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Cation Binding to Biomolecules

VI. SCF *ab initio* (Pseudopotential) Computations on the Interaction of Zn^{2+} with the Purine and Pyrimidine Bases of the Nucleic Acids

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The binding of Zn^{2+} to the purine and pyrimidine bases of the nucleic acids was studied by SCF *ab initio* (pseudopotential) computations. The order of affinity of the bases is guanine $\simeq$ cytosine > adenine $\gg$ uracil. Many geometrical features of the binding are similar to those observed previously in the interaction of the bases with Na^+. A new feature is the possibility of chelation by Zn^{2+} between N_7 and the rotated NH_2 group of adenine.

Key words: Zn^{2+} binding to nucleic acid bases

1. Introduction

In previous papers of this series we have investigated, among other things, the binding of an alkali (Na^+) and an alkaline-earth (Mg^{2+}) cation to the nucleic acid bases [1, 2]. This work is hereby extended to Zn^{2+}, one of the most important and ubiquitous metal cations in biological systems, involved in the catalytic site of many enzymes, forming an essential component of many DNA- and RNA-polymerases and also known to bind directly to the bases and the phosphates of nucleic acids [3, 4]. At the same time the work reported here is also a part of a more general investigation carried out in our laboratory [5–8] in relation to the large utilizations of Zn^{2+} by biological systems.

2. Method

The combination of the purine or pyrimidine bases of the nucleic acids with Zn^{2+} representing relatively large systems for which SCF *ab initio* computations are expensive, we have utilized the possibility to replace the inner shells of the atoms by pseudopotentials using those recently developed by Topiol *et al.* [9, 10]. Demoulin

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and Pullman [6] have established that this technique was able to reproduce to a good accuracy their results on zinc-ligand interactions obtained by full SCF computations with double-zeta quality basis sets. In the present work, the size of the ligands imposes the use of more contracted sets. Hence we have adopted for the ligands the (7*s*, 3*p*/3*s*) basis contracted to a single zeta set used in earlier work on the same systems [11], adapted to the pseudopotential computation by replacing the 2*s* valence orbitals by Topiol's fully contracted least-squares-fitted functions [12]. For the cation we have adopted the (9*s*, 5*p*, 3*d*) basis set of Roos, Veillard and Vinot [13] modified into a (8*s*, 6*p*, 4*d*) basis by deleting the *s* function of lowest exponent which becomes redundant when suitable *d* functions are present, and adding a diffuse *p* function ($\zeta_p = 0.4627$) and a diffuse *d* function ($\zeta_d = 0.2786$). This basis contracted into a double ζ set for the valence shell plus the diffuse functions yields an SCF energy for the zinc cation of -1771.3272 a.u. Even for single zeta contraction, the energy (-1769.3553 a.u.) remains better than that (-1767.8698 a.u.) obtained with a more extended, but less balanced (12*s*, 6*p*, 4*d*), basis used earlier [6]. For the present pseudopotential computation, the three valence *d* functions contracted single ζ were kept out of the core as well as the diffuse *p* and *d* orbitals. Test computations were performed on $Zn^{2+}-NH_3$ and $Zn^{2+}-H_2O$ yielding binding energies of -104.8 and -90.2 kcal/mole respectively, with a charge transfer to zinc of 265 and 184 (10^{-3} e) respectively. The energies are 10 percent smaller than those obtained in the full SCF computation with the same basis set at the double ζ level [7], but they are in the correct order as is also the amount of charge transferred to zinc, an agreement which appears sufficient to permit an exploratory study of the binding characteristics of the larger compounds.

The geometries adopted for the bases of the nucleic acids are those derived from averaged values by Arnott [14].

3. Results and Discussion

Because of the great computational time required, we have used the previous results on the shape of the electrostatic potential maps of the bases [15, 16] and on their interaction with Na^+ [1] to limit our study to what appeared *a priori* to be the most probable binding sites for the associations of the bases with Zn^{2+}. The results are summarized in Fig. 1 and Table 1.

3.1. Interaction of Zn^{2+} *with Uracil*

The explored directions of approach of the cation were located along the $C_2 = O_2$ and $C_4 = O_4$ bonds and along an axis making an angle of 10° with $C_4 = O_4$ on the side of C_5 (Fig. 1a).

As in the previous studies with Mg^{2+} [2] and Na^+ [1], the preferred binding site is O_4 along the 10° axis (Fig. 1). The binding energy (-120 kcal/mole) is larger than with Mg^{2+} (-108.8 kcal/mole) and Na^+ (-32.9 kcal/mole). The optimum distance (1.8 Å) is shorter than in the case of Na^+ (2.0 Å) and slightly larger compared to Mg^{2+} (1.75 Å).

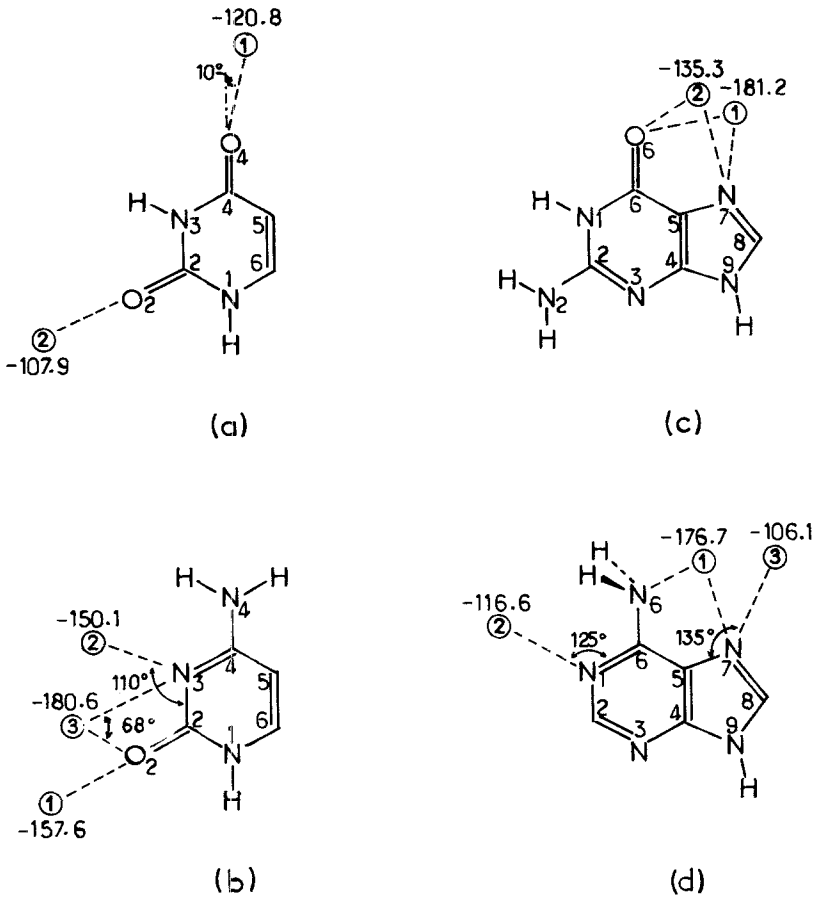


Fig. 1. Interaction energies (kcal/mole) of Zn^{2+} with: a) uracil, b) cytosine, c) guanine, d) adenine, in the sites indicated

3.2. Interaction of Zn^{2+} with Cytosine

Figure 1b gives the binding energies of Zn^{2+} to cytosine in the positions numbered 1) to 3), corresponding to approaches: 1) in the direction located along the $O_2 = C_2$ bond, 2) in the direction making an angle of 110° with the N_3–C_2 bond and 3), aiming at a bridged interaction with both O_2 and N_3. The maximum binding energies obtained for these positions are -157.6 kcal/mole for binding to O_2 ($d = 1.78$ Å), -150.1 kcal/mole for binding to N_3 ($d = 1.97$ Å) and -180.6 kcal/mole for the bridged position ($Zn^{2+} \cdots O_2 = 1.97$ Å, $Zn^{2+} \cdots N_3 = 2.11$ Å). The bridge position represents thus the strongest binding site. Considered individually the carbonyl oxygen exerts a somewhat stronger attraction on the cation than the ring N_3 atom.

3.3. Interaction of Zn^{2+} with Guanine

For this case only two different positions corresponding both to simultaneous binding to O_6 and N_7 have been studied. The distances were taken equal to those

Table 1. Binding energies of Zn^{2+} with the bases[a]

	Distance (Å)	$-E$ (kcal/mole)
Uracil		
1	$O_4Zn = 1.7$	117.0
	$O_4Zn = 1.8$	120.3
	$O_4Zn = 1.9$	118.0
	$O_4Zn = 1.8$, $\theta = 10°$[a]	120.8
2	$O_2Zn = 1.7$	104.0
	$O_2Zn = 1.8$	107.8
	$O_2Zn = 1.9$	106.0
Cytosine		
1	$O_2Zn = 1.7$	156.1
	$O_2Zn = 1.78$	157.8
	$O_2Zn = 1.8$	157.6
2	$N_3Zn = 1.9$	150.0
	$N_3Zn = 1.92$	150.1
	$N_3Zn = 2.0$	148.3
3	$O_2Zn = 1.93$ $N_3Zn = 2.07$	180.0
	$O_2Zn = 1.97$ $N_3Zn = 2.11$	180.6
	$O_2Zn = 2.08$ $N_3Zn = 2.22$	176.9
Guanine		
1	$O_6Zn = 1.97$ $N_7Zn = 2.11$ Zn in-plane	181.2
2	$O_6Zn = 1.97$ $N_7Zn = 2.11$ Zn out-of-plane 60°	135.3
Adenine		
1	$N_6Zn = 2.0$ $N_7Zn = 2.0$	176.7
	$N_6Zn = 2.1$ $N_7Zn = 2.1$	176.0
	$N_6Zn = 2.2$ $N_7Zn = 2.2$	170.1
2	$N_1Zn = 1.8$	112.8
	$N_1Zn = 1.9$	116.6
	$N_1Zn = 2.0$	115.5
3	$N_7Zn = 1.8$	102.6
	$N_7Zn = 1.9$	106.0
	$N_7Zn = 2.0$	104.8

[a] See Fig. 1 for the sites.

found for the $Zn^{2+}\cdots$ cytosine interaction. The binding energies found are -181.2 kcal/mole for the in-plane position and -135.3 kcal/mole when the cation is out of plane (in a plane making an angle of 60° with the guanine plane). Thus the in-plane position is significantly more favorable energetically.

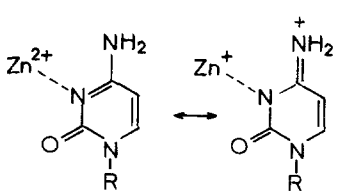
3.4. Interaction of Zn^{2+} *with Adenine*

The interaction energies were computed for the positions of the cation in the regions of N_1 and N_7 of the base and also for Zn^{2+} bound simultaneously to N_6 and N_7 with the NH_2 group rotated 90° around the CN bond in a pyramidal configuration, with the two hydrogens on the N_1 side of the molecule. The binding energy of the chelated Zn^{2+} (-176.7 kcal/mole) is much larger than those corresponding to the interactions with N_1 (-116.6 kcal/mole) or with N_7 (-106.1 kcal/mole).

The overall order of affinity of the bases for Zn^{2+}, judged by the maximum value of the interaction energy is: guanine $\simeq$ cytosine $>$ adenine $\gg$ uracil.

Altogether the results obtained for Zn^{2+} are similar in a number of their essential (qualitative) features to those found for Na^+. This concerns, for instance, the slight preference for a carbonyl oxygen over a ring nitrogen in compounds containing both types of atoms and the further preference for bridged binding in cytosine and guanine, over localized binding to individual O or N atoms. A new feature put into evidence in this paper is the possibility of a bridge binding between N_7 and the rotated NH_2 group in adenine.

The theoretical results obtained here find support in experimental studies, carried out in particular by proton magnetic resonance. The most extensive such studies, performed on nucleosides $-Zn^{2+}$ association in dimethyl-sulfoxide medium, seem to be those of Wang and Li [17]. Their results confirm that the complexation of Zn^{2+} with guanosine leads to a chelate ring involving N_7 and O_6 of the base, and that the complexation with adenosine induces the formation of a chelate between N_7 and the NH_2 group of the base. No complex formation occurs with uracil which in our computations is by far the less efficient ligand. For cytidine the authors suggest binding to N_3, which they consider to be representable by the structure:



However, in a recent very careful reinvestigation of the subject using Raman and ^{13}C NMR spectroscopy, Marzilli *et al.* [18] brought forward evidence indicating a general tendency of hard metal ions to bind to O_2 of cytidine. For the particular

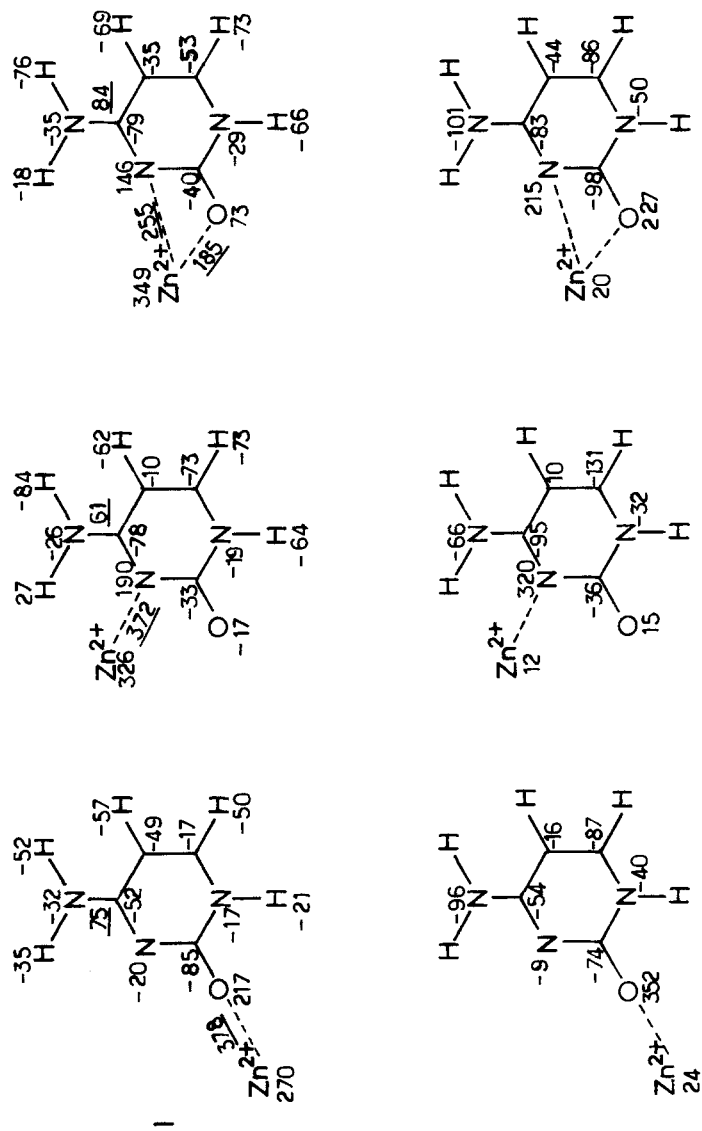


Fig. 2. Charge gains (+) and losses (−) by the atoms of cytosine upon binding to Zn^{2+} (10^{-3} e). Numbers underlined are gains in overlap populations

case of Zn^{2+} the results of these authors suggest that this metal ion forms two types of complexes involving C_2 and N_3 binding, respectively. However, as they admit themselves, they cannot exclude simultaneous binding of one metal to both sites with differing degrees of interaction.

In order to clarify this aspect of the problem and also some related questions relevant to the representation of the Zn^{2+}–base complexes we present in Fig. 2 the evaluation of the distribution of the electronic charges and of the overlap populations in the adducts of Zn^{2+} with cytosine. It can be seen that in the bridged complex the overlap population is appreciably greater on the $Zn^{2+} \cdots N_3$ side than on the $Zn^{2+} \cdots O_2$ side indicating a stronger interaction with N_3 than with O_2. Another interesting observation relates to the increase of the overlap population, *in the three complexes*, along the C_4–NH_2 bond and the concomitant increase in the delocalization of the nitrogen π lone-pair, indicating the increase of the double bond character of C_4N, hence a parallel increase in the torsion potential along this bond. This increase is particularly visible in the bridged complex.

It must be added that in distinction to the above-quoted works, Shimokawa *et al.* [19], studying similarly by proton magnetic resonance the complexation of Zn^{2+} with purine nucleosides in dimethyl sulfoxide, estimate that the binding site of this cation with adenine is at N_7 of the base and that its binding site to guanosine occurs above the center of the base plane. Insofar as these results are in contradiction to those of Wang and Li [17] we may say that our computations support rather the latter.

Before finishing we would like to underline that our theoretical results relate to the free bases. They are apparently significant also for nucleosides. It is obvious, however, that they must be used with caution in more complex systems, in particular in nucleotides and polynucleotides in which the presence of the anionic phosphate, with which the cation has a strong tendency to interact, may lead to a more complex scheme of binding. In crystal structures there is also, of course, the effect of crystal packing forces. A possible situation may involve the interaction of the cation with the phosphate and the reactive sites on the bases. Thus e.g. in the crystal structure of the polymeric complex of Zn^{2+} with cytosine-5′-phosphate [20], the metal is tetrahedrally coordinated to N_3 of the pyrimidine, to two phosphate oxygen atoms and to one water molecule. It forms also weak intramolecular interactions with C_2 of the base. On the other hand, chelation between N_7 and O_6 of the 3′ bound guanosine was advocated, on the basis of CD studies, for the *syn* conformer of the Zn^{2+} complex of Guo-3′-*P*-(*anti*)-5′-Guo [21].

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