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Short Communication

Study of Anion Binding to Protonated Nucleic Acid Bases Using Electrostatic Molecular Potentials

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Theory shows and experiment confirms that the binding of anions to protonated bases of the nucleic acids is not limited to the vicinity of the nitrogen atom carrying the added proton but may occur at other even quite distant sites.

Key words: Nucleic acid bases, protonated, anion binding to ~

In a recent paper [1] we have investigated the affinity of the purine and pyrimidine bases towards the binding of simple anions such as e.g. Cl^-. The method adopted uses in a distinctive way the information produced from computing the electrostatic molecular potentials around these bases [2]. In a first step we consider the negative ion as a point negative unit charge. Then its electrostatic energy of interaction with the molecule considered is given at every point of space by $-V$, where V is the value of the molecular electrostatic potential at this point. The corresponding interaction isoenergy lines drawn in the space surrounding the molecule are thus the same but of opposite signs as the isoenergy contours used for describing the interaction with a bare proton [2]. In order to use these inversed maps properly for a real anion, we must, however, take into account the fact that the anion carries an electron cloud which, overlapping with that of the molecule, gives rise to an exchange repulsion, and thus prevents the ion from collapsing into the molecular skeleton. In order to account for this situation, we delimit the permitted zones of approach for the different anions by drawing appropriate circles centered on all heavy atoms and exclude from consideration all the attractive regions inside these circles. For instance the radius chosen in an exploratory study with Cl^- was fixed at 3.2 Å for all atoms, this value corresponding to the equilibrium distance obtained in a supermolecule computation of the energy of interaction in $Cl^- \cdots H_2O$, using for H_2O the same basis set as that used to compute the wave functions and the corresponding potentials of the nucleic bases.

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In the present note this work is extended to protonated nucleic acid bases, which when occurring in biosystems may *a priori* be presumed to represent stronger anion binding units than the neutral bases. Our investigations involved N_3-protonated cytosine and N_7-protonated guanine. As anion, we took into practical consideration Cl^-.

The principal results obtained are summed up in Fig. 1. In this figure the dashed lines represent the limit of approach of 3.2 Å fixed for the closest contact between the Cl^- and N or C atoms of the bases. The full lines are isoenergy curves of interaction in kcal/mole in the zones explored.

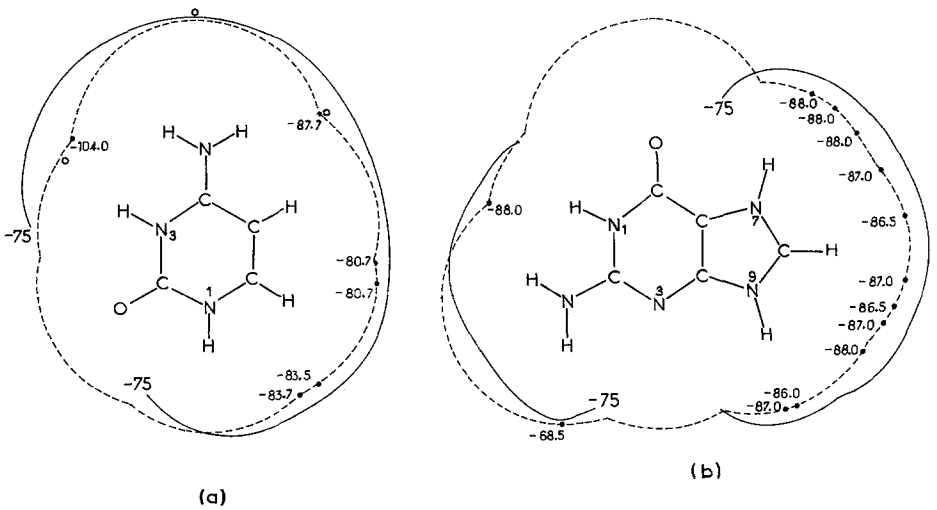

Fig. 1. Interaction energies of Cl^- with protonated nucleic acid bases (kcal/mole) (a) cytosine, (b) guanine.

(-----) limit of closest approach allowed for Cl^-.

(———) isoenergy curves for the interaction of the bases with a point negative charge.

(●) values of interaction energies at selected points on the lines of closest approach.

(○) in Fig. 1a: experimental positions of Cl^- in the crystal of cytosine hydrochloride [4]

The figure confirms the existence of attractive zones for Cl^- binding in specific regions of the bases studied, and the values of the energies involved indicate that, as expected, these interactions should be much stronger than with the neutral bases. One of the essential features of the results pertains, however, to the finding that the binding of the anions to the protonated bases is not necessarily limited to the vicinity of the nitrogen atom carrying the added proton, as might perhaps be expected by superficial reasoning, but may occur at other, sometimes quite distant sites. Thus in the case of protonated cytosine, while the strongest site of binding (-104 kcal/mole) does occur in the vicinity of the N_3^+H bond, the interaction energies at a number of places on the 3.2 Å curve exceed 80 kcal/mole and are thus still very attractive potential binding sites. The situation is even more striking with protonated guanine. In this case there are two equally strong sites of

maximum binding (88 kcal/mole), one of which is in the vicinity of the protonated N_7 but the other on the side of the pyrimidine ring, in a position between the N_1H and the NH_2 groups, very close to the position most effective for anion complexation in the neutral base. Moreover, there is in fact around the pentagonal ring of protonated guanine a large zone of practically constant interaction energy of the same order of magnitude than at the maximum.

This interesting result indicates that protonation of the bases produces, certainly through a large delocalization of the positive charge [3, 4], a strong activation of large portions of the molecular periphery towards anion binding.

The theoretical estimation seems to be in agreement with the scarce available experimental data. Figure 1a indicates the sites of location of Cl^- ions in the crystal structure of cytosine hydrochloride [5]. It is extremely gratifying to observe that two of these sites correspond to the two strongest, quite distant from each other interaction sites predicted by the computations. No results are available for the interaction of Cl^- with protonated guanine. However, in the closely related case of the crystal structure of 9-methylguanine hydrobromide [6], the location of the Br^- ions conforms satisfactorily to the theoretical pattern (one Br^- coordinated with N_1H and NH_2, another one with N_7, the presence of the methyl group at N_9 eliminating, of course, the possibility of coordination of the anion with the neighbouring part of the molecular periphery).

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