# Geometrical and vibrational features of phosphate, phosphorothioate and phosphorodithioate linkages interacting with hydrated cations: A DFT study

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## ABSTRACT

The effect of hexahydrated monovalent and divalent cations on the geometrical and vibrational features of dimethyl phosphate, dimethyl phosphorothioate and dimethyl phosphorodithioate anions (simple suitable model compounds representing the anionic moieties of natural and some modified nucleic acids) was studied. For this purpose, density functional theory (DFT) calculations were carried out at the B3LYP/6-31++G* level.

Our results indicate that only $K^+$ and $Mg^{2+}$ prefer to be located in the bisector plane of the $PO_2^-$ angle, whereas $Li^+$ and $Na^+$ deviate from this plane. Monovalent and divalent cations are slightly deviated from the $OPS^-$ bisector plane and are found closer to the free oxygen atom. Moreover, the present calculations have shown that in contrast to the general belief, the $g^- g^-$ conformer (with respect to the torsion angles defined around the P–O ester bonds) is not always the energetically most favorable. For instance, the $g^- t$ conformer presents the lowest energy in the case of dimethyl phosphorothioate. The calculated vibrational wavenumbers obtained for dimethyl phosphate and dimethyl phosphorothioate interacting with hydrated sodium counterion, were compared with those previously recorded by Raman scattering and infrared absorption (IR) in aqueous solutions. It has been evidenced that the use of explicit solvent versus dielectric continuum, considerably improves the agreement between the theoretical and observed characteristic wavenumbers.

## 1. Introduction

Water molecules and counterions are of key importance in stabilizing secondary structures of nucleic acids (NAs). For instance, the B form double stranded DNA, presumably present inside the cell, is stable at high humidity. Thanks to the high resolution X-ray diffraction patterns [1–10], it has been evidenced that water molecules can be found principally close to free phosphate oxygens, nitrogen and oxygen atoms on the edges of base pairs, and to the O1′ atom of sugars. Estimation on the number of water molecules hydrating a nucleotide varies from 5 and 12 depending on the relative humidity of nucleic acid chains [7]. Moreover, it has also been revealed that the occupancy of the six possible hydration sites per phosphate, depends on the conformation and the type of the nucleotide. When hydration is decreased, the water molecules are first removed from the grooves and are principally localized around phosphate groups.

In fact, the low mobility of water molecules bound to the phosphate group is believed to be related to the electrostriction effect produced in the vicinity of charged molecules such as NAs [11].

Vibrational spectra of NAs are sensitive to their local (nucleoside or nucleotide levels) and global (double- and multi-stranded chain formation) conformational features. Valuable data on the conformational transitions of NAs, depending on the hydration and counterion binding, as obtained by Raman scattering [12,13] and IR absorption [14] techniques, are now available. Quantum mechanical calculations with the consideration of electronic correlation effect and extended atomic basis sets are now used as a powerful tool to analyze both geometrical and vibrational features of NA constituents at nucleoside and nucleotide levels [15–19].

As far as the geometrical and vibrational features of the phosphate linkage and its interaction with water and counterions are concerned, dimethyl phosphate (DMP) has been considered in several previous investigations as a simple model for performing quantum mechanical calculations. In fact, DMP with a $C–O–P(O_2^-)–O–C$ backbone, has the advantage of involving the phosphate anion as well as two carbons connected each to one of

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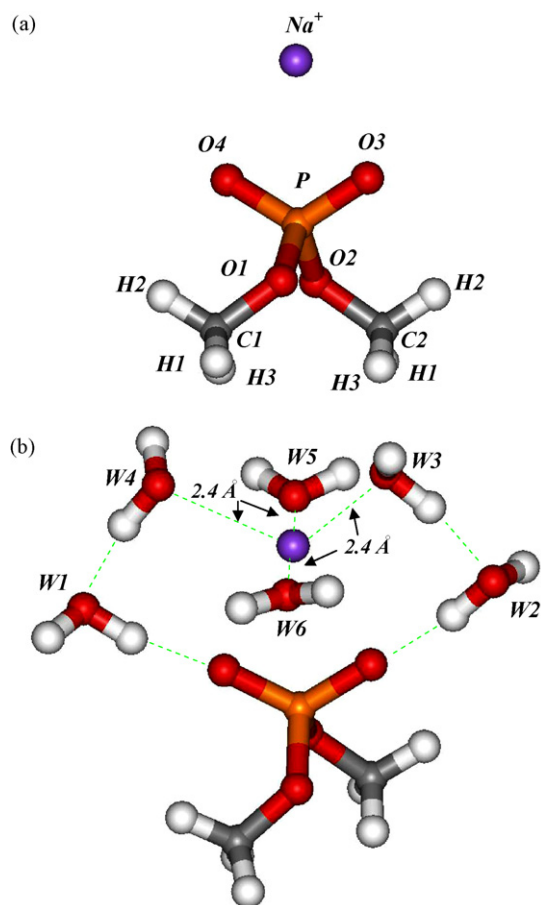*E-mail address:* mahmoud.ghomi@univ-paris13.fr (M. Ghomi).

**Fig. 1.** (a) Chemical structure and atom numbering of a dimethyl phosphate anion (DMP-OO)− interacting with a Na+ cation. (b) Intitial configuration (prior to the geometry optimization) of a hexahydrated cation. Note that 4 over 6 water molecules are directly bound to the cation (via their oxygen atoms), the two others directly interact with the anion. The initial distances between the cation and water oxygens were 2.4 Å. For final distances, see Tables 2 and 3.
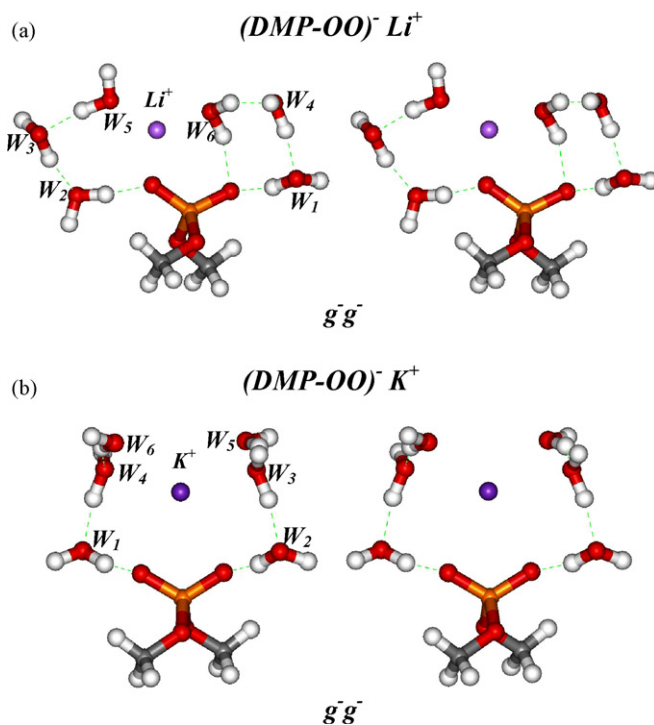


**Fig. 2.** Stereoview representation of the geometry optimized supermolecules constituted by a dimethyl phosphate anion interacting with a hexahydrated cation. (a) $g^- g^-$ conformer with Li+ cation. (b) $g^- g^-$ conformer with K+ (see Tables 1 and 2 for details).

its ester O–P bonds. These two carbons mimic somehow C3′ and C5′ carbons in a NA chain. Thanks to the presence of these carbons, two torsion angles can be defined at each side of the phosphorous atom (mimicking α and ζ torsion angles in a NA chain) [20]. Consequently, gauche (g) and trans (t) orientations of the DMP backbone carbons with respect to the phosphate group can be considered. Furthermore, detailed vibrational data from aqueous [21–23] and solid (powder) [23] samples of DMP/Na+ are available in the literature. Several groups have devoted previously theoretical investigations to DMP model. We can recall here those calculations: (i) by means of

**Table 1**
Energetics of dimethyl phosphate, dimethyl phosphorothioate and dimethyl phosphorodithioate as revealed by the calculations at the DFT/B3LYP/6-31++G* level of theory.

| Anion | Cation | Hydration | Conformers | ($E_e$) | ZPVE | $E_{tot}$ | $\Delta E$ |
|---|---|---|---|---|---|---|---|
| DMP(OO)− | | | | | | | |
| | Li+ | 6H₂O | $g^- g^-$ | −1188.4670 | 0.2483 | −1188.2187 | – |
| | Na+ | Continuum | $g^- g^-$ | −884.6048 | 0.0948 | −884.5100 | 0.00 |
| | | | $g^- t$ | −884.6031 | 0.0946 | −884.5085 | 0.94 |
| | Na+ | 6H₂O | $g^- g^-$ | −1343.2218 | 0.2469 | −1342.9749 | 0.00 |
| | | | $g^- t$ | 1343.2205 | 0.2471 | −1342.9735 | 0.88 |
| | K+ | 6H₂O | $g^- g^-$ | −1780.8210 | 0.2436 | −1780.5774 | – |
| | Mg²+ | 6H₂O | $g^- g^-$ | −1380.8615 | 0.2471 | −1380.6145 | 0.00 |
| | | | $g^- t$ | −1380.8634 | 0.2490 | −1380.6144 | 0.06 |
| (DMP-OS)− | | | | | | | |
| | Na+ | 6H₂O | $g^- t$ | −1666.1701 | 0.2432 | −1665.9269 | 0.00 |
| | | | $g^- g^-$ | −1666.1670 | 0.2441 | −1665.9229 | 2.51 |
| | Mg²+ | 6H₂O | $g^- t$ | −1703.8120 | 0.2464 | −1703.5657 | 0.00 |
| | | | $g^- g^-$ | −1703.8120 | 0.2471 | −1703.5649 | 0.50 |
| (DMP-SS)− | | | | | | | |
| | Na+ | 6H₂O | $g^- g^-$ | −1989.1130 | 0.2409 | −1988.8721 | 0.00 |
| | | | $g^- t$ | −1989.1067 | 0.2403 | −1988.8664 | 3.58 |
| | Mg²+ | 6H₂O | $g^- t$ | −2026.7516 | 0.2442 | −2026.5074 | 0.00 |
| | | | $g^- g^-$ | −2026.7482 | 0.2426 | −2026.5056 | 1.13 |

$E_e$: electronic energy (hartrees); ZPVE: zero point vibrational energy (hartrees); $E_{tot}$: total energy (hartrees); $\Delta E$: relative energy of a conformer with respect to the most stable one (kcal/mol). (DMP-OO)−, (DMP-OS)− and (DMP-SS)− represent dimethyl phosphate, dimethyl phosphorothioate and dimethyl phosphorodithioate, respectively. Calculated results obtained with a polarizable dielectric medium (continuum) and with a hexahydrated cation (6H₂O), are reported.