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Ab initio and charge study of phospholipids in gas phase and solution

M. Monajjemi[1*], A.Poorazizi [3], R.A.Khavari- Nejad [2], F.Falahian [3], M.Movehdi [3], S.Saki [3], F.Mollaamin[4], B. Khalili Hadad[5]

[1]Department of Physical Chemistry, Science & Research Branch, Islamic Azad University,P.O.Box:14155-775,Tehran Iran
[2] Biology Department, University for Teacher Education, Tehran, Iran
[3] Biology Department, Science & Research Branch, Islamic Azad University,Tehran,Iran
[4] Department of Chemistry, Qom Branch, Islamic Azad University, Qom,Iran
[5]Department of Biology ,Roodehen Branch,Islamic Azad University, Roodehen, Iran

ABSTRACT

phospholipids are important for the biological lipid and are commonly used in biophysical studies.A quantum calculation for two phospholipids Dipalmitoylphosphatidylethanolamine and dipalmitoylphosphatidic acid were performed using the abinitio software. Geometry optimization structures were obtained at RHF level using 3-21G, 6-31G*. These basis sets were used To understanding the effects of environmental polarity on the conformation, geometry optimization in various different solvents by SCRF theory. The introduction of a dielectric medium has significant effects on the energy, atomic charge distributions and dipole moments. As the polarity of the medium increase, the conformational stability and total dipole moment of these molecules increases. In this work, the changes of atomic charge distribution for some of selected atoms also were investigated.

*. Corresponding author

INTRODUCTION

Despite extensive studies have done on the structure, molecular conformation, lateral interaction, and dipole arrangement the head group and how these feature surface affect the properties and topology of the membrane.
An understanding of static properties of membrane is an essential prelude to the study of movement of molecules within the membrane. Biomembranes are dynamic assemblies of a wide variety proteins and lipids in aqueous environment (1). Lipids are essential for cellular signaling (2). In addition, they function as second messengers in several cellular processes (3). This molecular approach is a prerequisite in the understanding of the functions and organization of the biological membrane One of the main lipid constituents of cellular membrane are phospholipids. Phospholipid bilayers form the basic framework of the biological cell membrane (4,5). Phospholipids are amphiphilic molecules that have three regions:hydrophilic polar headgroup (α-chain), glycerol and hydrophobic long hydrocarbon chains (β- and γ-chains)(6). Two of these are dipalmitoylphosphatidylethanolamine (DPPE) and dipalmitoylphosphatidid acid (DPPA) (see fig.1). Despite very studies in laboratories, the specific role and the significance of its asymmetric distribution phosphatidylethanolamine for biological membranes are still poorly understood. Phospholipids have complicated phase properties, but for the lipid bilayer structure are considered two phase (gel phase and liquid – crystal phase) (8). in each of the phases, phospholipids show different mobility, ordering and packing (8). The packing of phospholipids in the bilayer membrane is determined by size and orientation of headgroups and acyl/alkyl chains (9). Phospholipids hydrocarbon chain conformations in these phases are different. For example, in the liquid-crystalline state, phosphatidylethanolamine is converted into inverted hexagonal (HII) structure (10, 11). NMR studies of phosphatidylethanolamines show that a preferred conformation is predominant in dynamic systems (12). For studying of biomembrane at the molecular level requires knowledge of the preference conformation of phospholipids. The flexibility to conformational changes in phospholipids occurs around the α, β and γ chains (13). The head group of the phospholipids prefers highly folded structures with strong intramolecular hydrogen bonds (14). For example, the most stable conformation of phosphoethanolamine headgroup is ring-like structure, that stabilized by a hydrogen bond between the ammonium and the phosphate group (15). Some properties of the lipid bilayers can be directly attributed to the intramolecular structural and dynamical characteristics of single (gas phase) phospholipids molecules (16-22).

Computational Calculation

The geometry of phospholipids were full optimized at the RHF/
6-31G*, 6-31G, 3-21G and STO-3G levels of the theory in the gas phase without any constraints and then optimizing all remaining geometrical parameters were bond angles. Geometry optimization was repeated to consider solvent effects on geometry and conformation dependence on the surroundings. All standard ab initio calculations were performed using Gaussian 98 molecular orbital software at hartree fock level of theory (22). To examine the effect of basis set on the structure of phospholipids we have first optimized the molecular geometry of two molecules with four basis sets including sto-3G, 3-21G, 6-31G and 6-31G* in gas phase. Fully geometry optimized structures and conformational energies were obtained. Then the standard 6-31G* basis set was employed in next calculation. Atomic charge of some atoms that are near dihedral angle θ, were calculated by CHELP method (23). Atomic charges were determined by fitting to the electrostatic potential calculated at the points selected according to CHELP scheme (24).

optimization in solvents

Solvent Model

The simplest SCRF model is Onsager reaction field the basic assumption. In this model is that the solute is placed in a spherical cavity of radius ao inside the solvent, cavity / dispersion effect are neglected and only the electrostatic effects of solvation, the net charge and dipole moment of the molecule are taken into account.

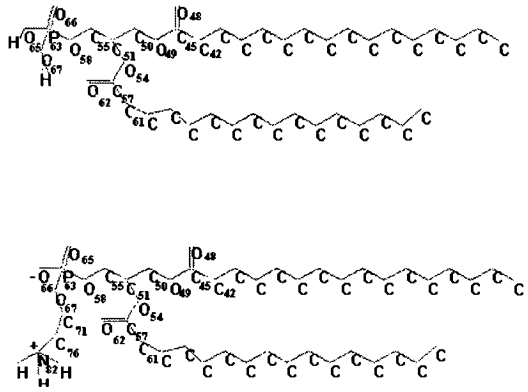
The total energy of solute and solvent, which depends on the dielectricity constant and also the solute dipole moment, induces a dipole moment of opposite direction in the surrounding medium .

The GIAO type method was introduced by Ditchfield and relies on the London orbitals. This technique is invariant with respect to the choice of the gauge for any basis set size. Therefore, the geometries of all the compounds were full optimized at the RHF/ 6-31G*, 6-31G, 3-21G, STO-3G levels of theory. Then the restricted Hartree-Fock (RHF) approach combined with the 6-31G basis set was employed for full optimization of the relevant geometries, and then the restricted Hartree-Fock (RHF) approach combined with the 6-31G basis set was employed for full optimization of the relevant geometries, and then GAIO was used for computation of corresponding energies and nitrogen NMR shielding;

To investigate the effect of the medium, we have employed the self-consistent reaction field (SCRF) method(25). We have chosen the 6-31G* basis set for SCRF calculations, this method is based on onsager reaction field theory of the electrostatic solute-solvent interaction. The onsager reaction field model has been incorporated in molecular orbital calculations by Tapia and Goscinski (26). In this reaction field model, the solvent is represented by a continuous dielectric, characterized by a given dielectric constant (ε). The solute assumed to be embedded into a cavity (usually spherical), with radius a_0 in the medium.A dipole in the molecule will induced a dipole in the medium, and the electric field applied to the solute by the solvent dipole will interact with the molecular dipole to lead to net stabilization (27). Note that solvation energy calculated by the SCRF method is the electrostatic distribution to the free energy of salvation. In the present work, the cavity radius of DPPE and DPPA (a_0) was calculated and fixed during optimization. The volume of two molecules (DPPE and DPPA) was obtained using the "volume" keyword. The calculated values of a_0 for DPPE and DPPA were 7.80 and 6.63 respectively. The molecular geometry resulted from rotation around dihedral angle θ (in gas phase) were optimized in nineteen different solvents with different dielectric constant (Heptane (ε =1.92), ...water (ε=78.39)). Because of the atomic charge distribution are altered in the presence of a solvent reaction field, we have investigated the atomic charge distribution of atoms in gas phase and different solvent for two molecules. Also total dipole moments in different solvents were investigated.

Results

The molecules were shown schematically in figure 1. Atomic labeling and dihedral angle notation for two molecules were defined (see fig.1).



θ: (O (49) – C (50) –C (51) –O (54))

Fig1: Atomic labeling and dihedral angle notation for DPPE (above) and DPPA (below).

First, geometry optimization was performed using four basis sets (sto-3G, 3-21G, 6-31G and 6-31G*) for two molecules. Then conformational energies of DPPE and DPPA obtained (see table 1).

Table 1. calculated energies for DPPE and DPPA using four basis set (sto-3G, 3-21G, 6-31G and 6-31G*).

Basis set	DPPA Energy
Sto-3g	-1428786.967
3-21g	-1438500.838
6-31g	-1445806.516
6-31g*	-1446444.712

The standard 6-31G* basis set was employed in next calculation. Optimized geometries at HF/6-31G* level of theory for two molecules were shown (see fig.2).

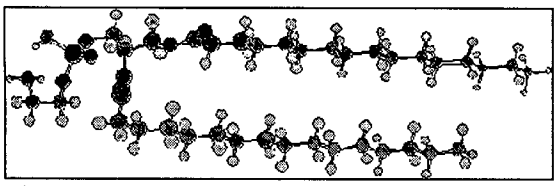


Fig 2. Gas phase minimum energy conformation of DPPE

For DPPE and DPPA, conformational energies corresponding to the rotations around the C(50)-C(51) bond as dihedral angle θ were calculated and the lowest energy conformation obtained (geometry optimization was performed using 6-31G* basis set). The minimum energy of DPPE and DPPA are respectively in internal dihedral angles of rotation θ = 180 ° and 110 ° (see Fig. 3). Optimized structures at mentioned dihedral angles were shown in Figure 4.

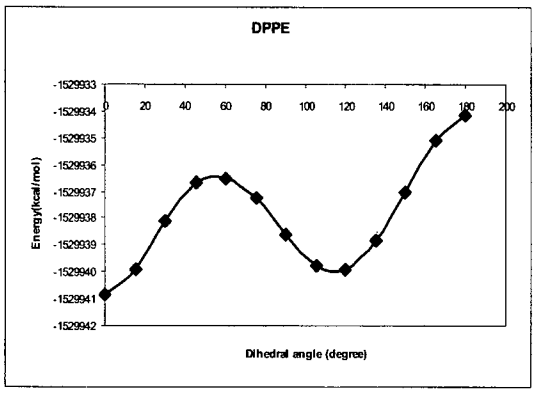


Fig 3: variation of energy with dihedral angle for DPPE

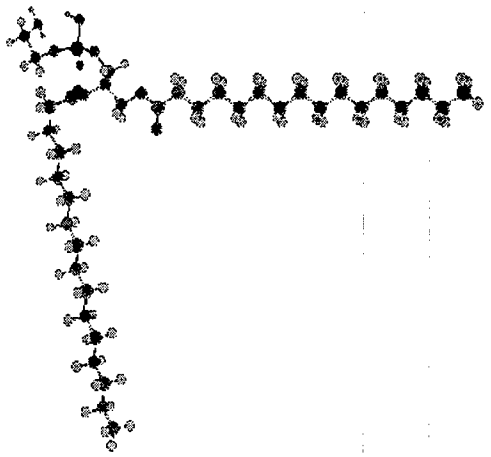
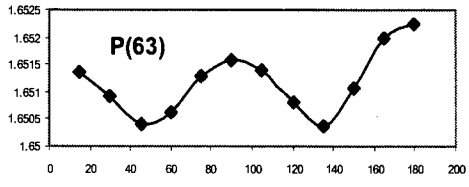
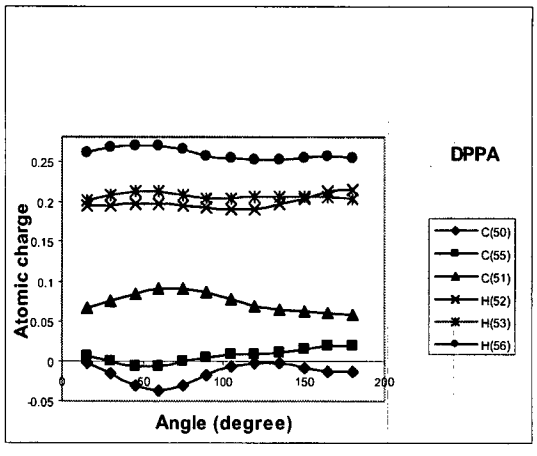


Fig4. Minimum energy conformations of DPPE

The lowest energy conformation of DPPE gives the unexpected result that NH3+ group losing one of its hydrogens to the oxygen attached to phosphorus. That is, a hydrogen bond, N---O-H, was formed. Therefore, the importance of hydrogen bonds in stabilizing the structure of phospholipids in a membrane was illustrated.

In the present study, atomic charge of some atoms was investigated using CHELP method. For two molecules, atomic charge values versus different dihedral angles (θ) were presented in Fig 5.





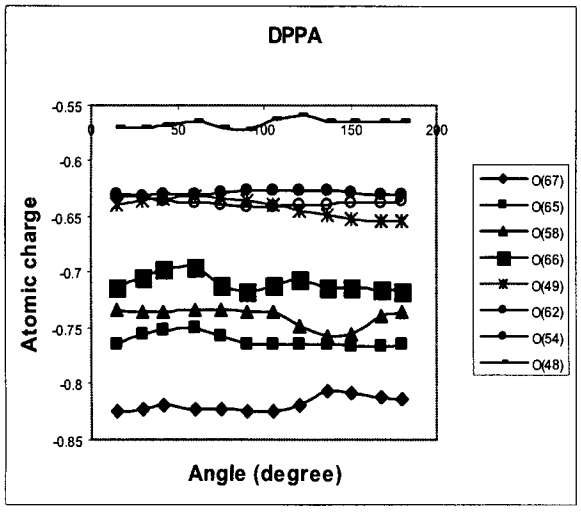


Fig 5: Variation of atomic charge with dihedral angle for DPPA.

We conclude when dihedral angle (θ) changes, the atomic charge of all atoms changes. It is interesting that carbon C (55) in DPPA had negative charge at θ=35°-75°; out of this range charge was positive (see fig. 6).

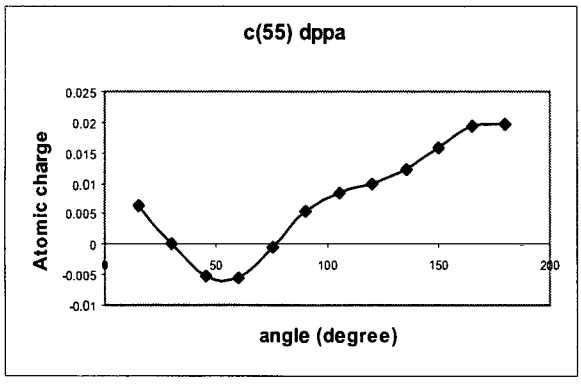


Fig 6: Variation of atomic charge with dihedral angle for C (55).

Solvent effect

Phospholipids are dynamic structures and solvent effects are crucial in determining their structure. The solvent catalyzes rapid conformational fluctuations in phospholipids. Information on the effects of solvent can be gained from theoretical studies. In this paper, we optimized the molecular geometry of DPPE and DPPA in 19 solvents using 6-31g* basis set (SCRF method). Energy calculations with different solvents revealed that the energy decreases with increasing dielectric constant (see fig. 7). That is, with increasing of solvent polarity, stability of two molecules increases. Therefore, the structures are more stable in solvents with high polarity.

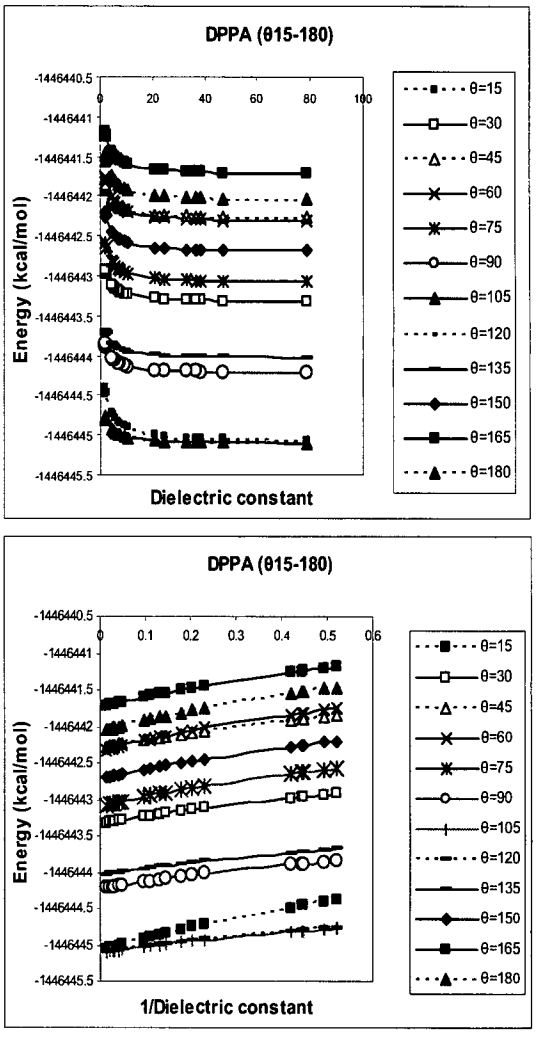


Fig 7: calculated energies DPPA in different solvents and its relationship with dielectric constant and 1/ dielectric constant.

The strength and orientation of the dipole moments of phospholipids is one of the main factors that determine the orientation of phospholipids relative to the bilayered membrane structure. The atomic charges and dipole moment in different solvents were studied. The relationship between calculated atomic charge and dipole moments with dielectric constant were presented (see fig. 8,9).

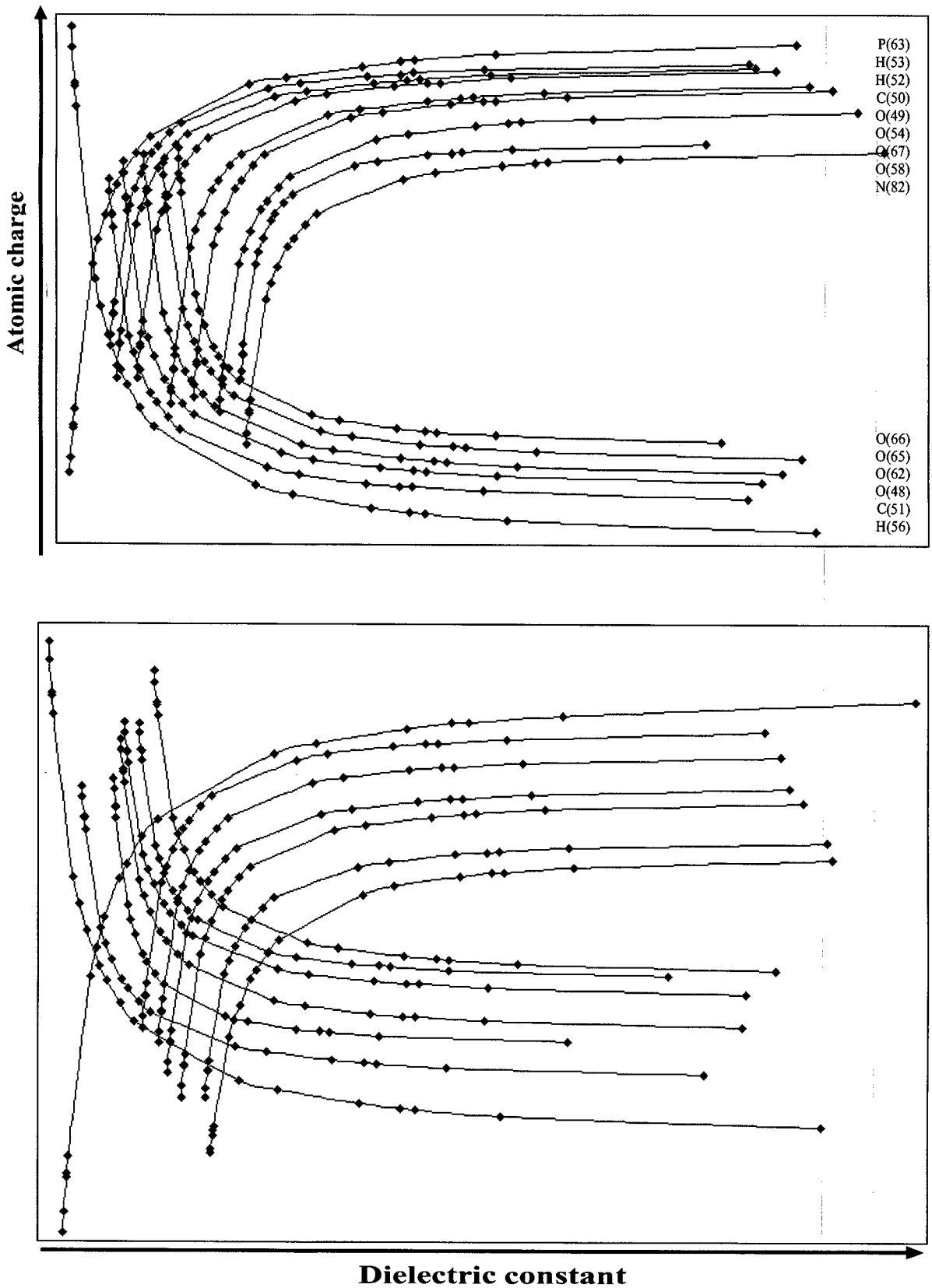


Figure 8: Atomic charge values versus dielectric constant for DPPE (a) and DPPA(b).

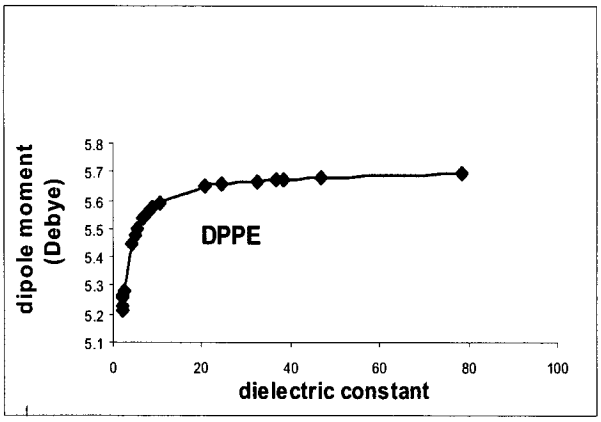


Fig 9: Dipole moment values versus dielectric constant for DPPE.

As expected, the atomic charge of selected atoms of DPPE and DPPA are found to be influenced by a dielectric medium. The charges of the some atoms are increasing when the dielectric constant is increasing. But the charges of other atoms are decreasing. A linear relationship can be found in plot of atomic charge and dipole moment versus 1/ dielectric constant. As shown in figures 8,9 the changes of atomic charge and dipole moment in range 1.92-10.36 of dielectric constant are considerable.

Conclusion

The conformational energies and atomic charge of some atoms were investigated in gas phase. Also we report the result of the effect of solvent on the energy, atomic charge and dipole moment. As expected, with increasing dielectric constant, stability of two molecules and dipole moment values were increased. When the dielectric constant increased, atomic charge of some atoms increased and others decreased. This study indicates that intermolecular and intramolecular interactions play an important role in determining stable structures of these molecular systems.

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