the reduction wave A at $E_p = -1.07$ V (Hg electrode) is again chemically irreversible [8]; no reoxidation wave is found in the reverse scan even at scan rates as high as 5.0 V s^{-1} or at temperatures as low as −30 °C. Similar behaviour is found for $Co_2(CO)_6$(PE) (**2**) (Table 1). Since it has been reported that the lifetimes of the electrogenerated radical anions $Co_2(CO)_6(RC_2R)^{\cdot-}$ depend on the electron-withdrawing capability of R substituents [8,14], we conclude that estradiols behave as electron-donating groups causing instability on reduction (though their large bulk may play a role).

The isoelectronic $Mo_2Cp_2(CO)_4$(EE) (**3**) complex also shows a chemically irreversible one-electron reduction at a more negative potential ($E_p = -1.59$ V). This shift is likely due to the electron-donating properties of the cyclopentadienyl ligands [15]. The same trend has been reported for the parent compounds, namely $Co_2(CO)_8$ and $Mo_2Cp_2(CO)_6$ [16].

In Fig. 6 the LSV responses of an acetone solution of **1** at a Pt (a) and at a mercury-plated Au (b) electrode are reported. The reproducibility at the Pt electrode is fairly good, especially when such an electrode is preconditioned at +0.8 V for few seconds before running of a set of measurements, (probably the deposited Co is removed by anodic stripping.) On the other hand, the mercury-plated Au electrode suffers from severe fouling: running repetitive scans causes the peak to broaden and to decrease in intensity. (The formation of "Co–Hg" derivatives at the electrode surface may be responsible for this.)

On the other hand, the heterogeneous electron transfer rate for the reduction process A is higher at a Hg than at a Pt electrode as testified by the $|E_p - E_{p/2}|$ values for **1**: 70 mV at Hg (reasonably close the Nernstian value of 59 mV), and 95

Table 1

Electrochemical parameters for the reduction process A (0/1−) of complexes **1**–**4** in acetone solutions containing $[NBu_4][BF_4]$ (0.1 *M*) supporting electrolyte at a Pt or a mercury-plated gold electrode

No.	Compound	Pt		Hg		D^b (10^{-5} cm^2 s^{-1})
		E_p ^{a} (V)	$E_p - E_{p/2}$ (mV)	E_p ^{a} (V)	$E_p - E_{p/2}$ (mV)	
1	$Co_2(CO)_6$(EE)	−1.10	95	−1.07	70	0.7
2	$Co_2(CO)_6$(PE)	−1.20	100	−1.07	75	0.7
3	$Mo_2Cp_2(CO)_4$(EE)	−1.62	105	−1.59	80	0.6
4	$Co_2(CO)_6(HC_2H)$	−1.05	60	−1.05	60	1.8

[a] Evaluated by LSV at 200 mV s^{-1}, [b] At 10 °C.

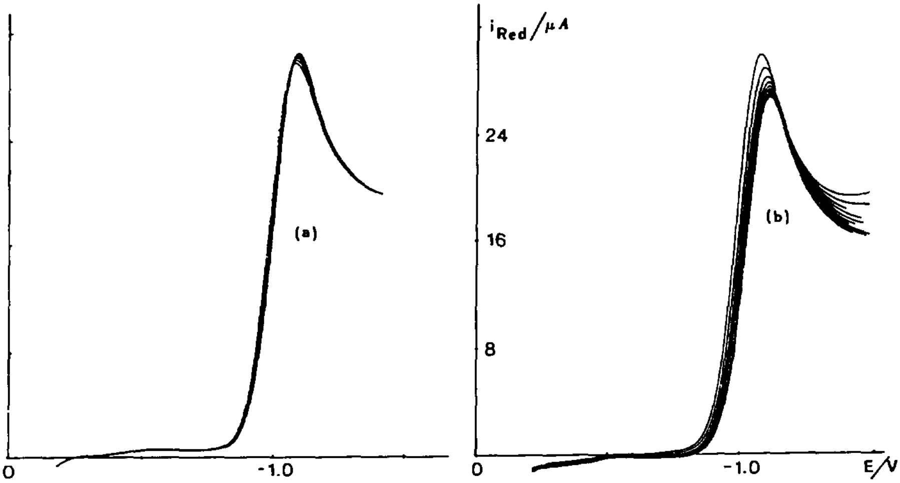

Fig. 6. Cathodic LSV response of an acetone solution of **1** (5 mM) containing $[NBu_4][BF_4]$ (0.1 *M*) at a Pt electrode (a) or at a mercury-plated gold electrode (b). Scan rate 200 mV s^{-1}.

mV at Pt. Similarly larger values are found for other solid electrodes (e.g. glassy carbon, 100 mV). These features confirm once again that Hg is not an "innocent" electrode but forms surface compounds [17].

Evaluation of diffusion coefficients and molecular mobility

It is interesting to evaluate the reduction of the diffusion coefficient (D) on passing from the model complex **4** to the larger alkyne-estradiol ones, since the LSV response depends on the square root of D [11].

For the calculation of the D values reported in Table 1, solutions of complexes **1**–**4** and ferrocene (both 5 mM) are prepared and their CV responses recorded at Pt electrode and at 10 °C (Fig. 7).

According to the Randles–Sevcik equation [11]:

$$i_p = kn^{3/2}AD^{1/2}C_0v^{1/2}$$

and to coulometry experiments [the reduction process A consumes one-electron per molecule ($n = 1$)], the ratio of the peak currents of the oxidation (0/1 +) of $FeCp_2$ and of the reduction A (0/1 −) of each complex under investigation gives the ratio between the square root of their diffusion coefficients. The D value of ferrocene in acetone has been extrapolated from literature data by application of Walden's rule [18].

$$\frac{i_{pFeCp2}}{i_pA} \approx \sqrt{\frac{D_{FeCp2}}{D_{complexes\ 1-4}}}$$

The reduction process A is assumed to show Nernstian behaviour (Actually at a Pt electrode the reduction step A is quasi-reversible for **1**–**3** complexes).

On passing from $Co_2(CO)_6(HC_2H)$ to complexes **1**–**3**, the D values roughly decrease by three times in according with the increase of the molecular moment of inertia.

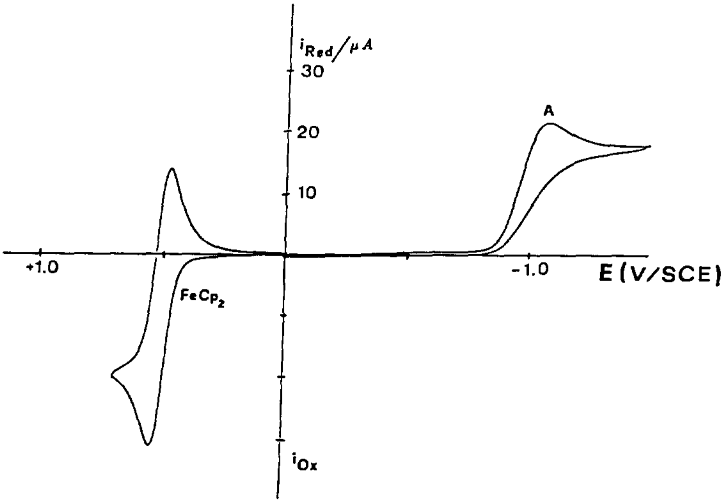

Fig. 7. CV response of an acetone solution of 1 and $FeCp_2$ (both 5 mM) containing $[NBu_4][BF_4]$ (0.1 *M*) at a Pt electrode. Scan rate 100 mV s^{-1}, 10 °C.

In order to make an alternative evaluation of the molecular mobility of such complexes, we recorded the ^{13}C-NMR spectra of acetone-d_6 solutions of $Co_2(CO)_6(EE)$ (**1**) and $Co_2(CO)_6(HC_2H)$ (**4**) at 10 °C. Both spectra exhibit an averaged resonance of the CO groups at 200.7 (**1**) and 200.2 (**4**) ppm, with a with at half-height ($W_{1/2}$) of 24 and 100 Hz, respectively (Fig. 8).

The carbonyl ^{13}C-NMR line-width values can be rationalized in terms of the scalar coupling relaxation between ^{13}C and ^{59}Co, the latter nucleus having a very efficient relaxation mechanism of its own, i.e. the quadrupolar one (scalar relaxation of second kind [19]).

The line-width effect at ^{13}C can be formulated as:

$$W_{1/2} = \frac{1}{\pi T_{2(c)}} = \frac{4\pi J^2 I(I+1)}{3}\left[T_{1(Co)} + \frac{T_{2(Co)}}{1 + (\omega_c - \omega_{Co})T^2_{2(Co)}}\right]$$

where the subscripts refer to ^{13}C and ^{59}Co nuclei, J is the ^{13}C–^{59}Co scalar coupling, I is the ^{59}Co nuclear spin quantum number (7/2), $(\omega_c - \omega_{Co})$ is the difference between the resonance frequencies of the two nuclei. Since this value is very large ($\approx$ MHz) compared with the ^{59}Co relaxation rates ($\approx$ kHz) [20], the previous equation can be formulated as:

$$1/\pi T_{2(C)} = 21\pi J^2 T_{1(Co)}$$

In the extreme narrowing limit, the ^{59}Co relaxation times T_1 and T_2 entirely depend on the quadrupolar relaxation mechanism, therefore:

$$\frac{1}{T_{1(Co)}} = \frac{1}{T_{2(Co)}} = \frac{2}{49}\pi^2\left(1 + \frac{\eta^2}{3}\right)\left(\frac{e^2qQ}{h}\right)^2 \tau_c$$

where η is the asymmetry parameter, (e^2qQ/h) is the electrical quadrupolar coupling constant (QCC) and τ_c is the rotational correlation time (roughly the mean time for the molecule to rotate through an angle of 1 radian). Providing η and QCC

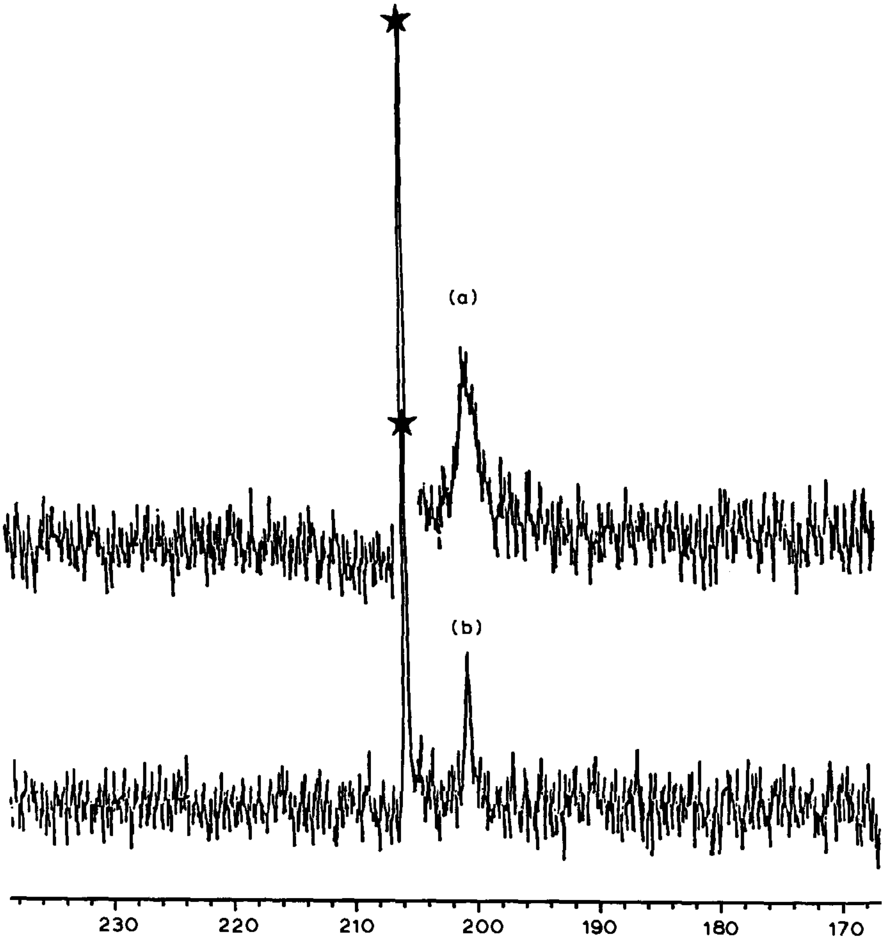

Fig. 8. ^{13}C-NMR spectra of $Co_2(CO)_6(HC_2H)$ (4) (a) and $Co_2(CO)_6(EE)$ (1) (b) in acetone-d_6 at 67.9 MHz and at 10 °C. Peak* denotes the carbonyl resonance of acetone solvent.

are very similar for complexes 1 and 4, the ratio of their $W_{1/2}$ values roughly corresponds to the inverse of the ratio of the relative correlation times:

$$\frac{W_{1/2}(1)}{W_{1/2}(4)} = \frac{24}{100} \approx \frac{1/T_{2(C)}(1)}{1/T_{2(C)}(4)} = \frac{T_{1(Co)}(1)}{T_{1(Co)}(4)} = \frac{1/\tau_c(1)}{1/\tau_c(4)} = \frac{\tau_c(4)}{\tau_c(1)}$$

The reduction of the molecular tumbling by a factor of ca. 4 on passing from $Co_2(CO)_6(HC_2H)$ to $Co_2(CO)_6(EE)$ compares fairly well with the reduction of the linear diffusion by a factor of ca. 3 found under the same conditions.

Concluding remarks

The diffusion-controlled behaviour of wave A should involve a linear relationship between the peak current (i_p) and the concentration of metal-labelled steroids. This has been verified in the concentration range $1 \times 10^{-2} - 1 \times 10^{-5}$ *M* at a Pt electrode of 2 mm i.d. The straight line has a slope of 11 μA mM^{-1} and a correlation coefficient of 0.93. The estimated standard deviation (from a set of 5 measurements) is 10%.

In conclusion, the electrochemical detection at a stationary Pt electrode and in acetone of metal-labelled steroids, although less sensitive than the FT-IR detection, could be useful especially when associated with separation of different compounds by HPLC.

Labelling of steroids with Ru_3 and Os_3 clusters, which form very stable bio-organometallic compounds, is in progress.

Experimental section

The $Co_2(CO)_6$(alkyne) and $Mo_2Cp_2(CO)_4$(EE) derivatives were synthesized by published procedures [9,10]. Their purities were checked by IR and ^{1}H-NMR spectroscopy. Voltammetric measurements were performed with two sets of instruments: a PAR 273 analyser connected to an interfaced IBM microcomputer, and an AMEL 553 potentiostat modulated by an AMEL 567 function generator and connected to an X–Y recorder.

A standard three-electrode cell was designed to allow the tip of the reference electrode (SCE) to approach closely the working electrode. Positive feedback *iR* compensation was applied routinely. All measurements were carried out under N_2 in anhydrous deoxygenated solvents; solutions were 1×10^{-3} *M* with respect to the compounds under study and 1×10^{-1} *M* with respect to the supporting electrolyte, $[Bu_4N]BF_4$. The temperature of the solution was kept constant within ±1°C, by circulation of thermostatted water–ethanol mixture through the double wall of the cell. The working electrode was a Pt disk-electrode embedded in a Teflon seal or a similar gold disk-electrode amalgamated by dipping in mercury. The Pt disk-electrode was soaking in nitric acid, rinsed with distilled water and dried with a paper-tissue. Before each set of measurement, it was preconditioned at +0.8 V.

Potential data (vs. SCE) were checked against the ferrocene (0/1 +) couple; under the experimental conditions used the ferrocene/ferrocenium couple is located at +0.49 in acetone, and at +0.54 V in dichloromethane [21].

^{13}C-NMR spectra were recorded on a JEOL GX270/89 spectrometer at 67.9 MHz, chemical shifts are reported in ppm downfield positive from $SiMe_4$. Traces of paramagnetic decomposition products were removed by passing the acetone-d_6 solutions through a small cellulose column in N_2 flux immediately before the NMR spectra were recorded

Acknowledgments

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