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Comparison of Direct and Through-Water Binding of Platinum Ammines to the Phosphate Anion

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Abstract: The structure of the *cis*-diammineplatinum adduct to DNA depends on the hydrogen binding of the polarized ammine ligand to nucleophilic sites in DNA. The possibility of water bridges significantly increases the number of types of structures. Molecular mechanics (MM) modeling with kinked oligomer duplex models suggested that both "direct" and "through-water" binding conformations to phosphate are possible. The intrinsic energetics of this binding is modeled for the $Pt(NH_3)_4^{2+}\cdots H_2O\cdots H_2PO_4^-$ cluster with valence self-consistent field molecular orbital calculations, which support the classical modeling. The energetics of direct and through-water clusters are calculated to be competitive. The binding of water to $Pt(NH_3)_4^{2+}$ and $H_2PO_4^-$ is also reported for a variety of conformations.

I. Introduction

Metal cation bonds to nucleic acid bases have large intrinsic bond energies. It is not surprising then that the binding of *cis*-$\{Pt(NH_3)_2\}^{2+}$ (*cis*-DP) to single- or double-strand oligomers of DNA can substantially alter the local geometry at the bond. The extent of the distortion of the structure of DNA will depend on not only the Pt bond to the bases but also hydrogen bonds that involve the ammine ligands. The experimental evidence suggests that *cis*-DP binds preferentially to the N7 sites in a GpG chelate.[1] A theoretical model for the binding of *cis*-DP to a tetramer duplex of DNA showed that a kinked structure is feasible without seriously disturbing the duplex base-paired hydrogen binding.[2] A kinked structure was also suggested by NMR experiments[3] and by crystallographic modeling.[4] Molecular orbital calculations of base binding energies[5] were combined with a molecular mechanics (MM) analysis of kinked tetramer duplex structures[6] to determine that binding to the N7 in a GpG chelate is energetically very favored over other base sequences.[2]

Various models have been constructed by Kozelka et al.[7–9] They have determined conformations in which base pairing is perturbed[7,9] and in which base pairing is substantially maintained leading to a kinked duplex.[8,9] These structures are distinguished by a direct phosphate–ammine hydrogen bond, which is related to that found in the crystal structure of *cis*-$[Pt(NH_3)_2\{d(pGpG)\}]$.[10] It is evident from the MM modeling done to date that a number of families of conformational structures are found with comparable energies. Our recent MM calculations determine that *cis*-DP can bind to phosphate in a through-water H bond as well as by a direct H bond.[11] Molecular orbital analyses of the platinum ammine–phosphate direct binding or mediated by an intervening water will be presented here.

The energetics of "direct" and "through-water" binding to the phosphate anion will be studied with the $Pt(NH_3)_4^{2+}\cdots H_2O\cdots H_2PO_4^-$ cluster. These two types of interactions were shown to be energetically competitive by Pullman et al.[12] in the case of Na^+ and Mg^{2+} interacting with nucleotide models. The Pt model geometries for the two types of binding were guided by MM calculations to allow only a single anionic oxygen of the phosphate to approach the ammine in two general ways. The oxygen can approach the ammonia ligand in a roughly linear hydrogen bond, which is called "planar", or it can attack the Pt atom along the axis perpendicular to the plane of the nitrogens. Both approaches are considered direct, and the modeling structures suggest intermediate approaches. The through-water complex is constructed to allow for an intervening water molecule hydrogen bonded to both the cation and anion. The ionic hydrogen bonds to water are strong and will lead to large binding energies for through-water clusters. Intervening water molecules can be placed in both planar and axial orientations. Solvation can also be envisaged with water oriented along the O···H–N bond, but calculation of such models do not find structures that are more stable than those considered below. The energy surface is found to be relatively flat and suggests that the direct and through-water structures are accessible to one another.

II. Platinum Ammine–Phosphate Binding

Method of Calculation. Valence-electron self-consistent field (SCF) calculations were performed with the HONDO code,[13] which had been modified to use compact effective core potentials (CEP) reported for atoms of the first two rows[14] and for the Pt atom[15] in place of the chemically unimportant core electrons. The double-ζ (DZ) basis for P was augmented with a d polarization function with an exponent of 0.55.[16] Gradient energy optimization was used to study the $Pt(NH_3)_4^{2+}$ and $H_2PO_4^-$ monomers, but such calculations are not possible in the model studies of the cluster since the energy surface is flat and dependent on too many degrees of freedom. The open and closed cluster geometries were guided by our MM results and those of Kozelka et al.[7–9] A wide angular

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Table I. Energy of Water Binding to $Pt(NH_4)_4^{2+}$ and $H_2PO_4^-$

complex	R(O···H), Å	ΔE, kcal/mol	figure	
PtA_4···W	1.8	22.7	1a	planar
PtA_4···W	3.25	15.5	1b	axial
PtA_4···W_3	1.8	57.0		planar
P···W (DZ)	1.8	12.9	2	E″
	1.8	14.1		E
P···W(DZP)	1.8	13.6		E″
	1.8	12.2		E

approach of the anionic oxygen is allowed by the electrostatic potential of the phosphate anion,[17] and this leaves space for a water molecule in the first hydration sphere of the cation. The O–N distances are about 2.8 Å and exceed 4.0 Å, respectively, for the direct and through-water cases. The phosphate approaches the ammine from above the plane defining the square-planar complex, and the g^+g^+ torsional conformation of the anion[12] is roughly maintained. The complete hydration spheres for the cation and anion could not be maintained in the SCF calculation. This will be examined later in an effective Hamiltonian study. The present calculations will yield higher binding energies than a more complete model, since ligand–ligand repulsions are neglected. However, the water ligands are sufficiently separated from one another that the qualitative results should not be affected. A cluster with three water ligands bound to the same ammonia ligand is examined below to support this contention.

$Pt(NH_3)_4^{2+}$ Electronic Structure and Binding to Water. The $Pt(NH_3)_4^{2+}$ (TeP) cation is the simplest square-planar molecule with four Pt–N bonds. For all the calculations involving binding to this molecule, the Pt–N bond distance was fixed at 2.05 Å. The energy differences among the many rotamers are small, and no attempt was made to quantify them. The square-planar array of Pt and N atoms is in the x–y plane. The present calculation finds the HOMO to be predominantly the d_{z^2} orbitals, and the LUMO is the Pt $6p_z$ orbital. However, the Pt 6s and $d_{x^2-y^2}$ orbitals, which have large antibonding orbital components on the ligands, are nearly degenerate in energy with the $6p_z$ orbital. The ordering of the remaining occupied d orbitals as the binding energy increases is d_{yz}, d_{xz}, and d_{xy}, with the d_{xz} and d_{yz} orbitals degenerate for this molecular symmetry. This agrees with a recent analysis of the spectra of this cation.[18]

There are substantial shifts in the charge distribution in the ammine ligands, which require that any attempt to represent the electrostatic potential of the complex uses the wave function or charge distribution obtained for the entire cluster or considers the effect of the metal interaction on the ligand charge distribution. A fit of the electrostatic potential of the TeP wave function using atom-centered partial charges[19] is dependent on the choice of atom van der Waals radii. The potential generated by the partial charges is least-squares fit to the accurate potential on a fixed grid of 1500 points distributed uniformly in a volume defined by the interaction of concentric spheres about each center of partial charge. The inner radius is chosen at 1.9 and the outer radius at 3.0 times a standard set of radii.[20] For these radii the Pt fractional charge is only +0.18 while the charges found for N and H are −0.50 and +0.32, respectively. On the other hand, an analogous fit to *cis*-DP finds the charges are +1.36, −1.43, and +0.58, respectively, for the Pt, N, and H atoms. The *cis*-DP cation exhibits a strong attraction for nucleophilic sites, obviously, and this is reflected in the large charge on Pt. The potential for TeP is determined by the dipoles in the ammonia ligands in the region that was used for the fit. In using the potential for TeP the Pt–N bonds cannot be substantially distorted without expecting the fitted charges to be altered. As expected, the ammonia ligands are polarized, and the hydrogens should bond strongly to electron donors.

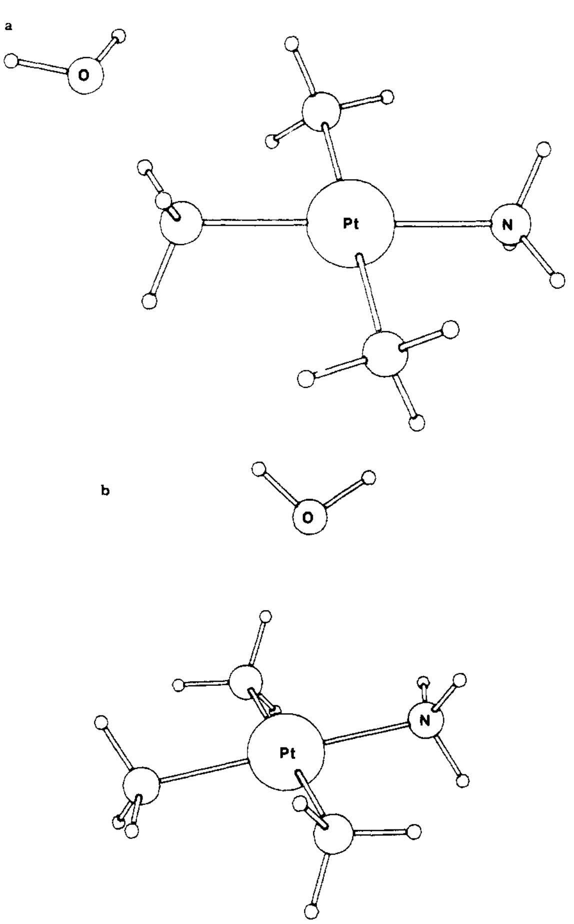

Figure 1. Orientation of water binding to PtA_4: (a) in a "planar" conformation with a hydrogen bond to the ammine ligand; (b) in an "axial" conformation and electrostatically bound to Pt.

In addition to the local interaction with the hydrogen, there is the large charge–multipole interaction of water, a polar ligand, to the doubly charged cation. The hydrogen bond to the ammine is calculated to be strongest for the linear O···H–N geometry as seen in Figure 1a, which bisects the water molecule and maximizes the charge–dipole attraction. The energetics for the water binding is summarized in Table I. The effect of binding three waters on a single ammonia ligand was also examined. The waters are sufficiently far apart, and the dipoles are oriented so that the binding per ligand is only reduced by 3.7 to 19.0 kcal/mol per ligand. The binding energy of water to a divalent cation substantially exceeds that of binding to the ammonium cation. However, it is still a strong hydrogen bond, and the average enthalpy of binding also is reduced by about 3 kcal/mol as the first coordination shell is saturated.[21]

Another possible approach of the water ligand is along the axial direction of the square-planar molecule as seen in Figure 1b. An axial ligand is not strongly bound in Pt(II) complexes. A calculation of a strictly axial water ligand does not find binding at the usual bond distance of 2.0 Å due to the antibonding character of the formed bond. However, at large distances, where the orbital overlap of the ligand and Pt d_{z^2} orbitals becomes small, there is substantial binding of an electrostatic origin. If space is available in a kinked structure, an axial water could still be positioned at a Pt–O distance greater than 2.4 Å and provide a bridge to Pt.

$H_2PO_4^-$ Structure and Binding to Water. The torsional energy surface of $H_2PO_4^-$ was examined at a few points and the global minimum determined by an energy gradient calculation to obtain the appropriate torsional angles for the model. Only one published study has included d orbitals in the phosphorus basis in a study of the hydration and torsional energy surface of the dimethyl-

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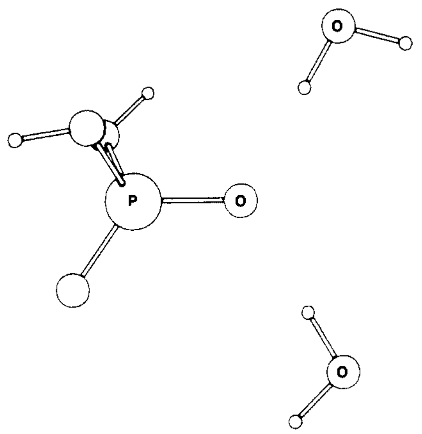

Figure 2. Orientation of water in the plane of O–P–O to a g^+g^+ conformer of $H_2PO_4^-$.

phosphate anion (DMP).[17] When all bond distances are fixed, the g^+g^+ conformation with torsion angles of 90°, 90° is reported as lowest for DMP. This position is shifted somewhat from the g^+g^+ conformation of 60°, 60° reported as the global minima with a small basis set that did not include the d functions. The relative energetics of the tt, g^+g^-, and gt conformations were also reported,[17] but these values are not reliable unless a complete geometry optimization is done for fixed torsion angles.[22] A complete geometry optimization was first performed to determine the global minima with a DZP basis for all atoms. The most stable conformation was for 92.9°, 92.9° in agreement with the earlier study of DMP.[17] This agreement is sufficient to confirm the model global minimum is g^+g^+, which qualitatively agrees with the structure in the MM calculation and in a wide range of DNA structures.[23] However, comparison of calculations, using bases near the Hartree–Fock limit,[24] with experimentally determined X-ray structures[25] shows that the ester P–O bond is more than 0.08 Å shorter than calculated here. The environmental effect on the bond distances in a crystal must also be considered as well as correlation effects and larger molecule models.

The binding of water to the phosphate group has been studied extensively.[17,26,27] However, the calculations with small basis sets substantially overestimate the binding energies. A complete study of binding energies was not attempted at this time, since a much large basis than used here is needed for anion hydrogen binding. However, a double-ζ plus polarization (DZP) basis for all the atoms was used to study the binding at two typical points. The bifurcated conformation was not studied, since it is not likely in the binding to DNA and is not significant in the hydration of the phosphate anion. The conformation of the phosphate anion was fixed for g^+g^+ (90°, 90°), and the hydrogen-bonding distance was also fixed at 1.8 Å. Binding of a single water to the anion alone will certainly lead to a shorter equilibrium hydrogen-bonding distance. However, the larger distance is representative of the general situation where there is ligand–ligand repulsion. A cone of substantial binding about the anionic oxygens has already been predicted for monodentate binding.[26] Binding to the ester oxygens is not significant, because the electrostatic potential at these sites is much smaller than at the anionic oxygens. The electrostatic potential for the phosphate anion is sufficient to predict the likely binding regions and their relative binding energies.[28] The E and E'' sites, described in Figure 2, are representative[26,27] of the extremes of binding on the cone, but the energies in Table I show that there is a very small difference in the binding energy as indicated by the potential. The water is in the plane of O1–P–O2 and hydrogen bonded to O1. The second hydrogen is arranged approximately cis to the O2 atom in E'' and trans in E. The present results with the basis that is DZ on all atoms plus d functions on P predict the binding to the E site slightly exceeds that in the E'' site. This agrees with the conclusions of Pullman et al.,[26] but Alagona et al.[27] find that for an all-electron DZ basis the reverse is true, although they agree at the minimal basis level. For the valence DZP basis the binding to E'' slightly exceeds that to E. Since more accurate calculations of the electronic structure of the phosphate anion[24] using even larger bases show that the

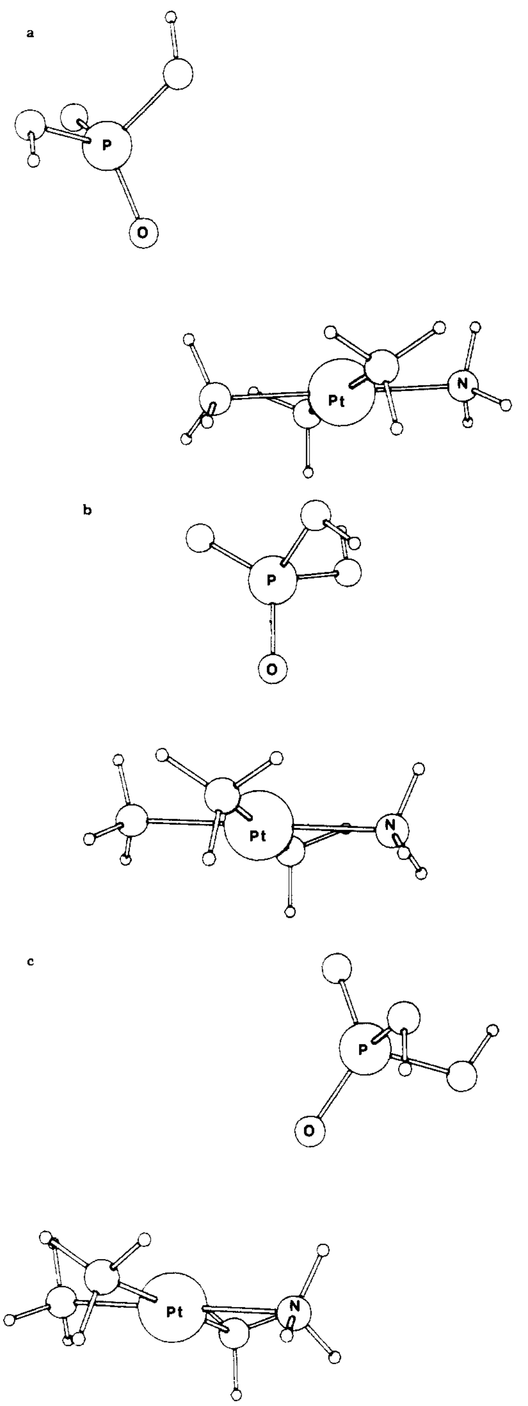

Figure 3. Phosphate anion in "direct" bond to platinum ammine: (a) with a hydrogen bond between P–O1···H–N; (b) with an "axial" P–O1···Pt interaction; (c) with the hydrogen bond between P–O1···H–N maintained while O1 is rotated toward Pt in the P···H–N–H plane.

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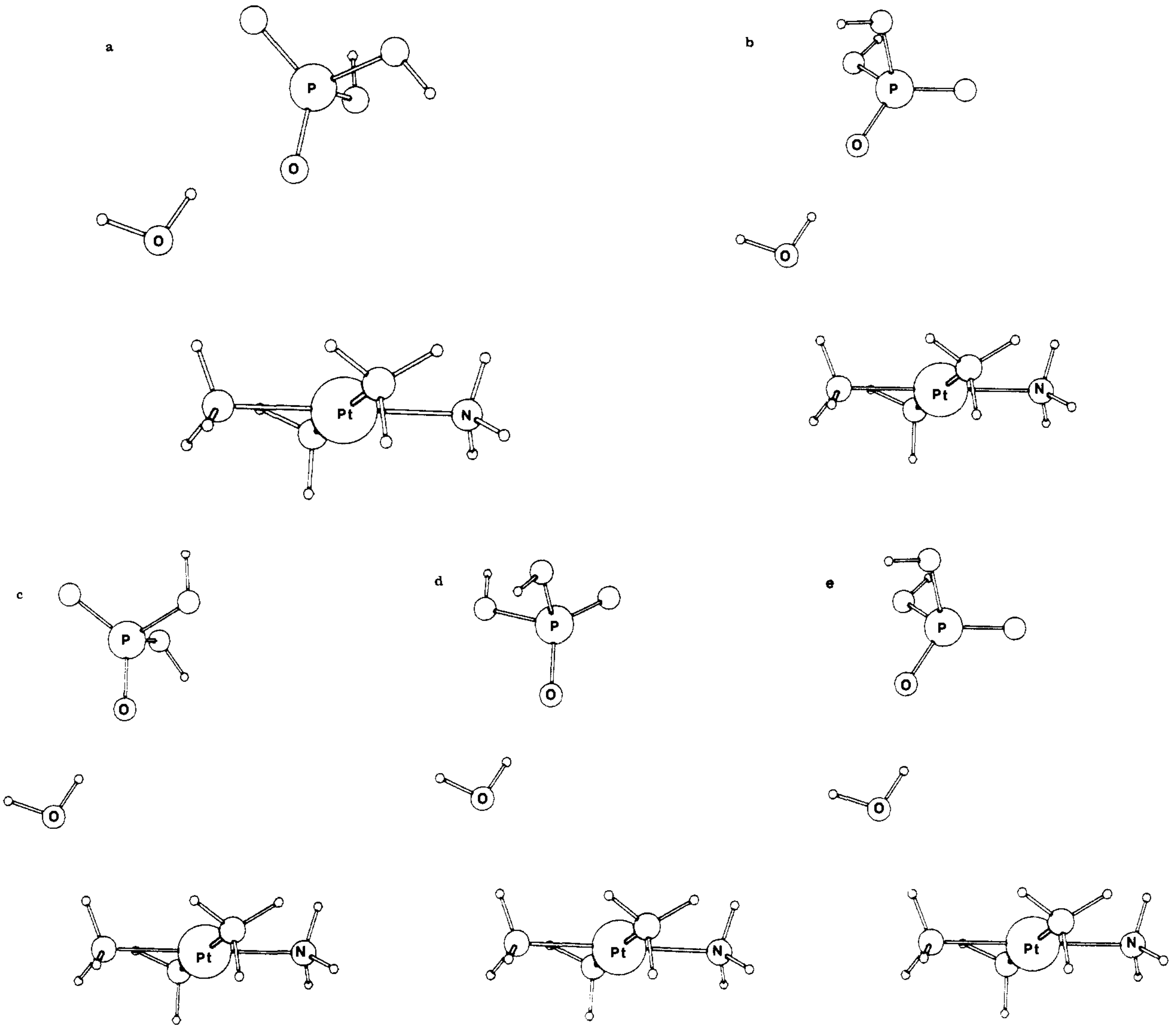

Figure 4. Phosphate anion in "through-water" bond to platinum ammine: (a) with anionic oxygen, O1, in hydrogen bond P–O···H–O but also interacting electrostatically with Pt; (b) with O1, in linear hydrogen bond to water and O2 oriented toward Pt; (c) with O1, in linear hydrogen bond to water at optimum electrostatic position; (d) with O1 in bent hydrogen bond and O2 oriented toward the Pt; (e) with O1 in bent hydrogen bond and O2 oriented away from the Pt.

electrostatic potential is slightly larger for the cis arrangement, the E″ site would then be favored energetically. This suggests that the DZP relative energies will be maintained as further improvements are made in the SCF calculation.

Platinum Ammine Binding to Phosphate Anion. The phosphate conformation was maintained as g^+g^+ throughout the study of the clusters, $Pt(NH_3)_4\cdots H_2O\cdots H_2PO_4$, reported in Table II. Two approaches are explored here. For direct binding, the P–O bond was kept linear with the H–N bond as seen in Figure 3a or the approach is axial toward the Pt atom as seen in Figure 3b. In Figure 3c, the anionic oxygen is still hydrogen bonded to the ammine, but the oxygen is allowed to approach the Pt from above the planar complex. Through-water binding is modeled with an analogous approach of the phosphate anion toward the TeP with the water interposed as seen in Figure 4. When the P–O···H–O hydrogen bond is maintained to be 1.8 Å, the phosphate was moved relative to the water in order to explore the through-water binding energy surface. Representative cases are shown in Figure 4. The P–O···H–O bond is also maintained in the Pt–N–H plane, so that it would encounter only a single water in the TeP hydration sphere. The waters of hydration of the phosphate anionic oxygen are initially arranged in a tetrahedral fashion, but, with the displacement of one water, the other two would rearrange to avoid the remaining hydration sphere on the ammine. For the present it is assumed that the reorganized hydration spheres are at comparable energies for both direct and through-water cases. At most, one water is then included in any cluster. The direct-binding case involves the ejection of two waters of hydration, one each from the cation and anion, while the through-water case displaces only one water. For the axial approach, more than two waters are probably disturbed, but for comparative purposes, all the cases will be treated the same. The energies of representative direct and through-water clusters are compared in Table II. The waters that are ejected can form new bonds in the bulk, but since only one H-bond is disrupted for each water, the energy differential for the direct case is at most 5 kcal/mol. Since the model is

Table II. Direct and Through-Water Binding to Phosphate

	$-\Delta H$, kcal/mol	figure
	Direct	
$PtA_4\cdots P + 2W$	111.2	3a
	119.7	3b
	113.3	3c
	Through Water	
$PtA_4\cdots W\cdots P + W$	120.5	4a
	118.0	4b
	112.1	4c
	112.6	4d
	113.0	4e

simplified, this energy difference will not determine whether the direct and through-water cases are competitive energetically and can be ignored for the moment.

In Figure 4a, the O···Pt distance is about 4.5 Å and the anionic O also interacts with the water solvating the ammine. Increasing the O···Pt distance is energetically compensated by hydrating the cation and anion. The second anionic oxygen is directed away from the Pt complex as suggested by the results in the MM modeling. In Figure 4b the P–O bond is linear with the H–O bond in the water, but the O2 atom points toward the cation to test the energy surface variation. The O···Pt distance is now 5.2 Å, but again the total energy differs slightly from previous structures. The structure in Figure 4c has the P–O bond make an angle of 30° with the linear hydrogen bond, and the O2 atom is pointed away from the cation. This reduces the binding energy by about 6 kcal/mol. In parts d and e of Figure 4, the O1 atom is rotated 30° away from the O–H bond in water, with the O2 away from the cation in Figure 4d and toward it in Figure 4e. Energetically, these orientations are found to be equivalent. When the P–O bond is linear with the H–O bond in water and the O2 atom points toward the cation as in Figure 4b, there is a stronger electrostatic interaction. Rotating the phosphate 90° about the P–O1 bond reduces the binding energy by only 2 kcal/mol. Within the usual cone of electrostatic attraction associated with the anion lone pair, the binding does not alter significantly and the energy surface is flat.

The simplest comparison of the energetics of direct and through-water interactions is found in the following equations:

$$PtA_4\cdots H_2O + H_2PO_4\cdots H_2O \rightarrow PtA_4\cdots H_2PO_4 + 2H_2O$$

$$PtA_4\cdots H_2O + H_2PO_4\cdots H_2O \rightarrow PtA_4\cdots H_2O\cdots H_2PO_4 + H_2O$$

The direct interaction will displace at least two waters, one each from the cation and anion. This involves a loss of about 37 kcal/mol of hydration energy. As can be seen from Figure 4 the through-water configurations can maintain the two hydrogen bonds in the single interposed water. The present calculation was done with a DZ basis, so cooperative polarization effects likely with such an arrangement are underestimated. Nonetheless, it is clear from the results summarized in Table II that the direct and through-water conformations are energetically competitive.

III. Discussion

The difference in the energetics of direct and through-water phosphate–ammine interactions is determined by the strong ionic hydrogen bonds to the interposed water. The small size of the water allows optimum hydrogen donor and acceptor bonds to be made with a relatively small increase in separation of the cation and anion. The competitive character of direct and through-water binding of cation to phosphate anion is likely to hold for all cases where electrostatic interactions dominate. Competitive binding was reported earlier for Ca^{2+}, and both types of binding are found experimentally for this cation.[12] As yet, there is no experimental evidence of through-water binding, but only one direct case for *cis*-DP binding has been observed in a dinucleotide to date.[10] A theoretical study of water binding between the anion ($H_2PO_4^-$) and cation (NH_4^+, Na^+, or Mg^{2+}) also concluded that two waters bound to the anionic oxygens in the phosphate will stabilize anion complex formation with the cation.[29]

The model structures are relevant to those observed in the MM calculations.[7–9,11] Water bridges between both anionic oxygens and a single ammine ligand are not found in the MM structures. The direct structure in Figure 3 is self-evidently related to the experimental observation of direct binding.[10] Approximately axial attack is possible because of steric constraints, but the positioning of a axial water does allow for hydrogen-bonded bridges, which are found in the MM calculations. The intermediate structure in Figure 3c positions the anionic oxygen to interact with the proton of an approximately axial water. The energy surface is flat, and the fragments can adjust orientation and distances to optimize hydrogen binding. Direct-binding structures like the one in Figure 3c are likely to be stabilized by additional water bonds. Such stabilization could be important since the axial attack is likely to disturb all three waters hydrogen bonded to the anionic oxygen, O1. The inclusion of the entire first hydration sphere of both ions is needed but is not possible with all-electron methods. A more accurate representation of both the environment and the reacting fragments is required before further examination of the energy surface is warranted. Since electrostatics dominates the interactions, effective Hamiltonian methods have been introduced in the HONDO code to treat this type of problem.

A chelate structure was studied where both anionic oxygens interact with the ammine. This cluster is not relevant to the MM structures found in binding to DNA, but it illustrates the importance of positioning the fragments in the cluster with respect to the electrostatic potential. In the chelate both anionic oxygens point toward the oxygen atom in water and significantly reduce the binding between the phosphate and the water. The additional binding of phosphate due to the interaction with at least two N–H bonds of the ammine is sufficient only to bring the total binding up to that for the complexes shown in Figure 4. A higher energy phosphate conformer (g^+g^-; 60°, –60°) was also used in the cluster calculations, and the direct and through-water binding is competitive for this conformer also, suggesting that this result is not dependent upon phosphate conformation.

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