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Relationes

Ab initio Molecular Electrostatic Potentials

Guanine Compared to Adenine

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The *ab initio* isopotential map of guanine is given and compared to that of adenine.
It shows that in contrast to the situation in adenine, the most basic site of guanine is N_7 with a secondary potential minimum at O_6. These results as well as those concerning the secondary out-of-plane attractive regions over the NH_2 group and C_8H bonds of the two molecules are discussed in connection with the available experimental knowledge concerning the bonding of alkylating carcinogens and mutagens.

Key words: Isopotentials – Guanine – Alkylating agents

1. Introduction

In a previous paper [1] we have presented the molecular electrostatic potentials created in the surrounding space [2] by three of the bases of the nucleic acids: adenine, cytosine and thymine, using *ab initio* wave functions computed in a small Gaussian basis set [3], and have shown that these potentials enable a satisfactory discussion of the preferred protonation and alkylation sites of these molecules. The *ab initio* wave function of guanine not being available to us at that time, a tentative computation of its potential was made [4] using a CNDO wave function. Although the results indicated, in remarkable agreement with experimental facts that the most basic sites are displaced from the N_1, N_3 region in adenine to the N_7, O_6 region in guanine, the defects inherent in CNDO isopotential maps [4–7] did not allow a more thorough discussion. In view of the importance of guanine in the chemistry of the nucleic acids and more particularly as a preferred site of electrophilic attack by various alkylating agents [8] it was felt necessary to obtain an image of its electrostatic potential derived from an *ab initio* wave function of reasonable accuracy. We present below such a potential for guanine with a brief discussion of its essential features compared to those of adenine, in connection with the available experimental data.

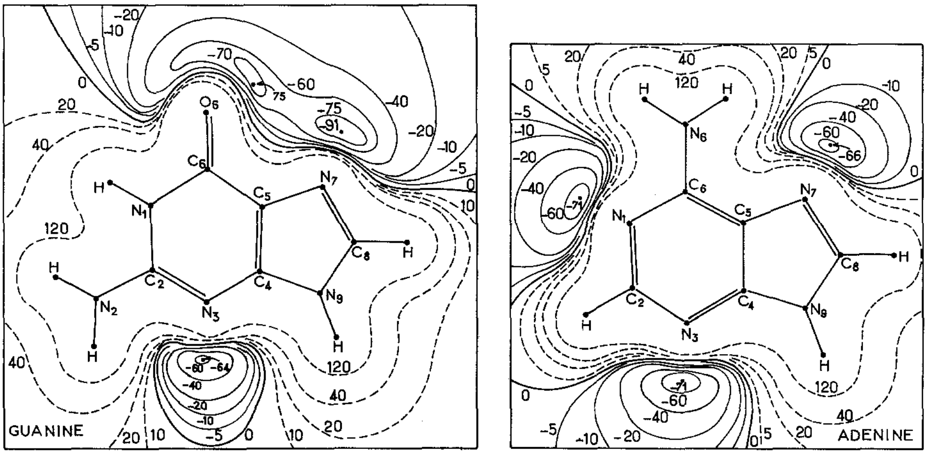


Fig. 1. Isoenergy curves (kcal/mole) for the interaction with a unit positive charge in the molecular planes of guanine and adenine. (Repulsive regions in dotted lines)

2. Results and Discussion

Since the publication of Ref. [3], a computation of the nucleic bases including guanine became available in a larger basis set [9]. We have used the wave functions of this latter computation[1] to obtain the isoenergy maps for the interaction with a point positive charge in the way described before [2]. The atomic basis set being different from that of Ref. [1] we have also recomputed the maps for adenine in the larger basis. This permits an assessment of the effect of the basis and provides a ground for a meaningful comparison of the two molecules.

The in-plane isoenergy maps are given in Fig. 1.

A first observation is that the present map of adenine resembles closely that obtained in our earlier work: it confirms the more attractive character of the N_1, N_3 region compared to the N_7 region, and the difficulty to discriminate between N_1 and N_3 previously discussed [1]. The numerical values of the minima obtained in Clementi's basis set are smaller than those found with the smaller basis as was also observed in the case of formamide [10].

As to the comparison of guanine with adenine, the in-plane maps of Fig. 1 show very clearly the switching-over of the most attractive region to an area encompassing N_7 and O_6 present already in the CNDO maps. They allow moreover a discrimination between two distinct minima, one connected with N_7, the other with O_6 (situation similar to that obtained for cytosine [1]) with a large preference in favor of the N_7 position, in complete agreement with the experimental observations concerning protonation and alkylation of guanine and its nucleosides or nucleotides [11, 12]. Worth noting is the fact that the N_7 minimum is appreciably larger than any of the minima in adenine, indicating that guanine is intrinsically more attractive towards an electrophilic agent than adenine, a feature in keeping with the fact that it is the base most easily alkylated in the alkylation of the nucleic acids [13]. Another observation of interest in connection with the

[1] The wave functions have been kindly communicated to us by Dr. E. Clementi.

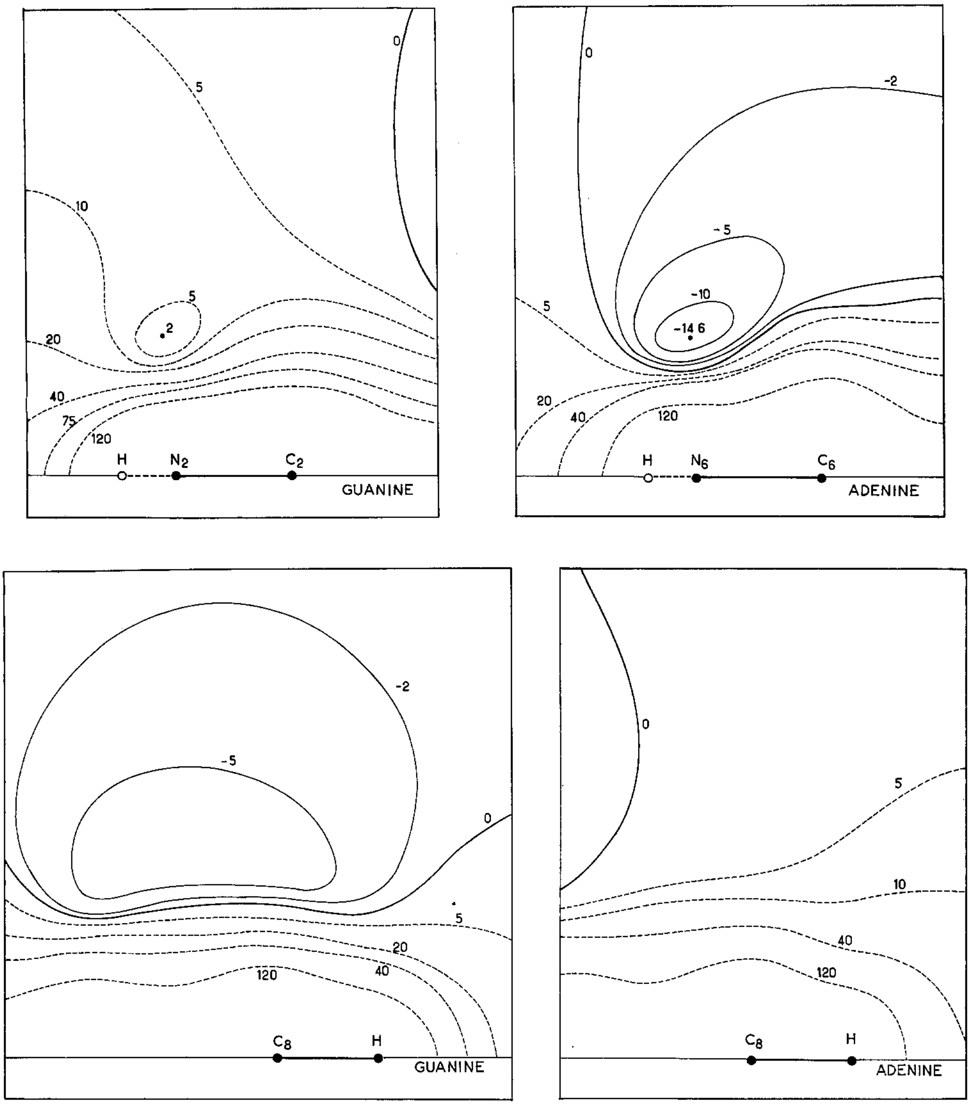
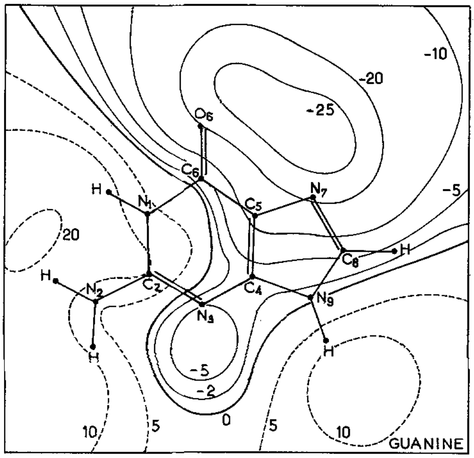


Fig. 2. Isoenergy curves (kcal/mole) in four sections perpendicular to the molecular plane, and containing the extracyclic CN and C_8H bonds of guanine and adenine as shown

presence of the second potential minimum near the oxygen atom is the fact that O_6 has been found to be a secondary alkylation site in deoxyguanosine [14, 15].

This sums up what concerns the favorable possibilities of in-plane approach of an electrophile towards the two molecules. As was found earlier [1, 10], the rest of the molecular periphery is repulsive for the in-plane approach of a positive charge towards NH, CH and NH_2 groups.

As concerns the out-of-plane approach, Fig. 2 illustrates the situation in four planes perpendicular to the molecule and corresponding to the most in-



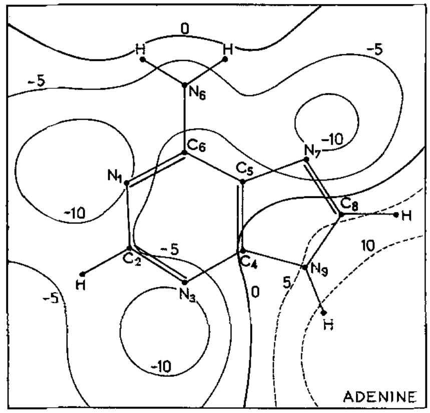


Fig. 3. Same as Fig. 1 in a plane at 2 Å of the molecular plane and parallel to it

teresting areas, namely above (and below) the amino group and above (and below) the C_8H bond of each molecule.

The small minimum found above the amino nitrogen of adenine is similar to that obtained in Ref. [1] in the smaller basis set. It shows the same qualitative feature encountered above the amino nitrogens in cytosine [1] and formamide [10] and indicates their much smaller basicity compared to that of the ring nitrogens (pyridine-like). In guanine, although the curvature of the lines indicates the existence of an attractive contribution in the potential, no negative value is found above the amino group. From the purely electrostatic point of view, the amino group of adenine appears more attractive than the amino group of guanine for an electrophile. It has been found recently that alkylation of nucleic acids by large aralkyl agents (7-bromomethylbenz(a)-anthracene, 7-bromomethyl 12-methyl-benz(a)-anthracene), while occuring (as for the small alkylating agents) on the "normal" ring nitrogen sites in non-polar solvents, takes place on the extranuclear amino groups in water [16–18]. Recent evidence seems in favor of the attack of guanine over adenine for the first regent [17], but in favor of adenine for the second reagent [18]. The preference for attack on the amino groups in the case of bulky aralkyl agents may be favored by an appropriate geometrical arrangement due to the possibilities of stacking of the aromatic group over the purine moiety in water [19], a circumstance not involved in the case of protons or small alkyl groups.

The remaining site of interest concerning electrophilic attacks is the C_8H region in these molecules [20]. A search in these regions, which we did not explore in our earlier study, appeared all the more interesting in view of the considerable amount of experimental observations [21] on the covalent binding of the carcinogens of the acetylaminofluorene family to the C_8 atom of guanine through an electrophilic substitution reaction [22]. Figure 2 indicates the existence in guanine of an attractive region above the imidazole ring extending well over carbon 8. In adenine, the small attractive region on the left part of the figure does not extend as far as to reach over the C_8 H bond. Thus the electrostatic component of the interaction energy with a positive charge points to a higher reactivity of guanine compared to that of adenine towards direct electrophilic attack on C_8. The experimental evidence seems to follow this trend both for halogenation, much easier in guanine than in adenine [20], and for the covalent binding of *N*-acetoxy-2-acetylaminofluorene which occurs essentially on C_8 of guanine in DNA and in various polynucleotides [21, 23–25] with very little, if any, covalent binding to adenine [25]. Figure 3, which gives the out-of-plane potentials for both molecules in a plane situated at 2 Å units above the molecular plane, helps visualizing the differences in the shape and characteristics of the attractive regions, particularly of its displacements from the hexacycle in adenine towards the pentacycle in guanine.

In conclusion, it appears once more that *ab initio* molecular electrostatic potentials provide us with a useful tool for studying protonation and electrophilic reactions in complex molecules, and it may be hoped that when supplemented by the inclusion of the second-order polarization and charge transfer effects, as was done in the case of formamide [26], they will contribute towards a better understanding of the differences in mechanisms involved in the action of the electrophiles of the various types [8, 27].

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