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Relationes

Metal Ion Interaction with Dimethyl Phosphate Anion

A Model System to Study the Conformational Changes at the Phosphate Site of Nucleic Acids

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The influence of metal ions on the conformation of dimethyl phosphate anion around its O–P bonds, has been studied theoretically. The perturbation caused due to metal ions like Na^+ and Mg^{2+} seems to affect the free dimethyl phosphate anion conformation to a considerable extent. In particular, the fully extended conformation becomes much more favourable in the metal ion dimethyl phosphate complex.

Key words: Dimethyl phosphate anion, metal ion interaction with ~ – Nucleotide-metal ion interaction

1. Introduction

Metal ions play a key role in many biological processes like translation, transcription and replication [1] and catalyse many enzyme reactions by acting as electron donor or acceptor [2]. Metal ion interaction with nucleic acids and their constituents have been the subject of investigation by several workers. The results have been reviewed [3, 4]. Since there are a large number of potentially active sites in nucleic acids for the attachment of metal ions experimental investigations have been very complex and different workers have proposed different models to explain their results. In order to resolve the ambiguity a sound theoretical investigation is necessary. A perturbative approach has been used [5] to explain the phenomena on a theoretical basis. These studies reveal that the perturbation due to metal ions is fairly large. Therefore, a detailed molecular orbital calculation is required to study the nature of metal-nucleic acid binding and alteration in the properties of nucleic acids as a result of such binding. In case of nucleic acids the rotation about the O–P bonds, usually designated by the rotational angles ω' and ω [6] is of key importance in deciding their configuration since rotation about other bonds in the backbone has been shown to be restricted [7]. In this paper we report the effect of metal ion binding with the phosphate group on the (ω', ω) conformational energy map of dimethyl phosphate anion (DMP^-) (Fig. 1) which serves as a good model system.

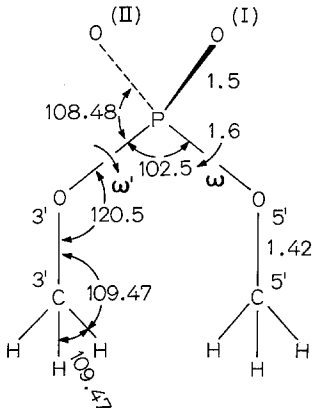

Fig. 1. Figure of DMP^- with its torsion angles ω' and ω which fix the conformation of this molecule

2. Method

The standard Complete Neglect of Differential Overlap method (CNDO/2) has been used in these calculations with minor modifications [8]. The Slater exponent for the Mg^{2+} ion has been chosen as 1.05 (cf. 0.95 in the original program) so as to predict the exact bond length (2.1 Å) in MgO. The bond length and bond angles for DMP^- are the same as given in Refs. [9] and [10]. The positions of Mg^{2+} and Na^+ ions in the metal ion-DMP complex was fixed as discussed later. The cartesian co-ordinates for different molecular conformations as defined by the torsional angles ω' and ω were computed and fed as input to the CNDO program. The energy differences between the various conformations are shown in the form of iso-energy contours to indicate regions of stability in the (ω', ω) map.

3. Results and Discussion

The iso-energy map for the free DMP^- has been studied in its staggered and eclipsed form (Figs. 2 and 3). The maps show that the regions (60°, 60°) and (300°, 300°) in the (ω', ω) space are preferred over other local minima in the map. The energy corresponding to fully extended (180°, 180°) structure is fairly high (~ 5 Kcal mole^{-1}). The phosphate geometry being chosen as symmetric, equal preference for (60°, 60°) and (300°, 300°) regions is observed. The results by CNDO/2 shows the same nature as two other theoretical methods namely PCILO [9] and *ab initio* calculations [10]. The relative preferences of the global minima is unaffected by changing the methyl group from staggered to eclipsed conformation. The (60°, 60°) and (300°, 300°) region in the (ω', ω) space correspond to a left handed and a right handed helix respectively for a linear polynucleotide chain. With the other torsional angles fixed at their preferred values the (300°, 300°) region leads to a conformation which is acquired in DNA double helices [7]. Other local minima which can satisfy the requirements of a double helix are the regions (180°, 300°) and (300°, 180°) and these are found to be ~ 1.5 kcal mole^{-1}

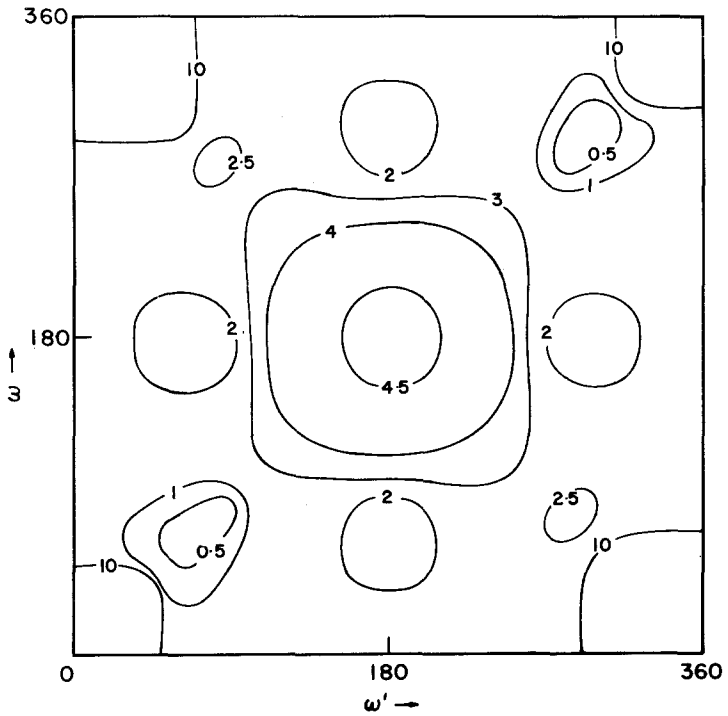

Fig. 2. The (ω', ω) conformational energy map of DMP^- with the methyl groups in staggered arrangement. The isoenergy contours are drawn in kcal $mole^{-1}$

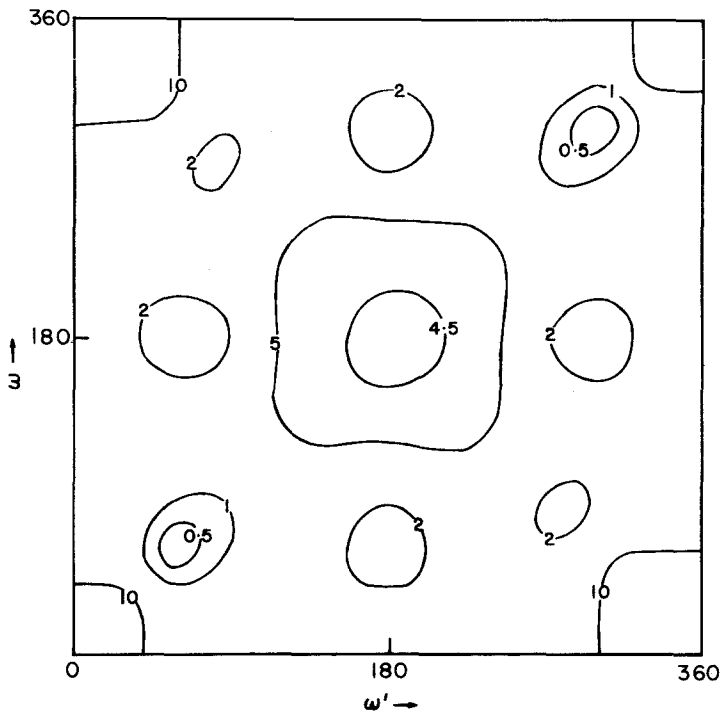

Fig. 3. The (ω', ω) conformational energy map of DMP^- with the methyl groups in eclipsed arrangement

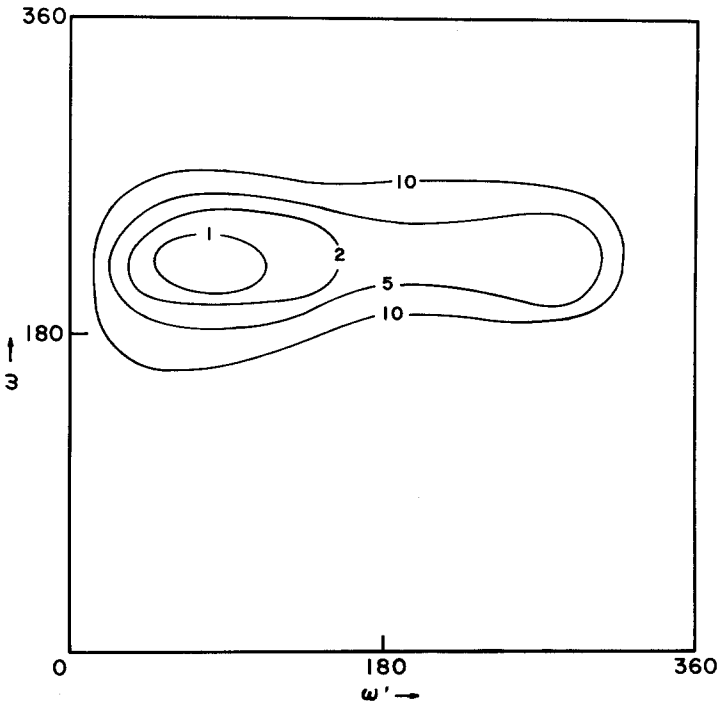

Fig. 4. The (ω', ω) conformational energy map of DMP^- with Na^+ ion attached to O(II) which shows result of one centre interaction

higher than the global minima. Because of the mirrorplane symmetry of the DMP^- we also find the (60°, 180°) and the (180°, 60°) regions to be equally probable.

Metal ion can interact with the phosphate group in two possible ways.

(a) Along the direction of one of the free oxygen atom, namely through a one centre interaction.

(b) Along the bisector of the angle between O–P–O and remaining in the plane of the two free oxygens and the phosphorus i.e. via a two centre interaction.

Both cases have been considered and the metal ion positions have been calculated by studying potential energy of the metal ion-DMP complex as a function of distance between metal ions and phosphate oxygens in DMP^-. The binding energies show a shallow minimum for Mg–O distance of 2.1 Å for one centre interaction and $\simeq 2.0$ Å for two centre interaction. The corresponding values for Na^+ complex are 2.3 Å and $\simeq 2.2$ Å respectively. These distances have been incorporated in the results shown in Figs. 4–7.

In case of one centre interaction, the reflection symmetry of the ligand is lost and one gets two metal ion DMP^- complexes which are optical isomers. The conformational maps for the two complexes are related by a mirror plane symmetry. Thus, a point (ω', ω) in the map for one complex corresponds to $(-\omega', -\omega)$ in its optical isomer. In case of Na^+ interaction with DMP^- the conformational freedom is rather restricted and is confined to the global minimum around

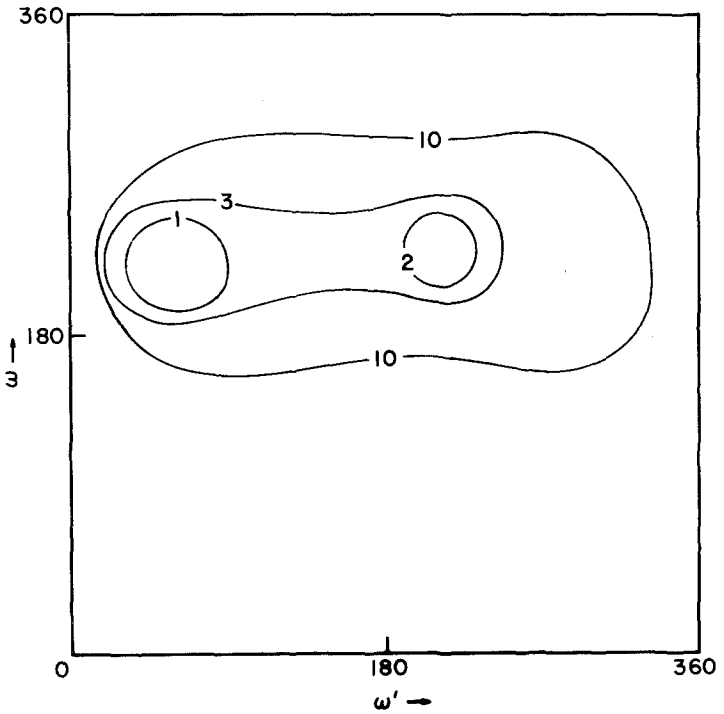

Fig. 5. The (ω', ω) conformational energy map of DMP^- with Mg^{2+} attached to O(II) which shows the result of one centre interaction

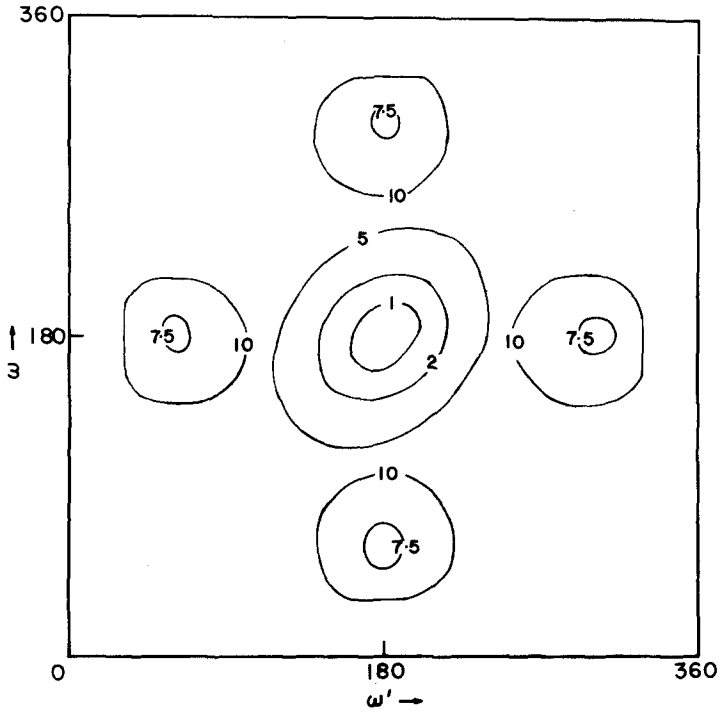

Fig. 6. The (ω', ω) conformational energy map of DMP^- when Na^+ ion is situated in the bisector of O(I) and O(II) and lies in the plane of O(I)–P–O(II)

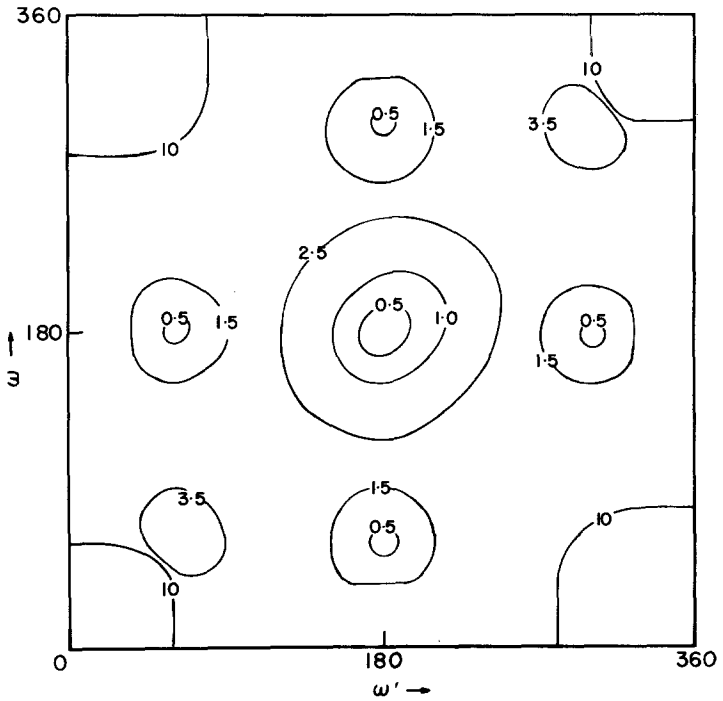

Fig. 7. The (ω', ω) conformational energy map of $DMP^- Mg^{2+}$ is situated in the bisector of O(I) and O(II) and lies in the plane of O(I)–P–O(II)

(80°, 220°) (or 280°, 140° for its optical isomer). The same nature of the map is observed in case of Mg^{2+} except that the conformation is relatively flexible due to the presence of another minimum around (240°, 220°) which is 3 kcal mole^{-1} higher than the global minimum.

The two centre interaction of Na^+ and Mg^{2+} with DMP^- preserves the symmetry of the molecular ion but the conformational preferences are altered. Energetically, such an interaction is found to be more favourable than one centre interaction by about 40 kcal mole^{-1} in case of Na^+ and 170 kcal mole^{-1} for Mg^{2+}. Here, the most stable region is predicted to be (180°, 180°). It is important to note that such a configuration is fairly unstable in free DMP^-. The regions (60°, 60°) and (300°, 300°) correspond to local minima with energy about 3 kcal mole^{-1} higher than the global minimum. The region (180°, 60°), (180°, 300°), (60°, 180°) and (300°, 180°) are found to be $\simeq 0.5$ kcal mole^{-1} higher up in energy compared to the fully extended form. These regions are not very high in energy compared to the extended form and the stability of the helix can be retained through compensation of energy due to stacking or hydrogen bonding etc.

The structures of a few metal ion complexes with diethyl phosphate (DEP^-) have been investigated using X-ray diffraction [11–13]. The metal ion binding in these crystals does not correspond to the two schemes discussed above but to a situation where metal ion binds simultaneously to more than one molecule of DEP. The observed conformations of DEP lie in the low energy regions of (ω', ω)

map, but do not correspond to the global minimum in the maps shown in Figs. 4–7. These observations are understandable in view of the sensitivity of (ω', ω) map to minor perturbations brought about by binding schemes.

The most important point that emerges from these studies is the fact that the nature and mode of the binding of metal ions have significant effect on the O–P bond rotations in the nucleotide backbone. In particular, the extended region becomes much more favourable in presence of metal ions. This has important bearing on the configurational properties of polynucleotide chains. The results also have important implications on experimental results of conformational studies of nucleotides based on metal ion induced pseudo contact shifts in NMR or X-ray diffraction studies of metal ion–nucleotide complexes, since the structure of free nucleotide may be different from the complex with metal ion. Further these studies point out to the possibility of metal ions being responsible for the opening of a double helix during replication or transcription through a conformational change of the individual strands from a right handed helical structure to a fully extended one.

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