Rotation and Conformation of Purine Ligands in *cis*-Bis(6-oxopurine)-platinum Compounds

A. T. M. MARCELIS, J. L. VAN DER VEER, J. C. M. ZWETSLOOT and J. REEDIJK*

Department of Chemistry, Gorlaeus Laboratories, State University of Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Received September 17, 1982

Several platinum(II) compounds containing two 6-oxopurines in the cis *position have been prepared and studied by nuclear magnetic resonance. As other ligands both methyl-substituted 1,3-propanediamines and pyridines or pyridine derivatives were used. As 6-oxopurines, guanosine and 9-methylhypoxanthine were selected. Rotation of the 6-oxo-purines about their Pt–N7 bonds appears to be fast on the NMR time scale, when no methyl groups are present on the nitrogens of the 1,3-propanediamine ligands. Rotation of the purines about their Pt–N7 bonds is slow on the NMR time scale, when two methyl groups are present on one nitrogen of a 1,3-propanediamine chelate. A single methyl group on a nitrogen hardly seems to interfere with this rotation of the purines about the Pt–N7 bonds. Coordinated pyridines do not hinder rotation of the 6-oxopurines. In compounds containing 2-methylpyridine ligands, the rotation of the pyridines is slow on the NMR time scale at room temperature, but becomes fast at higher temperatures. Rotation of the 6-oxopurines, however, is fast on the NMR time scale from −30 to +90 °C. In compounds containing 1,2-bis(pyridin-2-yl)ethane as a chelating ligand, rotation of the purines is slow on the NMR time scale at low temperatures, but becomes fast at room temperature. Furthermore, the results obtained with these compounds show that the purines are preferentially oriented in a head-to-tail arrangement. The results of this study are of relevance for the study of the proposed second stage of the interaction of* cis-$Pt(NH_3)_2Cl_2$ *with DNA. In the case of formation of an intrastrand crosslink, rotation of the purine about the Pt–N7 bond may be important.*

Introduction

A key step in the mechanism of action of antitumor platinum compounds, like *cis*-$Pt(NH_3)_2Cl_2$, appears to be their binding to DNA [1, 2]. These platinum compounds are known to bind preferentially to the N7 atoms of the guanine bases [3–13]. Recent studies have shown that this may lead to several types of intrastrand crosslinks, *e.g.* crosslinks between adjacent guanines [14–17] or between guanines separated by a third base [18, 19]. The antitumor properties of *cis*-platinum compounds depend on the nature of the amine ligands. It was found that the cytotoxic activity of PtA_2Cl_2 compounds decreases along the series A = NH_3 ~ NH_2R > NHR_2 > NR_3, where A is an aliphatic amine [20, 21]. Compounds with heterocyclic aromatic nitrogen donor ligands, such as pyridine, show only marginal activity [22–24]. The ineffectiveness of platinum compounds with secondary or tertiary amines and pyridines as antitumor drugs may have several reasons. Such compounds may have a limited ability to pass cell walls or nuclear membranes. If that is the case, they will not easily reach DNA. The ability of antitumor active platinum compounds to form hydrogen bonds *via* their N–H groups has been suggested to be essential for activity [24]. Therefore, the inability of compounds containing tertiary amines or pyridines to form hydrogen bonds may be one of the reasons for their poor antitumor properties. Steric hindrance by the amine substituents may also play a role. As a result of steric hindrance, the reaction rate with a nucleic acid base will be decreased. Once a platinum compound is monofunctionally bound to a nucleic acid base, it must be able to accommodate a second base, in order to form the crosslinking lesion. In this respect, steric hindrance of a platinum adduct and the ability to rotate about its platinum–base bond may be of great importance.

A NMR study of (N,N,N′,N′-tetramethyl-1,2-ethanediamine)bis(guanosine)platinum(II) showed that in this compound rotation of the purines about the Pt–N7 bonds is slow on the NMR time scale [25], even at high temperatures. Other ethylenediamine ligands containing no other substituents on

*Author to whom correspondence should be addressed.

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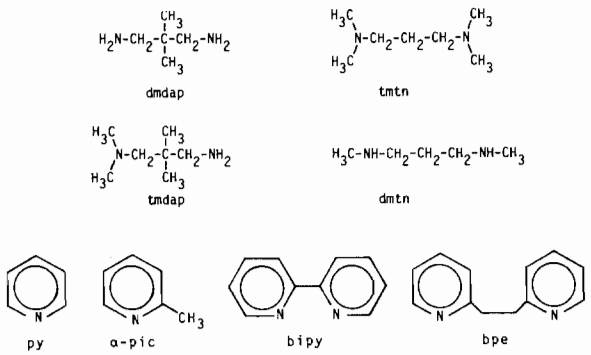

Fig. 1. Structures and abbreviations of the ligands used in this study.

their nitrogen atoms were reported to hinder rotation of guanosine ligands by hydrogen-bond formation between the NH_2 groups of the diamine and O6 of guanosine [26].

Recently, we have shown that rotation of the 6-oxopurine ligands in (1,2-bis(pyridin-2-yl)ethane)-bis(9-methylhypoxanthine)platinum(II) bis(nitrate) is fast on the NMR time scale at room temperature, but becomes slow upon cooling to −50 °C [13]. Furthermore, the 6-oxopurine ligands have a strong preference for a head-to-tail arrangement, *i.e.*, with the bulk of the purines pointing in opposite directions.

This has been concluded from the low-temperature NMR spectra and the crystal structure of this compound [13]. In all crystal structures reported up to date of platinum compounds containing two 6-oxopurines in a *cis*-position, the purines were invariably found to be in a head-to-tail arrangement [5–13].

From a recent CD and NMR study of (1,2-diamine)bis(6-oxopurine)platinum(II) compounds it was concluded that in solution the 6-oxopurines are also present in a head-to-tail arrangement [26]. However, this is not the most likely arrangement when platinum forms a crosslink between two adjacent guanines in DNA [1, 2, 27]. In this case a head-to-head arrangement is more likely.

To learn more about the ability of purines to rotate about the Pt–N7 bonds and about the arrangement of the purines in *cis*-bis(6-oxopurine)-platinum(II) compounds, a NMR study was undertaken of a series of compounds containing either 1,3-propanediamines or pyridines as other ligands. As substituted 1,3-propanediamine ligands were used; 2,2-dimethyl-1,3-propanediamine (dmdap), N,N,N′,N′-tetramethyl-1,3-propanediamine (tmtn), 2,2,N,N-tetramethyl-1,3-propanediamine (tmdap) and N,N′-dimethyl-1,3-propanediamine (dmtn). As pyridines were used: pyridine (py), 2-methylpyridine (α-pic), 2,2′-bipyridine (bipy) and 1,2-bis(pyridin-2-yl)ethane (bpe) (see Fig. 1).

The properties of 1,3-propanediamine chelates with platinum(II) have been studied extensively [28–30]. It appears that the 6-membered chelate is flexible, giving rapid interconversions between the various chair and boat conformations [28]. These interconversions remain fast on the NMR time scale at least down to −50 °C [28].

Two different diastereomers of a platinum chelate with dmtn occur. Both methyl groups on the nitrogens may point in the same direction with respect to the coordination plane (meso), or in opposite directions (racemic forms) [29, 30]. Interconversion between these isomers can occur through a base-catalyzed inversion on the nitrogen atoms [31, 32]. At neutral pH this interconversion is slow on the NMR time scale, and both isomers are generally observed in the NMR spectra of these compounds [29, 30]. Platinum compounds with py [33, 34], bipy [35] and α-pic [36] have been described in the literature. NMR spectra of *cis*-$Pt(\alpha\text{-pic})_2$ compounds have not been reported before. Therefore, they will also be discussed in this paper. As 6-oxopurines the non-chiral purine 9-methylhypoxanthine (9MeHX) and the chiral nucleoside guanosine (guo) have been used (Fig. 2).

Experimental

Starting Materials

$Pt(dmdap)Cl_2$ [37, 38], $Pt(dmdap)I_2$ [38], $Pt(tmtn)Cl_2$ [29], $Pt(tmdap)Cl_2$ [24], $Pt(tmdap)I_2$ [24], $Pt(dmtn)Cl_2$ [39], *cis*-$Pt(py)_2Cl_2$ [34], $Pt(bipy)Cl_2$ [35], *cis*-$Pt(\alpha\text{-pic})_2Cl_2$, $Pt(bpe)Cl_2$ [13] and $Pt(bpe)I_2$ [13] were prepared from K_2PtCl_4 by published methods. All amines, pyridines and guanosine used were commercially available. 9MeHx was prepared from 9-methyladenine [39] by treatment with $NaNO_2$ [40].

Syntheses [26, 41]

A suspension of the proper dichloro-1,3-propanediamineplatinum(II) compound with two equivalents of 9MeHX or guo in water was allowed to react for several days at 70 °C. The resulting almost colourless solution was concentrated to 3 ml. Any precipitate that formed at 5 °C was filtered off. The compound was precipitated by the addition of a large excess of a 1:1 acetone/diethyl ether mixture. In several cases an oil was obtained upon precipitation, which did not solidify. The corresponding nitrate compounds were obtained by the same procedure, starting from the diiodoplatinum compounds, from which the iodides were removed by reaction with $AgNO_3$. The precipitate of AgI was filtered off and

TABLE I. NMR Chemical Shifts of the H8 and H2 Resonances of Guanosine or 9-Methylhypoxanthine in Their Complexes with 1,3-Propanediamine-Platinum Compounds. Coupling Constants J_{Pt-H8} are also given.[a]

Compound	δH8 (ppm)	J (Hz)	δH2 (ppm)
$Pt(dmdap)(9MeHX)_2^{2+}$	8.40	20	8.27
$Pt(dmdap(guo)_2^{2+}$	8.35	22	–
$Pt(tmtn)(9MeHX)_2^{2+}$	8.54	23	8.26
$Pt(tmtn)(guo)_2^{2+}$	8.430; 8.420	26	–
$Pt(tmdap)(9MeHX)_2^{2+}$	8.79; 8.41	23	8.37; 8.35
$Pt(tmdap)(guo)_2^{2+}$	8.73; 8.71; 8.40; 8.35	22	–
$Pt(dmtn)(9MeHX)_2^{2+}$ [b]	8.35; 8.29	25	8.12
$Pt(dmtn)(guo)_2^{2+}$ [b]	8.300; 8.295; 8.255; 8.23	22	–

[a]Neutral pH*; ambient temperature. [b]pH* in these cases was 8.5. pH*: uncorrected meter reading from D_2O solutions.

TABLE II. A Selection of Relevant NMR Chemical Shifts of the Described Platinum Compounds. Observed coupling constants with ^{195}Pt are given in parentheses.[a,b]

Compound	Pyridine		Purine	
	H6	C2 substituent[c]	H8	H2
cis-$Pt(py)_2Cl_2$	8.96 (42)	–	–	–
cis-$Pt(py)_2(MeHX)_2^{2+}$	8.74 (35)	–	8.62 (25)	8.21
cis-$Pt(py)_2(guo)_2^{2+}$	8.79 (39)	–	8.62 (24)	–
cis-$Pt(\alpha\text{-pic})_2Cl_2$	9.17[d] [e]	3.18[d] [e]	–	–
cis-$Pt(\alpha\text{-pic})_2I_2$	9.43 / 9.14 (39)	3.24 / 3.14 (10)	–	–
cis-$Pt(\alpha\text{-pic})_2(9MeHX)_2^{2+}$ [f]	9.02 (37)	3.33 (8)	8.54 (23)	8.23
cis-$Pt(\alpha\text{-pic})_2(guo)_2^{2+}$ [f]	9.06 (36)	3.31 (8)	8.45 (24)	–
$Pt(bipy)Cl_2$	9.70 (36)	–	–	–
$Pt(bipy)(9MeHX)_2^{2+}$	8.39 [e]	–	8.70 (20)	8.34
$Pt(bipy)(guo)_2^{2+}$	8.37 [e]	–	8.66 / 8.62 (25)	–
$Pt(bpe)Cl_2$	9.05 (45)	4.64; 3.58	–	–
$Pt(bpe)I_2$	9.08 (45)	4.43; 3.57	–	–
$Pt(bpe)(9MeHX)_2^{2+}$	8.92 (39)	5.26; 3.86	8.87 (22)	8.23
$Pt(bpe)(guo)_2^{2+}$	8.72 [e]	5.05; 3.70	8.64 [e]	–

[a]Chemical shifts are given in ppm; coupling constants in Hertz. [b]Spectra of the neutral complexes were recorded in $(CD_3)_2SO$ (reference TMS), and those of the ionic compounds in D_2O (reference tetramethylammonium nitrate, 3.18 ppm downfield from TSP). Spectra were recorded at ambient temperature from approximately 0.05 *M* solutions. [c]These resonances originate from the $\alpha-CH_3$ group of the α-pic ligand and from the ethylene bridge protons of the bpe ligand. Two distinct resonances are observed for the bridge protons of the bpe ligand. [d]These resonances were very broad. [e]Coupling constants with ^{195}Pt could not be determined because the satellites were not sufficiently resolved. [f]Spectra of these compounds were recorded at 80 °C.

the filtrate was allowed to react with 9MeHX or guo, in the same manner as the chlorides.

The composition of the obtained products was verified by NMR. The integration of resonances from the diamine were compared with those from the 6-oxopurine. Downfield shifts for the H8 resonances of the purines, and the presence of satellites due to coupling of H8 with the ^{195}Pt nucleus, confirmed the coordination of platinum to the N7 atom. In a few cases minor impurities were removed by Sephadex G-25 gel chromatography.

TABLE III. Theoretical Number of Sets of Resonances Expected in the NMR Spectra for the 6-Oxopurines in *cis*-Bis(6-oxopurine)platinum(II) Compounds.

Class	Diamine ligand	Chelate symmetry[d]			Number of sets of resonances in NMR					
					9MeHX			guo		
		$C_2(x)$	$\sigma(xz)$	$\sigma(xy)$	fast r.	slow r. hth	slow r. htt	fast r.	slow r. hth	slow r. htt
A	dmdap, tmtn	+	+	+	1	1	1	1	2	2
B	dmtn (meso)	–	+	–	1	2[a]	2	2	4[a]	4
C	dmtn (rac.)	+	–	–	1	2	2[a]	2	4	4[a]
D	tmdap	–	–	+	2	2[b]	2[b]	2	4[b]	4[b]
E	–[c]	–	–	–	2	4[a,b]	4[a,b]	4	8[a,b]	8[a,b]

r. = rotation, rac. = racemic, hth = head-to-head, htt = head-to-tail.
[a]Due to the absence of a mirror plane in the coordination plane of the platinum chelate, the amine may favor particular conformations of the 6-oxopurines by steric hindrance. In the extreme case, which some conformations are effectively prevented by steric hindrance, half the number of sets of resonances may be found in the indicated cases. [b]The indicated number of sets of resonances is also valid when only one of the purines would rotate slowly on the NMR time scale. [c]Class E would comprise chelates of platinum(II) with, for example, N-methyl-1,3-propanediamine. Compounds with such chelates were not studied, due to the expected complexity of the NMR spectra of these compounds. [d]The reference axes are defined in Fig. 3.

NMR Spectroscopy

^1H NMR spectra were routinely obtained from approximately 0.05 *M* solutions in D_2O at room temperature on a JEOL PS-100 spectrometer. The pH of the solutions was usually between 5 and 6, where the N1 of the 6-oxopurine is expected to be protonated. In some cases spectra were also recorded on a Varian T-60, Bruker HDX-360 or Bruker WM-300 spectrometer. Tetramethylammonium nitrate was used as an internal reference for the aqueous solutions (δ = 3.18 ppm downfield from TSP). For the low-temperature studies the compounds were dissolved in a D_2O/CD_3OD mixture with tetramethylsilane (TMS) as an internal reference. The temperature was determined before and after each measurement from the chemical shift difference between the $-CH_3$ and $-OH$ resonances from a methanol sample, or from the HDO–TMA chemical shift difference in the high-temperature studies. $^{13}C\{^1H\}$ NMR spectra of $[Pt(dmdap)(guo)_2]Cl_2$ and $[Pt(tmdap)(guo)_2]Cl_2$ were obtained on a JEOL PS-100 spectrometer at ambient temperature. Dioxane (δ = 67.73 ppm downfield from TMS) was used as an internal shift reference.

Results and Discussion

General

The chemical shifts, especially of the purine H8 resonances are slightly dependent upon the temperature, the concentration and the nature of the counter ion. With increasing temperature the H8 resonances shift upfield. This effect has been observed earlier for [Pt(N,N,N′,N′-tetramethyl-1,2-ethanediamine)-$(guo)_2]Cl_2$ [25]. Upon lowering the concentration an upfield shift of the H8 signals is observed. Both these effects can amount to 0.1–0.2 ppm. Typical NMR chemical shifts of some of the 9MeHX and guo resonances of the platinum compounds are listed in Tables I and II. Ligand exchange or dissociation of the compounds containing four nitrogen-donor ligands is unlikely, and is not observed in aqueous and methanolic solutions under the conditions employed.

Stereochemical Considerations

Two purines coordinated to a square-planar platinum(II) atom in a *cis*-position through their N7 atoms may have a different chemical environment. This is obvious when the other coordinating groups are different.

Crystallographic studies of platinum compounds with N7 bound purines [5–13], show that the angle between the coordination plane and a plane through the purines is large. This means that in a *cis*-bis-(purine)platinum compound the bulk of the purines can be either on the same side of the coordination plane or on opposite sides. These conformations will be called head-to-head and head-to-tail, respectively. Generally, there will be an energy difference between these conformations, and one of them can be expected to predominate. When the purines are in a head-to-tail arrangement, they will also have a different chemical environment when the other ligands are the same, but cause a different chemical environment

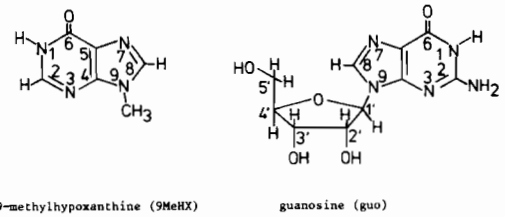

Fig. 2. Structures and numbering schemes of the used 6-oxopurines.

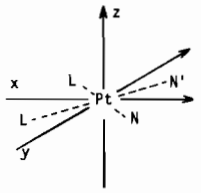

Fig. 3. Figure belonging to Table III.

with respect to the coordination plane, as for example in the Pt(meso-dmtn) chelate.

Upon coordination of two nucleosides with their chiral D-riboses, two diastereoisomers are formed, at least when the purines are in a head-to-tail arrangement. If the purines are in a head-to-head arrangement, their chemical environments are different from one another within the same molecule.

NMR is a powerful tool to study the environments of molecules or ligands. If, however, the interconversion between isomers, for example by ligand exchange or by rotation is fast on the NMR time scale, 'time-averaged' signals will be observed. The theoretical numbers of sets of resonances for the purines in *cis*-bis(6-oxopurine)platinum(II) compounds have been summarized in Table III. This table is based on the assumption that the possible conformers of the 1,3-propanediamineplatinum(II) chelate rings are in fast equilibrium on the NMR time scale. The 6-membered 1,3-propanediamineplatinum(II) chelates and bis(pyridine)platinum(II) compounds used in this study cover four of the symmetry classes indicated in Table III. The reference axes are given in Fig. 3. To illustrate how the numbers in Table III were derived, one case (Pt(tmdap)$(guo)_2^{2+}$) will be treated in more detail. Schematic representations of the possible conformers are given in Fig. 4. The head-to-tail conformers are represented by structures *a* and *b*; the head-to-head conformers are represented by *c* and *d*. In all conformers the two guanosines are different from one another, because A and B are different.

Therefore, in the case of slow rotation of the purines, four sets of resonances are expected when

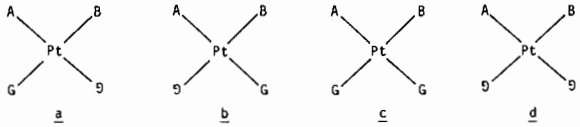

Fig. 4. Schematic representation of the possible different conformers of Pt(tmdap)$(guo)_2^{2+}$. A and B represent the two different coordination sites of tmdap. G and Ɔ represent guanosines with their relative orientations.

the purines are in a head-to-tail arrangement (*a* and *b*), and also four sets when the purines are in a head-to-head arrangement (*c* and *d*). Interconversion between all four conformers is possible by rotation about the Pt–G bonds. Therefore, only two sets of resonances are expected in the NMR spectra if rotation of the guanosines is fast on the NMR time scale.

[Pt(dmdap)L_2]X_2 (L = 9MeHX or guo, X = Cl^- or NO_3^-) (Class A)

In these compounds only one set of resonances is observed for the purine protons in the 100 and 360 MHz NMR spectra. This indicates that rotation of the purines about the Pt–N7 bonds is fast on the NMR time scale. NMR spectra of [Pt(dmdap)$(guo)_2$]$(NO_3)_2$ dissolved in a D_2O/CD_3OD mixture were recorded down to about −50 °C. At low temperatures no essential differences were observed with spectra recorded at room temperature, although some broadening of the resonances occurred. For the diamine ligand two singlets are observed for the $-CH_3$ and $-CH_2$ groups. The ^{13}C NMR spectra of the guanosine compound show also one set of resonances for the guo ligands (see Table IV). The coordination shifts are comparable with the results obtained earlier for other bis(guanosine)platinum compounds [33].

[Pt(tmtn)L_2]Cl_2 (L = 9MeHX or guo) (Class A)

100 MHz ^1H NMR spectra of [Pt(tmtn)$(9MeHX)_2$]Cl_2 show one set of resonances for the 9MeHX ligands. However, in this case two N-CH_3 resonances for the aliphatic diamine ligand are observed. This clearly indicates that rotation about the Pt–N7 bonds is slow. The 360 MHz NMR spectrum of [Pt(tmtn)$(guo)_2$]Cl_2 shows two sets of resonances for the guo ligands. Unfortunately, the expected splitting of the two N-CH_3 resonances was not observed. These results agree with the findings by Cramer *et al.* for [Pt(N,N,N′,N′-tetramethyl-1,2-ethanediamine)$(guo)_2$]Cl_2 [25], although in our case the splitting of the guo H8 resonances (0.010 ppm) is much smaller. This is probably due to the greater flexibility of the 1,3-propanediamine chelate compared with the 1,2-ethanediamine chelate. The results with both compounds indicate that, due to steric hindrance by the $N(CH_3)_2$ groups, rotation of the

TABLE IV. ^{13}C NMR Chemical Shifts of Guanosine[a], $[Pt(dmdap)(guo)_2]Cl_2$[b] and $[Pt(tmdap)(guo)_2]Cl_2$.[b]

Compound	C6	C2	C4	C8	C5
guo	157.8	154.6	152.4	136.9	117.6
$[Pt(dmdap)(guo)_2]Cl_2$	157.8	155.6	151.7	141.0	115.4
$[Pt(tmdap)(guo)_2]Cl_2$	157.43	155.67	151.94	140.6	115.1
	157.34	155.52	151.88		
	157.25		151.58		
	157.16		151.45		

[a]Taken from Reference 42 ($(CD_3)_2SO$ solution). [b]Ambient temperature, D_2O solution, approximately 0.2 *M*.

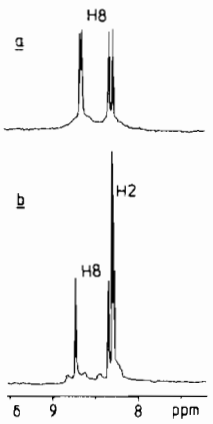

Fig. 5. Aromatic region of the ^1H NMR spectra (D_2O, 0.1 *M*, 20 °C, 100 MHz) of a) $[Pt(tmdap)(guo)_2]Cl_2$, showing the four H8 resonances, and of b) $[Pt(tmdap)(9MeHX)_2]Cl_2$, showing two sets for the H8 and H2 resonances and weak satellites, due to coupling of ^{195}Pt with H8.

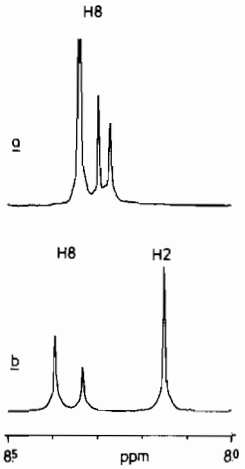

Fig. 6. Aromatic region of the ^1H NMR spectra (D_2O, 25 °C, 300 MHz, pH* 8.5) of a) $[Pt(dmtn)(guo)_2]Cl_2$, and of b) $[Pt(dmtn)(9MeHX)_2]Cl_2$, showing the H8 resonances of guo and the H8 and H2 resonances of 9MeHX. The two expected H2 resonances of 9MeHX coincide.

purines about the Pt–N7 bonds is slow on the NMR time scale. Whether the purines are in a head-to-tail or head-to-head arrangement cannot be concluded from these results.

$[Pt(tmdap)L_2]X_2$ (L = 9 MeHX or guo, X = Cl^- or NO_3^-) (Class D)

As is seen from Table III two sets of resonances for the 9MeHX ligands of $Pt(tmdap)(9MeHX)_2^{2+}$ should be observed in the NMR spectra. This is indeed the case (see Fig. 5b). $[Pt(tmdap)(guo)_2]Cl_2$ shows four sets of resonances for the guo ligands (Fig. 5a). This indicates that rotation of the purines about their Pt–N7 bonds is slow on the NMR time scale. It does not necessarily mean that rotation of both purines is slow. In this compound there is only one $N(CH_3)_2$ group, so at least the purine *cis* to this group will be hindered in its rotation. On the other side of the diamine ligand there are no methyl

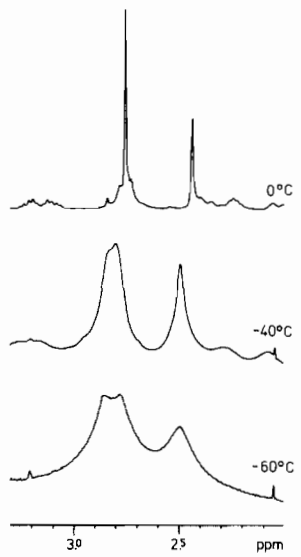

Fig. 7. Part of the ^1H NMR spectra of $[Pt(dmtn)(9MeHX)_2]Cl_2$, showing the N-CH_3 resonances of the dmtn ligand at various temperatures (70% CD_3OD/30% D_2O, 300 MHz).

substituents. Therefore, it is still possible that rotation of the purine on this side of the molecule is fast. Upon heating a solution of this compound, two of the four H8 resonances merge. However, because no sign of coalescence is found and there remain three resonances, we have to conclude that even at 90 °C rotation of the sterically hindered purine is slow on the 100 MHz NMR time scale; this means less than $10-10^2$ rotations of the purine per second. The ^{13}C NMR spectra of this compound show four resonances for the guo C4 and C6 atoms. A splitting of the resonances in two signals is observed for C2 and C5′. For the other carbon atoms only one signal is observed, although the C8 resonance is very broad (see Table IV). These results illustrate that ^{13}C NMR is also useful for the study of the rotational phenomena, although the expected number of sets of resonances is only observed for a few signals.

[Pt(dmtn)L_2]X_2 (L = 9MeHX or guo, X = Cl^- or NO_3^-) (Class B and C)

The compound [Pt(dmtn)(9MeHX)$_2$]Cl_2 shows two unequal sets of resonances for the 9MeHX ligands (see Fig. 6b). There are also two sets of resonances for the diamine ligand. In the compound [Pt(dmtn)(guo)$_2$]Cl_2 four sets of resonances for the guo ligands are observed in the 300 MHz spectra (Fig. 6a).

As is seen form Table III four possibilities would agree with these results:

i) Fast rotation of the purines with the Pt(dmtn) chelate in the meso and racemic form,

ii) slow rotation of the purines, with the purines in the sterically less hindered conformation, imposed by the meso and racemic isomers of the Pt(dmtn) chelate,

iii) a meso isomer of the chelate, with the purines in a head-to-head arrangement, and

iv) a racemic isomer of the chelate with the purines in a head-to-tail arrangement.

Possibilities iii) and iv) not only imply a blocking of the rotation of the purines, but also a strong influence of the purines on the meso/racemic ratio of the Pt(dmtn) chelate. This seems possible only with the purines in the sterically less hindered positions. Therefore, in these cases one set of resonances would be expected for the compound with 9MeHX as a ligand.

There are two arguments that suggest that fast rotation of the purines indeed occurs. If the dmtn ligands force the purines into a particular arrangement, then the purines should also be able to force the dmtn chelate into a particular arrangement. Since the 6-oxopurines have a strong preference for a head-to-tail arrangement [13], one isomer of the Pt(dmtn) chelate would be expected to predominate strongly, as is found in Pt(dmtn)(2,2′-bipyridine)$^{2+}$, where the bipyridine ligand forces the Pt(dmtn) to adopt the meso form [30]. In the Pt(dmtn)(6-oxopurine)$_2^{2+}$ compounds, two isomers of the Pt(dmtn) chelate are clearly present (see Fig. 7). Furthermore, at low temperature (approximately –60 °C) one of the N-CH_3 resonances of the dmtn ligand in the 300 MHz NMR spectra of [Pt(dmtn)(9MeHX)$_2$]Cl_2 appears to be very broad and close to a doublet (Fig. 7). This could indicate that, at this temperature, rotation of the purines has become slow. Alternatively, it is possible that the platinum chelate is no longer flexible at these low temperatures. Apparently, the presence of one methyl substituent on one of the nitrogens of a 1,3-propanediamine-platinum chelate hardly interferes with the rotation of the purines. Because the chelate ring remains flexible, the methyl groups can easily adopt an axial position to allow fast rotation of the purines.

[cis-Pt(py)$_2L_2$]Cl_2 (L = 9MeHX or guo)

In the 100 MHz NMR spectra of these compounds only one set of resonances is observed for the 6-oxopurine ligands, even at –30 °C. This indicates that rotation about the Pt–purine N7 bonds is fast on the NMR time scale.

[cis-Pt(α-pic)$_2L_2$]X_2 (L = 9MeHX or guo, X = Cl^- or NO_3^-)

NMR spectra of *cis*-Pt(α-pic)$_2Cl_2$ obtained from solutions in $(CD_3)_2SO$ at room temperature show broad resonances for the α-CH_3 and H6. Upon heating to 50 °C these resonances become much sharper. NMR spectra of *cis*-Pt(α-pic)$_2I_2$ show two separate signals for the α-CH_3 and H6 resonances, both with satellites resulting from coupling with the ^{195}Pt nucleus. Upon heating to 50 °C these resonances remain sharp. At higher temperatures the compound rapidly decomposes, probably through ligand exchange reaction with the solvent [43].

Due to hindered rotation about the Pt–N bond, two rotational isomers are possible for *cis*-Pt(α-pic)$_2X_2$: one with both methyl groups on the same side of the coordination plane, and one with both methyl groups on opposite sides of this plane. As a result of steric hindrance the pyridines will tend to be perpendicular to the platinum coordination plane.

In the chloride compound rotation of the α-pic ligands becomes fast on the 100 MHz NMR time scale above 30 °C where they give rise to one averaged set of resonances. At 50 °C the satellites, due to coupling of ^{195}Pt with H6 (~40 Hz) become distinguishable. In the iodide compound rotation of the α-pic about the Pt–N bond is still slow on the NMR time scale at 50 °C. This is probably due to steric hindrance by the iodide groups, which are larger than chloride groups. A hindered rotation of *ortho*-substituted pyridines has been suggested before [44].

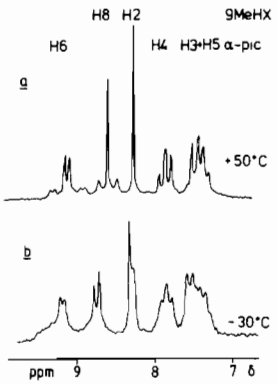

Fig. 8. Aromatic region of the ^1H NMR spectra of [*cis*-Pt(α-pic)$_2$(9MeHX)$_2$](NO$_3$)$_2$, showing the aromatic resonances of the α-pic ligand and the H8 and H2 resonances of 9 MeHX. Spectra were obtained at a) 50 °C and b) −30 °C. At 50 °C satellites are seen due to coupling of ^{195}Pt with H8 of 9MeHX and H6 of α-pic (70% CD_3OD/30% D_2O, 100 MHz).

At high temperatures the spectra of the compounds [*cis*-Pt(α-pic)$_2$L$_2$]X$_2$ (L = 9MeHX or guo, X = Cl^- or NO_3^-) show one set of resonances for the 6-oxopurines (Table II). Also one set of resonances for the α-pic ligands is observed. This indicates that rotation of the purines and of the α-pic ligands is fast at this temperature. Upon cooling coalescence is observed for the α-CH_3 resonances of α-pic at about 50 °C. At room temperature and below two separate resonances are observed for these protons. This implies that two different rotamers are present in solution; one with methyl groups on the same side of the coordination plane, and one with the methyl groups on opposite sides. At −10 °C [*cis*-Pt(α-pic)$_2$(9MeHX)$_2$](NO$_3$)$_2$ indeed shows two sets of resonances for the 9MeHX ligands. No further spectral changes are observed upon cooling to −30 °C (Fig. 8). This agrees with a fast rotation of the 9MeHX ligands at this temperature for both *cis*-Pt(α-pic)$_2$ rotamers. Fast rotation of the guo's in both rotamers of *cis*-Pt(α-pic)$_2$(guo)$_2^{2+}$ should yield four sets of resonances (see Table III; Class B and C); however, the resonances are rather broad at −30 °C and only two sets are observed.

[Pt(bipy)L$_2$]Cl$_2$ (L = 9 MeHX or guo)

Two sets of purine resonances are found in the NMR spectra of [Pt(bipy)(guo)$_2$]Cl$_2$, and only one set for [Pt(bipy)(9MeHX)$_2$]Cl$_2$. This indicates that rotation of the purines about the Pt–N7 bonds is slow in these compounds, most likely caused by steric hindrance by the planar bipyridine ligand.

[Pt(bpe)(guo)$_2$](NO$_3$)$_2$

Upon coordination of bpe to platinum a rigid 7-membered chelate is formed. This is clearly indicated by NMR spectra of compounds containing this chelate [13]. This ligand introduces different environments above and below the platinum coordination plane. This has been confirmed by crystal structure determinations of compounds containing the Pt–bpe moiety [13, 45]. A recent NMR and crystallographic study of [Pt(bpe)(9MeHX)$_2$](NO$_3$)$_2$ showed that the 9MeHX ligands are preferentially in a head-to-tail arrangement, and that rotation of the purines becomes slow on the NMR time scale at low temperatures [13]. [Pt(bpe)(guo)$_2$](NO$_3$)$_2$ should exhibit two sets of resonances in its NMR spectra for the guo ligands when there is fast rotation about the Pt–N7 bonds (see Table III; Class B). The H8 and H1′ resonances seem to be too broad at room temperature, but even at 360 MHz these resonances are not split (spectra not shown). However, two separate H2′ resonances are observed. Upon cooling the H8 resonance strongly broadens and at −40 °C two H8 resonances appear. This is probably due to the fact that rotation about the Pt–N7 bonds becomes slow, just as in [Pt(bpe)(9MeHX)$_2$](NO$_3$)$_2$, although in fact four resonances should be observed in this case, when the purines are in a head-to-tail arrangement.

Conclusions

From the above-discussed results it is concluded that rotation of 6-oxopurines about their Pt–N7 bonds may be hindered by ligands in *cis* positions. The presence of two methyl groups on one nitrogen of a 1,3-propanediamine chelate effectively hinders rotation. When there are no substituents, rotation of the purines remains fast on the NMR time scale between −50 and +90 °C. One methyl group on a nitrogen hardly seems to interfere with the rotation of the purine, probably because in this case the methyl groups can easily adopt an axial position to allow rotation of the purines.

Pyridines, which can be oriented perpendicular to the platinum coordination plane, like pyridine and 2-methylpyridine do not hinder rotation of the purines. 2,2′-Bipyridine, whose pyridines lie in the platinum coordination plane, however, appears to hinder the rotation of the purines about the Pt–N7 bond.

The ligand bpe was found to be very suitable for the study of the conformation and rotational behaviour of *cis*-bis(6-oxopurine)platinum compounds.

This study has also provided profound evidence for the assumptions made by Cramer and Dahlstrom [25], and confirms their conclusions about the rotation of the purines about Pt–N7 bonds.

Rotation about a Pt–purine or Pt–pyrimidine bond may be important for intrastrand crosslinking in DNA. Such crosslinking will be easier if, after an

initial monofunctional binding, the Pt adduct can rotate to accommodate a second base, to which it is able to bind.

Acknowledgements

This work has been carried out under the auspices of S.O.N., with financial aid from the Netherlands Organization of Pure Research (Z.W.O.).

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