Kinetics of the Reaction of Dichloro-*trans-rac-* and *-cis-meso-* 1,2-diaminocyclohexaneplatinum(II) with Pyridine

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The kinetics of the reaction [Pt(dach)Cl$_2$] + py $\longrightarrow$ [Pt(dach)(py)Cl]Cl (dach = either *trans-rac-* or *cis-meso-*1,2-diaminocyclohexane, py = pyridine) has been studied in dimethylformamide (dmf) solution, under pseudo-first-order conditions (excess of pyridine), in the range 50–80 °C, by measuring the increase in conductance of the solution. In dmf the products behave like weak electrolytes, with dissociation constants of about 1.4×10^{-3} mol dm^{-3}. The reactions were found to be reversible under the experimental conditions. Owing to the uncertainty in evaluating the equilibrium concentrations, the kinetic constants k_{obs} have been calculated from the initial slopes (up to 15% conversion) of first-order plots. Their values obey the equation $k_{obs} = k_1 + k_2[py]$, k_1 being about two orders of magnitude lower than k_2. The values of k_{obs} for the *cis* derivative are always slightly but significantly higher than those of the *trans*. The activation parameters have been evaluated only for k_2, since the k_1 values are affected by too high uncertainties: $\Delta H^\ddagger$ *trans* 76(1), *cis* 79(1) kJ mol^{-1}; $\Delta S^\ddagger$ *trans* −101(3), *cis* −92(3) J K^{-1} mol^{-1}. The higher rate for the *cis* isomer is interpreted in terms of higher flexibility of the diamine chelate ring.

Complexes of the type [Pt(dach)X$_2$] (dach = 1,2-diaminocyclohexane, X = anionic leaving ligand) have been proposed many years ago as second-generation analogues of the antitumour complex [PtCl$_2$(NH$_3$)$_2$] (cisplatin), because of their improved biological properties.[1–3] It was recognized at a very early stage that the three isomers of dach (*trans-R,R*, *trans-S,S* and *cis-meso*) give platinum complexes having different biological properties. For instance the activity towards experimental tumours usually follows the order *R,R* > *S,S* > *cis*.[4–7]

A number of studies have been aimed at understanding the origin of this difference, including reactions with nucleosides,[8] nucleotides[9] or DNA.[10–12] The currently accepted explanation is that, as the result of different steric requirements, the derivatives of the *trans* isomers, especially that with the *R,R* configuration, 'match' with the DNA double helix better than do the complexes of *cis*-dach.[9,12] These considerations are based on static (ground state of the reactants and products, or equilibrium) considerations, but to our knowledge very few detailed studies have been performed on the influence of the structure and the conformation of the spectator diamine ligands on the kinetics of the substitution of X by nucleophiles, although such an influence has been noted a few times.[13–15] As a first approach to this problem we report here the results of a kinetic investigation of reaction (1) (py = pyridine), in dimethylformamide (dmf), with either the *trans-rac* (racemic) or the *cis-meso* isomers of dach. To our knowledge, there is only one report which compares the rates of substitution of one chloride ligand of *rac-* and *cis-***1**: the solvolysis of the latter in Me$_2$SO has been found to be slightly faster than that of the former.[14]

$$\underset{\mathbf{1}}{[\mathrm{Pt(dach)Cl_2}]} + \mathrm{py} \longrightarrow \underset{\mathbf{2}}{[\mathrm{Pt(dach)(py)Cl]Cl}} \qquad (1)$$

Reaction (1) has been chosen for two reasons: (*i*) the aromatic nitrogen atom of pyridine can be taken as a rough model of N(7) of guanine, which is believed to be the main target of [Pt(diamine)X$_2$] type compounds;[16] and (*ii*) since pyridine is not chiral, there is no diastereoisomeric interaction in the formation of **2**, therefore the results of these measurements can give information on the relation between the conformation of the dach chelate ring and the reactivity of the complexes.

Owing to the very low water solubility of [Pt(dach)Cl$_2$] the measurements have been performed in dimethylformamide solutions. Although this choice neglects the aquation-assisted pathways, which are believed to be important under biological conditions,[16] the use of such a solvent may mimic the environment of some active sites of target macromolecules, where the effective relative permittivity may be lower than that of bulk water.[17]

Experimental

The reagents *cis-* and *trans*-dach (Aldrich) were used as received for the synthesis of [Pt(dach)Cl$_2$], performed according to literature methods.[18] Pyridine (Merck) was distilled under N$_2$ over KOH just before use. The solvent dmf (Fluka) was stored under N$_2$ over 4 Å molecular sieves and distilled under reduced pressure before use. It was transferred under N$_2$ using oven-dried glassware.

The calibrations and the kinetic runs were performed in an oven-dried Schlenk vessel, with two screw caps (for the conductance cell and for introducing the reagents). The vessel was plunged in a Haake F3 thermostat (±0.1 °C). The conductance was measured with an Amel 133 instrument (cell model 192, platinum plates), connected to a Shimadzu recorder for automatic acquisition of the data, at intervals set by a BASIC program.

Data processing was performed with laboratory-written routines executed by the 386-MATLAB software (The MatWorks Inc.), running under MS-DOS.

The NMR spectra were acquired on a Bruker 80 WP instrument.

Syntheses.—[Pt(*trans*-dach)(py)Cl]Cl. A 400 mg (1.05 mmol) sample of [Pt(*trans*-dach)Cl$_2$], suspended in dmf (90 cm^3), was treated with pyridine (10 cm^3, 124 mmol). The solution was heated in an oil-bath at 60 °C for 24 h, and the white precipitate was isolated by filtration. Concentration of the mother-liquors to 20 cm^3 under vacuum gave a second fraction of precipitate. The two precipitates were collected, washed with Et$_2$O and dried in vacuum (389 mg, 0.847 mmol, isolated yield 80.5%). ^{1}H NMR (D$_2$O): δ 8.75 (m, 2, J_{HPt} 32 Hz), 8.1 (m, 1), 7.6 (m, 2), 2.6 (m, 2), 2.1 (m, 2) and 1.3 (m, 6) [Found (Calc.): C, 28.95 (28.75); H, 3.90 (4.15); N, 8.90 (9.15)%].

$[Pt(\textit{cis}\text{-dach})(py)Cl]Cl$. The reaction was performed as above, using $[Pt(\textit{cis}\text{-dach})Cl_2]$ (353 mg, 0.928 mmol), and obtaining 225 mg (0.490 mmol, isolated yield 52.8%) of the product. ^1H NMR (D_2O): δ 8.75 (m, 2, J_{HPt} 34), 8.05 (m, 1), 7.6 (m, 2), 3.1 (m, 2, J_{HPt} *ca.* 30 Hz), 1.9 (m, 6) and 1.6 (m, 2) [Found (Calc.): C, 28.90 (28.75); H, 4.00 (4.15); N, 8.90 (9.15)%].

Calibrations.—Freshly distilled dmf (25 cm^3) was introduced, under N_2, into the measurement vessel, which was thermostatted at the appropriate temperature. The conductance of the solvent was always in the range 0.1–0.2 μS cm^{-1}. Several aliquots (each ranging from 250 μl to 1 cm^3) of a mother solution about 2×10^{-3} mol dm^{-3} {prepared by dissolving 50 mg of [Pt(dach)(py)Cl]Cl in 50 cm^3 of dmf} were then added to the solvent, by a microsyringe, through a rubber septum, giving solutions in the range 2×10^{-5}–9×10^{-4} mol dm^{-3}. After each addition the vessel was carefully shaken and then left in the thermostatted bath for 15 min, before measuring the conductivity.

Attempts to fit the data through Onsager's equation (2)

$$\Lambda = \Lambda_0 - Sc^{\frac{1}{2}} \qquad (2)$$

(which gives the variation of the equivalent conductance Λ from its value at infinite dilution Λ_0, as a function of the concentration *c*, for strong electrolytes) led to unreasonably high values of the slope *S* (*ca.* 1300 S cm^2 $l^{\frac{1}{2}}$ $mol^{-\frac{3}{2}}$, *vs.* expected values of *ca.* 300),† suggesting that the dissociation of complex **2** increases with the dilution, according to the classical Ostwald law (3). In agreement with this, plots of 1/Λ against the specific

$$1/\Lambda = (1/\Lambda_0) + c\Lambda/(K\Lambda_0{}^2) \qquad (3)$$

conductance χ were linear, allowing estimates of Λ_0 and of *K*, the dissociation constant of the ion pair. The knowledge of such parameters would allow one to relate, through equation (3), the values of the specific conductance χ ($\chi = c\Lambda/1000$), measured during the kinetic runs, to the concentration of compound **2**. Ostwald's equation, however, is a crude approximation, and therefore the more accurate equation (4), due to Fuoss and

$$F/\Lambda = (1/\Lambda_0) + c\Lambda f^2(KF\Lambda_0{}^2)^{-1} \qquad (4)$$

Accascina,[20] was used to correlate the conductance of the solution to the concentration of **2**. To compute the values of *f* and *F* in the latter equation, according to ref. 20, the values of the relative permittivity *D* and of the viscosity η (not available at the temperatures of interest) were extrapolated from data available for lower temperatures,[21,22] assuming that the temperature variation is linear for *D* and of the Arrhenius type for η (with slope equal to $\Delta H_v/3$,[23] ΔH_v for dmf being 47.57 kJ mol^{-1}).[22] As to Λ_0, the value obtained from the fitting of Ostwald's equation was used as the entry value for the calculation of *F*. A few iterations led to the values of Λ_0 and 1/*K* reported in Table 1. No significant variation of these parameters was observed when the calibration was repeated in the presence of an amount of pyridine comparable to that used in the kinetic runs.

Kinetic Runs.—A weighed amount of $[Pt(dach)Cl_2]$ (about 15 mg, 0.04 mmol) was introduced, under N_2, in an oven-dried reaction vessel, containing freshly distilled dmf (30 cm^3) and the conductance cell. The mixture was stirred until complete dissolution, then the vessel was plunged in the thermostatic bath at the appropriate temperature. After 10 min freshly distilled pyridine (150–500 μl) was added, with a microsyringe, through a rubber septum. The vessel was carefully shaken, then the automatic acquisition of the data was started. The conductance data were corrected by subtracting the conductance of the solution measured immediately before the addition of pyridine (usually 1–2 μS cm^{-1}). The transformation of the conductance data into values of concentrations according to equation (4) was performed by a laboratory-written minimization routine, working in MATLAB.

Table 1 Values of the parameters of equation (4) estimated from the calibrations for dmf solutions of the complexes [Pt(dach)(py)Cl]Cl **2** *

T/°C	Isomer	Λ_0/S cm^2 mol^{-1}	K^{-1}/dm^3 mol^{-1}
50	*trans*	111.4(2)	685(6)
60	*trans*	121.5(1)	673(2)
70	*trans*	133.1(2)	721(5)
80	*trans*	143.0(1)	710(2)
50	*cis*	111.4(4)	662(12)
60	*cis*	122.3(4)	667(11)
70	*cis*	133.1(4)	662(10)
80	*cis*	143.9(2)	661(6)

* The numbers in parentheses represent the uncertainties (referred to the last digits) computed from the errors in the slope and in the intercept of the least-squares straight lines.

Measurement of pK_a.—The ligands *cis*- and *trans*-dach were purified by distillation under vacuum and stored for a short time under N_2. Samples of the amine (about 80 mg, 0.7 mmol) were dissolved in water (25 cm^3, degassed by double distillation and stored for a short time under N_2) and were titrated, under N_2, with 0.1 mol dm^{-3} HCl, using a pH-meter. The values of pK_a were obtained by least-squares fit of the relationship $pH = pK_a + \log(c_b/c_a)$, where c_b and c_a are the concentrations of the base and of its conjugated acid, respectively, in the range $0.15 < c_b/c_a < 0.85$.

Evidence for the Reversibility of Reaction (1).—(*i*) Typically, a solution of *trans*-**2** (15.4 mg, 0.034 mmol) in dmf (50 cm^3) was treated with LiCl (14.2 mg, 0.33 mmol) and heated at 80 °C for 24 h. The solvent was removed under vacuum, trapped and analysed by GLC (Carbowax 20M, 50 °C), which showed the presence of pyridine. (*ii*) The conductance of dmf solutions of *trans*- and *cis*-**2** (about 9×10^{-2} mol dm^{-3}) in a thermostat at 50–80 °C was measured at fixed intervals for 24 h. The conductance decrease in that time was *ca.* 9% at 80 °C and *ca.* 3% at 70 °C, while at lower temperatures the decrease was too low to be measured.

Results and Discussion

The reaction of concentrated (> 10^{-2} mol dm^{-3}) dmf solutions of $[Pt(dach)Cl_2]$, *trans-rac* or *cis-meso* isomers (compounds **1**), with a large excess of pyridine (*ca.* 100 equivalents) gives in about 48 h, at 60 °C, a white precipitate, identified by IR and NMR spectroscopy and elemental analyses, as the monosubstitution derivatives [Pt(dach)(py)Cl]Cl (compounds **2**). No other product has been isolated nor spectroscopically detected. In particular, under these conditions, the tendency of **2** to react further with pyridine to give disubstitution derivatives can be considered negligible, as we found no such products even in the presence of 1000 equivalents of pyridine. Even reactions (1) have unfavourable equilibrium constants, as will be discussed later.

If reactions (1) are performed in more dilute solution (*ca.* 10^{-3} mol dm^{-3}), compounds **2** do not precipitate, thus allowing kinetic measurements.

Conductance Measurements.—Since compounds **2** are ionic, the increase in the conductance of the solution during the

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† The theoretical values of the slope *S* for equation (2) have been computed through the relationship $S = \alpha\Lambda_0 + \beta$, where α and β are constants which depend on the temperature, the relative permittivity and the viscosity of the solvent.[19]

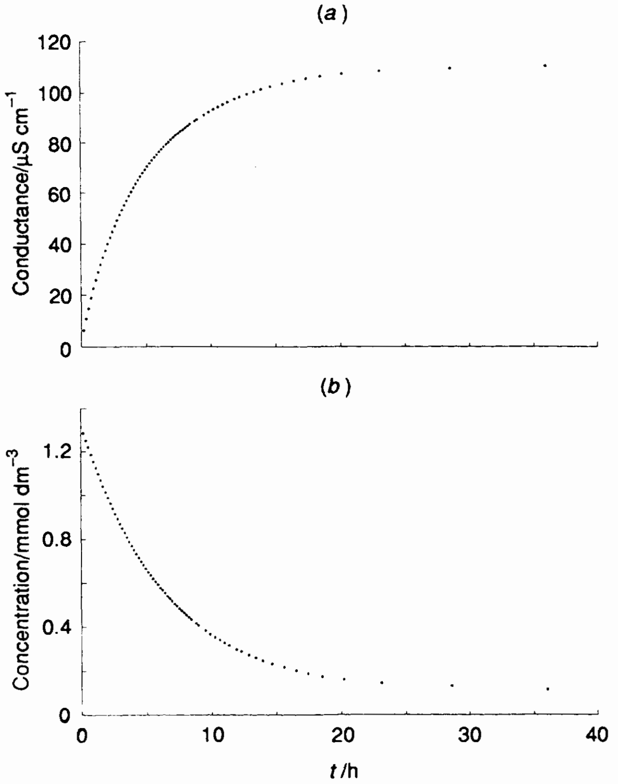

Fig. 1 Variation (*a*) of the conductance of the solution and (*b*) of the concentration of *trans*-**1**, calculated through equation (4), during a kinetic run ([*trans*-**1**] = 1.33×10^{-3} mol dm^{-3} in dmf, [py] = 0.15 mol dm^{-3}, T = 80 °C)

reaction [Fig. 1(*a*)] is a convenient method to follow the kinetics, provided the occurrence of side reactions, leading to other ionic species, can be safely neglected, as is the case. We have also verified that the addition of pyridine to carefully dried dmf results in only a negligible increase in the conductance ($\chi < 0.2$ µS cm^{-1} after 15 h at 80 °C). On the other hand, the conductance of dmf solutions of **1** in the absence of pyridine did show a small, but significant, increase with time (up to about 8 µS cm^{-1} in 48 h at 60 °C for a 1.3×10^{-3} mol dm^{-3} solution). This can be attributed to the solvolytic reaction (5). Such a

$$[Pt(dach)Cl_2] + dmf \rightleftharpoons [Pt(dach)(dmf)Cl]^+ + Cl^- \qquad (5)$$

reaction, however, is one step of one path normally followed by substitution reactions of square-planar complexes (the solvent-assisted substitution pathway),[24] since in the presence of pyridine compounds of the type [Pt(dach)(dmf)Cl]$^+$ convert readily into **2**.[25] The kinetic experiments have confirmed the existence of such a path, which, however, in the presence of an excess of pyridine, was less important than the direct pyridine attack. The values of the kinetic constants k_1 in Table 3 substantially account for the rates of reactions (5).

In order to correlate the conductance of the solution to the concentration of compounds **2**, calibrations have been performed by measuring the conductance of solutions containing known amounts of either *trans-rac-* or *cis-meso-***2**, at various temperatures (see Experimental section). These calibrations have shown that in dmf solution compounds **2** behave like weak electrolytes and the values of Λ_0 and $1/K$ (the association constant of the ion pair) have been evaluated for both isomers of **2**, at various temperatures (see Table 1). The $1/K$ values obtained compare well with those reported in the literature for other electrolytes, in dmf solution: for instance 400 dm^3 mol^{-1} for AgNO$_3$, 300 dm^3 mol^{-1} for NEt$_3$HBr and 787 dm^3 mol^{-1} for TlMe$_2$I (25 °C).[19] From the values of $1/K$, it is easily computed that in 10^{-3} mol dm^{-3} solutions about 30% of compounds **2** exist in solution as ion pairs.

Table 2 Values of k_{obs}/s^{-1} provided by least-squares fits of first-order plots for reaction (1), using data up to a 0.15 conversion of complex **1** *

		$10^6\ k_{obs}$	
T/°C	[py]/mol dm^{-3}	*trans*	*cis*
50	0.06		1.55(2)
	0.10	2.30(2)	2.38(3)
	0.15	3.30(3)	3.47(3)
	0.20	4.36(3)	4.50(5)
60	0.06		3.71(4)
	0.10	5.14(2)	5.93(6)
	0.15	7.45(5)	8.51(8)
	0.20	9.85(5)	11.47(10)
70	0.06		9.22(11), 8.97(10)
	0.10	12.85(8)	13.03(13), 14.23(14)
	0.15	17.52(28)	19.55(18), 19.78(21)
	0.20	23.17(11)	25.05(19), 25.55(20)
80	0.06		20.25(25)
	0.10	28.48(19)	30.76(28)
	0.15	41.13(62)	45.73(138)
	0.20	52.12(32)	59.28(36)

* The numbers in parentheses are referred to the last digits and give the errors in the estimate of the slope.

Kinetic Experiments.—The kinetic data for reaction (1) have been acquired by recording [Fig. 1(*a*)] the increase with the time of the conductance of dmf solutions of [Pt(dach)Cl$_2$] (about 1.4×10^{-3} mol dm^{-3}) in the presence of a large excess of pyridine, to ensure pseudo-first-order conditions. The experiments (Table 2) have been performed at four temperatures, using three (*trans*) or four (*cis*) different concentrations of pyridine. The concentrations of **2** [and consequently of **1**, see Fig. 1(*b*)] were calculated from equation (4), through a minimization routine, using the values of Λ_0 and K previously obtained.

The analysis of the data at long reaction times shows that, even in the presence of a large excess of pyridine, reactions (1) do not go to completion [Fig. 1(*b*)], indicating their reversibility. This has been confirmed by two experiments: (*i*) pyridine (detected by GLC) is obtained, upon heating [Pt(dach)(py)Cl]Cl in dmf, at 80 °C, in the presence of LiCl, and (*ii*) the conductance of dmf solutions of [Pt(dach)(py)Cl]Cl slowly decreases with time (the decrease being less than 10% after 24 h at 80 °C). Such reverse reactions are exceedingly slow in the absence of an excess of chloride ions, which however precludes the possibility of conductivity measurements. We could make a rough estimate only at 80 °C, obtaining rate constants about one order of magnitude higher than that of the direct reaction. This indicates that the excess of pyridine favours not only the 'kinetics' but also the 'thermodynamics' of the substitution reaction.

In all the experiments the equilibrium was attained at very long times, when the data (due to the increased possibility of side reactions) could be affected by too high uncertainties to allow a reliable estimate of the equilibrium concentrations. Therefore, instead of using the kinetic equations for reversible reactions, which require equilibrium data,[26] we calculated the kinetic constants from the initial slopes of first-order plots (data up to a conversion of 15% were used for all the runs). This procedure has the advantage that it minimizes any error due to side reactions, including disubstitution. Table 2 lists the values of k_{obs} so obtained.

The values of k_{obs} at each temperature increase linearly with the pyridine concentration (Fig. 2), according to equation (6),

$$k_{obs} = k_1 + k_2[py] \qquad (6)$$

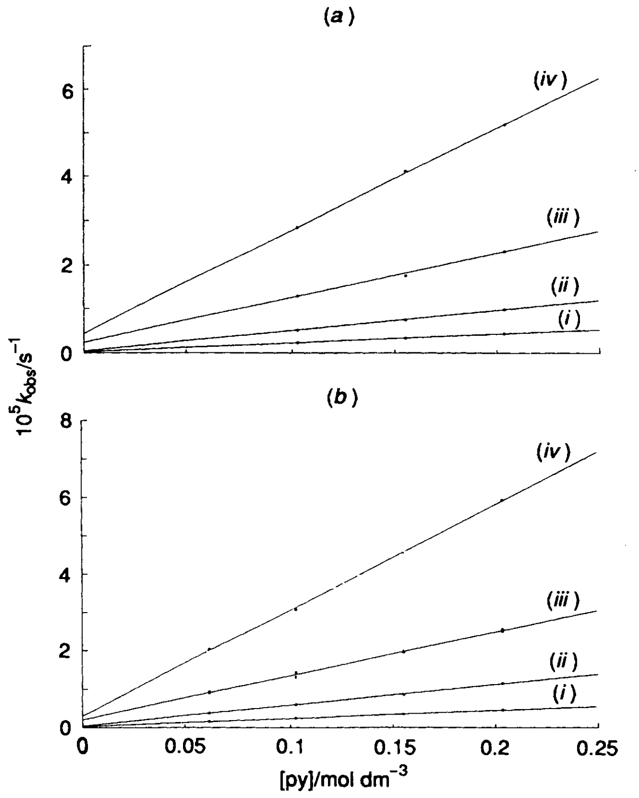

Fig. 2 Variation of k_{obs} with the pyridine concentration for the (*a*) *trans* and (*b*) *cis* derivatives at 50 (*i*), 60 (*ii*), 70 (*iii*) and 80 °C (*iv*)

which is the classical rate equation for substitution reactions of square-planar platinum(II) complexes[24,27] characteristic of a double-pathway mechanism involving a solvolytic assisted path (ligand-independent, k_1) and a direct attack of the nucleophile through an associative mechanism (k_2). The values of k_1 and k_2 provided by least-squares fits are given in Table 3. Under our conditions the rate of the solvolytic assisted path is lower, but not negligible, with respect to that of the direct attack of pyridine.

*Comparison between the Reactivity of Isomers trans-rac- and cis-meso-*1.—From Table 2 it appears that the overall rate of substitution of *cis*-1 is always slightly, but significantly, faster than that of the *trans* isomer [*i.e.* $k_{obs}(cis) > k_{obs}(trans)$]. This difference increases with pyridine concentration: the values of k_{obs} are in fact mainly determined by the values of k_2 (Table 3), which are always higher for the *cis* isomer. On the other hand, little can be said about the solvent-assisted path, because the values of k_1 are affected by too large errors to allow a meaningful comparison.

The higher rate of reaction (1) for the *cis* complex is comparable with the previously cited faster solvolysis of *cis*- with respect to *trans*-1, in neat Me_2SO (k_{obs} *cis*, 1.06(1) × 10^{-4}; *trans*, 9.1(5) × 10^{-5} s^{-1}, at 30 °C).[14] Interestingly, also in the case of the new class of antitumour cationic platinum complexes $[Pt(dach)(O_2CC_6H_4OSMe\text{-}2)]^+$, it has been observed[28] that the *cis*-dach derivative always displays a higher rate of reaction towards various nucleophiles in water solution.[29] This kinetic difference seems therefore rather general.

As to its origin, we have tried to relate the different rates to the different basicities of *trans*- and *cis*-dach: in the absence of π-acidic ligands, the *trans*-labilizing power of a ligand is related to its σ-donating ability and hence, for an amine, to the first approximation to its basicity.[24a] We have re-evaluated such values [*cis* pK_{a2} 9.99(1), pK_{a1} 6.20(1); *trans* pK_{a2} 9.96(1), pK_{a1} 6.47(1), in water at 25 °C] and found them to be in good agreement with literature data.[30,31] The only significant difference was found in pK_{a1}, the *trans* isomer being slightly more basic than the *cis*. The different reactivity of the two isomeric complexes is therefore not related to this property.

Table 3 Values of k_1/s^{-1} and k_2/dm^3 mol^{-1} s^{-1} obtained by least-squares fits of equation (6)*

	trans		*cis*	
T/°C	$10^7 k_1$	$10^5 k_2$	$10^7 k_1$	$10^5 k_2$
50	2.1(11)	2.02(7)	2.7(2)	2.07(1)
60	3.9(16)	4.61(12)	4.0(15)	5.35(14)
70	23.6(49)	10.19(33)	20.0(33)	11.37(29)
80	44.3(24)	23.43(18)	29.5(55)	27.54(46)

* In parentheses are given the errors (referred to the last digits) in the estimate of the intercept and of the slope of the straight line.

Table 4 Activation parameters for k_2*

	trans	*cis*
E_a/kJ mol^{-1}	79(1)	81(1)
ln *A*	18.4(4)	19.5(4)
$\Delta H^‡$/kJ mol^{-1}	76(1)	79(1)
$\Delta S^‡$/J K^{-1} mol^{-1}	−101(3)	−92(3)

* In parentheses are given the errors (referred to the last digits) in the estimate of the intercept and of the slope of the Arrhenius and Eyring plots.

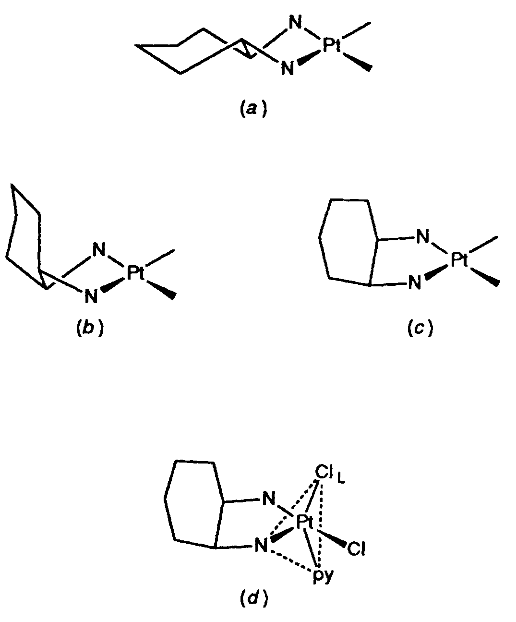

Fig. 3 The possible conformations of the dach chelate ring: (*a*) *trans*; (*b*) and (*c*) *cis*; (*d*) *cis* in the five-co-ordinate transition state

Some clues are provided by the analysis of the activation parameters, which could be determined with accuracy only for the direct attack because of the errors affecting k_1 (Table 4). As expected, the activation parameters are typical of an associative mechanism (large negative activation entropies). From these data it appears that the higher rate for the substitution in *cis*-1 should be attributed to its less unfavourable activation entropy (the difference being once again small, but significant). Since, as stated above, the greater reactivity of *cis* derivatives seems to be independent of the medium, the nucleophile and the charge of the complex, it is likely that solvation factors play a minor role. More important could be the higher flexibility of the *cis*-dach chelate ring with respect to the rigid *trans*-dach chelate ring. In the latter the two fused rings (the cyclohexane and the chelate rings) are fixed in a *trans*-diequatorial conformation [Fig. 3(*a*)], whereas in the case of *cis*-dach both conformations (*b*) and (*c*) of Fig. 3 are possible and their interconversion requires such a small energy barrier that even intermediate, non-*gauche*, conformations of the chelate ring have been reported to be stable.[8,32,33] The flexibility of the chelate ring of *cis*-dach would favour the attainment of the trigonal-bipyramidal five-co-ordinate transition state typical of substitution reactions of d^8 square-planar complexes [Fig. 3(*d*); Cl$_L$ = leaving chloride].

It should be noted that in the only case in which the different rates for *cis*- and *trans*-**1** have been studied in some detail, a different explanation has been suggested.[14] In complexes of *cis*-dach the cyclohexane ring resides always on one side of the co-ordination plane, whereas in the case of *trans*-dach the ring lies approximately in the co-ordination plane (dihedral angles between the co-ordination plane and the mean plane through the cyclohexane ring in crystal structures: about 67° for *cis*-dach and 11–19° for the *trans*-dach platinum complexes).[34] Consequently, in *cis*-**1** one side of the co-ordination plane should be free for the attack of the incoming nucleophile.[14] However, one could argue that in *trans*-**1** both sides are not effectively shielded. This type of steric effect is therefore difficult to evaluate unambiguously.

Conclusion

This study has confirmed a small, but systematic difference in the rates of reaction of the two isomeric platinum complexes toward nucleophiles. We think that, at least in the present case, the difference arises from the different conformational freedoms of the two isomers, which makes the attainment of the transition state more easy in the case of the *cis*-dach derivative. The observed difference is rather small, probably too small to account for (and difficult to correlate with) the reported different biological properties. Presumably the reaction studied is a model too naive to mimic successfully the reactions occurring under biological conditions and more refined models should be envisaged, taking into account the aquation step (for instance, on using water–dmf mixtures) and the steric hindrance of the target molecule.

The results presented, however, have evidenced the existence of a subtle relationship between the conformation of the spectator dach ligand and the reactivity of the Pt–X bonds. Work is in progress in order to evaluate the general validity of this finding.

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