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Molecular Mechanics Modeling of the Interaction of *cis*-Diammine- and *cis*-Diamineplatinum(II) Complexes with the A-DNA fragment d(GCC):dCGG)*

TREVOR W. HAMBLEY

Department of Inorganic Chemistry, University of Sydney, Sydney 2006, Australia

Abstract

The calculations described in this work aim to model the interaction of *cis*-diammineplatinum(II) anticancer drugs with DNA and to establish a structure–activity relationship for these drugs. They have been centered on the premise that the mode of action of these drugs involves intrastrand crosslinking of adjacent guanine bases.

We have developed a force field for molecular mechanics analysis of the interaction of platinum with guanine bases by modeling $[Pt(NH_3)_2(9\text{-ethylguanine})_2]^{2+}$, $[Pt(NH_3)_2(guanosine)_2]^{2+}$, and $[Pt(NH_3)_2(inosine\ 5'\text{-monophosphate}]^{2+}$. Using this force field the complexes between the nucleotide fragment deoxyguanyl-(3′,5′)-deoxycytidyl-(3′,5′)-deoxycytidine: deoxycytidyl-(3′,5′)-deoxyguanyl-(3′,5′)-deoxyguanosine (GpCpC;CpGpG) and various diammineplatinum(II) moieties have been studied. The influence of the specific diammine ligand(s) employed, and of the role of hydrogen bonding, on the ability of platinum to bond to DNA has been analysed.

The modeling has revealed that on covalent binding of the *cis*-diammineplatinum(II) moiety to N7′s of adjacent guanines, two hydrogen bonds are formed between the drug and DNA. One is from an ammine ligand to an oxygen atom of the phosphate backbone and the other from the other ammine to O6 of the covalently bonded guanine on the 3′ side. The formation of these hydrogen bonds accords well with the observation that drugs with tertiary diammine ligands are very poor antitumor agents.

The interactions have been modeled for a range of drugs in which the diammine is $(NH_3)_2$, λ-en, δ-en, *R*,*R*-chxn, *S*,*S*-chxn, and *R*,*S*-chxn (en = 1,2-ethanediamine, chxn = 1,2-cyclohexanediamine). The calculations suggest that the steric bulk of the ligand generally has little effect on the binding interaction energy but that the conformation of the ligands influences the dispositions of the ammine hydrogen atoms and so varies the strength of the hydrogen bonds described above.

Diammine ligands which test the hypothesis that the two hydrogen bonds predicted by the calculations are essential for antitumor activity, are currently being developed.

Introduction

The use of molecular mechanics to model the interaction of drugs with their targets is currently an area of enormous research effort. It is an approach which many pharmaceutical companies pursue vigorously as is exemplified by the recent report that a consortium of pharmaceutical and computing companies is to spend US$ 1 million over the next three years to attempt to develop a second generation force field for molecular mechanics modeling. Very little has been reported, however, of comparable studies on the interactions of metallo-drugs with their targets.

My aim was to attempt to model the interaction of *cis*-diammineplatinum(II) type drugs with their intracellular targets. Application of molecular mechanics to this system is particularly appropriate since very little information on the details of these drug/target interactions is available from crystallographic studies.

Experimental

I shall begin with a brief background of the molecular mechanics method. The method is based on building up of a model of the molecule of interest using potential functions which define the energy cost associated with deforming internal coordinates and with interatomic interactions. Bond lengths and angles are treated as harmonic oscillators and are modeled using Hooke's Law functions:

$$E = (1/2)k(x - x_0)^2$$

where the force constant k is derived from infra-red data and the undeformed value for the coordinate, x_0, is taken from crystal structure data. Torsion angles are treated using functions which have maxima and minima for eclipsed and staggered conformations respectively:

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$$E = (1/2)k(1 + \cos(3\text{phi}))$$

where the force constant k is derived from rotation barriers determined by microwave spectroscopy. Non-bonded interactions are modelled using Buckingham functions:

$$E = ae^{-br} - cr^{-6}$$

which have a repulsive exponential term and an attractive, r^{-6}, term. Electrostatic interactions are calculated assuming point charges on the atoms:

$$E = q_1q_2/er$$

where e is the dielectric constant. Hydrogen bonds are modeled using an empirical function of the form:

$$E = cr^{-12} - dr^{-10}$$

The force field used was derived from that reported by Kollman *et al.* [1]. Parameters associated with the interaction of the atom and the guanine base were adjusted to reproduce structures of small Pt/nucleotide and nucleoside complexes. The combination of all the energy terms gives the total steric energy which is minimized by the Newton–Raphson method to give a value for the strain-energy and a minimum energy structure.

Results and Discussion

I will now turn to the modeling of the cisplatin/DNA interaction. The first point to be established is what particular interaction type is to be modeled since for cisplatin the interaction type responsible for cytotoxic activity is not unequivocally established. The bulk of the current evidence indicates that up to 90% of cisplatin bound to DNA is bonded to the N7 atoms of adjacent guanine bases of the one strand [2]. I therefore set out to model this interaction.

The program used for these calculations employs a Newton–Raphson minimization method, the best of the methods currently available, and the only one precise enough to distinguish small differences in binding energies. However, the speed of this method and the amount of computer memory used are approximately proportional to N^3, where N is the number of atoms. This limits the size of the problem which can be tackled and it had been suggested that the largest problem which could be done was 70–100 atoms. Modeling the interaction between cisplatin and two base pairs gives a problem with about 180 atoms. This was where I began; modeling cisplatin:pGpG:CpC. No difficulties were experienced in refining these structures and the interaction was successfully modeled. However, it was clear from the results obtained that at least a three base-pair model was required to give meaningful results. Encouraged by the success of the earlier calculations I attempted the modeling of cisplatin:GpCpC:CpGpG and again experienced no problems except for the considerable amount of computer time this 220 atom problem required.

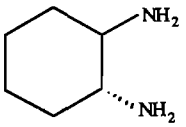
The first step in the modeling was to refine the structure of the three base-pair fragment taken from the crystal structure of CCGG:CCGG. All small DNA fragments containing suitable GpG sequences, including this one, are found to adopt the A-DNA structure. Therefore, modeling was carried out on this structure. The geometry obtained by energy minimization of the fragment agreed well with that found in the crystal structure from which the fragment was taken. The next step was to bond the platinum complex to N7 of one of the guanine bases. When this was done the distance between the Pt and the N7 atom of the adjacent guanine base was 3.7 Å while the expected bonding distance is 2.04 Å. In order to form the bifunctional attachment this distance was decreased in a stepwise fashion using the method of Lagrangian multipliers to constrain the separation distance and minimizing the strain-energy at each step. Once the correct bonding distance was reached the constraint was released and the structure refined to what appears to be a sensible model for the bifunctional attachment.

So what do we see in this model? First the coordinated guanine bases are no longer parallel but are both tilted toward the Pt atom. This distorts the interstrand interactions but interstrand hydrogen bonds persist in accord with the observations of NMR spectroscopic studies of these interactions [3]. The more interesting observation though was that of two close contacts between the ammine hydrogens of the cisplatin complex and two oxygen atoms of the DNA; one from the phosphate on the 5′ side of the GG pair and the other to the O6 atom of the guanine on the 3′ side. In the initial model both O···H contacts were found to be less than 2.1 Å which correspond to very unfavorable interactions unless they are hydrogen bonds. The refinement was continued with these interactions modeled explicitly as hydrogen bonds and sensible geometries resulted. The observation of these two interactions is in accord with the only clearly established structure–activity relationship for cisplatin-type drugs; that is that replacement of one or two of the hydrogen atoms on each of the ammine ligands with alkyl groups does not destroy cytotoxic activity but replacement of all three gives inactive compounds [4].

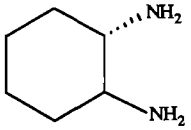
This correlation is an encouraging result, but if we are to show that we are modeling the interaction responsible for cytotoxic activity then a more general correlation between experimental structure–activity relationships and the calculated binding energies is required. The problem of course is that changing the structure of the complex might alter not only its interaction with DNA but also its chemical stability,

transport properties and other properties which affect antitumor efficacy. For instance, in the example above, the loss of activity on replacement of all ammine hydrogen atoms may be a consequence of poor transport into the cell. One way of obtaining structure–activity relationships which avoid these problems is to study the two enantiomers of racemic drugs. Since the DNA molecule is chiral, each hand of such drugs will interact differently but their chemical and transport properties will be identical (assuming only passive transport processes).

Different antitumor activities have been reported for the *R,R* and *S,S* hands of the drug [Pt(*trans*-chxn)X_2], where chxn = 1,2-cyclohexanediamine [5, 6].



R,R-chxn



S,S-chxn

Therefore, I undertook modeling of the interaction of each of these in turn with the DNA fragment described above.

The first observation from this modeling was that the bulky amine ligand did not interact significantly with the DNA molecule and therefore it appears that such interactions are not responsible for different binding of the two enantiomers. Differences were observed, however, in the interaction of the amine hydrogen atoms with two oxygen atoms described above. The chirality at the two carbon atoms adjacent to the nitrogen atoms of the chxn ligand confers a preference for a different orientation of the amine hydrogen atoms in each enantiomer. As a result the hydrogen atoms in the *S,S* enantiomer are more directly disposed toward the oxygen atoms to which they are hydrogen bonded than is the case for the *R,R* enantiomer. This is reflected in a 10 kJ mol^{-1} lower binding energy (described as the strain energy of the DNA/drug complex minus the total strain energy of the isolated species) for the *S,S* enantiomer. Whether this relatively small difference is sufficient to account for the reported difference in cytotoxic activity cannot be determined and it should also be noted that in some systems the *S,S* enantiomer is more active while in others the *R,R* is better. However, it is encouraging that the modeling suggests a difference in binding ability for these enantiomeric drugs.

Conclusion

In conclusion the calculations suggest that the ability of the ammine ligand(s) of cisplatin-type drugs to form two hydrogen bonds to DNA is an important determinant of binding ability. What is needed to test this hypothesis is a pair of enantiomers, one of which can form both hydrogen bonds and one of which can form neither.

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