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LETTER

Model Calculations on Zn(II)/Cd(II) Interaction with Nucleic Bases

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Binding of smaller metal ions to DNA/RNA bases has been studied intensively by means of theoretical methods [1–10]. Various techniques have been used, ranging from semiempirical [5, 6] and *ab initio* SCF [7–9] to Monte Carlo methods [10]. Some studies of Zn(II) binding to DNA/RNA bases have been reported [1–4]. In experimental work [11] it has been found that zinc ion can unwind and rewind double-helical DNA by heating and cooling, respectively. Furthermore, Zn(II) is an essential ion in enzymes of nucleic acid metabolism, including replication [12, 13]. Binding of Cd(II) to purine and pyrimidine bases of DNA and RNA has not been studied yet by means of quantum chemical calculations, despite its similarity to Zn(II) and its supposed ability to replace this ion under certain circumstances, possibly leading to detrimental effects. Cd(II) is considered as a carcinogenic cation and, when replacing Zn in enzymes, it can cause damage to living organisms [14].

The relative stability of binding sites for Zn(II) to guanine have been reported so far only on the basis of minimal basis set calculations, so that reinvestigation using a more accurate method seemed desirable. Also, by this a comparison of relative binding affinities of guanine for Cd(II) and Zn(II) [15] becomes possible.

Calculations

Effective core potentials (ECP) were used to describe the core electrons of all heavier atoms [16]. For the valence electrons, double-zeta (DZV) basis sets were used [17]. The SCF calculations were performed with the HONDO program, version VII [18], adapted for the CDC-Cyber 840 computer of Innsbruck University.

The geometry of the guanine base was taken from the experimental data of Spencer [19], and kept constant throughout the calculations, as it is known that the geometry of this base does not change significantly upon interaction with metal ions [20]. The positions of Zn(II) and Cd(II) in the field of guanine were selected only in the molecular plane according to the molecular potential maps for guanine [21]. The coordination considered included all possible binding sites according to previous calculations [1, 2], N_7, O_6 and the chelate position involving both of these atoms (Fig. 1). First, a grid of ion positions was calculated and, after having evaluated the local minima for binding, distances of the metal ions from the site were optimized with a step width of 0.01 Å.

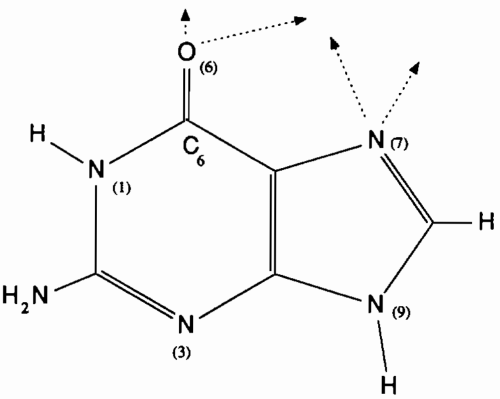

Fig. 1. Binding sites of guanine for metal ions.

Results and Discussion

The local energy minima for the metal ions binding to the reactive sites of guanine are listed in Table 1, together with their binding energies. Guanine has actually another reactive site at N_3, but since previous work [1, 4] found that N_3 is by far less favoured for ion binding, this site could be neglected in our work. In both systems, Zn(II)-guanine and Cd(II)-guanine, it was found that simultaneous binding of metal ions to N_7 and O_6 is energetically most favoured.

Considering the relative binding energies for both systems, Zn(II) can form more stable complexes with guanine than Cd(II), as expected. The factor by which Zn(II) is favoured over Cd(II) is identical for N_7 and the chelate position, but slightly larger for O_6, indicating the higher binding affinity of Zn(II) for O as coordination site. In the case of

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TABLE 1. Energy-optimized metal ion binding positions at various reaction sites of guanine, together with corresponding binding energies

Site	Distances (Å)		Angles (deg)		Binding energies (kcal/mol)		Factor (Zn/Cd)
	Zn^{2+}	Cd^{2+}	Zn^{2+}	Cd^{2+}	Zn^{2+}	Cd^{2+}	
N(7)	1.90	2.06	129.4[a]	129.5[a]	−187.9	−164.0	1.15
O(6)	1.80	1.95	155.6[b]	134.3[b]	−171.6	−140.2	1.22
$N_7 + O_6$	2.03[c] 2.05[d]	2.20[c] 2.21[d]	100.5[a]	100.3[a]	−217.1	−189.6	1.15

[a] $Zn-N_7-C_5$ angle. [b] $Zn-O-C_6$ angle. [c] $Ion-N_7$ distance. [d] $Ion-O_6$ distance.

chelate complexes, distances from metal ions to N_7 and O_6 are larger than the distances in complexes where metal ions bind to N_7 or O_6 of guanine alone.

The energy surfaces for metal ion/guanine interactions are presented in Figs. 2 and 3, respectively. Differences can be observed especially for the areas of maximal binding stability, which are considerably larger for Cd(II) than for Zn(II), indicating a better mobility and flexibility of this ion in its choice of location. This might play some role when guanine is embedded in a larger molecular structure such as RNA/DNA. The experimental investigation of guanine complexation with Zn(II) and Cd(II) has shown that the Cd(II) complex is slightly more stable in aqueous solution than that of Zn(II). Since the interaction energies calculated in this work do not reflect this behaviour, this enhanced stability should probably be attributed to the smaller hydration energy of Cd(II) and/or entropic effects. The preference of a chelate position for Cd(II), as concluded from the *ab initio* energy surface here, is well supported by experimental NMR data [15]. Summarizing the results of this study, it can be concluded that binding of Zn(II) and Cd(II) to guanine/guanosine should not differ too much, as far as structure and affinity are concerned and that, because of these small differences, it seems quite possible that the noxious Cd(II) can easily replace Zn(II) in biological environments under suitable conditions.

From a methodical viewpoint, a comparison of our results based on DZV–ECP basis set accuracy with those obtained with minimal GLO basis seems

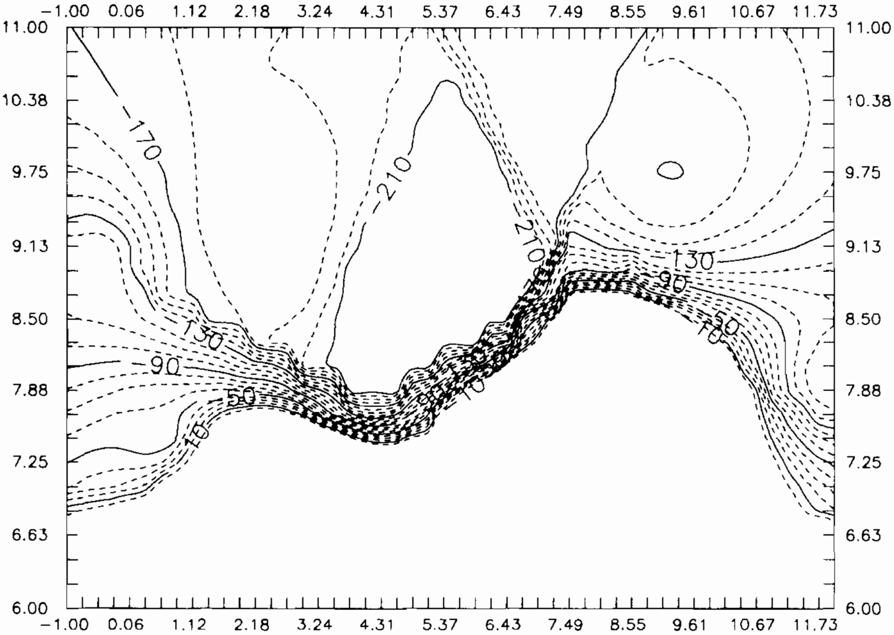

Fig. 2. In-plane energy surface for Zn(II)/guanine interaction. The local minimum on the left corresponds to interaction with N_7 only; that on the right to interaction with O of guanine. The absolute minimum area in the centre represents chelate binding to both coordination sites.

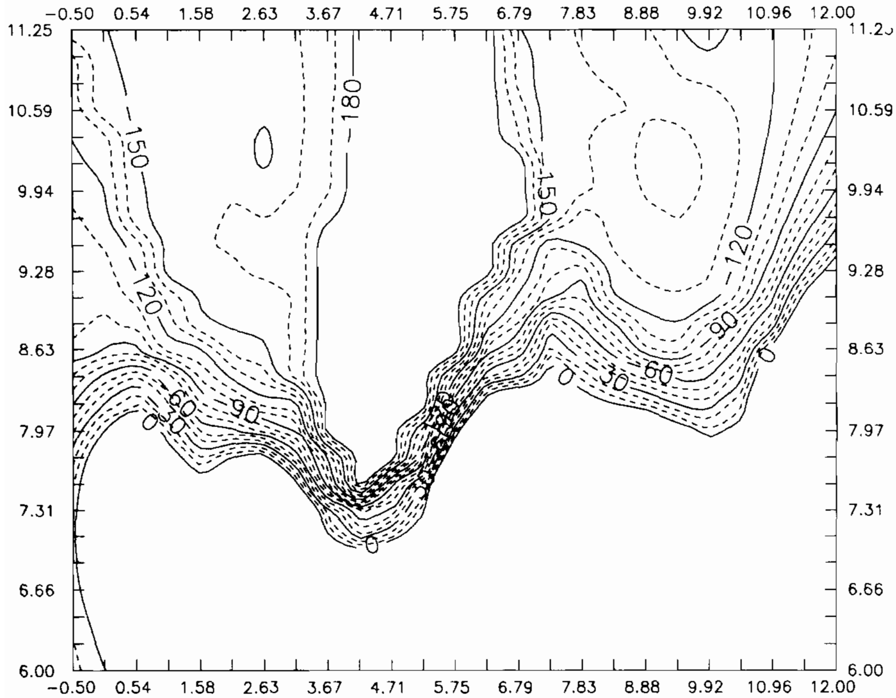

Fig. 3. In-plane energy surface for Cd(II)/guanine interaction. The local minimum on the left corresponds to interaction with N_7 only; that on the right to interaction with O of guanine. The absolute minimum area in the centre represents chelate binding to both coordination sites.

worthwhile. The corresponding data for Zn(II)-guanine (Zn–O = 1.85 Å, Zn–N = 1.72 Å, Zn–N_7–C_5 = 88°, BE = 260.7 kcal/mol) reveal that data obtained for the geometry of the ion binding site are not too reliable for either distances or angles when using the minimal basis set, nor are the absolute interaction energies, but that the correct binding site is predicted. Since the use of effective core potentials brings about a considerable reduction of computer time, thus allowing the use of higher quality basis sets for the valence electrons, this method seems to be the better solution in dealing with MO SCF calculations on heavier ions and/or larger ligands.

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