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Platinum Complexes with One Monodentate Ligand (1-Methylbenzimidazole or Antiviral Ribavirin) Flanked by Two *cis*-NMe_2 Groups: Informative Models for Assessing Interligand Interactions

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Platinum complexes with a tridentate amine ligand (A_3) and a nucleobase (L) represent very useful models for investigating nucleobase/*cis*-amine interactions without the complications arising from nucleobase/nucleobase interferences present in the more frequently used *cis*-A_2PtL_2 model systems (A_2 = two monodentate amines or a diamine). In this context, the Me_3dienPtL complexes (Me_3dien = *N1*,*N4*,*N7*-trimethyldiethylenetriamine), previously investigated, were particularly informative. The presence of a methyl group on each terminal nitrogen atom renders the rotation of L about the Pt–L bond slow on the NMR timescale and the two half spaces defined by the coordination plane inequivalent. Thus, guanine and deoxyguanine derivatives were found to have comparable rates of rotation by way of a H-bond interaction between the O6 atom of the rotating guanine and the NH group of the *cis*-amine. We have now extended the investigation to Me_5dien complexes (Me_5dien = *N1*,*N1′*,*N4*,*N7*,*N7′*-pentamethyldiethylenetriamine). The results indicate that the absence of a proton on the terminal nitrogen atoms not only reduces the rate of rotation of L by a factor of 10^{10}, but also dramatically increases the difference in the rates between the L ligands mimicking guanine and deoxyguanine.

Introduction

Cisplatin [*cis*-$PtCl_2(NH_3)_2$] displays exceptional anticancer activity when employed in the treatment of testicular, ovarian, cervical, head and neck, oesophageal, and non-small-cell lung cancers.[1,2] Continued research into the mechanism for the action of cisplatin[3–5] is being carried out in order to understand why it is so extraordinarily effective, especially against testicular cancer, and to allow for the rational design of new derivatives that could overcome the toxic side effects and the resistance to cisplatin of several tumors.

The major DNA adduct formed by cisplatin, the intrastrand cross-link between adjacent G groups, is mimicked by *cis*-A_2PtG_2 models, where A_2 stands for two monodentate or a bidentate amine and G is a guanine derivative. Models with bulky A_2 ligands, designed to reduce the rate of rotation around the Pt–G bonds, have been extensively investigated in our laboratories and have contributed to the elucidation of some relevant features of cisplatin adducts.[6–12] In some instances, in order to investigate the role of nucleotide/*cis*-amine interactions without the complications arising from interactions between *cis*-nucleotides, model compounds containing only one G group have also been constructed.

The most widely used model compound for platinum adducts with just one coordinated purine base is represented by dienPtL (dien = 1,4,7-triazaheptane = diethylenetriamine). *N4*-methyldien, *N1*,*N4*,*N7*-trimethyldien, and *N1*,*N1′*,*N4*,*N7*,*N7′*-pentamethyldien (abbreviated as Medien, Me_3dien, and Me_5dien, respectively) are systems of increasing steric bulk, which can differently affect the rate of rotation of a purine base about the Pt–N7 bond. All these ligands are nonsymmetrical with respect to the platinum coordination plane. In particular the single Me group on the N4 atom occurs only on one side of the platinum coordination plane. Therefore, coordination of a nonsymmetrical ligand L, such as a purine base, can lead to the formation of two Me_ndienPtL conformers differing in the orientation of the purine base with regard to the Me_ndien ligand (Scheme 1). The six-membered ring of the purine base and the central *N*-methyl group of Me_ndien can be either on the same side (*endo* rotamer) or on opposite sides (*exo* rotamer) of the platinum coordination plane.[13–17]

MedienPtL complexes[18] are very dynamic and the four hydrogen atoms on the terminal nitrogen atoms exert negligible hindrance to the *endo*/*exo* interconversion process; therefore, similar to the case of dienPtL complexes, only one set of signals, which is the coalescence of the sets of signals of the two conformers, is observed in the NMR spectra.[19]

Me_3dienPtL complexes represent a case in which the interconversion is sufficiently slow (already at ambient temperature) to be studied by NMR spectroscopic techniques.

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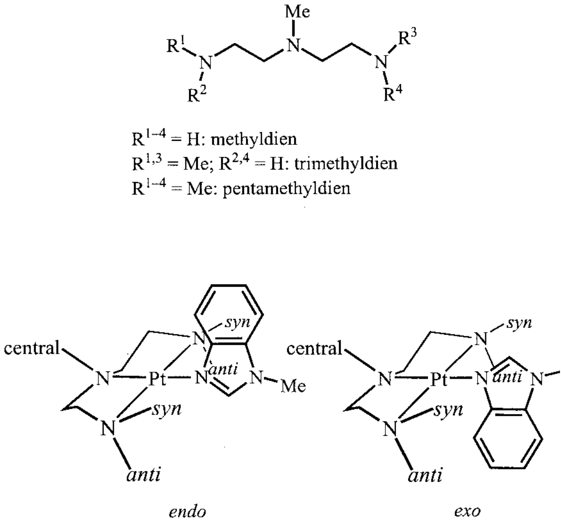


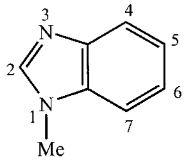
Scheme 1. Schematic view of the Me$_n$dien ligands (top) and of the two possible conformers (*endo* and *exo*) for Me$_5$dienPt(1-methylbenzimidazole) (bottom).

The rate of *endo*/*exo* interconversion has been found to depend upon the nature of the purine derivative investigated, and the factors influencing the rotation around the Pt–L bond have been elucidated.[11–14]

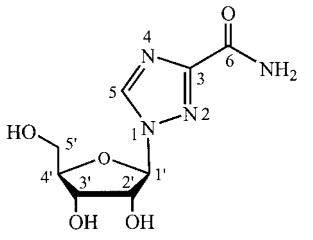
In particular, Me$_3$dienPtL compounds could be prepared in the form that has all three methyl groups of Me$_3$dien on the same side of the platinum coordination plane [*syn*-(*R*,*S*) isomer];[12] moreover, under acidic or neutral conditions no change in ligand configuration could be detected after several days in aqueous solution. Me$_3$dienPtL complexes were found to be the most informative for assessing steric, solvation, and electronic factors influencing stability and dynamic behavior.

A first interesting result of the investigation was the large tendency of a coordinated 5′-nucleotide to place the phosphate group on the same side of the platinum coordination plane as the NH groups of Me$_3$dien; such a conformation allows for phosphate/*cis*-amine H-bonding. Therefore, the *endo* rotamer was the exclusive form in adducts with 5′-GMP, while in adducts with 9-EtG and 3′-GMP, in which such an interaction cannot take place, the *endo* and *exo* rotamers were present in comparable amounts. The effect of the substituent at the 6-position of the purine ring on the rate of rotation about the Pt–N7 bond was also investigated. The rate of interconversion between rotamers was comparable for guanine and deoxyguanine derivatives notwithstanding the greater bulk of the C6 substituent in the guanine complex. In contrast, the rate of rotation was far slower for the adenine derivative although the bulk of the C6 substituent is comparable for adenine and guanine. Activation parameters for rotation suggest that an attractive interaction between the negatively charged O6 atom of the guanine (an H-bond acceptor) and the positively charged *N*-hydrogen atom of the *cis*-amine (an H-bond donor) could lower the rotational barrier and render the rate of rotation of guanine only one order of magnitude slower than that of deoxyguanine. Finally, in the case of adenine derivatives in which the substituent at the 6-position of the purine ring is bulky and positively charged (as positively charged as the *N*-hydrogen atoms of the triamine) the barrier to rotation could be expected to be far greater than that observed for guanine and deoxyguanine derivatives with the consequence that the interconversion between rotamers becomes very slow.

In order to prove further the correctness of the explanation given above, we extended the investigation to fully methylated dien derivatives (Me$_5$dienPtL compounds) lacking protons on the terminal aminic groups. Some Me$_5$dienPtL complexes have already been investigated (L = a guanine derivative such as 9-EtG, guanosine, 5′-dGMP, 5′-GMP,[11] and penciclovir,[10] or a deoxyguanine such as famciclovir[10]); however, in none of the cases was it possible to observe an interconversion between rotamers and the *endo*/*exo* ratio was in the range 0.6–1 in the case of the guanine derivatives and ca. 2 in the case of the deoxyguanine derivative. We therefore looked at other N-donor heterocycles that could mimic guanine and deoxyguanine derivatives but be more reactive and allow for the detection of a kinetically controlled composition, which could possibly be different from that at thermodynamic equilibrium. The search has been successful. We found two bases (Scheme 2), 1-methylbenzimidazole (bzim) and 1-D-ribose-1*H*-[1,2,4]triazole-3-carboxamide (ribavirin, riba) for which the reaction was completed in 2 d at ambient temperature. Moreover, the initially formed rotamer composition appears to be under kinetic control (*endo*/*exo* ratio of 7–8) and in one case (bzim) it has been possible to measure the rate of isomerization to the thermodynamically controlled composition and to evaluate the activation parameters.



1-methylbenzimidazole, *bzim*



ribavirin, *riba*

Scheme 2. Structures and numbering schemes for the two ligands L used in this work.

New insights into steric, electronic, and solvation factors influencing the dynamic behavior of these model compounds have been gained.

Results

Me_5dienPt(bzim)

The reaction of [Pt(Me_5dien)(NO_3)](NO_3) with bzim was complete after 48 h at room temperature. In the ^1H NMR spectrum two sets of signals of very different intensities (ca. 8:1) were detected. For each set of signals the resonance at the lower field belongs to H2 and reveals a downfield shift with respect to the corresponding signal for the free bzim of ca. 0.8 ppm. This is a clear indication that both sets of signals belong to complex species in which bzim is *N3*-coordinated to the platinum atom. Therefore, most likely, the two sets of signals arise from the presence of two conformers, *endo* and *exo* (Table 1).

A 2D NOESY experiment showing connectivities between bzim protons and *N*-Me protons of Me_5dien enabled the assignment of the two sets of signals to the corresponding conformers (Figure 1). Previous investigations on strictly related compounds have demonstrated that *syn*-*N*-Me signals of Me_5dien are always at a higher field with respect to *anti*-*N*-Me signals and the latter are at a higher field with respect to the central *N*-Me signals.[13–17]

The major conformer exhibits intense NOE crosspeaks between bzim-H2 and *anti*-*N*-Me groups of Me_5dien and between bzim-H4 and *syn*-*N*-Me groups of Me_5dien, therefore it is identified as the *endo* rotamer (the six-membered ring of bzim is on the same side of the platinum coordination plane as the central *N*-Me group of Me_5dien). Consequently, the minor form is identified as the *exo* rotamer (the six-membered ring and the central *N*-Me group are on opposite sides of the platinum coordination plane). A common feature of the Me_ndienPtL compounds is a signal for the L proton adjacent to the coordinating nitrogen atom,

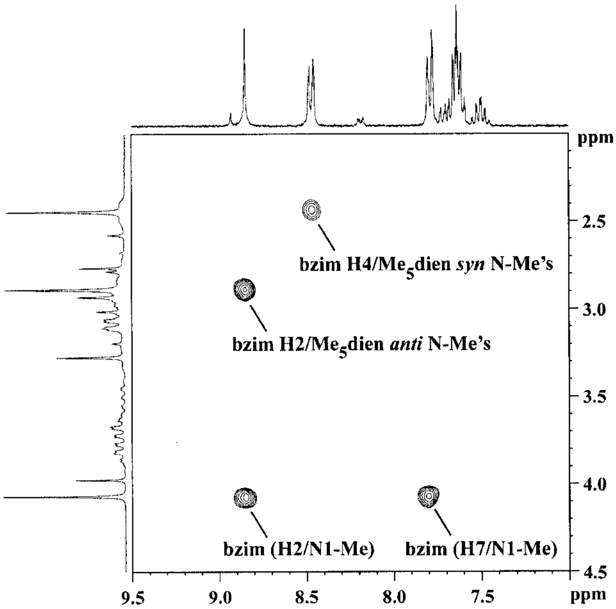


Figure 1. 2D NOESY spectrum of Me_5dienPt(bzim). All crosspeaks belong to the major set of signals that result from the *endo* conformer. The second set of signals has intensities that are too weak to generate observable crosspeaks, and, by exclusion, it is assigned to the *exo* rotamer.

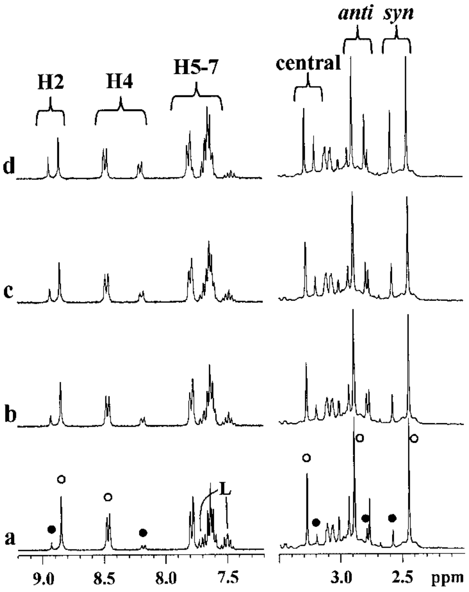


Figure 2. ^1H NMR spectra of Me_5dienPt(bzim) after standing for different times in D_2O solution at 353 K (a, b, c, and d correspond to 0, 1800, 3600, and 12000 s, respectively). The signals of the bzim aromatic protons fall in the region δ = 9–7 ppm, while the Me_5dien protons fall in the region δ = 4–2 ppm. The intensity of the aromatic proton signals is increased by a factor of two with respect to the intensity of the aliphatic proton signals. Peaks labeled with ○ belong to the *endo* rotamer, peaks labeled with ● belong to the *exo* rotamer, and peaks labeled with L belong to unreacted bzim.

Table 1. Chemical shift values (ppm) for the Me_5dienPtL complexes (L = riba or bzim), and the starting $[Pt(Me_5dien)(D_2O)]^{2+}$, bzim, and riba compounds. The sugar protons of Me_5dienPt(riba) not listed in the table underwent rather small chemical shift changes (values for free riba are given in parenthesis): H2′ 4.75 (4.66), H3′ 4.46 (4.50), H4′ 4.30 (4.22), H5′/5′′ 3.91/3.76 (3.87/3.76).

		H2/H5[a]	H4	H7	H5	H6	*N1*-Me/H1′[b]	*N*-Me (Me_5dien)		
								central	*anti*	*syn*
Me_5dienPt(D_2O)								3.04	2.92	2.75
Bzim		8.08	7.72	7.64	7.51	7.49	3.86			
Me_5dienPt(bzim)	*endo*	8.85	8.47	7.79	7.64	7.62	4.07	3.27	2.89	2.44
	exo	8.93	8.18	7.77	7.63	7.60	4.08	3.19	2.79	2.58
Riba		8.75					6.05			
Me_5dienPt(riba)	*endo*	9.81					6.14	3.21	2.80	2.47
	exo	9.90					6.15	3.10	2.71	2.58

[a] H2 for bzim and H5 for riba. [b] *N1*-Me for bzim and H1′ for riba.

Table 2. Experimental C_{endo}/C_{exo} ratios [for Me$_5$dienPt(bzim) complex] evaluated from NMR spectroscopic data. For each temperature (first column) the C_{endo}/C_{exo} value was evaluated at different time intervals (given in parenthesis) starting from the kinetically controlled composition and ending when the equilibrium composition was reached (last value on each line). The values of the equilibrium [$K = (C^{\infty}_{exo}/C^{\infty}_{endo})$] and kinetic constants (k_{endo} and k_{exo}) are also given.

T [K]	C_{endo}/C_{exo} (time [10^3 s])									K	$k_{endo}+k_{exo}$ (10^{-6} s^{-1})	k_{endo} (10^{-6} s^{-1})	k_{exo} (10^{-6} s^{-1})
323	7.69	5.94	3.30	2.48	2.14	2.00	1.83	1.78	1.77	0.565	6.16	2.22	3.93
	(0)	(18.0)	(104)	(187)	(270)	(335)	(594)	(680)	(767)				
333	6.47	6.00	4.25	3.83	2.10	1.83	1.75			0.572	17.1	6.22	10.9
	(0)	(7.20)	(18.0)	(27.0)	(88.2)	(153)	(583)						
343	7.25	3.37	2.58	2.14	1.88	1.72				0.583	146	53.7	92.1
	(0)	(3.60)	(7.20)	(10.8)	(17.0)	(45.0)							
348	5.51	4.33	3.61	2.95	2.40	2.20	2.06	1.86	1.71	0.584	185	68.1	117
	(0)	(0.900)	(1.86)	(2.82)	(5.58)	(7.50)	(9.36)	(12.8)	(35.0)				
353	7.55	4.81	3.76	3.14	2.79	2.48	2.21	1.91	1.70	0.590	239	88.8	150
	(0)	(0.900)	(1.80)	(2.70)	(3.60)	(4.50)	(6.30)	(9.90)	(12.0)				
363	6.23	3.09	2.60	2.13	1.84	1.78	1.67			0.600	769	288	481
	(0)	(0.600)	(1.20)	(1.80)	(3.00)	(3.66)	(6.50)						

more shielded in the *endo* rotamer than in the *exo* rotamer.[13,14,16,17]

The 8:1 ratio between rotamers reflects a kinetic rather than a thermodynamic preference for the *endo* form. As a matter of fact, with time, the *endo*/*exo* ratio decreases until a constant value (representing the thermodynamic equilibrium) is reached (Figure 2). The rate of isomerization is very slow at room temperature, requiring weeks; however, it can be increased by increasing the temperature. In order to evaluate the activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$), the rates of isomerization were measured at different temperatures in the range 323–363 K (Table 2).

The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for the rate of isomerization of the *endo* (k_{endo}) and *exo* (k_{exo}) conformers were found to be almost identical ($\Delta H^{\ddagger} = 118 \pm 9$ and 119 ± 9 kJ mol^{-1} for the *endo* and *exo* rotamers, respectively; and $\Delta S^{\ddagger} = 15 \pm 20$ J K^{-1} mol^{-1}), indicating that the two rotamers have very similar ground-state enthalpy and entropy values (Table 3).

Table 3. Collection of activation enthalpies ($\Delta H^{\ddagger}$ [kJ mol^{-1}]) and entropies ($\Delta S^{\ddagger}$ [J K^{-1} mol^{-1}]) for interconversion between rotamers in Me$_{3/5}$dienPtL complexes. Standard deviations are given at the 95% confidence limit.

Compound	$\Delta H^{\ddagger}_{endo}$	$\Delta H^{\ddagger}_{exo}$	$\Delta S^{\ddagger}_{endo}$	$\Delta S^{\ddagger}_{exo}$
Me$_3$dienPt(penciclovir)[a]	61 ± 2	54 ± 2	-8 ± 4	-29 ± 4
Me$_3$dienPt(9-EtG)[b]	65 ± 2	56 ± 2	2 ± 4	-28 ± 4
Me$_3$dienPt(deoxypenciclovir)[c]	111 ± 2	105 ± 2	181 ± 4	159 ± 4
Me$_5$dienPt(bzim)	118 ± 9	119 ± 9	15 ± 20	15 ± 20

[a] Penciclovir = 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine.[17] [b] 9-EtG = 9-ethylguanine.[16] [c] Deoxypenciclovir = 6-deoxy-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine.[17]

Me$_5$dienPt(riba)

The reaction of [Pt(Me$_5$dien)(NO$_3$)](NO$_3$) with riba was also complete after 48 h at room temperature. Two sets of signals (intensity ratio 7:1) were observed. For both sets of signals the chemical shift of the aromatic proton of riba (H5) is more than 1 ppm at a lower field with respect to the corresponding signal for the free ligand indicating that in both cases the riba ligand is *N4*-coordinated to the platinum atom. Therefore, the two sets of signals have to be ascribed to two conformers, most likely the *endo* and *exo* rotamers (Table 1).

As in the the case of bzim, a 2D NOESY experiment enabled the assignment of the two sets of signals to the corresponding conformers. In particular, the presence of a crosspeak between the riba H5 proton and the *anti-N*-Me signal of Me$_5$dien for the more intense set of signals indicates that in this case the major rotamer also has the *endo* conformation (Figure 3). No isomerization was observed for this compound, even after prolonged heating at 363 K.

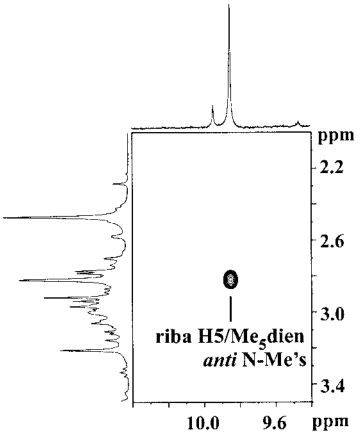


Figure 3. 2D NOESY spectrum of Me$_5$dienPt(riba). The crosspeak belongs to the major set of signals and this set is assigned to the *endo* rotamer. The second set of signals has intensities that are too weak to generate observable crosspeaks and, by exclusion, it is assigned to the *exo* rotamer.

Discussion

In Table 3 we compare the activation parameters for rotamer interconversion in the series of Me$_{3/5}$dienPtL complexes investigated so far. In the case of Me$_3$dien complexes the most remarkable difference was between the guanine and deoxyguanine derivatives. The enthalpy of activation was ca. 50 kJ mol^{-1} higher in the case of the deoxyguanine derivative, notwithstanding the fact that deoxyguanines carry a much smaller group (H) in the 6-position of the purine ring as compared to guanines for which the substituent at the 6-position is much bulkier (O). We argued that in the transition state (in which the purine base is dragged through the platinum coordination plane) the O6 atom of the guanine ligand (negatively charged) and the *N*-hydrogen atom of the *cis*-amine (positively charged) can give rise to an attractive interaction which helps in lowering the rotational barrier. In contrast, in the case of deoxyguanine derivatives, both the purine H6 and the *cis*-amine *N*-hydrogen atom carry a partial positive charge; therefore, the electrostatic repulsion between the two positively charged moieties, when coming close to one another, would increase the rotational barrier, notwithstanding the small size of H6 as compared to O6 of guanine. In the case of deoxyguanine the greater enthalpy of activation is also accompanied by a rather large entropy of activation (average 170 ± 4 as compared to –18 ± 4 J mol^{-1} K^{-1} for guanine derivatives). We suggested that, in the presence of an electrostatic repulsion between the two groups, there could be a large desolvation process (particularly of the amine groups) with the consequent release of water molecules and increase of activation entropy. The explanation given for the Me_3dien derivatives is fully confirmed by the behavior of the Me_5dien derivatives reported in this paper. The major difference between Me_3dien and Me_5dien derivatives is the absence, in the latter case, of positively charged *N*-hydrogen atoms on the *cis*-amine groups. In principle, there could also be a change in steric bulk of the terminal amines (an additional methyl group attached to each terminal nitrogen atom in the case of Me_5dien); however, such a change in steric bulk could be rather small. It has been widely demonstrated that the rotation of a coordinated purine base is mainly affected by substituents on the *cis*-amine, which have "quasi-equatorial" character, and Me_3dien and Me_5dien both have one "quasi-equatorial" methyl group on each terminal nitrogen atom.[14]

The Me_5dienPt(bzim) complex has an activation enthalpy for rotamer interconversion that is very similar to that observed for the Me_3dienPt(deoxyguanine) derivative. The stereochemistry of the H4 proton of bzim is coincident with that of the H6 proton of deoxyguanines; therefore, it is expected to generate a similar steric interaction with the "quasi-equatorial" *N*-Me group on the *cis*-amine, while it is dragged through the platinum coordination plane. Accordingly, the measured $\Delta H^{\ddagger}$ value for rotation is very similar for Me_3dienPt(deoxyguanine) and Me_5dienPt(bzim) complexes. In contrast, the $\Delta S^{\ddagger}$ value was much greater for Me_3dienPt(deoxyguanine) (average 170 ± 4 J K^{-1} mol^{-1}) than for Me_5dienPt(bzim) (average 15 ± 20 J K^{-1} mol^{-1}). The large value of $\Delta S^{\ddagger}$ for the former complex was explained by a desolvation (particularly of the amine NH group) taking place in the transition state; such a desolvation cannot occur in the Me_5dienPt(bzim) complex lacking amine *N*-hydrogen atoms.

The rate of interconversion was found to be extremely low for the Me_5dienPt(riba) complex in which the riba ligand has the O6 substituent stereochemically equivalent to the O6 atom of a guanine group. In the case of Me_3dienPt(guanine) derivatives the $\Delta H^{\ddagger}$ value for rotamer interconversion was found to be lowered by an electrostatic attraction between the negatively charged O6 atom and the positively charged *N*-hydrogen atom of the *cis*-amine. Such an interaction cannot take place in the Me_5dienPt(riba) complex lacking amine *N*-hydrogen atoms. Therefore, contrary to the case of Me_3dienPtL derivatives (for which the $\Delta H^{\ddagger}$ value was significantly lower for guanine as compared to deoxyguanine derivatives), Me_5dienPtL compounds are expected to have a much larger $\Delta H^{\ddagger}$ value for guanine-type derivatives (like the riba complex) having a bulkier substituent at the C6 position than for deoxyguanine-type derivatives (like the bzim complex) having a small proton at the C6 position. This fully explains the much slower rate of rotation observed in Me_5dienPt(riba) as compared to Me_5dienPt(bzim).

Conclusions

This investigation has highlighted two features of Me_5dienPtL compounds (a kinetic preference for the *endo* rotamer and a rate of rotation depending upon the substituent at the *peri* position with respect to the coordinated L nitrogen atom) that further contribute to deepening our understanding of interactions between a rotating platinum(II)-coordinated ligand L and *cis*-amine groups. For the first time in Me_ndienPtL complexes, it has been shown that the kinetically preferred product has the bulkier portion of the ligand L on the sterically less hindered side of the platinum coordination plane (that is the side where the "quasi-equatorial" *N*-methyl substituents are located). In the case of Me_3dienPtL derivatives, the rate of rotamer interconversion was too fast to enable the observation of the kinetically controlled composition.

The investigation of rotamer interconversion in the case of Me_5dienPt(bzim) has fully confirmed the previous observation that an amine proton can play a key role in modulating the rate of rotation of a *cis* ligand, also in the case in which an alkyl substituent is attached to the same nitrogen atom (as in the case of Me_3dienPtL compounds). The presence of such a proton can increase the rate of L rotation by 10 orders of magnitude [compare the rates of rotation of L in Me_3dienPt(deoxyguanine)[17] and in Me_5dienPt(bzim)] and can greatly reduce the difference in the rate of rotation between ligands L having a bulky oxygen atom or a small proton substituent in the *peri* position with respect to the coordinated nitrogen atom. Therefore, for Me_3dienPtL complexes the rate of rotation is only ten times smaller in guanine than in deoxyguanine derivatives (at ambient temperature), while for Me_5dienPtL derivatives the rate is far smaller in the case of riba (mimicking a guanine) than in the case of bzim (mimicking a deoxyguanine).

Recent results from studies on oligomers led to the hypothesis that the very small size of the NH group, and not its hydrogen-bonding ability, is responsible for the good activity exhibited by antitumor Pt compounds with amine carrier ligands bearing multiple NH protons.[7,8,22] In contrast, for amines lacking NH groups, bulky substituents projecting out of the coordination plane could clash with neighboring nucleobases. Since the biological activity of cisplatin is widely considered to be associated with a definite arrangement of the nucleic bases (guanines in first place) linked by the metal center,[6–12] the lack of significant biological activity for platinum complexes bearing bulky ligands can be attributed to the conformational restrictions that the coordinated bases are subjected to in these compounds. On the other hand, it has been recently demonstrated that platinum complexes with specially designed bulky ligands can sort out other interesting effects in the case of coordination to single-strand oligonucleotides.[23] In particular, the negatively charged phosphate groups of the oligonucleotide are no longer able to wrap around the positively charged metal core with the consequence of favoring the hybridization of the oligonucleotide with the complementary strand and tightening the double-strand form. Therefore, we can envisage a possible employment of the platinum complex with Me$_5$dien in the modification of single-strand oligonucleotides to be used in antisense and antigene therapy.

Experimental Section

Materials: [Pt(Me$_5$dien)(NO$_3$)](NO$_3$) was prepared as previously described.[20] Bzim was purchased from Sigma–Aldrich, riba was a gift from Joze Kobe of the Institute of Chemistry of Ljubljana, Slovenia.

Preparation of the Adducts: Solutions of the adducts were prepared by treatment of [Pt(Me$_5$dien)(NO$_3$)](NO$_3$) (5 mM solution in D$_2$O) with a stoichiometric amount of ligand. The reactions were monitored by ^{1}H NMR spectroscopy. When the reaction was complete, the pD of the solution was found to be 7.2 in the case of both bzim and riba.

NMR Spectroscopy: Spectra were collected in D$_2$O at 298 K with a Bruker DPX 300 MHz spectrometer. ^{1}H NMR chemical shifts were referenced to internal TSP. For 2D NOESY experiments a standard pulse program with gradient pulses during the mixing time was used. 2048 complex points in the direct detection dimension and 256 in the indirect dimension were collected. A 3000 Hz spectral width was used in both dimensions with a 500 ms mixing time. Chemical shift values are reported in Table 1.

Kinetic Measurements: NMR tubes containing solutions of the bzim adduct were sealed and kept at a fixed temperature in a water bath. ^{1}H NMR spectra were taken from time to time by collecting 64 scans. Selected nonexchangeable proton signals were integrated and used to determine the relative abundance of the two rotamers. Equilibrium was considered reached when the changes in signal intensities became negligible (after a time that was five-fold larger than the estimated half life at a given temperature). The kinetic constants were determined at six different temperatures covering a range of 40° (323, 333, 343, 348, 353, and 363 K). At equilibrium the *exo*/*endo* ratio (K) was found to be rather constant (comprised between 0.56 and 0.60). The kinetic equation for the $endo \underset{k_{exo}}{\overset{k_{endo}}{\rightleftarrows}} exo$ process has the following expression:

$$\ln \frac{KC^{t}_{endo} - C^{t}_{exo}}{KC^{0}_{endo} - C^{0}_{exo}} = -(k_{endo} + k_{exo})t$$

[in which k_{endo} and k_{exo} are the kinetic constants for the *endo* → *exo* and the *exo* → *endo* conversions, respectively; $K = (C^{\infty}_{exo}/C^{\infty}_{endo}) = (k_{exo}/k_{endo})$ is the equilibrium constant; C^t, C^0, and C^{∞} are the concentrations of a given rotamer (*endo* or *exo*) at time t, at time 0, and at equilibrium]. The graphical representation of the logarithmic term as a function of time (Figure 4) corresponds to a straight line whose slope gives $k_{endo} + k_{exo}$. From the values of k_{endo}/k_{exo} (corresponding to the equilibrium constant K) and of $k_{endo} + k_{exo}$ (kinetically determined) the individual k_{endo} and k_{exo} constants

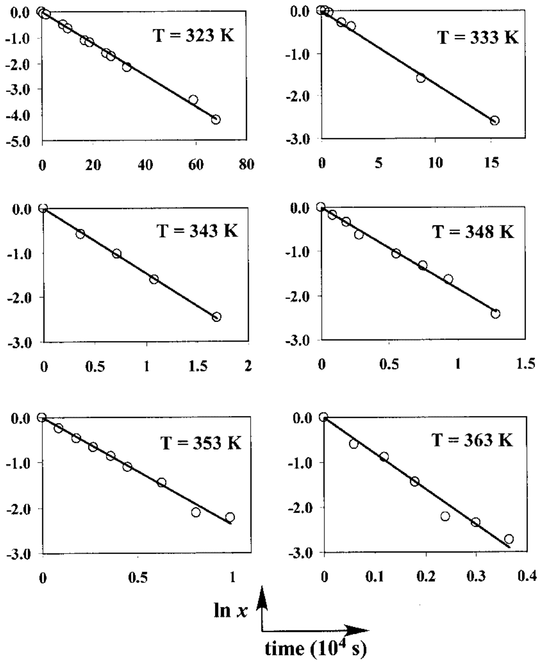


Figure 4. Plots of ln x {$x = [(KC^{t}_{endo} - C^{t}_{exo})/(KC^{0}_{endo} - C^{0}_{exo})]$} as a function of time for the isomerization of Me$_5$dienPt(bzim) at different temperatures.

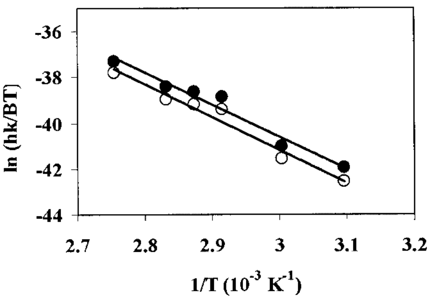


Figure 5. Plots of $\ln(h/B)\cdot(k/T)$ as a function of $1/T$ for the *endo* → *exo* (○) and *exo* → *endo* (●) interconversion of Me$_5$dienPt(bzim). According to the Eyring equation, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be derived from the slope $[(\Delta H^{\ddagger})/R]$ and intercept $[(\Delta S^{\ddagger})/R]$ of the straight line fitting the experimental points.

could be determined. Enthalpies and entropies of activation ($\Delta H^\ddagger$ and $\Delta S^\ddagger$) were estimated (for direct and inverse reactions) from plots of $\ln(h/B)\cdot(k/T)$ vs. $1/T$ (Figure 5), according to the Eyring equation:

$$\ln\frac{h}{B}\frac{k}{T} = -\frac{\Delta H^{\#}}{RT} + \frac{\Delta S^{\#}}{R}$$

[k = kinetic constant (k_{endo} or k_{exo}) at temperature T; h, B, and R, are the Planck, Boltzmann, and gas constants, respectively].[21] Values of C_{endo}/C_{exo} at different time intervals for a given temperature together with the estimated values of K, k_{endo}, and k_{exo} are reported in Table 2. Activation parameters are reported in Table 3.

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