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Interactions between phosphate and water in solution:

a Natural Bond Orbital based analysis in a QM/MM framework

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Abstract

The Natural Bond Orbital (NBO) and Natural Energy Decomposition Analysis (NEDA) calculations are used to analyze the interaction between mono-methyl phosphate-ester (MMP) and its solvation environment in a combined quantum mechanical/molecular mechanical (QM/MM) framework. The solute-solvent configurations are generated using a specific parameterization of the self-consistent-charge density functional tight-binding (SCC-DFTB) model for the MMP and TIP3P for water. The NBO and NEDA calculations are done with several QM/MM partitioning schemes with the HF/6-31+G** as the QM level. Regardless of the size of the QM region, a notable amount of charge transfer is observed between MMP and the neighboring water molecules and the charge-transfer interactions are, in the NEDA framework, as important as the electric (electrostatic and polarization) components. This work illustrates that NBO based analyses are effective tools for probing intermolecular interactions in condensed phase systems.

Introduction

The analysis of intermolecular interactions is an important subject in quantum chemistry.¹ Most of these studies, however, focused on gas-phase systems and systematic investigations in the condensed phase have only started to appear in recent years.²⁻⁴ Depending on the framework of analysis, there are controversies regarding the relative importance of different contributions, especially concerning charge-transfer (CT) type of interactions.²⁻⁴ For example, based on linear-scaling semi-empirical methods, Merz and co-workers² are among the first to propose that charge transfers between protein residues and water make an essential contribution to the protein-water interactions, even greater than the polarization interactions. This proposal has been questioned by Gao and co-workers³ based on the block-localized wavefunction (BLW) theory at the Hartree-Fock level.⁵ Their analyses of small charged molecules in solution found that the solute-solvent interactions are dominated by electrostatic and polarization interactions and charge transfers make very small contributions. It was argued that the large charge transfer contributions found by Merz and co-workers² were due largely to the minimal basis nature of the semi-empirical methods used. Klein and co-workers⁴ studied the similar systems using Car-Parrinello molecular dynamics.⁶ Analysis using the atoms in molecules (AIM) theory⁷ found larger amounts of charge transfers between the solute and water than that in Ref. 3; it was concluded that charge transfers are likely important to solute-solvent interactions, although a quantitative decomposition was not carried out.

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Supporting Information Available: More details for the 40 studied systems are provided, including the local solvent structure of MMP, NEDA energy component analysis, orbital occupancy change, NPA analysis, second-order perturbative estimate of the donor-acceptor interactions from NBO analysis. Similar information is also included for an analysis with a large QM region (34 QM water molecules plus MMP). This material is available free of charge via the internet at <http://pubs.acs.org>.

In the current work, we apply the Natural Bond Orbital (NBO) analysis⁸ and Natural Energy Decomposition Analysis (NEDA),⁹ which are well established in the quantum chemistry literature for analyzing intermolecular interactions in gas phase applications, to examine phosphate-solvent interactions in water solution in a combined quantum mechanical/molecular mechanical (QM/MM) framework.¹⁰ This is particularly interesting since biologically relevant phosphate molecules are usually highly charged and therefore a proper treatment of solute-solvent (or substrate-enzyme) interactions is crucial to a quantitative theoretical description for their reactivity.¹¹ In a more general context, we hope that this first application of the NBO based techniques to solution system underlines the general value of such analysis in the assessment and improvement of QM/MM models for increasingly complex molecular systems.

Methods

The solute chosen is mono-methyl phosphate- ester (MMP), which bears a -1 charge. Four different solvated MMP configurations are used in the NBO analysis and NEDA, which are randomly collected from a 50 ps QM/MM molecular dynamics simulation in which MMP and its closest 34 water molecules are treated quantum mechanically. The QM model is a recently parameterized SCC-DFTB approach^{12(a)} for phosphate compounds (SCC-DFTBPR),^{12(b)} which describes the structure and hydrolysis energetics of a series of small phosphate compounds rather well compared to high level DFT and *ab initio* calculations; the analysis in the current work is not expected to be sensitive to the details of how the solute-solvent structures are generated. The remaining water molecules are described with a modified TIP3P model. The internal geometries of all water molecules are constrained using SHAKE.¹³

The NBO analyses and NEDA are done in a QM/MM framework using HF/6-31+G** as the QM level; the MMP is always treated as QM and the MM water appear as point charges. In each solute-solvent configuration, typically six to seven water molecules are in the first coordination sphere of the unprotonated oxygen atoms in MMP. Accordingly, different numbers of nearby solvent molecules are treated quantum mechanically (see Fig. 1 for an example) to probe the dependence of the local solute-solvent interactions on the size and structure of the QM region; calculations are also done with both the first and second solvation shells (34 water molecules) treated as QM and the results are very similar to that of QM5 (see **Supporting Information**). To explore the electrostatic effect of the MM solvent on the solute-solvent interactions, MM charges are either turned “on” or “off”. In total, forty systems (five QM/MM partitions combined with two MM charge states for four configurations) are examined.

The SCC-DFTBPR/MM molecular dynamics simulations are carried out using a local version of CHARMM.¹⁴ The NBO analyses and NEDA are carried out using the CHARMM/GAMESS-US¹⁵/NBO¹⁶ package, where CHARMM is of version c32a2, GAMESS-US of version July-2003 and NBO of version 5.0.

Results and Discussions

The solvent structure around the phosphate oxygen atoms from the SCC-DFTBPR/MM simulations (Fig. 2) has the expected trends. The two unprotonated oxygen atoms are better solvated than the protonated oxygen, as reflected by the higher peak value in the OO radial distribution functions associated with the former. Integration of the radial distribution functions over the first solvation-shell gives approximately 8.2 water molecules around the unprotonated phosphate oxygens and 4.1 for the protonated phosphate oxygen.

In the NEDA framework, CT is found to make a significant contribution to the MMP-water interaction for all the forty cases studied, with the magnitude comparable to that of the electrical

interactions (EL), which include both the electrostatic (ES) and polarization (POL) contributions. The average ratio between CT and EL over the forty systems is 73%; except for the QM1 partition of configuration 4, all the ratios are above 63% (see **Supporting Information** for structures and detailed decomposition results; for results for configuration 1, see Table 1). These observations highlight the fundamental significance of CT to the MMP-water interaction regardless of the QM/MM partitioning scheme, water structure near the solute and the electrostatic effect of the MM environment.

The presence of charge transfers between MMP and water is also indicated by the significant variations of orbital occupancies due to orbital delocalization in the NEDA calculations, and the magnitude of the effect depends on the number of QM water molecules. When the entire first solvation shell for the unprotonated MMP oxygen atoms is treated quantum mechanically (scheme QM5 in Fig.1), approximately 0.130e on average are transferred from the lone pairs of the unprotonated MMP oxygen atoms to the anti-bonding orbitals of the QM water molecules. In the other extreme, when only one water molecule is treated quantum mechanically (scheme QM1 and QM3), there are about 0.022e and 0.028e, respectively, transferred from MMP to the corresponding QM water molecule. The amount of transferred electrons with different QM/MM schemes scales well with the size of the QM region, while the presence of MM charges typically makes only a small contribution; for example, for QM5 of configuration 1, about 0.01 more electrons are transferred from MMP to water when the MM charges are turned on.

To further support the quantitative significance of electron transfers from the MMP oxygen lone pairs to the anti-bonding orbitals of nearby QM water molecules, second-order perturbation theory analysis of the Fock matrix in the NBO basis is carried out. Overall, the interactions between the MMP oxygen lone pairs and the antibonds of water acceptors are found significant and much larger in magnitude than other MMP-water orbital interactions. For example, for QM1 of configuration 1 without MM charges, the interaction energy between the MMP oxygen lone pairs and the O-H antibond is 10.88 kcal/mol, while all other orbital interactions are less than 1 kcal/mol; this magnitude of donor-acceptor orbital interaction and the observed amount of charge transfer (0.02-0.03e, see above) per hydrogen bond are consistent with the trend observed in a more extensive set of surveys.^{1(d)} As a general trend, the orbital interaction energies and the CT contribution to the interaction energy are sensitive to the relative distance and orientation between the MMP oxygen donor and the water acceptors, which emphasizes that CT is due to orbital delocalization. As illustrated in Fig. 3, one of the MMP oxygen lone pairs and one of the O-H antibonds of a nearby QM water have significant overlaps.

In addition to the NEDA calculations, the ratio of the electrons transferred out of the MMP oxygen lone pairs to the total electrons transferred out of the MMP molecule is calculated based on the Natural Population Analysis (NPA).¹⁷ For all the forty cases studied, the ratio ranges from 80% to 120%, indicating that the “electron loss” from the oxygen lone pairs accounts for the major channel for the electron transfer between MMP and the QM water molecules. For cases with the ratio larger than 100%, there are notable electrons transferred back from the QM water to MMP between the doubly occupied O-H bonding orbital(s) in water and the empty Rydberg orbitals of the MMP oxygen atoms. For example, for QM5 of configuration 2 without MM charges, the electron loss ratio is 120% and there are 0.014 electrons transferred from water O-H bonds to the Rydberg orbitals of MMP oxygen atoms.

Our general finding regarding the significant amount of CT between MMP and water is qualitatively consistent with the study of Klein and coworkers, who found on the order of 0.10 e transfer between the GlyGly-dipeptide and water based on Car-Parrinello simulation and atoms in molecules (AIM) theory.⁴ In fact, NPA at the HF/6-31+G** level for configurations

collected from SCC-DFTB/MM simulation of the same peptide-water system found a similar degree of charge transfer (results not shown). To certain degree, the results here are different from the findings in the study of Mo and Gao,³ who found rather small ($<0.03 e$) amount of charge transfer between molecular ions (acetate and methyl-ammonium) and water; the charge transfer energies calculated in the block-localized wavefunction framework were also substantially smaller than those due to electrostatics and polarization. Since it is clear that the magnitude of charge transfer energy depends rather sensitively on the framework of energy decomposition, we don't intend to directly compare our CT interaction energies with those from Ref. 3⁻⁴. It is interesting to point out, however, that the solvent structure around the solute in Ref. 3 and ⁴ has systematic differences; e.g., the peak location in the water-acetate O-O radial distribution function is longer by $\sim 0.2 \text{ \AA}$ in Ref. 3 than the Car-Parrinello results in Ref. 4. Since the magnitude of CT is very sensitive to the distance and relative orientation, it is conceivable that the difference in solvent structure may influence the contribution of CT in a significant manner. For the MMP studied here, experimental solvent-solute radial distribution is not available; however, the peak values around $2.8 \text{ \AA}$ found in the simulation results (Fig. 2) are within the expected range.

Concluding Remarks

The NBO analysis and NEDA are well-established techniques for analyzing intermolecular interactions with a well-defined and self-consistent quantum mechanical formulation. In the current work, we report the first application, to be best of our knowledge, of these techniques to condensed phase problems within a QM/MM framework. Specifically, SCC-DFTBPR/MM simulations are used to sample the configurations of the solute with explicit solvent molecules; representative microscopic solute-solvent structures are then analyzed with QM/MM calculations at a higher QM level. For MMP in solution, the NBO and NEDA results clearly illustrate that there is significant charge transfer between MMP and nearby solvent molecules. This is not only shown by the solute charges from NPA but also NEDA, which underlines that charge-transfer interactions are almost as important as the electrical (electrostatic plus polarization) contributions; the magnitudes observed here based on HF as the QM method are likely slightly underestimated since electron-correlation is known to further enhance the importance of charge-transfer by 20-30%.^{1(d)}

Although this result is partially a consequence of the NBO and NEDA formulation, their self-consistent nature makes the application of NBO and NEDA in the QM/MM framework a useful approach for analyzing intermolecular interactions in the condensed phase. We anticipate that NBO analysis and NEDA will be valuable for a deeper understanding of catalysis in solution and enzyme systems as well as for the benchmark and improvement of approximate QM/MM methods at a fundamental level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- (1) (a). Kitaura K, Morokuma K. *Int. J. Quantum Chem* 1976;10:325. (b) Reed AE, Curtiss LA, Weinhold F. *Chem. Rev* 1988;88:6–899. (c) Gordon MS, Jensen JH. *Acc. Chem. Res* 1996;29:536. Weinhold, F.; Landis, CR. *Valence and Bonding: A Natural Bond Orbital Donor-Acceptor Perspective*. Cambridge University Press; 2005.
- (2) (a). Nadig G, Van Zant LC, Dixon SL, Merz KM Jr. *J. Am. Chem. Soc* 1998;120:5593. (b) van der Vaart A, Merz KM Jr. *J. Am. Chem. Soc* 1999;121:9182.
- (3). Mo Y, Gao J. *J. Phys. Chem. B* 2006;110:2976. [PubMed: 16494296]
- (4). Peraro MD, Raugei S, Carloni P, Klein ML. *ChemPhysChem* 2005;6:1715. [PubMed: 16080223]
- (5) (a). Mo Y, Peyerimhoff SD. *J. Chem. Phys* 1998;109:1687. (b) Mo Y, Gao JL, Peyerimhoff SD. *J. Chem. Phys* 2000;112:5530.
- (6). Car R, Parrinello M. *Phys. Rev. Lett* 1985;55:2471. [PubMed: 10032153]
- (7). Bader, RFW. *Atoms in Molecules—A quantum theory*. Oxford University Press; Oxford: 1990.
- (8). Foster JP, Weinhold F. *J. Am. Chem. Soc* 1980;102:7211.
- (9) (a). Glendening ED, Streitwieser A. *J. Chem. Phys* 1994;100:2900. (b) Glendening ED. *J. Am. Chem. Soc* 1996;118:2473. (c) Schenter GK, Glendening ED. *J. Phys. Chem* 1996;100:17152.
- (10) (a). Washel A, Levitt M. *J. Mol. Biol* 1976;103:227. [PubMed: 985660] (b) Field MJ, Bash PA, Karplus M. *J. Comput. Chem* 1990;11:700.
- (11) (a). Herschlag D, Jencks WP. *J. Am. Chem. Soc* 1989;111:7579. (b) Florian J, Warshel A. *J. Am. Chem. Soc* 1997;119:5473.
- (12) (a). Elstner M, Porezag D, Jungnickel G, Elsner J, Haugk M, Frauenheim T, Suhai S, Seifert G. *Phys. Rev. B* 1998;58:7260. (b) Yang YY, York DC, Cui Q, Elstner M
- (13). Ryckaert J, Ciccotti G, Berendsen HJC. *J. Comput. Phys* 1977;23:327.
- (14). Brooks BR, Bruccoleri RE, Olafson BD, States DJ, Swaminathan S, Karplus M. *J. Comput. Chem* 1983;4:187.
- (15). Schmidt MW, Baldridge KK, Boatz JA, Elbert ST, Gordon MS, Jensen JH, Koseki S, Matsunaga N, Nguyen KA, Su SJ, Windus TL, Dupuis M, Montgomery JA. *J. Comput. Chem* 1993;14:1347.
- (16). NBO 5.0
Glendening ED, Badenhoop J, K Reed AE, Carpenter JE, Bohmann J, Morales CM, Weinhold F. 2001. Theoretical Chemistry Institute, University of Wisconsin-Madison
- (17) (a). Reed AE, Weinhold F. *J. Chem. Phys* 1983;78:4066. (b) Reed AE, Weinstock RB, Weinhold F. *J. Chem. Phys* 1985;83:735.

Figure 1. Different QM/MM partition schemes used in the NBO and NEDA analyses. Hydrogen-bonds are indicated by dot lines with H...O distances given in angstroms.

Figure 2. Radial distribution functions, $g(r)$ (black), and running coordination numbers, rcn (blue dashed line) of water oxygen around different oxygen atoms of MMP from SCC-DFTBPR/MM simulations.

Figure 3. Preorthogonal Natural Bond Orbitals (PNBO) for one MMP oxygen lone pair and an O-H antibond for a nearby QM water molecule. The result is from a calculation with the QM1 partition for configuration 1 with full electrostatic interaction with the MM charges.

Table 1

NEDA analysis for solvated MMP (Configuration 1)^a

	MMP+H ₂ O (QM1)		MMP+4 H ₂ O (QM2)		MMP+ H ₂ O (QM3)		MMP+3 H ₂ O (QM4)		MMP+7 H ₂ O (QM5)	
	Uncharged	Charged	Uncharged	Charged	Uncharged	Charged	Uncharged	Charged	Uncharged	Charged
Interaction Energy	-3.8	-2.9	-34.4	-31.1	-10.1	-8.0	-32.4	-33.8	-58.9	-67.1
ΔE total	-14.7	-14.3	-63.1	-60.3	-14.6	-14.2	-45.6	-46.2	-103.6	-108.1
EL	7.4	7.2	33.3	31.9	7.3	7.2	24.2	24.4	54.6	56.8
SE	42%	41.6%	43%	42%	30%	29%	33%	34%	37%	39%
(POL+SE)/ES	-5.1	-4.9	-15.2	-14.9	-4.78	-4.8	-11.4	-11.0	-26.5	-25.5
EX	52.4	51.7	185.2	182.0	65.1	66.7	160.2	158.0	342.3	338.4
DEF										
Electron Loss^c										
MMP	0.019	0.017	0.065	0.063	0.040	0.038	0.084	0.085	0.130	0.143
(MMP O LP→Water	111%	106%	112%	111%	93%	95%	98%	97%	112%	108%
Antibonds)/Total (%)										

^aThe NEDA is done at the HF/6-31+G**/MM level, where the different QM regions are specified separately; the rest water molecules are treated with the TIP3P model. All energies are given in kcal/mol. "Charged" and "Uncharged" refer to results with and without the effect of the MM partial charges in the HF/MM calculations. For results of all other configurations, see **Supporting Information**.

^bES: Electrostatic interaction; POL: Polarization; SE: Electrical self energy; EX: Exchange interaction; DEF: Deformation energy. See Ref. 9c.

^cThe amount of electron loss is calculated based on NPA at the same level.