

Dimethyl Phosphate: Stereoelectronic versus Environmental Effects

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Structure and bonding of dimethyl phosphate (DMP) in vacuo and in the crystal phase is investigated using density functional theory calculations with gradient corrections for the exchange-correlation functional. Calculated structural properties agree well with experiment and previous high-level *ab initio* results. Analysis of the chemical bonding in terms of localized Wannier orbitals allows us to compare stereoelectronic effects to those of the environment. It is found that the latter play a much more critical role for the conformational flexibility of DMP.

1. Introduction

The phosphate diester group is a fundamental building block of several molecules of biological interest, such as DNA/RNA, phospholipids, and ATP. Its conformational flexibility plays a crucial role in several fundamental processes in biology, from the ATP-based cell energy cycle to the biosynthesis of nucleic acids^{1–6} and the molecular recognition between proteins and DNA.^{1–4}

By far the most frequent conformation of phosphodiester compounds in crystals is the *gauche*–*gauche* (gg), in which the torsional angles along the nonester P–O bonds (χ (O5'–P–O3'–C) and α (O3'–P–O5'–C) in Figure 1) are $\approx \pm 60^\circ$.^{1,6,7} Early quantum chemical calculations have attributed the preference for the gg conformation to a specific stereoelectronic effect, the hyperconjugative delocalization.^{8–13} By relating calculated bond lengths to overlap populations,^{9,14–19} it has been proposed that stabilizing interactions which occur between the P–O σ^* orbital with a hybrid sp^3 σ orbital (characterized as an ester oxygen electron lone pair) are key factors for the conformational flexibility of DMP, as they are at a maximum in the gg conformation.¹¹ Problems related with this type of approach include the errors associated with the calculations of overlap population¹² and the dependence of the results on the type of analysis of the electronic structure.^{20–23}

Environmental effects may also be important. Theoretical studies have been focused mostly on the role of the aqueous solvent at various levels of sophistication.^{24–34} A Monte Carlo study has pointed out the relevance of water/water interactions for the stabilization of the gg conformation.^{25–27} In contrast, early quantum chemical investigations on water–phosphodiester clusters have emphasized the role of solvent/solute interactions.^{25,28–31,34} Very recently, high level *ab initio* calculations, in which the solvent was included as a continuum model,²⁴ have

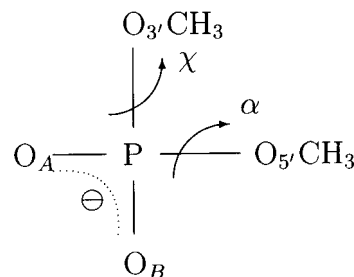


Figure 1. Molecular structure of the phosphodiester linkage. The α and χ angles are also indicated.

provided accurate estimations of the free energies indicating a key role of solvent/solute interactions.

Because of the importance of the above problem, we have decided to explore the relevance of *intra*- versus *intermolecular* effects by performing density functional theory (DFT) calculations on dimethyl phosphate (DMP), one of the most used models of the phosphodiester linkage,^{12,24–26,32–36} in vacuo and in the presence of condensed matter effects. In contrast to the previous work, we consider here an *explicit* model of the environment by performing calculations on DMP in the crystal phase. To characterize the change in the chemical bonding on passing from the gas to the crystal phase we use a novel localized orbital method based on the Wannier functions.^{37,38} This approach has already been successfully applied in a variety of chemical and physical systems.^{37,38} Anticipating our results, we find that stereoelectronic effects are operative, yet they play a minor role for the conformational flexibility of this system in comparison to polarization due to the crystal field.

2. Computational Methods

Our quantum chemical calculations were performed within the framework of density functional theory. Gradient corrected exchange and correlation functionals with the Becke³⁹ and Lee–Yang–Parr⁴⁰ parameterizations were used. As the basis set, a plane-wave expansion up to an energy cutoff of 70 Ry at the Γ point of the Brillouin zone was used. The interactions between the ionic cores and valence electrons were described by Martins–Troullier-type⁴¹ pseudopotentials.

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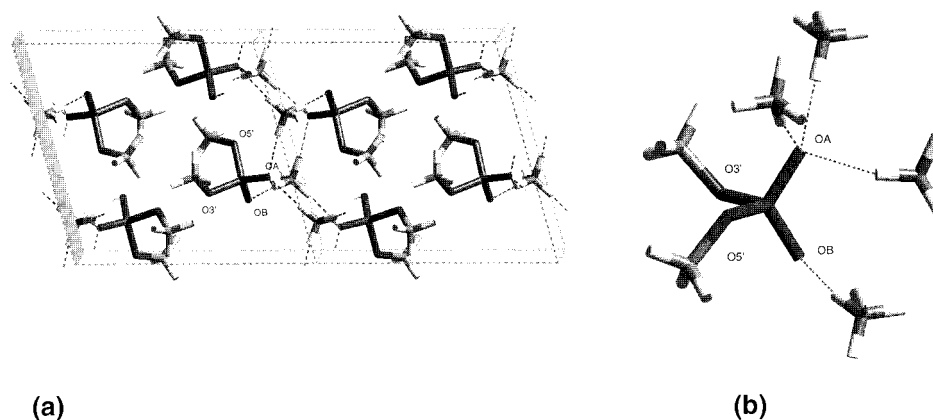


Figure 2. (a) Crystal structure of $\text{NH}_4\text{PO}_4(\text{CH}_3)_2$. The [100] plane is also shown. (b) H-bond network for one of the four equivalent phosphates present in the unit cell.

We optimized the structures of DMP in vacuo and in crystal phase, starting from the gg conformation it adopts in crystalline $\text{NH}_4(\text{CH}_3)_2\text{PO}_4$,^{42–44} ($\alpha = 62^\circ$ and $\chi = 57^\circ$). For crystalline $\text{NH}_4(\text{CH}_3)_2\text{PO}_4$, we optimized the molecular structure while keeping the cell parameters fixed at the experimental values.

The optimized structure of the isolated DMP (in which α and χ turned out to be 75°) was used as the starting model for the investigation of other conformers. The α angle, which is equivalent to χ in DMP, was chosen to have the following values: 20° , 40° , 60° , 75° , 100° , 120° .⁴⁵ The χ angle was set to 75° . Calculations were also carried out on a conformer characterized by $\alpha = 62^\circ$ and $\chi = 57^\circ$. Full geometry optimization was carried out for the conformers while keeping the α and χ angles constrained at their fixed values. Geometry optimization of the conformer characterized by $\chi = 75^\circ$ and $\alpha = 0^\circ$ resulted in an unstable structure, presumably because of the large van der Waals repulsions of the methyl groups.

Finally, we optimized the structure of the following molecules in the gas phase: MgH , H_2 , PH_3 , CH_4 , NH_3 , HCl , H_2O . The agreement between calculated and experimental geometrical parameters turned out to be very good (data available upon request).

All atomic positions have been optimized using the direct inversion of iterative subspace (DIIS) method^{46,47} for both electronic and ionic degrees of freedom. For the calculations of DMP in vacuo, nonperiodic boundary conditions were used as in refs 48 and 49.

The chemical bonding was characterized with the method of the maximally localized Wannier orbitals (WO),^{37,38} recently implemented in the Car–Parrinello scheme.³⁷

We have used the scalar and parallel version of the Car–Parrinello⁵⁰ code CPMD V3.0h.⁵¹ The calculations have been performed on IBM RISC 6000 workstations and on a Cray T3E.

3. Analysis of the Chemical Bonding: the Wannier Orbitals

Chemical concepts such as electron lone pairs and covalent bonds can be efficiently described using localized molecular orbitals.⁵² Recently, geometrical analysis of centers of maximally localized Wannier orbitals (WO) has emerged as a very useful tool to study bond properties in periodic systems.^{37,38} The methodology is equivalent to that of Boys used for isolated molecules⁵³ as the positions of the WO centers can individuate electron lone pairs and may provide an estimation of the ionicity of chemical bonds.

To analyze quantitatively displacements of the locations of the WO centers as a result of conformational changes and/or

the presence of the electric field of the crystal, it is first necessary to correlate the positions of the centers to more familiar measures of bond ionicity. In this work, we attempt to relate *displacements* of the WO centers of chemical bonds to the *differences* in Pauling electronegativity⁵⁴ between the atoms forming the bonds.

To this aim, let us consider a chemical bond formed by atoms A and B. We then define the bond ionicity indices (BI) of this bond as

$$\text{BI}_{\text{AB}}(\text{A}) = \left(\frac{d_{\text{A}}}{d_{\text{AB}}} - \frac{r_{\text{A}}}{r_{\text{A}} + r_{\text{B}}} \right)$$

$$\text{BI}_{\text{AB}}(\text{B}) = \left(\frac{d_{\text{B}}}{d_{\text{AB}}} - \frac{r_{\text{B}}}{r_{\text{A}} + r_{\text{B}}} \right)$$

where d_{A} (d_{B}) are the distances between atom A (B) and the WO center along the AB bond, d_{AB} is the bond length, and r_{A} , r_{B} the covalent radii⁵⁵ of the two atoms. The factors $r_{\text{B}}/r_{\text{A}} + r_{\text{B}}$ and $r_{\text{A}}/r_{\text{A}} + r_{\text{B}}$ take into account the difference in diffusivity of the valence orbitals of the two atoms.⁵⁶ Obviously, $\text{BI}_{\text{AB}}(\text{A}) + \text{BI}_{\text{AB}}(\text{B}) = 0$ for any chemical bond.

As a second step, we calculate the bond ionicity indices $\text{BI}_{\text{AB}}(\text{A})$ of simple molecules of the type AH_n where A spans a large range in electronegativity ($\text{A} = \text{Mg}, \text{H}, \text{P}, \text{C}, \text{N}, \text{Cl}, \text{O}$).

Finally, we attempt to relate the calculated bond ionicity indices to the Pauling electronegativity⁵⁴ of the atom A. Figure 3 shows a nice correlation between the two quantities. This suggests that the BI's can provide a quantitative estimate of the bond polarity of the A–H bond. In particular, negative (positive) values of the bond ionicity indices of atom A correspond to larger (smaller) electronegativity than that of hydrogen. Obviously, the hydrogen molecule is located at the origin of the graph.

From the above discussion, it is clear that the bond ionicity indices of the bond A–B are a measure of the polarity of the bond. Thus the displacements of WO centers and the resulting changes of BI's are a valuable tool for relating electronic structure calculations to specific bond properties.

4. Structure and Bonding of Dimethyl Phosphate in the Gas and the Crystal Phases

In this section, we describe structural and electronic properties of DMP in several conformations in vacuo, obtained by varying α from 20° to 120° , and in crystalline $\text{NH}_4(\text{CH}_3)_2\text{PO}_4$.

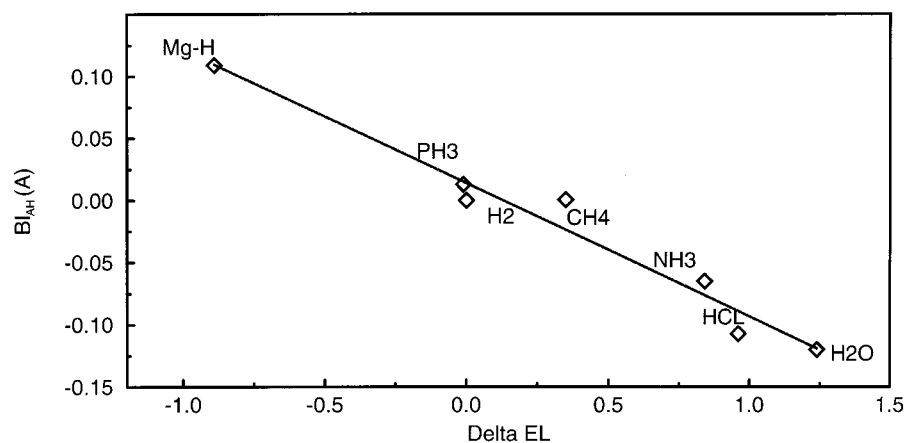


Figure 3. Bond ionicity indices (BI_{AH} (Å)) of molecules of the type AH_n plotted as a function of the difference of Pauling electronegativity⁵⁴ of atom A and H. Slope = -0.107 , least-squares deviation of the linear fit = 2×10^{-4} .

TABLE 1. Selected Structural Parameters of DMP in Vacuo and of Ammonium DMP in Crystal Phase

| | DMP in vacuo | | | crystalline ammonium DMP | |
|------------------------------|------------------|---------------------------------|--------------------------------|--------------------------|---------------------|
| | DFT this work | HF MP2/6-31G** ²⁴ | HF MP2/6-31G* ³⁶ | DFT this work | X-ray ⁴² |
| bond distances (Å) | | | | | |
| P–O3' | 1.68 | 1.68 | 1.64 | 1.61 | 1.54 |
| P–O5' | 1.68 | 1.68 | 1.64 | 1.62 | 1.58 |
| P–OB | 1.49 | 1.51 | 1.47 | 1.50 | 1.49 |
| P–OA | 1.49 | 1.51 | 1.47 | 1.52 | 1.50 |
| O3'–C | 1.44 | 1.43 | 1.40 | 1.47 | 1.48 |
| O5'–C | 1.44 | 1.43 | 1.40 | 1.47 | 1.43 |
| bond angles (deg) | | | | | |
| O3'–P–O5' | 99 | 99 | 100 | 105 | 105 |
| O3'–P–OB | 105 | 106 | | 104 | 105 |
| O5'–P–OA | 105 | 106 | | 106 | 106 |
| OA–P–OB | 125 | 126 | 125 | 118 | 117 |
| P–O3'–C | | | | 119 | 123 |
| P–O5'–C | | | | 119 | 118 |
| torsion angles (deg) | | | | | |
| C–O3'–P–O5' (χ) | 75 | 70 | 75 | 58 | 57 |
| C–O5'–P–O3' (α) | 75 | 70 | 75 | 65 | 62 |
| C–O3'–P–O5' (χ) | | | | –58 | –57 |
| C–O5'–P–O3' (α) | | | | –65 | –62 |
| intermolecular distances (Å) | | | | | |
| N–OA I | | | | 2.9 | 2.8 |
| N–OA II | | | | 2.9 | 2.8 |
| N–OA III | | | | 3.0 | 3.0 |
| N–OB I | | | | 2.8 | 2.8 |

Structural Properties. Our results for DMP in vacuo agree well with other ab initio calculations on this system^{13,24,36} (Table 1). All of the conformers investigated here, characterized by $20^\circ \leq \alpha \leq 120^\circ$ and $\chi = 75^\circ$ (Figure 1), exhibit similar structural properties. In particular, the P–O bond length changes upon rotation of the α angle reproduce previous high level ab initio calculations^{24,36,57} (data not shown).

On passing from the gas to the solid state (crystalline $NH_4(CH_3)_2PO_4$) significant rearrangements are observed (Table 1). In particular, the P–O ester bond lengths and the α and χ angles are reduced in the crystal structure.^{13,24,57} Note that here α and χ are not equivalent, owing to the anisotropy of the electric field and to the H-bond network in the crystal (Figure 2). The latter renders the two P–O bonds, which are not involved in the ester linkage (P–OA and P–OB in Figure 2), non equivalent: OA and OB point toward the polar and non polar regions of the crystal, respectively (Figure 2a), and they differ in the interaction with the ammonium counterions. OB forms one strong H-bond (O–H distance 1.7 Å), whereas OA is involved in three weaker H-bonds (O–H distances 1.8–1.9

Å). While most of the structural features are very well reproduced, we note deviations of some structural parameters involving the ester oxygen atoms (P–O bond length⁵⁸ and P–O–C bond angles). Because the ester methyl groups form a hydrophobic layer in the crystal, these deviations might be explained in part by the inability of DFT to reproduce the dispersion forces.^{59,60}

Energetics. The conformational energies reproduce nicely the previous high level ab initio calculations.^{13,57} Figure 4a, which plots the conformational energy of this molecule, exhibits a minimum at $\alpha = 75^\circ$ and increases at higher and more significant at lower α values.

Chemical Bonding. Several interesting features emerge from the analysis of WO centers (Figure 5) and bond ionicity indices of the optimized structure of DMP in vacuo. The averaged index of carbon in the methyl C–H bond $\langle BI_{CH}(C) \rangle = 0.007$ is consistent with the almost apolar character of the CH bond. In contrast, the corresponding index in the carbon–oxygen bond is rather positive $\langle BI_{CH}(C) \rangle = 0.100$. This indicates, as expected, that the bond is very polarized toward the oxygen. In

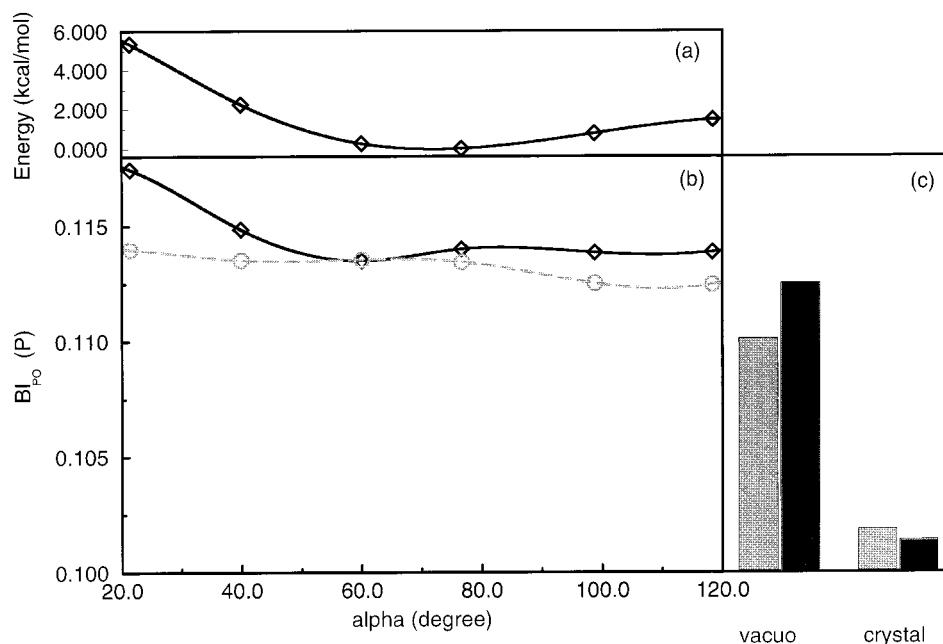


Figure 4. Energetics and chemical bonding in DMP. (a) Energy of the molecule in vacuo plotted as a function of the α -torsional angles. The calculated energies, indicated as squares, are interpolated using spline functions. For the sake of clarity, the energies are shifted to the energy minimum. (b) $BI_{PO5'}(P)$ (black line) and $BI_{PO3'}(P)$ (gray line) of DMP in vacuo plotted as a function of the torsion angle α . (c) $BI_{PO5'}(P)$ (black line) and $BI_{PO3'}(P)$ gray line of DMP in the conformation of the crystal phase without (left) and in the presence of (right) the crystal.

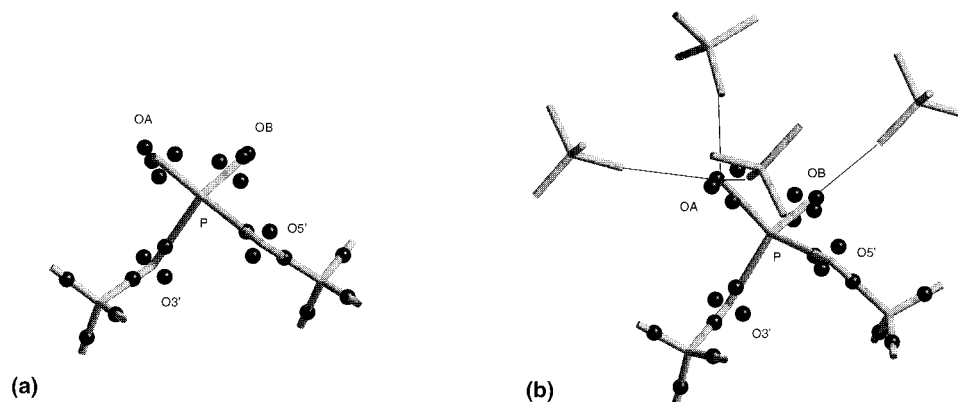


Figure 5. WO centers (represented as spheres) of the optimized structure of DMP in vacuo (a) and in crystal phase (b).

the other conformers investigated here, the bond ionicity indices of the carbon do not vary appreciably ($0.003 \leq \langle BI_{CH}(C) \rangle \leq 0.014$ and $0.099 \leq \langle BI_{CO}(C) \rangle \leq 0.100$).

We focus now on the change in chemical bonding of the ester P—O bonds⁶¹ upon conformational changes and in the presence of the crystal. These bonds are those involved in the P—O σ^* lone pair interactions,^{8–12} and thus they are those related to stereoelectronic effects.

Figure 4b shows that the averaged bond ionicity indices of phosphorus in these bonds are rather large ($BI_{PO}(P) \approx 0.114$), indicating, as expected, a very polar character of the P—O bond and a large difference in Pauling electronegativity between the two atoms. Furthermore, we see that the *change* of $BI_{PO}(P)$ due to conformational changes is very small, lying within 0.004 and 0.002 for the P—O5' and P—O3' bonds, respectively. A very small change in electronegativity (0.02–0.04 units) corresponds to these tiny displacements of the WO centers. The indices of the P—O3' bond almost do not vary in the conformational space explored which is consistent with the fact that the torsional angle of this bond is always kept with the same orientation. In contrast, the indices of the P—O5' bond (which has a different orientation in each conformer) correlate rather

nicely with the conformational energy and exhibit a minimum around 60 degrees. In this conformation, the proposed maximum back-donation of the oxygen lone pairs to the P—O σ^* orbital is achieved,^{1,6,11} which in turn renders the P—O bond less polar.

We conclude that the ester P—O chemical bonding is affected by stereoelectronic effects as this maximum back-donation can be related to reduced bond ionicity of the P—O5' bond.

On passing to the conformation as in the crystal phase ($\alpha = 62^\circ$, $\chi = 57^\circ$) (Figure 4c), the bond ionicity indices turn out to be rather similar to those of all the other conformers investigated here. In contrast, a dramatic rearrangement of the WO centers, and hence of the bond ionicity indices, is found in the presence of the crystal field: the indices decrease by as much as ≈ 0.01 (Figure 4c), which corresponds to a decrease of ≈ 0.11 units of Pauling electronegativity (Figure 3). Thus, the electric field and the intermolecular interactions of the crystal induce a substantial loss of bond ionicities of the ester P—O bonds.

The difference in magnitudes between the shifts of the WO centers in vacuo and those in the crystal phase (Figure 3b-c), about 1 order of magnitude, clearly show that *intermolecular* factors affect the P—O ester bonding to a much larger extent than *intramolecular* stereoelectronic factors do.

4. Discussion and Conclusion

We have presented a detailed investigation of structure and chemical bonding of DMP in vacuo and in the solid state using DFT calculations.

Our calculations agree well with experiments and with previous high-level ab initio calculations of both structural properties and energetics.

Furthermore, our analysis based on the localized Wannier orbitals, a generalization of the localized Boys orbitals⁵³ in periodic systems, provides a picture of the ester P–O chemical bonding which is absolutely consistent with previous work.^{13,24,36} First, the bond ionicity turns out to be dependent on the conformational state: in the most stable conformer, the ester P–O bonds exhibit the lowest ionic character. This is absolutely consistent with maximum P–O σ^* lone pair overlap,¹¹ since the oxygen lone pairs' back-donation to the P–O σ^* orbitals can be related to reduced bond ionicity. Second, we find a sizable effect of the crystal phase environment on the chemical bonding, consistent with the recent results of high-level ab initio calculations of this and similar molecules embedded in a continuum model.²⁴

New information is provided by the comparison between solvent-induced and conformation-induced changes of the chemical bonds.

It is found that the effects of the crystal play a much more critical role than those induced by conformational changes. Because effects of the environment also play a crucial role in aqueous solution,²⁴ we conclude that "solvent" effects should always be taken into account in order to describe adequately the conformational flexibility of DMP.

We should stress here that the conformational space sampled is rather limited to the regions around the gg conformation. However, the difference found in the magnitudes of the shifts between the in vacuo and the crystal phase is large (Figure 3c) which strongly suggests that the main conclusions of the paper are valid in a more general context.

Solvent effects are expected to be of equal or greater importance in the conformational flexibility and the reactivity of the phosphate moieties of DNA/RNA and ATP/ADP and their interactions with other biomolecules, such as proteins: specific protein–phosphate interactions (notably H-bonding and electrostatic interactions) are expected to dramatically affect their conformation and recognition.

A final remark concerns the use of the Wannier centers. This paper suggests that this type of analysis is very attractive for investigating the chemical bonding and the reactivity of phosphate-based systems. Particularly appealing is the possibility of calculating the Wannier Orbital centers on the fly in a Car–Parrinello ab initio molecular dynamics⁵⁰ simulation.

Work is in progress in our laboratories to characterize phosphorylation processes carried out by nucleotide binding enzymes.

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- (56) Note that: (i) The simple definition $BI(A) = d_A$ cannot be related to bond polarity whenever atoms A and B have significantly different atomic radii. For instance, in water $d_O = 0.53 \text{ \AA}$ (approximately half of the OH bond length (0.97 \AA), although the OH bond is obviously polarized towards

- the oxygen atom. (ii) Use of these indices is obviously restricted to a specific bond in different molecules and/or to the same molecule in different conformations.
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- (61) By definition, the maximally localized Wannier functions are not suited to describe strongly delocalized bonds. Thus, our analysis cannot be extended to the nonester P–OA and P–OB bonds.