Therefore, it might reasonably be predicted that the chemistry of the mixture would be dominated by the chemistry of NSCl. This is true, in some cases. Thus $(NSCl)_3$[27] and 3 $SNSAsF_6$ react in SO_2 quantitatively to give $ClSSNSNAsF_6$ (see Table I). The reaction likely proceeds by the symmetry-allowed cycloaddition of NSCl with SNS^+, as is observed for $SNSAsF_6$ and NSF leading to $FSSNSNAsF_6$.[20] Solutions of $(NSCl)_3$[27] (0.244 g, 1.01 mmol) in SO_2 (3.37 g) react with the perfluoro diene $F_2CCFCFCF_2$ (0.496 g, 3.06 mmol) to give $ClSCF_2CFCFCF_2N$ quantitatively (^{19}F NMR;[21] ^{14}N NMR δ −263, $\Delta\nu_{1/2}$ = 230 Hz). Presumably the reaction proceeds via the symmetry-allowed Diels–Alder type cycloaddition reported for NSF and the same diene.[21]

In view of the above, it would be reasonable to expect that a mixture of $(NSCl)_3$ in SO_2 (essentially NSCl in SO_2) and 3 $AgAsF_6$ would lead to the rapid formation of 3 AgCl (insoluble in SO_2) and 3 $NSAsF_6$ in solution at room temperature as described by eq 2. In fact, this does not occur. Addition of $AgAsF_6$

$$(NSCl)_3 + 3AgAsF_6 \rightarrow 3AgCl\downarrow + 3NSAsF_6 \qquad (2)$$

to solutions of $(NSCl)_3$ in SO_2 gave a mixture that did not contain $(NSCl)_3$, NSCl, or NS^+ (^{14}N NMR). Only on removal of the solvent and heating of the solid is reaction 2 completed and $NSAsF_6$ generated (^{14}N NMR and ref 14).

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cis-Diamminediaquaplatinum(II) Selectivity for GpG: Influence of the Adjacent Base on the First Platination Step

Sir:

One important point characterizing the binding of the anticancer drug *cis*-diamminedichloroplatinum(II) ("cisplatin") to DNA is the drug's high affinity for d(GpG) sites.[1] From studies on nucleosides and nucleotides, it is known that guanine N7 atoms are the best DNA ligands for Pt(II).[2] But in vitro[3] as well as in vivo[4] experiments have shown that cisplatin binds to d(GpG) sites with a frequency exceeding the statistical probability, assuming all guanines to be equireactive. Calculations of molecular potentials have revealed that the negative potential at the N7 atom of a guanine is enhanced in the presence of an adjacent guanine at both the 5′- and 3′-sides.[5] These effects are, however, small and not likely to explain solely the observed GpG affinity of cisplatin. We present here conclusive evidence that, for single-stranded ribodinucleotides, interactions of the platinum ligands with the adjacent base are an important factor making GpG more reactive toward *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$, the aquated form of cisplatin, which seems to be the active compound forming the adducts with the dinucleotides.[6] Although dinucleotides are not necessarily good models for DNA, the selective GpG (or d(GpG)) binding could have the same origin in both cases. Since platinum binding to DNA is controlled kinetically,[7] the binding site is determined by the first platination step. Thus, we measured and analyzed the rate constants for the first platination of XpG and GpX dinucleotides (X = G, A, C) by *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ (cation of **1**) and interpreted them by molecular mechanics modeling of the pentacoordinated reaction intermediate, which we expect to have a geometry similar to that of the transition state, since H_2O is a good leaving group.[8] A set of analogous experiments using $[Pt(NH_3)_3(H_2O)]^{2+}$ (cation of **2**) was done to reveal the role of the nonleaving H_2O ligand of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$.

Table I. Rate Constants of the First Platination Step of Dinucleotides by *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ (**1**) and $[Pt(NH_3)_3(H_2O)](NO_3)_2$ (**2**)[a]

		k_1, $M^{-1}\cdot s^{-1}$	
		1	**2**
$k_1(3')$	GpG	5.7 ± 1.0	0.61 ± 0.02
$k_1(3')$	ApG	1.7 ± 0.1	0.40 ± 0.02
$k_1(3')$	CpG	2.2 ± 0.1	0.52 ± 0.05
$k_1(5')$	GpG	2.8 ± 0.5	0.31 ± 0.02
$k_1(5')$	GpA	0.8 ± 0.1	0.31 ± 0.02
$k_1(5')$	GpC	0.95 ± 0.1	0.44 ± 0.05

[a] The kinetic studies were done under pseudo-first-order conditions, with **1** or **2** (0.1 to 0.4 mM) and the dinucleotide (0.01 mM) at pH 5.2 and 20 °C. UV data were recorded for the disappearance of the dinucleotide and appearance of the monocoordinated complex (λ = 280 nm). Differential UV monitoring of the reactions clearly showed two isosbestic points. The rate constants were obtained from the analysis of the UV absorbance data by nonlinear regression with the Marquardt algorithm,[12] as previously reported for the platination of ApG and GpA by **1**.[13] The rate constants obtained from the data of HPLC monitoring of the reactions (**1** or **2**, 10–15 mM; dinucleotide, 1 mM) were in good agreement with the UV results.

The kinetic data are summarized in Table I. They show that, for the diaqua complex **1**, (i) the presence of a 5′-guanine favors the platination of the 3′-guanine by a factor of $\simeq$3 ($\simeq$5.7/1.7 $\simeq$ 5.7/2.2) relative to the case where the 5′-neighbor is A or C and (ii) the presence of a 3′-guanine, instead of 3′-A or 3′-C, favors the platination of the 5′-guanine also by a factor of $\simeq$3 ($\simeq$2.8/0.8

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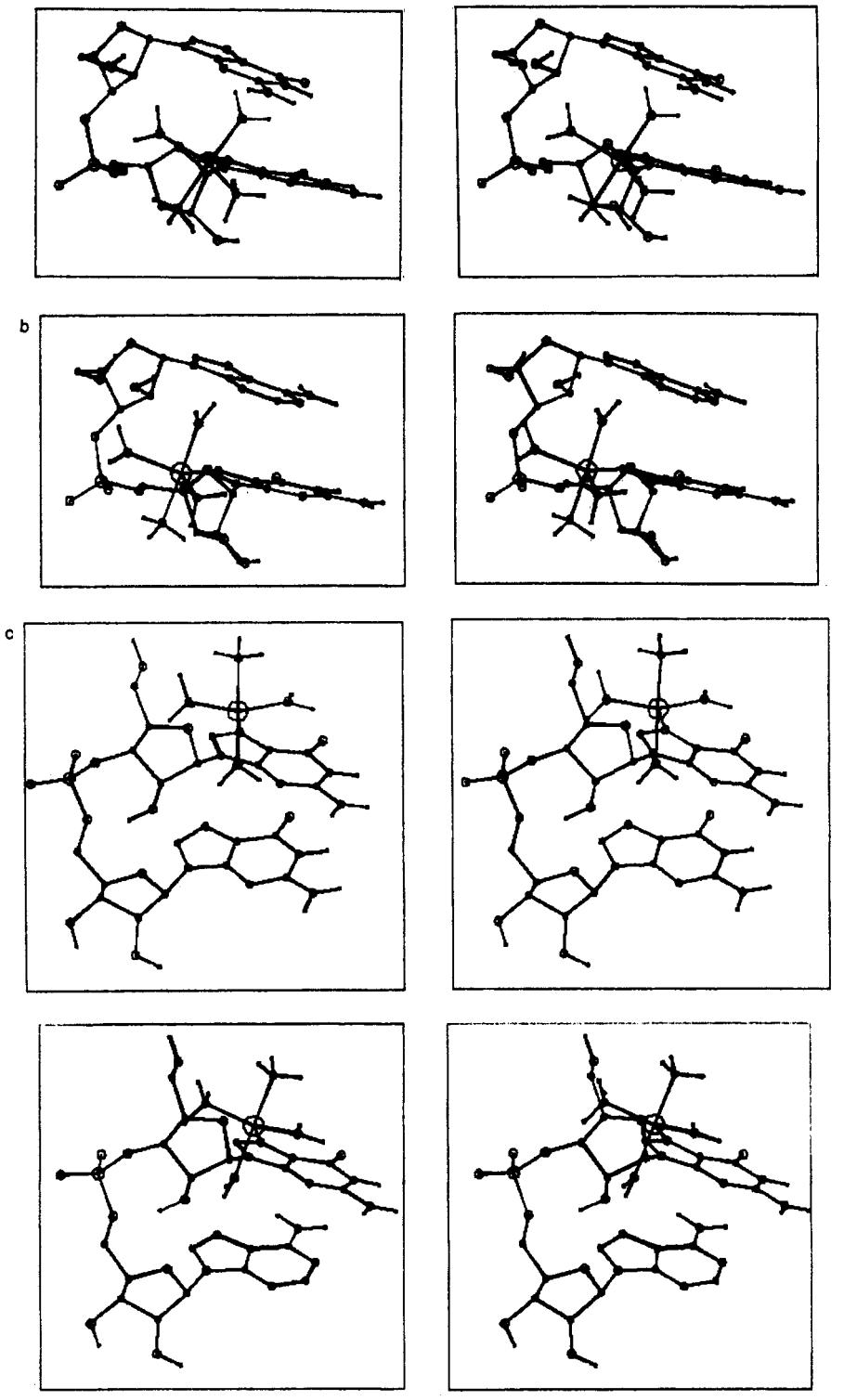

Figure 1. Stereoscopic views of structures modeling the pentacoordinated intermediates for the first coordination of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ to the 3′-G of (a) GpG and (b) ApG and to the 5′-G of (c) GpG and (d) GpA.

$\simeq$ 2.8/0.95). Furthermore, for $[Pt(NH_3)_3(H_2O)]^{2+}$, we see that (iii) all the rate constants are smaller than those obtained for **1** and (iv) preferences i and ii are considerably reduced or do not exist.

From the ratios of the rate constants shown in Table I, differences in the free energies of activation can be calculated. For instance, for *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ reacting with the 3′-G of GpG, compared to ApG, or with the 5′-G of GpG, compared to GpA, the difference between the free energies of activation is 0.7 $\pm$ 0.2 kcal/mol in favor of GpG in both cases.

Molecular models of the pentacoordinated intermediates were constructed by assuming trigonal-bipyramidal geometry around platinum, with bond lengths to axial ligands of 2.0 Å and to equatorial ligands of 2.07 Å.[9] Both possible configurations around

(9) The charges for the coordinated guanine were derived from a quantum-mechanical study of $[Pt(NH_3)_3(gua)]^{2+}$[10] and were as follows: C1′, +0.410; H1′, +0.043; N9, −0.081; C8, +0.333; H8, +0.113; N7, −0.660; C5, −0.111; C6, +0.721; O6, −0.460; N1, −0.758; H1, +0.381; C2, +0.939; N2, −0.772; HN2A, +0.358; HN2B, +0.369; N3, −0.682; C4, +0.564; Pt, +0.930. NH_3 ligands: N, −0.525; H, +0.240. H_2O ligands: O, −0.770; H, +0.460. The force constants used were as follows: Pt–X(axial), 180 kcal/(mol·Å^2); Pt–X(equatorial), 202 kcal/(mol·A^2); Pt–N–H, 35 kcal/(mol·rad^2); Pt–O–H, 55 kcal/(mol·rad^2); X(eq)–Pt–X(eq), 40 kcal/(mol·rad^2); X(eq)–Pt–X(ax), 30 kcal/(mol·rad^2); X(ax)–Pt–X(ax), 20 kcal/(mol·rad^2). Free rotations around the Pt–X bonds were assumed. All remaining parameters of the force field were employed as described previously[11] except that the new AMBER database[12b] was used.

platinum were considered. The models were energy-refined by using the program AMBER.[12] Figure 1 shows the most stable refined models for the ApG, the GpA, and both GpG intermediate adducts of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$. The calculated final energy of the 3′-bound GpG intermediate is 0.5 kcal/mol lower than that of the ApG adduct, and the energy of the 5′-bound GpG intermediate lies 1.3 kcal/mol below that of its GpA counterpart.[13] These differences in energy are very small, and the calculations do not yield free energies but enthalpies and do not take into account the solvation effects. Despite these limitations, the fair agreement between the calculated values and the kinetic data provides support for the molecular mechanics approach.

In the 3′-GpG and ApG adducts, two strong hydrogen bonds connecting the phosphate with the equatorial H_2O and the axial NH_3 ligands determine the structure. Within the remaining conformational freedom, the axial H_2O ligand orients itself so as to optimize its interactions with the groups at the positions 7 and 6 of the uncoordinated purine, i.e. by forming two hydrogen bonds with N7 and O6 in the case of the 3′-GpG adduct and only one to N7 in the ApG adduct (Figure 1a,b). In the 5′-GpG and GpA intermediates, the phosphate is too far away from the platinum complex to allow direct interaction. Under these conditions, the equatorial H_2O ligand is hydrogen bonded to the O6 atom of the coordinated guanine instead of the equatorial NH_3 in the former case and the 3′-purine optimizes the interactions between its groups 7 and 6 and the axial H_2O ligand, forming two hydrogen bonds with N7 and O6 in the 5′-GpG adduct and only one to N7 in the GpA adduct (Figure 1c,d).

The intermediates formed by $[Pt(NH_3)_3(H_2O)]^{2+}$ have geometries analogous to those of the *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ adducts. Since hydrogen bonds donated by the axial NH_3 ligand (replacing the H_2O ligand) are inherently weaker, the energy differences are smaller: the 3′-GpG and 5′-GpG adducts are respectively 0.1 and 0.5 kcal/mol more stable than the ApG and GpA adducts. This is in qualitative agreement with the smaller ratios between the rate constants found for these pairs (Table I).

In conclusion, we have shown that, for dinucleotides XpG and GpX, a guanine at the place of X accelerates the first platination. Molecular mechanics calculations suggest that the neighboring guanine stabilizes the pentacoordinated intermediate formed during the first coordination of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ by means of a hydrogen bond connecting its O6 atom with the nonleaving aqua ligand. For $[Pt(NH_3)_3(H_2O)]^{2+}$, the preference for GpG is much weaker (if any) than in the case of the diaqua complex. This clearly shows that the nature of the ligands (specifically the nonleaving water molecule) interacting with the adjacent base is an important factor determining the kinetics. Thus, inductive effects[5] alone cannot explain the high affinity of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ for GpG, as they should operate for both platinum complexes in the same way. Since, in DNA, each nucleotide has a phosphate at the 5′-side, only the formation of the 3′-base adducts of the XpG dinucleotides (X = G, A, C) is relevant to the *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ interaction with DNA. One expects large conformational differences between dinucleotides and double-stranded DNA. However, our results suggest that the major factor determining the structure of the transition state of the first platination of a guanine in DNA is hydrogen bonding between the 5′-phosphate and both the leaving H_2O and axial NH_3 ligands. This will probably preclude important interactions between the platinum complex and the base at the 3′-side. Under these conditions the presence of a 5′-guanine will stabilize the transition state of the first platination and determine the GpG selectivity. A series of experiments and calculations on deoxyribodinucleotides reacting with *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ have shown that the 2′-OH group does not have any appreciable influence on the results presented here. We are currently investigating the platination of the hexanucleotide duplex d [(TGGCTA)-(TAGCCA)]. Kinetic data indicate that the platinum coordination to GpG is favored over that to ApG by a factor of 9.

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