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A Theoretical Study of the Interaction of Ammonium and Guanidinium Ions with the Phosphodiester Linkage

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The different possible modes of interaction of the ammonium cation with the phosphate anion were explored both by the SCF *ab initio* method and by an empirical procedure developed in order to mimic the SCF results. The empirical procedure was then applied to the study of the guanidinium cation–phosphate anion system. The preferred modes of interaction are established.

Key words: Phosphate anion – Ammonium – Methylguanidinium

1. Introduction

Interactions involving the phosphate group and ammonium or guanidinium cations are ubiquitous processes in molecular biology. Most conspicuous interactions of this type occur in the formation of complexes between basic proteins (protamines and histones) and nucleic acids [1], polyamines and nucleic acids [2, 3], proteins and acidic phospholipids [4], biogenic amines and bioorganic phosphate-containing substrates (ATP, vitamin B_6 phosphate, etc.) [5–8] and local anaesthetics and phospholipids [9].

In this paper we present the results of a model theoretical study on fundamental aspects (configurational, energetic and electronic) of such interactions as apparent in the complexation of ammonium (NH_4^+) and methylguanidinium (MGD^+) cations with the phosphodiester linkage represented by the dimethylphosphate anion (DMP^-).

2. Methods

A series of computations on cation-ligand interactions carried out within the framework of the *ab initio* SCF method in the supermolecular approach have been

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presented recently from our laboratory [10–15]. While this procedure is certainly the most reliable for this relatively delicate and complex type of problems, its utilization becomes prohibitively expensive when the size of the interacting species increases.

For this reason we have attempted to establish an additive empirical procedure capable to reproduce to a fairly satisfactory degree the results of *ab initio* SCF computations of intermolecular interactions. The details of this procedure are presented elsewhere [16]. As in all additive procedures of this type [17, 18], the interaction energy is computed as a sum of components, each of which is evaluated separately. Here we would only like to indicate as a distinctive feature of our treatment that the computation of the electrostatic component, which brings about the major contribution to the total energy, is taken as a sum of multipole–multipole interactions, using the overlap multipole expansion of the exact electron density distribution [19, 20] corresponding to the SCF wave function of the individual molecules. The other contributions involve a polarization term computed with a corresponding multipolar expansion of the electrostatic field, a repulsion contribution and a R^{-6} attractive term appropriately fitted [16]. (The interactions considered in the present paper have not been used for the fitting.)

We present here the results of computations for the interactions of NH_4^+ with DMP^- obtained both by the SCF *ab initio* supermolecular treatment and by our empirical additive procedure, from the comparison of which an estimation may be made on the reliability of the empirical methodology. The computations on the interaction of the guanidinium ion with DMP^- have been carried out only within this last procedure.

The geometrical input data and the basis set used for DMP^- are the same as in our previous work of Ref. [11]. For NH_4^+ we have adopted an N-H bond length of 1.05 Å and an HNH valence angle of 109.5°, the basis set used being that of Ref. [10]. The input geometry for MGD^+ is taken from crystallographic results on the structure of MGD-PO_4H_2 complex [21], the basis set used for the computations of MGD^+ is that of Ref. [10] (Ref. [11] for the methyl group).

3. Results and Discussion

3.1. Interaction of NH_4^+ with DMP^-

The six principal modes of interaction investigated are illustrated in Fig. 1.

In mode I, NH_4^+ interacts symmetrically through two hydrogen atoms H_1 and H_2 with the two anionic oxygens of DMP^-, O_1 and O_3, the plane H_1NH_2 being coplanar with the plane O_1PO_3. Mode II is a somewhat distorted mode I in which the interaction between H_1 and O_1 exceeds that between H_2 and O_3. Mode III corresponds to the optimal arrangement involving a linear NHO bond in the O_1PO_3 plane; O_3 interacts then equally with H_1 and H_2. In mode IV, NH_4^+ interacts through one hydrogen atom (H_1) with the anionic oxygen O_1, and through H_1, H_2 and H_3, with the second anionic oxygen O_3 in a non-linear fashion, H_2 and H_3 being symmetrical above and below the O_1PO_3 plane. In mode V, NH_4^+

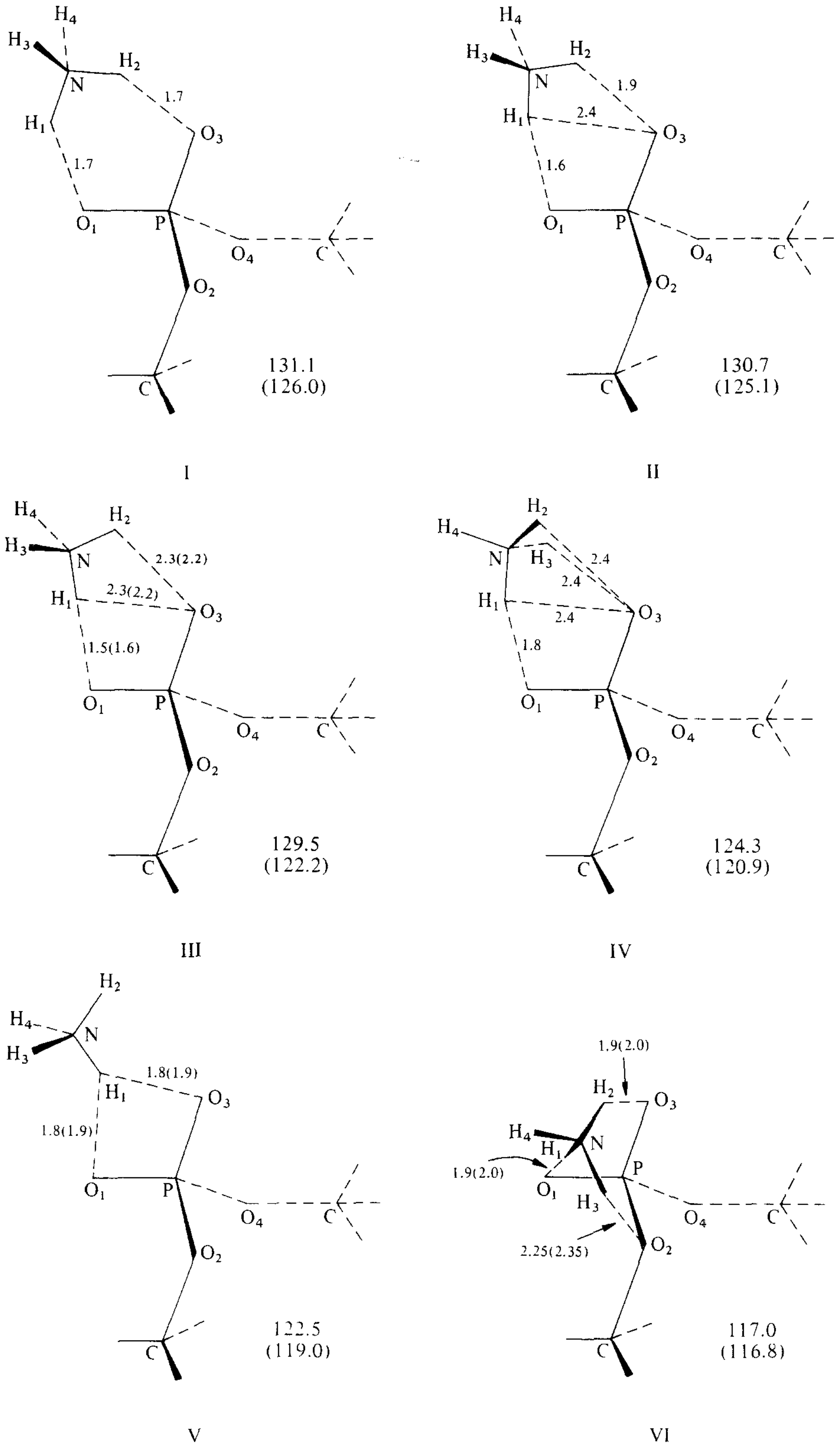

Fig. 1. Representation of the different investigated modes of interaction of NH_4^+ with DMP^- (distances in Å). SCF and (in parentheses) empirical binding energies in kcal/mole

interacts through H_1 with the two anionic oxygens, so that the H_1N axis coincides with the first bisector of the O_1PO_3 angle. H_3 and H_4 are symmetrically above and below the O_1PO_3 plane. Finally, in mode VI, H_1 and H_2 interact symmetrically with the two anionic oxygens and H_3 interacts with one esteric oxygen (O_2). The bonds N_4N and PO_4 are approximately coaxial.

Two types of conclusion may be drawn from the computed interaction energies associated with these different modes of interaction. One concerns the parallelism between the SCF *ab initio* and the empirical results, the two procedures indicating the same order of relative stabilities of the different modes of association. This result confirms thus the reliability of the empirical procedure to mimic qualitatively and to a large extent quantitatively the results of the SCF computations.

Concerning the association complexes themselves, the computations indicate that the coplanar approach of H_1NH_2 to the O_1PO_3 plane of DMP^-, as it occurs in modes I–III, is favored over the other approaches, the preferred arrangement corresponding to a symmetrical interaction of H_1 with O_1 and H_2 with O_3. Nevertheless, the remaining modes correspond to high interaction energies which do not differ by more than 10–15% from the most efficient one. Thus, the possibility of their occurrence in compounds with an ammonium cationic head, under the influence of specific environmental effects, cannot be excluded.

3.2. Interaction of MGD^+ with DMP^-

In view of the agreement between the SCF and empirical results for the $NH_4^+ \cdots DMP^-$ interaction the empirical procedure was the only one applied to the study of the large system $MGD^+ \cdots DMP^-$.

Five modes of interaction have been investigated, which are illustrated in Fig. 2.

In modes I and II the interaction involves the two anionic oxygens of the phosphate, O_1 and O_3, the plane of MGD^+ coinciding with the O_1PO_3 plane of DMP^-. However, while in mode I the interaction involves one amino group, through H_{21}, and the imino H_1 of MGD^+, in mode II it involves the two amino groups, through H_{22} and H_{31}. In modes III–V the interaction involves one anionic and one ester oxygen of DMP^-, O_3 and O_2 respectively, the plane of MGD^+ coinciding with the plane O_3PO_2 of DMP^-. In mode III the interaction occurs between the N_2 amino group of MGD^+ and O_2 of DMP^- and between the imino group of MGD^+ and O_3 of DMP^-. In mode IV this arrangement is reversed. In mode V, the interaction involves the two amino groups of MGD^+.

The results indicate that the preferred modes of association are I and II, it means those which involve the two anionic oxygens of DMP^- and that mode I which implies one of the amino groups and the imino group of MGD^+ represents the most stable arrangement.

The computed values of the interaction energy are smaller than the values found in the interaction $NH_4^+ \cdots DMP^-$. This is due, principally, to the large delocalization of the net positive charge of MGD^+ over its whole skeleton, which decreases the electrostatic contribution to the interaction energy.

The distribution of Mullikens net charges in MGD$^+$ is shown in Fig. 3, which indicates also that the amount of the net positive charge on atoms H_{21} and H_1 is greater than the corresponding amount on atoms H_{31} and H_{22}, a situation which plays a decisive role in determining the preference of arrangement I over arrangement II.

The energy differences between I and II and between these two configurations and

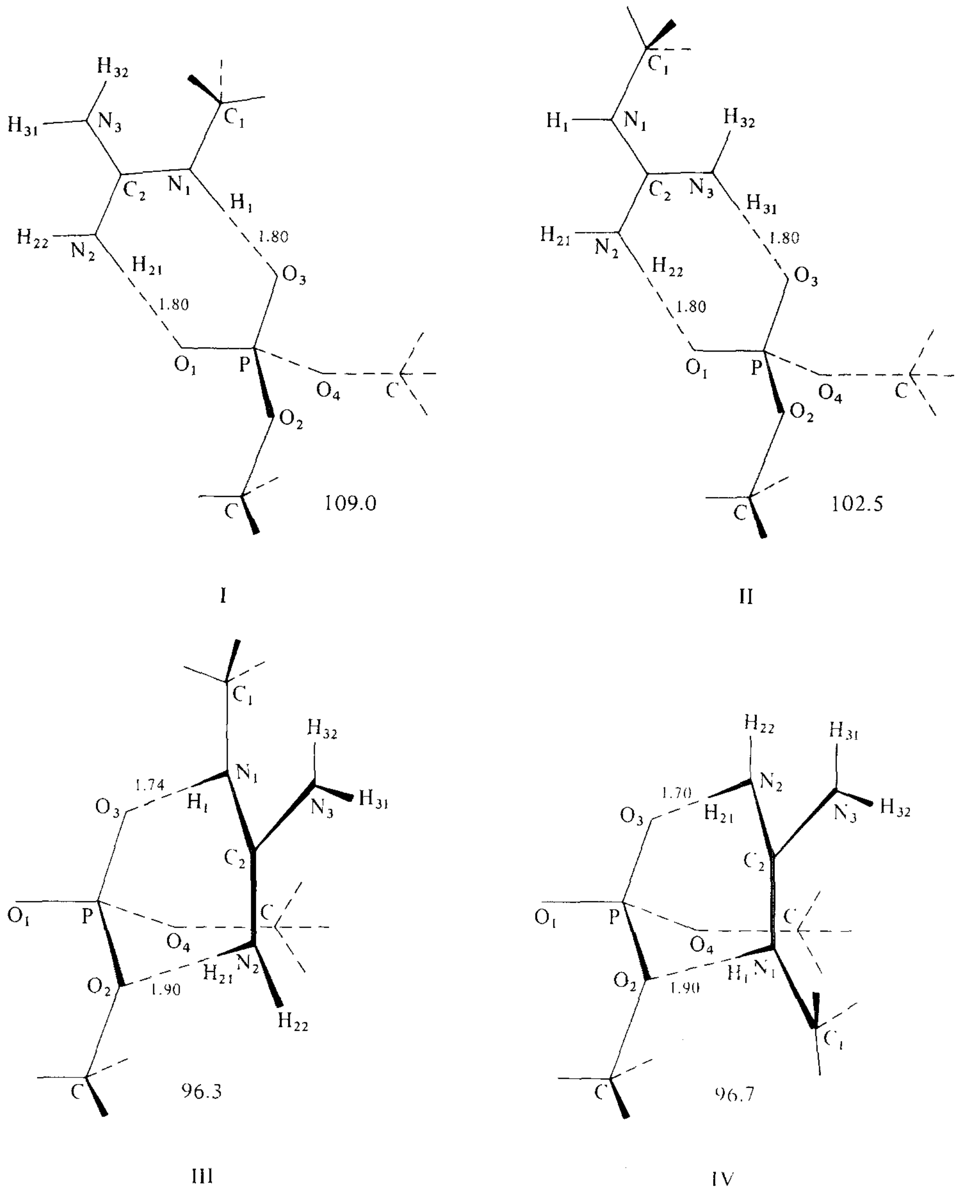

Fig. 2.

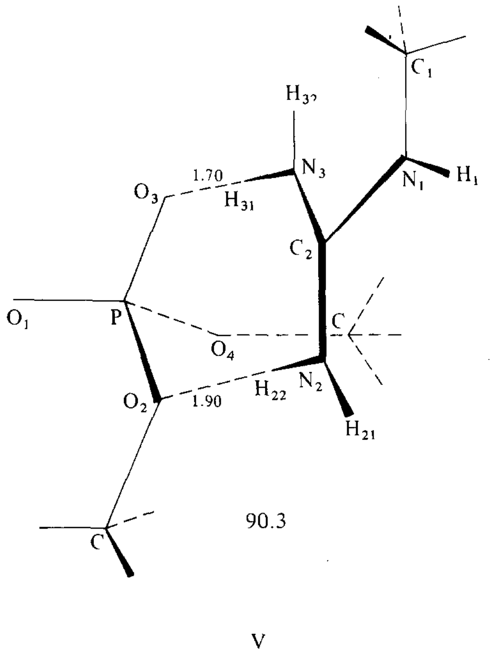

Fig. 2. Representation of the different investigated modes of interaction of MGD^+ with DMP^- (distances in Å). Empirical binding energies in kcal/mole

the remaining ones are sufficiently large to indicate most probably the order of their intrinsic preferences, but also sufficiently close to enable the different configurations to be produced under appropriate environmental influences. Examples illustrating this situation may be found in Ref. [21]. In this paper the authors report the results of a study on the structure of the ternary *staphylococcus* nuclease–thymidine diphosphate–calcium complex, in which two arginines, Arg-35 and Arg-87, play a specific role in binding simultaneously the inhibitor through H-bonds

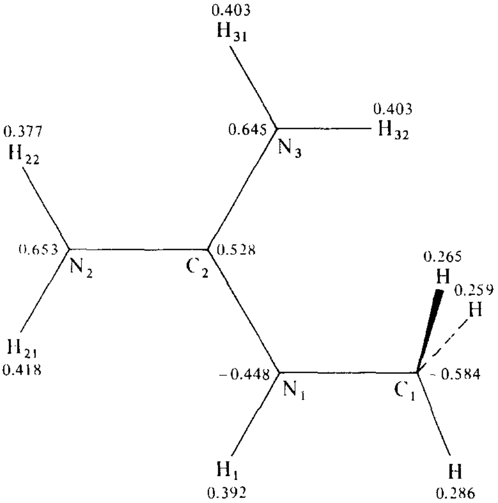

Fig. 3. Mulliken net charges in MGD^+ (in millielectron units)

with the 5'-phosphate group. This binding involves the modes I and V of interaction of the guanidinium groups with the phosphate. In the same publication the authors present also results of an X-ray crystallographic study of hydrogen bond interactions between MGD^+ and $H_2PO_4^-$ in (MGD) H_2PO_4. The mode of binding is of type III. In a similar crystallographic study of the interaction of two MGD^+ ions with HPO_4^{2-} ions in $(MGD)_2HPO_4$, both MGD^+ ions are bound to the phosphate ions through one NH_2 and their NH group. The preference for the utilization by MGD^+ of these two groups rather than of its two amino groups in binding associations seems thus to be a reality.

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