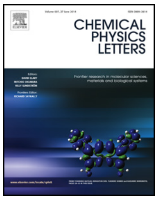
Chemical Physics Letters 635 (2015) 301–305

Contents lists available at ScienceDirect

Chemical Physics Letters

journal homepage: www.elsevier.com/locate/cplett



Molecular interactions in the microsolvation of dimethylphosphate

Natalia Rojas-Valencia, César Ibargüen, Albeiro Restrepo*

Instituto de Química, Universidad de Antioquia UdeA, Calle 70 No. 52-21, Medellín, Colombia

A R T I C L E I N F O

Article history:
Received 18 April 2015
In final form 23 June 2015
Available online 6 July 2015

A B S T R A C T

Molecular interactions in the microsolvation of anionic dimethylphosphate (DMP$^-$, a molecular model for the polar head in cell membranes), with up to three water molecules are studied. Charge assisted $PO_2^- \cdots H—O—H$ contacts are shown to be the stronger interactions. $CH_3O \cdots H—O—H$ interactions are also stabilizing and characterized as closed shell. Secondary $H_2C—H \cdots OH_2$ interactions are also at play. All dominant intermolecular interactions correspond to the general lone pair → antibonding ($n_O \rightarrow \sigma^*_{X-H}$) ($X = O, C$) form. The formal charge in DMP$^-$ has a strengthening effect in hydrogen bonds between water molecules in outer solvation shells.

1. Introduction

At the molecular level, cell membranes comprise two layers of phospholipids, whose molecular structures include a polar head and a large hydrophobic tail. In cell membranes, phospholipids are organized in such a way that the polar head of each layer faces either the interior or the exterior, with the hydrophobic tails in between; this particular configuration affords highly polar environments which dictate interactions that control physiologically relevant processes such as cell signaling, passive transport, cell adhesion, among others [1,2]. These processes are also heavily influenced by the presence of water in biochemical environments. $(CH_3O)_2PO_2^-$, the anionic dimethylphosphate group (DMP$^-$), also known as the phosphodiester linkage, is the major factor determining behavior of the polar head in phospholipids toward polar solvents such as water, accordingly, DMP$^-$ has recently been suggested as a molecular model to study the microsolvation of cell membranes [3]. Many other works have also dealt with the problem of explicitly describing DMP$^-$ ↔ water interactions [4–9].

There is no shortage of techniques to experimentally study microsolvation of biomolecules [10–13]. Experimental methods provide very good insights into the number of water molecules solvating polar heads and about the associated changes in spectra, but fail to give meaningful descriptions about the precise geometrical arrangements of solvent molecules around the polar heads of phospholipids and about the nature of the interactions leading to conformational preferences and to spectral shifts. This lack of information has been partially mitigated by an exhaustive description of the potential energy surfaces (PESs) for the interactions of DMP$^-$ with up to three water molecules by Ibargüen and coworkers [3]. In that study, the authors reported all possible structural motifs obtained after stochastic explorations of the corresponding PES. A total of 11, 24, 52 structures were identified for $n = 1, 2, 3$ respectively, using second order perturbation theory in conjunction with a fairly large basis set, MP2/6–311++G(d, p), and considering all three possible monomer conformations (gauche–gauche, *gg*, anti–gauche, *ag*, and anti–anti, *aa*) for DMP$^-$. This exhaustive description of the PESs involved in DMP$^-$ ↔ water interactions was nicely supported by calculations of the shifts in the asymmetric stretching vibrations of the PO_2^- group ($\nu_a PO_2^-$) which is commonly used as hydration sensor of solvation of polar heads in phospholipids [15–19].

The structures located in Ibargüen's work for the gas phase microsolvation of isolated DMP$^-$ with up to three water molecules [3] afforded a total down shift of $32\,\mathrm{cm^{-1}}$ in $\nu_a PO_2^-$, an outstanding match to the $30\,\mathrm{cm^{-1}}$ reported by Pohle and coworkers [20] for solvated phosphatidylcholine bilayers under experimental conditions. Those structures also provided valuable information not available with present day experimental techniques about the specific structural preferences for the disposition of water molecules around polar heads in phospholipids and about the strength of the interactions leading to cluster stabilization. A recent study of the microsolvation of anionic ibuprofen [21] also accurately matched the experimental and theoretical asymmetric vibrations of the CO_2^- group.

The extensive and very precise collective experimental and computational evidence relating several aspects of the interactions between water and phospholipids in cell membranes do not yet offer a detailed picture of the nature of those interactions at

---

* Corresponding author.
E-mail address: albeiro.restrepo@udea.edu.co (A. Restrepo).

http://dx.doi.org/10.1016/j.cplett.2015.06.064
0009-2614/

the molecular level. This letter is an attempt to contribute to this sensitive issue taking, as suggested by Ibargüen and coworkers [3], dimethylphosphate as a molecular model for the polar heads, specifically addressing the $\text{DMP}^- \leftrightarrow$ water molecular interactions, aiming at deciphering their nature using a variety of theoretical tools provided by Bader's quantum theory of atoms in molecules (QTAIM) [22] and by natural bond orbital (NBO) [23] methods.

2. Theory and methods

87 well defined local minima previously reported in the potential energy surfaces (PESs) for the interactions between dimethylphosphate and 1, 2, and 3 water molecules were borrowed from the literature [3] and made the subject of topological analyses of the electron densities and of orbital interactions. We focus on extracting information that would provide insight into the nature of intermolecular interactions that stabilize the clusters and keep them as discrete units.

In the QTAIM formalism, molecular interactions are thought to arise from closed shell interactions (ionic, long range, hydrogen bonds, etc.), from shared (covalent) interactions, and from intermediate types, with contributions from both closed shell and shared interactions. Detailed information about the nature of interactions between atom pairs can be obtained from the topological properties of the electron density, specifically, from properties of their critical points, those for which the gradient vanishes $\vec{\nabla}\rho(\mathbf{r}_c) = 0$. Bond critical points (BCPs), a subset of the critical points in the electron density located in the line of maximum density connecting pairs of atoms, carry loads of useful information, which can be extracted from quantities such as the electron density itself, its Laplacian $\nabla^2\rho(\mathbf{r}_c)$, and the total $\mathcal{H}(\mathbf{r}_c)$, potential $\mathcal{V}(\mathbf{r}_c)$ and kinetic energy densities $\mathcal{G}(\mathbf{r}_c)$ evaluated at BCPs.

Among the many QTAIM derived criteria available to analyze molecular interactions, we hand pick a few that we think are suitable to study intermolecular bonding in the title clusters. The Laplacian of the electron density measures local concentration or depletion of charge [24]. Thus, the sign of the Laplacian at BCPs tells that $\nabla^2\rho(\mathbf{r}_c) > 0$ correspond to local minima of the electron density and therefore the charge is displaced toward the nuclei, this is characteristic of closed shell (ionic) as well as of long range (van der Waals, hydrogen bonding, etc.) interactions. On the other hand, $\nabla^2\rho(\mathbf{r}_c) < 0$ characterizes local maxima and thus indicates that the electron density is concentrated in the region intermediate between the two interacting atoms, otherwise known as covalent bonding. Alternatively, because of the virial theorem, the Laplacian of the electron density is seen to act as local balance between kinetic and potential energy densities, effectively measuring the local quantum pressure exerted by the charge density [22,24–26].

Another useful indicator of atom–atom interactions is the total energy density evaluated at BCPs, $\mathcal{H}(\mathbf{r}_c) = \mathcal{V}(\mathbf{r}_c) + \mathcal{G}(\mathbf{r}_c)$. Since the kinetic energy density is positive (destabilizing) everywhere, and the potential energy density is negative (stabilizing) at all points of the charge distribution, the sign of the total energy density at BCPs also affords valuable information about the nature of the interactions, however, in some cases, the signs of $\nabla^2\rho(\mathbf{r}_c)$ and of $\mathcal{H}(\mathbf{r}_c)$ give conflicting information, thus alternative schemes combining the two criteria, each with proper formal justifications, have emerged in the literature [27]. For example, Cremer and Kraka [28] stated that in some cases where the Laplacians of the electron density at BCPs are positive (local depletion of charge), the interaction can still be considered as covalent if the total energy density at the BCP is negative (the absolute value of the potential energy density is larger than the kinetic energy density, hence stabilizing the BCP). In a set of more general criteria for hydrogen bonding (HB) cases, which are relevant to this work, Rozas and coworkers [29] argue that $\nabla^2\rho(\mathbf{r}_c) > 0$ and $\mathcal{H}(\mathbf{r}_c) > 0$ for weak to medium strength HBs, $\nabla^2\rho(\mathbf{r}_c) > 0$ and $\mathcal{H}(\mathbf{r}_c) < 0$ for strong HBs, while for very strong HBs, both quantities are negative. In addition, in this work, relative strength of interactions is properly quantified using the criteria derived by Espinosa and coworkers [30] after local application of the virial theorem to BCPs, according to the following scheme

$$\frac{|\mathcal{V}(\mathbf{r}_c)|}{\mathcal{G}(\mathbf{r}_c)} = \begin{cases} < 1, & \text{closed shell} \\ \in [1,2], & \text{intermediate} \\ > 2, & \text{covalent} \end{cases} \tag{1}$$

In the one-particle methods used to solve Schrodinger's equation for molecular Hamiltonians, molecular interactions, hydrogen bonds among them, are thought to arise from orbital interactions. In the specific case of the water dimer, the classic work by Reed and Weinhold [31] established that charge transfer from one of the oxygen non-bonding lone pairs to the O—H antibonding orbital in the vicinal water molecule ($n_{\text{O}} \to \sigma^*_{\text{O–H}}$) is the driving factor behind the water ↔ water interaction leading to dimer formation. Similar charge transfer mechanisms are thought to be involved in most cases of hydrogen bonding. Orbital interactions are conveniently analyzed under the natural bond orbitals (NBOs) picture [23]. NBOs result from successive transformations of the AO basis set to produce molecular orbitals of maximum occupancy, typically consisting of core, bonding and lone pairs, and virtual antibonding and Rydberg orbitals, thus closely resembling the Lewis electronic structure of atoms and molecules that provide familiar and intuitive insight into the orbital distribution of the total n-electron density. Interaction energies between occupied $|\phi_i\rangle$ and virtual $|\phi_j\rangle$ orbitals are obtained via second order perturbation corrections to the Fock matrix from [23]

$$E_{ij}^{(2)} = -\omega_i \frac{|\langle\phi_i|\mathcal{F}|\phi_j\rangle|^2}{\epsilon_j - \epsilon_i} \tag{2}$$

where ω_i is the occupancy of $|\phi_i\rangle$ and $\mathcal{F}$ is the Fock operator.

In this work, we apply the QTAIM and NBO methodologies to the set of structures previously found in the PESs for the interactions of dimethylphosphate with up to three water molecules, aiming at providing an integral picture that helps understanding the fundamental interactions leading to the microsolvation of DMP^- and by extension, the interaction of cell membranes with water.

3. Results and discussion

Internal rotation of methyl groups in DMP^- leads to three stable conformations in a 3 kcal/mol energy window: gauche–gauche (*gg*, the global minimum), anti–gauche (*ag*, ≈1 kcal/mol above *gg*) and anti–anti (*aa*, ≈3 kcal/mol above *gg*). The three DMP^- conformers are shown in Figure 1 along with a few selected structures, including the global minimum on each PES, the complete set of 87 structures analyzed here, together with their Cartesian coordinates can be found in the supplementary material. For all DMP^- configurations, two chemically different oxygen atoms are susceptible of interacting with water molecules, on one hand, the formal charge is delocalized among the two oxygens in the phosphinate group, PO_2^-, which we label O_{P}, on the other hand, there are the oxygen atoms belonging to the phosphoester group, C—O—P, labeled O_{C}. As shown in Figure 1, a variety of intermolecular interactions are uncovered by QTAIM via well defined BCPs and bonding paths: water ↔ phosphinate contacts ($\text{HOH}\cdots\text{O}_{\text{P}}$, all solvated clusters in Figure 1), water ↔ phosphoester interactions ($\text{HOH}\cdots\text{O}_{\text{C}}$, for example W_1S_1 in Figure 1), water ↔ water hydrogen bonds ($\text{HOH}\cdots\text{OH}_2$ as in W_3S_2 in Figure 1) and secondary water ↔ methyl hydrogen bonds ($\text{H}_2\text{O}\cdots\text{HCH}_2$, W_2S_1 in Figure 1).