Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Supplementary Material Available: View down the *b* axis showing the noncrystallographic 2-fold axis in **2** (Figure S1), diagram showing the fit of the two molecules of complex **3** present in the asymmetric unit (Figure S2), and crystal structure data for **1-3**, including complete lists of bond lengths (Tables S1-S3) and angles (Tables S4-S6), anisotropic thermal parameters (Tables S7-S9), and H-atom coordinates (Tables S10-S12) (14 pages); listings of observed and calculated structure factors (Tables S13-S15) (89 pages). Ordering information is given on any current masthead page.

Contribution from the Department of Inorganic Chemistry, The University of Sydney, Sydney, NSW 2006, Australia

Molecular Mechanics Analysis of the Stereochemical Factors Influencing Monofunctional and Bifunctional Binding of *cis*-Diamminedichloroplatinum(II) to Adenine and Guanine Nucleobases in the Sequences d(GpApGpG)·d(CpCpTpC) and d(GpGpApG)·d(CpTpCpC) of A- and B-DNA

Trevor W. Hambley

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Monofunctional and bifunctional binding of *cis*-diamminedichloroplatinum(II) (DDP) to the guanine and/or adenine bases of the sequences d(GpApGpG)·d(CpCpTpC) and d(GpGpApG)·d(CpTpCpC) of A- and B-DNA have been modeled by molecular mechanics. The stereochemical factors that influence the tendencies for sequence specific binding are described. Monofunctional binding of DDP produces significant changes in the conformational geometry of the DNA. In particular, the bases are rotated by up to 20°, altering the distance from the Pt atom to potential binding sites on adjacent residues and making the distances to the 5'- and 3'-bases approximately equal. This is in contrast to the unequal distances predicted on the basis of idealized models of A- and B-DNA. Models for bifunctional adducts with ApG sequences are similar to those seen for bifunctional adducts with GpG sequences in that an NH_3 ligand makes a hydrogen bond with O6 of the 3'-guanine. In contrast, models for bifunctional adducts with GpA sequences have a highly unfavorable contact between the equivalent NH_3 ligand and the NH_2 of the 3'-adenine. Five-coordinate transition-state models show that these interactions persist and are potentially important in determining the frequency of occurrence of the A*pG* and G*pA* adducts.

Introduction

It is now generally accepted that the mechanism of action of the anticancer drug DDP (DDP = *cis*-diamminedichloroplatinum(II), *cis*-[$Pt(NH_3)_2Cl_2$]) involves binding to DNA.[1,2] In vitro studies of the interaction of DDP with DNA or fragments of DNA show that the bulk of DDP is bound to the N7 atoms of the nucleobases guanine and adenine.[3-5] The major binding site was found to be adjacent guanine bases of the one strand [d(G*pG*)] with a smaller amount bound to the d(A*pG*) sequence.[3,4] Binding to d(GpA) sequences was not found, or occurred at very low frequency, in binding studies with DNA[3,4] and the trinucleotide d(GpApG).[5] The lower preference for d(A*pG*) binding compared with d(G*pG*) binding is understandable on the basis of the lower kinetic preference for binding to adenine compared with guanine.[6,7] However, this does not explain why binding does not occur to d(GpA) sequences. Dewan has pointed out that when DDP binds to the central guanine in a d(ApGpA) sequence of B-DNA, the distance from the Pt atom to the N7 of the adenine on the 5'-side is ~3 Å and the distance to the N7 of the adenine on the 3'-side is ~5 Å.[8] This observation is consistent with some kinetic preference for the formation of d(A*pG*) adducts over d(G*pA*) adducts. However, we question whether such a difference is sufficient to account for the apparently complete absence of the latter adduct in some binding experiments,[3,4] especially when it is remembered that DDP has been found to bind appreciably to d(G*pNpG*) sequences,[5] in which the initial separation of the bases is likely to be 7-8 Å.

In a preliminary molecular mechanics study of the binding of DDP to the sequences d(CpApG)·d(CpTpC) and d(GpGpA)·d(TpCpC), we have shown that formation of d(G*pA*) adducts results in an unfavorable interaction, between an ammine group of DDP and the NH_2 group of the adenine base, not observed in the formation of the d(A*pG*) adduct.[9] While direct conclusions cannot be drawn from these models because binding of DDP, particularly to adenine nucleobases, is probably kinetically rather than thermodynamically controlled,[10] we propose that this type of destabilizing interaction would occur during the binding process and so strongly inhibit formation of the d(G*pA*) adduct. In order to investigate further this and other factors that might stereochemically influence binding of DDP to adenine-containing sequences, we have modeled the monofunctional and bifunctional binding of DDP to the sequences d(GpApGpG)·d(CpCpTpC) and d(GpGpApG)·d(CpTpCpC) (hereafter GAGG and GGAG) and report the results herein. Five-coordinate models for the transition state leading to the formation of the bifunctional models have also been studied. Mindful of recent studies which have shown that the structure of DNA is strongly sequence dependent[11] and that its solution structure is not limited to the B form[11c] we have considered models based on both A-DNA and B-DNA.

Experimental Section

The Model. Strain energies were calculated according to the formalism

$$E_{tot} = \sum E_b + \sum E_\theta + \sum E_\varphi + \sum E_\sigma + \sum E_{nb} + \sum E_{hb} + \sum E_\epsilon$$

where E_b represents bond deformation energy, E_θ valence angle defor-

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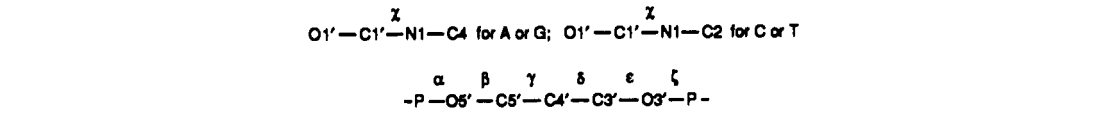
Table I. Comparison of Torsion Angles (deg) for DNA Fragments[a]

	χ	α	β	γ	δ	ε	ζ	ref
				A-DNA				
GAGG	−168	−72	172	61	80	−154	−67	this work
GGAG	−168	−71	174	60	80	−153	−67	this work
fiber	−154	−90	−149	47	83	−175	−45	26
d(GGGGCCCC)	−158	−76	178	62	84	−156	−70	27
				B-DNA				
GAGG	−119	−63	176	59	145	−176	−111	this work
GGAG	−120	−62	176	57	144	−178	−109	this work
fiber	−102	−41	136	38	139	−133	−157	26
d(CGCGAATTCGCG)	−117	−63	171	54	123	−169	−108	11a

[a] Torsion angles are defined as follows:



mation energy, E_φ torsion angle deformation energy, E_σ out-of-plane deformation energy, E_{nb} nonbonded interaction energy, E_{hb} hydrogen-bond energy, and E_ϵ electrostatic interaction energy.

The force field used to model the nucleic acids was based on the AMBER force field.[12] The parameters of the AMBER force field were modified by using the approach adopted in the development of Allinger's MM2 force field[13] and our force field for metal complexes.[14,15] Thus, force constants for valence angle deformation were reduced to 50% of the values derived from vibrational spectroscopy and the center of repulsion for hydrogen atoms was moved toward the heavy atom to which they were bonded by ~10% of the bonding distance. The 6-12 nonbonded interaction potentials of the AMBER force field were replaced by MM2 type potentials calculated by using a Buckingham function.

The force field for the platinum(II) complexes and their interactions with the nucleic acids has been fully described previously and used successfully to model the structures and dynamics of bis(purine)diammine- and bis(purine)bis(amine)platinum(II) complexes.[16] For the five-coordinate transition-state models, a Pt–N bond 0.05 Å longer than that in the ground state was used to reflect the effects of the expanded coordination sphere. Similar increases in bond lengths occur in Ni(II) and Zn(II) complexes on going from four- to five-coordination.[17,18] Force field parameters are given in a supplementary table.

Electrostatic charges were taken directly from the AMBER force field for the nucleic acids. For the complexes, estimated charges of +0.50 e^- were used for Pt and +0.20 e^- for ammine hydrogens, there being no data available for these values. The latter value has been found previously to give sensible hydrogen-bonding geometries,[16] and variation in the former did not significantly alter the model.

Electrostatic energies were calculated by using the function

$$E_\epsilon = q_i q_j / \epsilon r_{ij}$$

in which the dielectric constant, ϵ, was set to the distance-dependent value of $4r_{ij}$. This approach to electrostatic interactions has been found to yield the most realistic results.[19] It also mimics the effect of intervening solvent molecules, which are not otherwise included in our model.

Starting Structures. Coordinates for the initial, uncomplexed, A and B forms of the tetranucleotide duplexes were calculated by using a local modification of the program NAHELIX.[20] These starting structures were energy-minimized prior to construction of the DDP-complexed models. Complexed models were constructed by first attaching a Pt to one N7 atom and then either completing the coordination sphere about the Pt to model monofunctional binding or completing the coordination sphere to model bifunctional binding by using constraints to reduce the distance between the Pt and an adjacent N7 to the required bonding distance.

Models of B-DNA requiring sugar conformations other than the normal C_2'-endo were produced by using constraints to drive the torsion angles to values required for other conformations and then relaxing these constraints. These models are hereafter referred to as B′-DNA models.

Energy Minimization. Strain energies were minimized by the full-matrix Newton–Raphson method of Boyd,[21] using a program developed in these laboratories.[22] Minimization was continued until all shifts in positional coordinates were less than 0.001 Å. Constraints were applied by using the method of Lagrangian multipliers.[23,24]

Results

Native Tetradeoxynucleotide Duplexes. Starting coordinates for the uncomplexed DNA fragments were calculated by using a helix building program as detailed above. These structures required 30–50 cycles for energy minimization to reach convergence. The veracity of these structures as reasonable models for DNA might be assessed by comparing them with results from crystallographic analyses. There are, however, no crystal structures of the sequences under consideration here. However, the A conformation of the CCGG·CCGG sequence has been structurally characterized and has been subjected to energy minimization by using the same force field parameter set and energy minimization procedure as described above. Comparison with the X-ray crystal structure[25] is complicated by the iodination of the structure, but the best overlap gives an rms difference of 0.62 Å. The largest differences are in the region where the crystal structure adopts an anomalous sugar conformation.

Analysis of the conformational parameters of the energy-minimized structures shows that they are typical of parameters observed in a range of single-crystal and fiber diffraction studies of the A and B forms of DNA, though they are clearly closer to those of the single-crystal studies than those of the fiber studies[11a,26,27] (Table I). Some sequence-dependent variation in the conformational parameters is observed, but on the basis of these few models, no conclusions as to systematic variations can be drawn.

Monofunctionally Bound Platinum Complexes. There is evidence that DDP forms monofunctional as well as bifunctional adducts with DNA.[3,4] This, taken with the evidence that, following removal of excess, uncomplexed DDP, the frequency of bifunctional adducts continues to increase,[10] suggests that the monofunctional adducts are precursors of the bifunctional adducts. Thus, factors that influence the frequency of the monofunctional adducts will indirectly affect the frequency of the bifunctional

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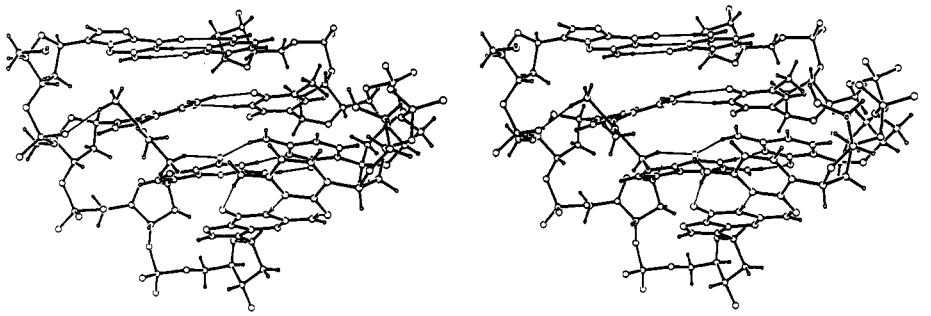

Figure 1. Stereoview of $[Pt(NH_3)_3]^{2+}$-GA*GG (A-DNA).

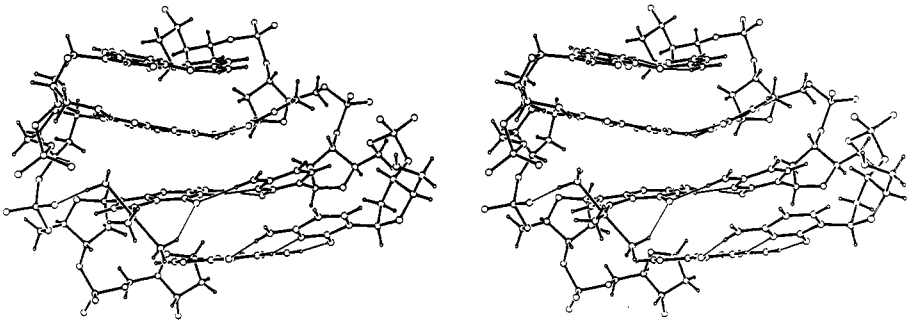

Figure 2. Stereoview of $[Pt(NH_3)_3]^{2+}$-GAG*G (A-DNA).

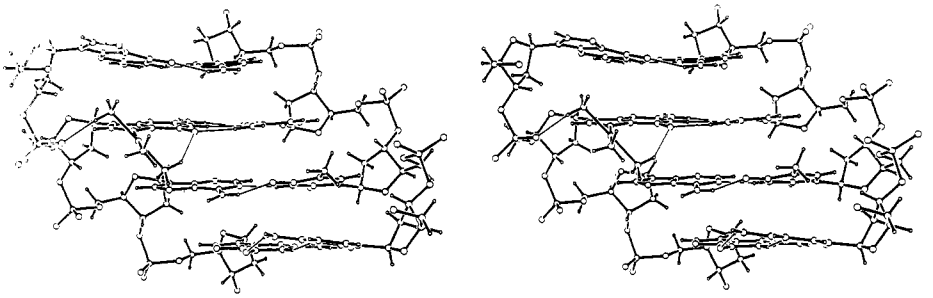

Figure 3. Stereoview of $[Pt(NH_3)_3]^{2+}$-GG*AG (A-DNA).

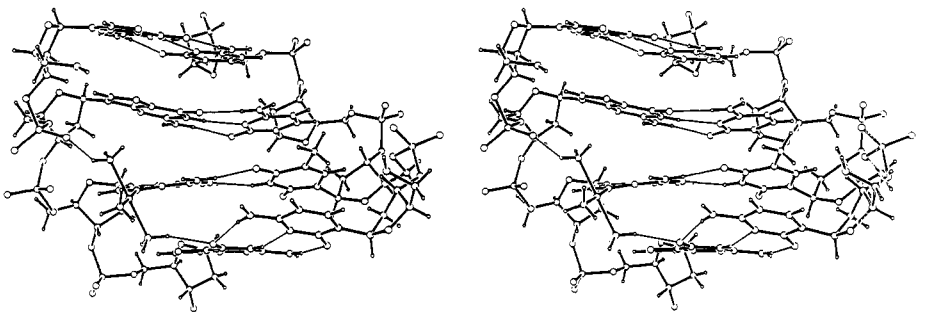

Figure 4. Stereoview of $[Pt(NH_3)_3]^{2+}$-GGA*G (A-DNA).

adducts. Also, the geometry of the monofunctional adduct may influence the propensity for formation of bifunctional adducts. Our aims in modeling monfunctional binding were 3-fold: (i) to look for any differences in the monofunctional binding of DDP to guanine and adenine bases, since monofunctional adducts are only observed with guanine bases, (ii) to analyze differences in the monofunctional adducts of DDP with A-DNA and B-DNA, and (iii) to analyze the models to look for differences that might influence the propensity for formation of bifunctional adducts and that depend on the adjacent 3′- and 5′-bases.

Formation of monofunctional adducts requires that one of the chloro groups of DDP be displaced. It is believed that, on entering the cell, DDP is hydrolyzed, resulting in replacement of both chloro ligands by aqua and/or hydroxo ligands.[28] In order to model the binding of the hydrolyzed complex to DNA, we have used the hypothetical moiety $-Pt(NH_3)_3$. The ammine ligands have similar hydrogen-bonding properties with regard to aqua and hydroxo ligands and the use of this moiety avoids the need to consider the various possible dispositions of ammine, aqua, and hydroxy ligands. These models are also directly applicable to the frequently studied Pt(dien)/DNA (dien = diethylenetriamine) interactions.

Monofunctional binding of the $-Pt(NH_3)_3$ moiety to N7 of the second and third purine bases of A, B, and B′ forms of GAGG and GGAG was modeled, viz. GA*GG, GAG*G, GG*AG, and GGA*G. The models were established by adding Pt at 2.02 Å from N7 of the purine base and then adding the three ammine ligands to give a square-planar arrangement. In all cases, little freedom in the orientation of these ligands was permitted by the

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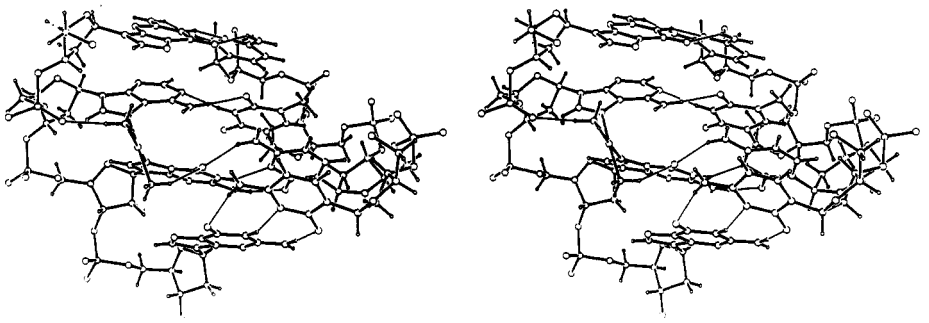

Figure 5. Stereoview of $[Pt(NH_3)_2]^{2+}$·GA*G*G (A-DNA).

steric constraints imposed by adjacent sugar and phosphate groups. Stereoviews of all adducts for A-DNA are shown in Figures 1–4.

When Pt binds to N7 of guanine or adenine, it is forced into close proximity with the substituent in the 6-position of the purine. In the case of guanine, this substituent is an O(carbonyl) atom and Pt···O contacts in the range 3.28–3.53 Å are observed. In the case of adenine, the substituent is an NH_2 group. The preference is for the NH_2 group to lie coplanar with the purine, and consequently close contacts between the Pt atom and the N atom and one of the H atoms results. In the energy-minimized structures these Pt···N and Pt···H contacts range over 3.36–3.52 Å 2.62–2.84 Å, respectively, comparable to the distances in [Pt(adenine)Cl_3] of 3.48 and 2.85 Å, respectively. The interactions with the NH_2 group are almost certainly more destabilizing than those with the O(carbonyl) oxygen and so contribute to the preference Pt(II) has for N7 of guanine over N7 of adenine. This preference is reflected in the binding of DDP to DNA by the observation that only monofunctional adducts with N7 of guanine, and not N7 of adenine, are found on digestion of DDP-treated DNA.[3,4]

Energy minimization of these models led in all cases to close contacts between the ammine ligands and the DNA. When Pt is bound to a guanine base, a hydrogen bond between an ammine and O6 of the same base results. This interaction is similar to those observed in models of DDP bifunctionally bound to GpG sequences.[30,31] In GAG*G the adjacent base in the 3′-direction is also a guanine, and alternative models with the ammine hydrogen-bonded to G4 were also refined. When Pt is bound to adenine, no hydrogen bond to the same base is possible but the adjacent base on the 3′-side in all of these models is a guanine that is available for hydrogen bonding. In models of A-DNA, a hydrogen bond between a second ammine and an O atom of the 5′-phosphate group was always observed. This too is similar to the interaction observed in models of bifunctional binding[30,31] and in the crystal structures of DDP bound to GpG[32] and CpGpG.[33] In B-DNA, however, this interaction is not seen when the 5′-sugar retains its normal C_2′-endo conformation, but when this sugar is in the C_3′-endo conformation, the hydrogen bond forms readily. It has been suggested, as an alternative arrangement, that a water molecule can link an ammine ligand and the 5′-phosphate by hydrogen-bonding to each of these groups.[34] It is clear from our models of unmodified B-DNA that this is feasible. However, NMR studies have shown that formation of DDP adducts generally causes a change in the sugar conformation from C_2′-endo to C_3′-endo[35] and since, following this conformational change there is no room for a bridging water molecule, we have not investigated this alternative arrangement further. It has also been suggested, on the basis of a low-resolution crystal structure of DDP bound to DNA, that a water molecule may form a bridge between O6 of the coordinated guanine and one of the ammine ligands.[36] Our models suggest that a direct H-bond between these groups is more likely but do not rule out this alternative arrangement.

The interactions between the ammine ligands and the DNA cause small but significant changes in the conformational geometry of the DNA. The largest changes in most cases are rotations, with respect to the sugar, of either the purine coordinated to the Pt atom and/or those adjacent to this purine. These changes facilitate the hydrogen-bonding interactions and/or relieve unfavorable nonbonded interactions. The rotations are reflected in the torsion angles χ (O4′–C1′–N9–C8), which change by up to 20° on complexation, and by the angles between adjacent purine bases, which change by up to 23°. Changes also occur in the conformation of the sugar rings and these are reflected in the changes of the pseudorotation angles (P) of up to 10°. The most significant effect of the rotations of the purine bases in relation to the formation of bifunctional adducts is on the distance between the Pt atom and the N7 atoms of the adjacent purine bases. When the models are initially established, with the Pt atom in an idealized position and the DNA having the energy-minimized geometry of the native (uncomplexed) form, the distances from the Pt atom to N7 on the 5′-side range from 3.25 to 3.85 Å and those to N7 on the 3′-side range from 4.94 to 5.94 Å. These distances are similar to those calculated by Dewan[8] for an idealized B-DNA structure. Following energy minimization of the complexed model, these distances change considerably; those on the 5′-side then range from 4.55 to 5.59 Å and those on the 3′ side from 3.86 to 5.25 Å. In nearly all cases, the distances are similar, with that on the 5′-side generally slightly longer than that on the 3′-side, which is the reverse of the situation seen in the idealized models.

Deviations of the Pt atom from the plane of the coordinated purine base by 0.1–0.6 Å also contribute to the change in distances to adjacent bases. The deviation of the Pt atom from the purine plane is generally greater when it is coordinated to adenine (ca. 0.4 Å) then when it is coordinated to guanine (ca. 0.2 Å), probably as a result of the unfavorable interaction between the Pt atom and the NH_2 group in the 6-position of adenine. Similar deviations (0.02–0.36 Å) of the Pt atom from the guanine or adenine plane are seen in a number of crystal structures of small-molecule complexes.[29,37,38] The distortions of the DNA that result from complexation are not notably dependent on sequence or on whether the DNA is in the A or B conformation. However, as noted above, and consistent with NMR studies, DDP complexation to B-DNA is likely to induce a change in the conformation of one sugar ring.[35] The observation of significant deformation of the DNA structure on formation of monofunctional adducts accords with the recent

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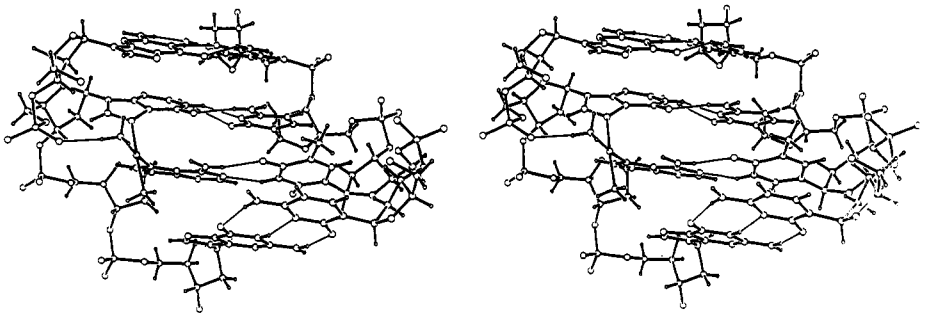

Figure 6. Stereoview of $[Pt(NH_3)_2]^{2+}$-GG*A*G (A-DNA).

reports by Reedijk et al.[39] that such adducts destabilize the DNA structure.

Bifunctionally Bound Diammineplatinum(II). While there is as yet no unequivocal evidence that bifunctional binding of DDP to adjacent purine bases is responsible for its cytotoxic activity, such interactions are unquestionably those which occur most frequently between DDP and DNA and have consequently attracted the greatest amount of attention. Our aims in modeling the interaction of DDP with the central ApG and GpA sequences of GAGG and GGAG, respectively, were to compare these interactions with each other and with the bifunctional interaction with GpG sequences. Models with DDP bound to A-DNA, B-DNA, and B-DNA with a modified sugar conformation were considered.

GA*G*G. Models with DDP bound to the ApG sequence of A-DNA (Figure 5) are very similar to those described previously for DDP bound to GpG sequences of A-DNA.[40,41] Thus, there is a hydrogen bond between one ammine ligand and O6 of the coordinated guanine and another between the other ammine and a terminal oxygen of the 5′-phosphate group. When bound to B-DNA, DDP makes the former of these hydrogen bonds with equal facility but the orientation of the backbone is such that the second does not form. Rearrangement of the 5′-sugar ring from C_2'-endo to C_3'-endo brings the phosphate group into a position where the hydrogen bond can form, yielding a model similar to that seen previously for DDP bound to B-DNA.[30,31]

GG*A*G. When DDP binds to the GpA sequence of A-DNA (Figure 6) or modified B-DNA, the hydrogen bond to the 5′-phosphate is observed as before. However, since the purine on the 3′-side is now adenine, which has an NH_2 group in place of the O6 of guanine, no hydrogen bond between this purine and an ammine is possible. Rather, there are repulsive H···H contacts in the range 2.59–2.64 Å.

Formation of bifunctional adducts with both GAGG and GGAG sequences of necessity causes large deformations in the conformational geometry of the DNA. Most notable is the angle between adjacent bases, in particular for those coordinated directly to the Pt atom. In uncomplexed DNA, these bases lie at 0–20° to each other and the primary rotation axis is the one linking the base to the sugar (χ). On formation of the bifunctional adduct, the coordinated bases tilt toward one another at angles ranging from 28 to 41°. In the A-DNA models, large changes also occur in the χ angle of the nucleoside on the 5′-side of the adduct. In B-DNA, the largest changes occur in the pseudorotation angles of the sugar on the 3′-side, which decreases by up to 30°, tending more toward the C_1'-exo sugar conformation rather that the more usual C_2'-endo conformation.

Five-Coordinate Transition-State Models. The models of bifunctionally bound DDP suggest that the preference for ApG over GpA sequences is the consequence of secondary interactions between an ammine ligand and groups on the purine base. However, binding of DDP is believed to be largely kinetically controlled.[10] Therefore, in order to determine whether these interactions might influence the kinetics of binding, we have modeled a possible transition state. It is widely believed that substitution reactions of square-planar Pt(II) complexes proceed via five-coordinate intermediates. Therefore, we have modeled structures intermediate between the monofunctional and bifunctional adduct models. A similar approach has been used to model the formation of the monofunctional interaction.[42]

For simplicity and consistency with monofunctional models, five-coordinate intermediates with Pt coordinated to the two purine bases and to three NH_3 ligands were modeled. Five equal Pt–N bond lengths of 2.08 Å were used.

In all cases the models refined with geometries about the Pt atom intermediate between the idealized five-coordinate geometries of square-pyramidal and trigonal-bipyramidal. In the square-pyramidal description, the square base lies in a position and an orientation similar to those of the coordination plane of the four-coordinate bifunctional models. Of particular interest are the interactions between the NH_3 ligands and the group in the 6-position of the purine on the 3′-side of the adduct. These interactions are similar to those in the models of the bifunctional interactions. However, the increased bulk about the Pt atom results in these contacts becoming shorter. Thus, for GA*G*G the O6···N(H_3) H-bond shortens from 2.91–2.93 to 2.72–2.76 Å, suggesting an increased stabilization. Conversely, for GG*A*G the unfavorable H(NH_2)···H(NH_3) contacts shorten from 2.59–2.64 to 2.45–2.47 Å, indicating an increased destabilization.

Thus, the suggestion that interactions between NH_3 ligands and groups in the 6-positions of the 3′-purine contribute significantly to the difference in the frequencies of occurrence of the A*pG* and G*pA* adducts is supported by models of five-coordinate transition-state complexes.

Discussion

The present study uses a modification of previously described force fields and an energy minimization technique that has rarely been applied to the modeling of nucleic acids. Therefore, we need to establish that together they produce a reasonable model of DNA. Comparison of conformational parameters for our models of uncomplexed DNA with those from single-crystal studies of short fragments of DNA shows excellent agreement (Table I). Thus, the modeling does appear to be reasonable. A second concern is that we are modeling only short fragments of DNA. This constraint is a consequence of the computational demands of full-matrix Newton-Raphson energy minimization. The agreement with experiment for the uncomplexed fragments suggests this is not a serious limitation in these cases. However, the bifunctional adducts cause large distortions in the DNA structure and our small fragments will be more flexible than DNA itself. We have recently carried out analogous calculations for DDP binding to the GG sequence of a six-base pair fragment and see no significant differences from equivalent models with a four-base pair fragment.[43] Thus, while the additional flexibility needs to be considered, we are confident that the present models offer a

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reasonable description of the likely interactions between DDP and DNA.

The primary aim of the present study was to investigate stereochemical explanations for the observation that DDP binds to ApG but not GpA sequences of DNA. It has been predicted on the basis of an idealized model of DNA that this dichotomy is the result of differences in the distance from a Pt atom bound monofunctionally to N7 of adjacent bases in the 3'- and 5'-directions.[8] We have modeled a number of monofunctional interactions in order to investigate this suggestion further. Our initial, idealized, models do show the difference in the distances to the 3'- and 5'-bases as proposed previously, but these differences disappear or are reversed on energy minimization. This is primarily the result of rotation of the plane of the purine base following monofunctional complexation, and in general the distances to the 3'- and 5'-bases are similar. Thus, our models do not provide support for the suggestion that differences in the distances to the 3'- and 5'-bases are responsible for the nonoccurrence of DDP binding to GpA sequences of DNA.

Since the monofunctional adducts do not appear to offer an explanation, we have modeled both the formation and the structure of the bifunctional adducts. Transition-state and ground-state models of bifunctional adducts with ApG and GpA sequences reveal significant differences. In the ApG adducts, there is an H-bond between an ammine ligand and O6 of the 3'-guanine, and in the GpA adducts, there is a repulsive contact between the equivalent ammine ligand and the $-NH_2$ of the 3'-adenine. We propose that the latter interaction destabilizes the transition state sufficiently to prevent formation of the DDP-GpA adduct.

The proposal that interactions between an ammine ligand and groups in the 6-position of the 3'-purine influence binding specificity might be tested by designing a compound able to interact favorably with the $-NH_2$ groups of adenine. Such a compound should be able to bind to GpA sequences. Recent molecular modeling suggests that a complex with one amine donor group and one sulfoxide donor group would be ideal stereochemically. We have prepared a number of these compounds and are currently studying their interaction with DNA.

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Supplementary Material Available: A listing of force field parameters and a chart showing the atom identifiers (6 pages). Ordering information is given on any current masthead page.

Contribution from the Department of Chemistry, University of Newcastle, New South Wales 2308, Australia, Institut für Anorganische Chemie, Universität Basel, 4056 Basel, Switzerland, and School of Chemistry, University of Sydney, New South Wales 2006, Australia

Coordination of the Sexidentate Macrocycle 6,13-Dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine to Iron(III)

Paul V. Bernhardt,[1] Peter Comba,[2] Trevor W. Hambley,[3] and Geoffrey A. Lawrance*,[1]

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The sexidentate polyamine macrocycle 6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine (diammac) reacts with iron(II) in aqueous solution to form the low-spin iron(III) complex Fe(diammac)$^{3+}$. Crystals of [Fe(diammac)](ClO$_4$)Cl$_2$ are monoclinic, space group C_2/c, with a = 15.6612 (8) Å, b = 7.4390 (7) Å, c = 18.061 (2) Å, and β = 108.626 (7)°. The Fe(diammac)$^{3+}$ ion is stable indefinitely in aerated aqueous solution, and its electronic and electron paramagnetic resonance spectra are consistent with a low-spin d^5 electronic ground state. In aqueous base, deprotonation (pK_a 10.2 ± 0.2) is accompanied by a color change to red, but the deprotonated species is not stable. The reversible $Fe^{III/II}$ redox couple occurs at a quite negative potential (−0.35 V vs Ag/AgCl; ΔE = 60 mV at 10–500 mV/s scan rate for cyclic voltammetry at glassy carbon) compared with other iron(III) complexes. Although the couple is reversible on the voltammetric time scale, monitoring the chemical reduction with zinc amalgam by NMR spectroscopy showed metal ion exchange occurs. Detailed analysis of the EPR and electronic spectra was possible; from the latter, along with comparisons with five other octahedral complexes of diammac, the empirical ligand spectroscopic parameter, g, for Fe(III) has been reassessed as 16.3 cm^{-1}, and sexidentate diammac has been defined as the strongest purely σ-bonded ligand extant.

Introduction

The nitrogen-donor coordination chemistry of iron(III) is dominated by complexes containing strong π-acceptor ligands such as porphyrins and bipyridine. In stark contrast, there have been very few reports of (hexaamine)iron(III) complexes in the literature.[4-6] Moreover, these complexes have in some cases been stable for extended periods only in the solid state, although the recent chemistry of (tacn)$_2$ complexes (tacn = 1,4,7-triazacyclononane)[5,6] indicates that solution-stable hexaamines can be accessible. As a consequence of the limited examples of (hexaamine)iron(III) compounds, the interesting spectroscopic and electrochemical properties of these complexes have remained relatively unexplored.

Hexaamine complexes are ideal for studying the electronic properties of metal complexes in strong ligand fields free from charge-transfer transitions, but only one assignment of the electronic spectrum of a (hexaamine)iron(III) complex has appeared in the literature. This comprised a report of the solid-state, diffuse-reflectance spectrum of tris(ethylenediamine)iron(III) chloride, which is not stable in aqueous solution.[4] Also, the low-spin d^5 electronic configuration typical of (hexaamine)iron(III) complexes is particularly amenable to analysis by electron paramagnetic resonance (EPR) spectroscopy without the complications of electron delocalization.

As a continuation of our studies of the coordination chemistry of the strong ligand field, pendant-arm macrocycle 6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine (diammac),[7-11] we have investigated its complexation of iron(III). A

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