Platinum(II) Complexes of Functionalized Malonato Ligands: Unequivocal Synthesis, Interaction with a Tetradeoxyribonucleotide and Deoxyribonucleic Acid

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The unequivocal syntheses of four cis-$[PtL_2\{(O_2C)_2CH(CH_2)_nCO_2H\}]$ complexes $[L_2 = (NH_3)_2$ or $trans$-cyclohexane-1,2-diamine, $n = 1$ or 4] has been achieved, avoiding any interaction between the pendant carboxyl group and the platinum. The complexes have been characterized by elemental analysis, ^{13}C NMR and FAB mass spectroscopy. Their interaction with a tetradeoxyribonucleotide d(T-G-G-T) (G = guanosine, T = ribosylthymine) and DNA (*in vitro*) has been investigated to show that they form adducts of the type $[PtL_2\{(GpG)$-$N^7,N^{7'}\}]$ as do the known therapeutically active platinum complexes. However the presence of the free carboxyl function increases significantly the reactivity with respect to that of the related non-functionalized malonato complexes $[PtL_2\{H_2C(CO_2)_2\}]$.

cis-Diamminedichloroplatinum(II) is one of the most effective oncolytic agents against cancers of the testes, ovaries, bladder, head and neck.[1–4] However there are drawbacks that limit its usefulness: it displays severe toxicities, is only active against a narrow range of tumours and results in the development of resistance in the tumour cells. Many attempts have been made to prepare new platinum complexes with improved therapeutic properties but only a few have been successful.[5,6] The second-generation platinum drugs resemble cis-$[Pt(NH_3)_2Cl_2]$ except that the chloride ligands are replaced by 1,1- or 1,2-dicarboxyl-ates.[7–9] They are well represented by cis-$[Pt(NH_3)_2(cbdca)]$ (cbdca = cyclobutane-1,1-dicarboxylate) which displays a reduced nephrotoxicity but still suffers from a narrow range of activity.[10] Thus the search for new complexes still continues. In this context, a possible strategy would be to introduce in the chelating dicarboxylato framework an additional function which can modify some relevant properties of the complex or even give rise to new complexes by reacting with suitable substrates. Complexes of this type have been described; they involve as chelating ligands benzene-1,2,3-tricarboxylic acid, aminomalonic acid and iminoacetic acid.[11–16]

The present paper is devoted to four platinum complexes formed by malonic acids containing, in addition to the two chelating carboxylates, an uncomplexed carboxyl group. They may be represented by the general formula cis-$[PtL_2\{(O_2C)_2CH(CH_2)_nCO_2H\}]$ [L = NH_3, $n = 1$ **1** or 4 **2**; $L_2 = trans$-cyclohexane-1,2-diamine (dach), $n = 1$ **3** or 4 **4**]. The first objective was to design an unequivocal preparation mode. Complexes of this type have been mentioned in one patent,[17] but, in our hands, the synthesis reported for complex **4** led to a mixture from which we did not succeed in isolating a pure sample. An additional objective was to decipher the influence exerted by the pendant carboxylic function upon the reactivity towards biological targets. Most studies devoted to unsubstituted or alkyl-substituted malonato complexes concern the contrast observed between the rapid inhibition of DNA synthesis and the high *in vivo* cytotoxicity of these complexes and their relatively unreactive nature *in vitro*.[10,18–22]
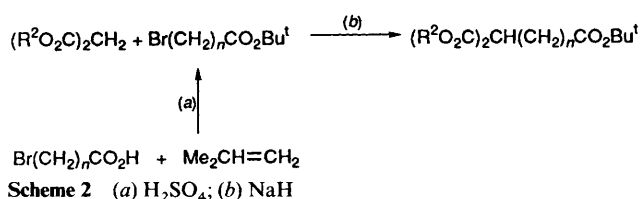
Results and Discussion

Synthesis.—Malonato complexes, $[PtL_2\{R(CO_2)_2\}]$ where

Scheme 1　(*a*) $[(O_2C)_2CH(CH_2)_nCO_2R^1]^{2-}$; (*b*) CF_3CO_2H, R^1 = Bu^t; (*c*) L^2
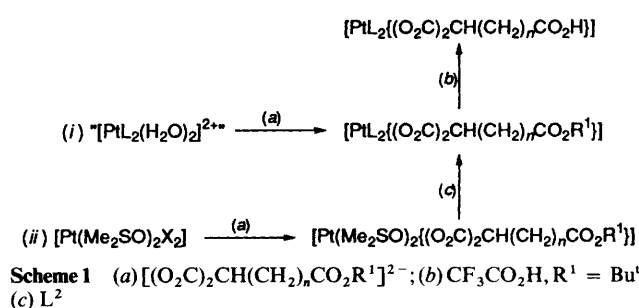
L = NH_3 or a primary amine and L_2 occasionally a chelating diamine while $R(CO_2)_2$ represents the dianionic form of a malonic acid, are generally prepared[23–25] by (*i*) reaction of a dihalogeno complex cis-$[PtL_2X_2]$ with silver nitrate (or sulfate) and subsequent reaction of the resulting diaqua species with the sodium (or barium) salt of the appropriate malonic acid, or (*ii*) reaction of the dimethyl sulfoxide complex $[Pt(Me_2SO)_2\{R(CO_2)_2\}]$ with an amine L (or L_2).

In order to apply these reactions (Scheme 1) to the synthesis of functionalized malonato complexes it is obviously of prime importance to prevent any interaction of the pendant function with the platinum. This is simply obtained by esterifying this function. However the protecting group R^1, in the ester form of the ligand ($^-O_2C)_2CH(CH_2)_nCO_2R^1$, has to be chosen so that it is not affected by complexation but is easily removable in the last step of the synthesis without disruption or modification of the complex structure. A further requirement results from the fact that the functionalized malonato ligands are obtained as triesters $(R^2O_2C)_2CH(CH_2)_nCO_2R^1$ which may be converted into the related dianions $(^-O_2C)_2CH(CH_2)_nCO_2R^1$ prior to complexation. A preliminary study showed that the choice of R^1 is extremely limited since the majority of the known deprotect-ing agents alter the nature of the complex. In practice the best R^1 group is Bu^t. This group is easily removed by trifluoroacetic acid which, under the conditions described in the Experimental section, does not modify the metal environment. Since *tert*-butyl esters are not affected by basic and/or reductive media, the choice R^1 = Bu^t dictates the choice of methyl or benzyl group for R^2. Indeed methyl and benzyl esters are cleaved by

$(R^2O_2C)_2CH_2 + Br(CH_2)_nCO_2Bu^t \xrightarrow{(b)} (R^2O_2C)_2CH(CH_2)_nCO_2Bu^t$

$(a)\uparrow$

$Br(CH_2)_nCO_2H + Me_2CH{=}CH_2$

Scheme 2 (a) H_2SO_4; (b) NaH

Table 1 Elemental analyses for $cis\text{-}[PtL_2\{(O_2C)_2CH(CH_2)_nCO_2H\}]$

			Analysis (%)*			
Complex	L_2	n	C	H	N	Pt
1	$(NH_3)_2$	1	15.3 (15.4)	2.8 (2.6)	7.0 (7.2)	49.7 (50.1)
2	$(NH_3)_2$	4	22.6 (22.4)	3.9 (3.7)	6.2 (6.5)	44.8 (45.2)
3	dach	1	27.6 (27.9)	4.9 (4.7)	5.7 (5.9)	—
4	dach	4	32.9 (32.6)	5.2 (5.5)	5.2 (5.4)	38.2 (37.8)

* Calculated values in parentheses.

Table 2 Carbon-13 NMR chemical shifts for $cis\text{-}[PtL_2\{(O_2C)_2\text{-}CH(CH_2)_nCO_2H\}]$

	dach		Malonate		
Complex	CH	CH_2	CO_2	CH	CH_2
1	—	—	185.1, 181.4	56.2	38.3
2	—	—	186.1, 181.1	60.3	37.6, 33.0
					28.9, 26.7
3	65.2	34.1, 26.8	186.1, 182.0	57.1	37.9
4	65.0	34.3, 26.4	186.4, 181.5	60.6	37.5, 33.1
					29.3, 27.8

hydrolysis and hydrogenation respectively. In practice we used the triesters $(MeO_2C)_2CH(CH_2)_nCO_2Bu^t$. By reaction with NaOH or $Ba(OH)_2$ they are easily converted into the sodium or barium salt used in (*i*); the silver salt involved in (*ii*) is obtained by treating the sodium salt overnight with silver nitrate. The synthesis of the triesters $(R^2O_2C)_2CH(CH_2)_nCO_2Bu^t$ is outlined in Scheme 2.

The purity of the final complexes 1–4 was checked by analysis (C, H, N, Pt) (Table 1). Their characterization was achieved by ^{13}C NMR spectroscopy (Table 2) and, in the case of complex 4, by fast atom bombardment (FAB) mass spectroscopy. The main feature of the latter spectrum is a four-peak pattern ($m/z = 511$, 512, 513 and 515) which is characteristic of the molecular ion $[4 + H]^+$. Peaks corresponding to the loss of one and two carboxyl groups are observed at $m/z = 467$ and 421, respectively.

The solubility of complexes 1–4 in water is rather good: 10 mg cm^{-3} for 1 and 2, 4 mg cm^{-3} for 3 and 4. As expected the sodium salts display a higher solubility, in excess of 20 mg cm^{-3} for the four complexes. The solubility of $[Pt(dach)\{H_2C(CO_2)_2\}]$ has been reported to be 0.23 mg m^{-3}.[26] Detailed kinetic studies of the displacement of the functionalized malonato ligands from their complexes have yet not been performed but we have verified (^{1}H and ^{13}C NMR spectroscopy) that aqueous solutions of the complexes are stable for at least 48 h in the absence of any nucleophile.

Interactions with a Tetradeoxyribonucleotide d(T-G-G-T) *and* DNA.—Strong evidence exists indicating that DNA is the primary target for $cis\text{-}[Pt(NH_3)_2Cl_2]$ and closely related platinum drugs in biological systems.[7,27,28] Among the purine and pyrimidine bases, platinum seems to favour guanine as a reactant so that the main type of adduct (55–65%) formed involves an intrastrand cross-link (GpG)-$N^7,N^{7\prime}$ between the N^7 position of two adjacent guanines of the guanosine (G) residues. The second most abundant adduct (25–35%) is an (ApG)-$N^7,N^{7\prime}$ intrastrand cross-link (A = adenosine).[7,27–29]

Among the various tools which have been used to assess the interactions between platinum complexes and DNA fragments, multinuclear NMR spectroscopy proved to be powerful.[7,30] The ^{31}P NMR studies of DNA and a variety of oligonucleotides treated with $cis\text{-}[PtL_2Cl_2]$ complexes have pointed in each case to the appearance of a signal downfield of the normal DNA ^{31}P signal range.[7,30–35] Interestingly the therapeutically inactive $trans\text{-}[Pt(NH_3)_2Cl_2]$ complex does not produce any abnormal ^{31}P signal. In some instances it has been definitely established that the platinum responsible for the shifted ^{31}P signal is in the platinum intrastrand (GpG) cross-link.[7,30,36]

We considered the systems resulting from reaction of complexes 1, 2 and 4 with d(T-G-G-T) (T = ribosylthymine). This oligonucleotide was chosen because its behaviour in the presence of platinum complexes is well documented.[30,35,37] Also examined were the systems formed by the tetranucleotide and $cis\text{-}[Pt(NH_3)_2Cl_2]$, which have been studied,[37] and $[Pt(NH_3)_2\{H_2C(CO_2)_2\}]$. In each case, the ^{31}P NMR spectra of freshly prepared mixtures were identical with that of d(T-G-G-T) alone: a cluster of signals from δ 1.6 to 1.8 was observed. After a delay (t_i) which varied from a few hours to several days, at least one downfield signal became perceptible. Judging from the intensity of this signal, the reaction was complete within 12 h for $cis\text{-}[Pt(NH_3)_2Cl_2]$ and complex 4, within 24 h for 1 and 2 and within 7 d for $cis\text{-}[Pt(NH_3)_2\{H_2C(CO_2)_2\}]$. Similarly, new signals were observed in the ^{1}H NMR spectrum of the non-exchangeable base protons. The relevant data are in Table 3. In the case of $cis\text{-}[Pt(NH_3)_2Cl_2]$–d(T-G-G-T) the ^{31}P and [1]H δ values are in agreement with those indicated by Marzilli and co-workers[35,37] and attributed beyond doubt to the adduct $[Pt(NH_3)_2\{d(T\text{-}G\text{-}G\text{-}T)\text{-}N^7,N^{7\prime}\}]$. Since almost identical $\delta(^{31}P)$ and $\delta(^1H)$ values are observed for the new signals appearing in the four systems in which the platinum is bonded to two NH_3 molecules, we can reasonably conclude that, in each of these systems, the adduct is formed by bonding of the $Pt(NH_3)_2$ entity to the N^7 position of the two guanines. Similar effects appear in the ^{31}P and ^{1}H NMR spectra of the fifth system in accordance with the formation of a $[Pt(dach)\{d(T\text{-}G\text{-}G\text{-}T)\text{-}N^7,N^{7\prime}\}]$ adduct. Two points deserve further comment. First the shifts are slightly but significantly smaller than those observed for $cis\text{-}[Pt(NH_3)_2\{d(T\text{-}G\text{-}G\text{-}T)\}]$. This is not unexpected since it has been shown that the nature of the amine group influences the ^{31}P and ^{1}H shifts *via* modification of hydrogen bonding between the 5′-phosphate group and these amines.[35] Then it appears that several of the signals attributable to $[Pt(dach)\{d(T\text{-}G\text{-}G\text{-}T)\}]$ are split. This is clearly observed in the ^{31}P NMR spectrum (δ 2.86 and 2.80) and in the ^{1}H spectrum, for 5′-G, H^8 (δ 8.06 and 8.03) and for 3′-T, H^6 (δ 7.57 and 7.54). This probably arises from the use as starting material of dach which actually is *rac*-(RR),(SS)-dach. Indeed $[Pt\{(RR)\text{-}dach\}X_2]$ and $[Pt\{(SS)\text{-}dach\}X_2]$ are optical isomers which cannot be discriminated by NMR spectroscopy but, due to the intrinsic chirality of d(T-G-G-T), the adducts $[Pt\{(RR)\text{-}dach\}\{d(T\text{-}G\text{-}G\text{-}T)\}]$ and $[Pt\{(SS)\text{-}dach\}\{d(T\text{-}G\text{-}G\text{-}T)\}]$ are diastereoisomers which are expected to give different NMR spectra. It has been recently reported[38] that, in the adducts $[Pt\{(RR)\text{-}$ or $[Pt\{(SS)\text{-}dach\}\text{-}\{d(GpG)\}]$, the 5′-G, H^8 protons experience a difference ($\Delta\delta \approx 0.1$ ppm) between the λ conformation [for $Pt\{(RR)\text{-}dach\}$] and the δ conformation [for $Pt\{(SS)\text{-}dach\}$] of the five-membered chelate ring formed by dach and the platinum. For the 3′-G, H^8 protons the difference is very small ($\Delta\delta \approx 0.01$ ppm).

At this stage of the discussion, the proper conclusion is that the functionalized malonato complexes 1–4 react with d(T-G-G-T) as do the previously investigated platinum drugs to form adducts of the general type $[PtL_2\{d(T\text{-}G\text{-}G\text{-}T)\text{-}N^7,N^{7\prime}\}]$. The period of time ($t_i$ in Table 3) necessary for the adduct ^{31}P NMR signal to become observable can be viewed as a (very crude) estimation of the rate of chelation of the PtL_2 moiety to the (GpG) fragment which is considerably increased by functionalizing the malonato ligand. This conclusion is supported by the observation that the reaction of d(T-G-G-T)

Table 3 Relevant ^{31}P and ^{1}H NMR data for d(T-G-G-T) and its platinum adducts

Complex	t_i*	$\delta(^{31}P)$	$\delta(^1H)$			
			3'-G,H^8	5'-G,H^8	3'-T,H^6	5'-T,H^6
Unreacted d(T-G-G-T)	—	1.6/1.8	7.81	7.91	7.57	7.35
cis-[Pt(NH$_3$)$_2$Cl$_2$]	5 ± 1	2.82	8.96	8.21	7.58	7.50
cis-[Pt(NH$_3$)$_2${H$_2$C(CO$_2$)$_2$}]	> 50	2.82	8.97	8.21	7.59	7.51
1	10 ± 1	2.82	8.97	8.20	7.58	7.51
2	10 ± 1	2.82	8.96	8.21	7.59	7.51
4	6 ± 1	2.86	8.90	8.06	7.57	7.47
		2.80		8.03		7.54

* See text.

Table 4 Half-life ($t_{\frac{1}{2}}$) of the kinetics of the *in vitro* DNA–Pt interaction

Complex	$t_{\frac{1}{2}}$/h
cis-[Pt(NH$_3$)$_2$Cl$_2$]	4.0
cis-[Pt(NH$_3$)$_2${H$_2$C(CO$_2$)$_2$}]*	24.0
2	13.0
3	8.0
4	10.5

* A value of 110 h has been reported for [Pt(dach){H$_2$C(CO$_2$)$_2$}].[41]

with cis-[Pt(NH$_3$)$_2$Cl$_2$] and **4** is complete within 12 h while 7 d are required in the case of cis-[Pt(NH$_3$)$_2${H$_2$C(CO$_2$)$_2$}].

Fluorescence-based methods have been used to differentiate the mode of fixation of different platinum complexes to DNA *in vitro* and to study the kinetics. It has been shown that chelating platinum entities of the type 'PtL$_2$' but not monodentate entities of the type 'PtL$_3$' inhibit intercalation of ethidium bromide (3,8-diamino-5-ethyl-6-phenylphenanthridinium bromide) and cause a decrease in the fluorescence of the DNA–ethidium bromide complex which has been correlated with the number of platinum atoms bound per nucleotide.[39–41] Data obtained for the functionalized malonato complexes and several reference complexes are in Table 4 in the form of $t_{\frac{1}{2}}$ which represents the time required to chelate half of the platinum to DNA.

All the complexes in Table 4 inhibit the fluorescence characteristic of the DNA–ethidium bromide complex and, therefore, react with DNA through chelation. However the rate characterizing the overall displacement of the labile ligand varies. Complexes **2–4** are 10–30 times more reactive than the related unsubstituted complexes [PtL$_2${H$_2$C(CO$_2$)$_2$}] so that functionalization confers on the malonato complexes a reactivity which is only slightly lower than that of cis-[Pt(NH$_3$)$_2$Cl$_2$]. This conclusion is consistent with that deduced from the study of the [PtL$_2$X$_2$]–d(T-G-G-T) systems. It is generally accepted[42] that the first step of the reaction of a platinum complex [PtL$_2$X$_2$] with DNA fragments concerns the replacement of one anionic ligand X by a water molecule to yield a monoaquated species which rapidly binds DNA, essentially at the N^7 position of guanosine, to form a monofunctional adduct [PtL$_2$X(G-N^7)]. Then hydrolysis of the second X occurs with subsequent reaction with a second base to yield the diadduct [PtL$_2${(GpG)-N^7,N^7}]. In keeping with data from a recent study[43,44] of the hydrolysis of malonato complexes, it is likely that the main effect of functionalizing the malonato ligands concerns the formation of the monoadduct.

Experimental

Materials.—The tetradeoxyribonucleotide d(T-G-G-T) was purchased from Appligène (Illkirch, France) and used without further purification. Salmon sperm DNA was obtained from Worthington Biochemical Corporation (Freehold, NJ) and treated as described in ref. 41. All other materials were of reagent grade obtained from standard sources.

Spectra.—The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker WM 250 MHz instrument. An internal lock on deuterium of the solvent D$_2$O was used in all cases. The ^{1}H and ^{13}C chemical shifts were relative to the methyl signal of 3-(trimethylsilyl)propanesulfonate, the ^{31}P to external H$_3$PO$_4$ (85% in water).

The FAB mass spectra were obtained with a VG-ZAB-SE spectrometer. The samples prepared by dispersing the complexes in glycerol were introduced in the high-vacuum region of the spectrometer where they were bombarded with a xenon-atom beam of 7 keV (1.12 × 10^{-15} J). The spectra were acquired by scanning over the range m/z 200–800.

Reaction with d(T-G-G-T).—This study was performed according to the conditions described in ref. 35. Briefly, the cis-[PtL$_2$X$_2$] complexes were added as solids to separate solutions of d(T-G-G-T) so as to make one platinum per strand. The oligomer solutions were adjusted to pH 6.5 with 0.01 mol dm^{-3} base, D$_2$O and 0.001 mol dm^{-3} ethylenediaminetetraacetate (edta). Reaction solutions were maintained at 35 °C and the reactions were followed by ^{31}P NMR spectroscopy; a spectrum was recorded every 2 h. To evaluate the time t_i (Table 3) we considered arbitrarily that the abnormal ^{31}P NMR signal was discernible when the related signal-to-noise ratio was 2:1. The ^{1}H NMR spectra were recorded at the end of the reaction. Assignments of the ^{1}H resonances in the δ 8–5 region (non-exchangeable base protons) were based on literature values.[35]

Reaction with DNA.—As described in ref. 41, platination of DNA was performed by adding to a DNA solution (0.25 mg cm^{-3} determined spectrophotometrically, water, 0.01 mol dm^{-3} NaClO$_4$) an amount of cis-[PtL$_2$X$_2$] which corresponded to a final bound complex to nucleotide ratio value of 0.2:1. At different times aliquots were taken and added to 2.4 cm^3 of an ethidium bromide solution (0.04 mg cm^{-3} determined spectrophotometrically, water, 0.4 mol dm^{-3} KNO$_3$). For each aliquot the intensity of the fluorescence emitted at 590 nm (excitation at 546 nm) was measured allowing the determination of the number of bound ethidium bromide molecules and consequently the number of chelated 'PtL$_2$' entities. Finally the data are presented in the form of the time ($t_{\frac{1}{2}}$) required to complex half of the platinum initially added to the DNA solution.

Ultraviolet spectrophotometric and spectrofluorometric measurements were obtained with a Zeiss PMQII spectrophotometer equipped with a ZFM4 fluorescence attachment.

Preparation of Ligands.—As represented in Scheme 2, the esters (MeO$_2$C)$_2$CH(CH$_2$)$_n$CO$_2$Bu^t were obtained by alkylation of dimethyl malonate by the bromo derivatives Br(CH$_2$)$_n$-CO$_2$Bu^t. *tert*-Butyl bromoacetate ($n = 1$) was commercially available. *tert*-Butyl-5-bromovalerate ($n = 4$) was prepared as follows. An autoclave chilled to 0 °C was charged with isobutene (250 cm^3), 18 mol dm^{-3} H$_2$SO$_4$ (5 cm^3) and 5-bromovaleric acid (50 g, 0.28 mol). The autoclave was stoppered and

the mixture allowed to react at 20 °C, with stirring for 5 d. After depressurizing the autoclave, the reaction mixture was poured into diisopropyl ether (500 cm^3). The solution was washed with an aqueous saturated solution of NaHCO$_3$ (250 cm^3). The aqueous phase was extracted twice into diisopropyl ether (200 cm^3). The combined organic extracts were washed with saturated NaCl, treated with MgSO$_4$ and then concentrated *in vacuo* to a yellow oil. Vacuum distillation (56–58 °C, 66 Pa) afforded *tert*-butyl 5-bromovalerate (yield: 47 g, 72%).

Dimethyl 2-(*tert*-butyloxycarbonylmethyl)malonate and barium 2-(*tert*-butyloxycarbonylmethyl)malonate were prepared as follows. To a suspension of NaH (0.52 mol) in 1,4-dioxane (500 cm^3, dried over activated 5 Å molecular sieves) cooled to 15 °C was added dropwise first dimethyl malonate (69 g, 0.52 mol) and then *tert*-butyl bromoacetate (100 g, 0.52 mol). The mixture was stirred at room temperature for 20 h and then filtered. The filtrate was evaporated to give an oil. Vacuum distillation (73–74 °C, 2.66 Pa) gave (MeO$_2$C)$_2$CHCH$_2$CO$_2$Bu^t (yield: 40%). The barium salt was obtained by adding a 3 mol dm^{-3} aqueous solution of Ba(OH)$_2$ (370 cm^3) to a solution of the triester (42 g, 0.17 mol) in acetone (200 cm^3). The mixture was stirred for 20 h at 20 °C. The resulting precipitate was filtered off, washed with water and acetone and dried *in vacuo* (yield: 57 g, 95%).

Dimethyl 2-[4-(*tert*-butyloxycarbonyl)butyl]malonate and barium 2-[4-(*tert*-butyloxycarbonyl)butyl]malonate were prepared as described above in almost identical yields.

Preparation of Complexes.—Preparation of *cis*-[PtL$_2$-{(O$_2$C)$_2$CH(CH$_2$)$_n$CO$_2$Bu^t}] *via* route (*i*) (Scheme 1) was performed as described in the literature.[23,26,45–48] Reaction of the diaqua species [PtL$_2$(H$_2$O)]X$_2$ with Ba[(O$_2$C)$_2$CH-(CH$_2$)$_n$CO$_2$Bu^t] resulted in a mixture of *cis*-[PtL$_2$-{(O$_2$C)$_2$CH(CH$_2$)$_n$CO$_2$Bu^t}] and BaX$_2$ which could be difficult to separate. This difficulty was overcome by a suitable choice of the anion X. If the platinum complex displayed a good solubility in water, as was the case for the complexes with L = NH$_3$, we used SO$_4^{2-}$ as the dianion. Conversely, the platinum complexes of the dach ligand being almost insoluble, were prepared from the nitrato form of the diaqua species. Crude samples of the four complexes were obtained with yields ranging from 60 to 70%. Preparation of *cis*-[PtL$_2${(O$_2$C)$_2$CH(CH$_2$)$_n$CO$_2$Bu^t}] *via* route (*ii*) was performed as described in the literature[24,25,49] with yields of *ca.* 70%. After recrystallization from warm water the complexes prepared according to procedure (*i*) or/and (*ii*) were used directly in the following step.

cis-[PtL$_2${(O$_2$C)$_2$CH(CH$_2$)$_n$CO$_2$H}]. The same procedure was used for the four complexes and so only one example is given. The complex *cis*-[Pt(NH$_3$)$_2${(O$_2$C)$_2$CH(CH$_2$)$_4$CO$_2$Bu^t}] (500 mg) was added to trifluoroacetic acid (6 cm^3). The mixture was stirred at 30–35 °C for 5 min. Then it was concentrated *in vacuo* to yield a yellow oil from which a white powder precipitated upon addition of diethyl ether. The precipitate was filtered off, washed twice with diethyl ether and recrystallized from warm water to give 245 mg of complex **2** (yield: 55%).

Acknowledgements

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