



Ab initio study of the influence of conformation on partial charge distribution of dioctadecylamine

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Abstract

The lipid dioctadecylamine (DODA) has been shown to self-organize in plate-like structures in aqueous solution. While in a previous model, we investigated by simulations its mesoscopic collective behaviour, here, we considered atomic partial charge distribution as determined by ab initio quantum chemical computations, and its relationship with different conformations of the DODA molecule. After comparison of the charges obtained at different levels of theory on the stretched form of DODA, we show that gas phase charges are sufficient to represent what appears to be an intrinsic property of the lipid, independently from the solvent. As the molecule becomes distorted, significant partial charge fluctuations appear along the aliphatic chains.

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1. Introduction

Atom-centered partial charges of molecules are extremely useful for apprehending a wide range of physicochemical problems. Indeed, the knowledge of the precise electronic distribution for given molecular states gives valuable insights into reactivity mechanisms. It may also shed light on complex self-organized systems such as biomembranes and viruses, solute-solvent interactions, or on protein folding and DNA behaviour. In this respect, the close partial charge-geometry rela-

tionship is interesting to analyze in details in order to further picture dynamical properties of such processes. While such charges are clearly not observables in contrast with electronic density matrix, we have to select the most reasonable description consistent with the size and properties of the system we study. There has been considerable interest in the relation between conformation and molecular charge distribution (see for instance [1,2]). Ab initio methods provide the best predictions of partial charge distributions. Unfortunately, computational limitations render this kind of calculations affordable only for systems composed of a maximum of two hundreds of atoms, and for not too high levels of theory. Integration of accurate partial charges in molecular mechanics

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force fields is crucial, but in current force fields (e.g. GROMOS [3]), the charges are independent on the conformation of molecules. Recent developments start to take polarizability into account, notably integration of ab initio methods with the application of a novel torsional fitting technique [4,5]. In AMBER 7 [6,7], atom-centered induced dipoles (determined by a Car-Parrinello dynamics approach) allow charge description to depend upon the environment, but it is not an electronically polarizable force field.

The aim of our study was to analyze the partial charge distribution of the neutral dialkylamine dioctadecylamine (DODA, $(C_{18}H_{37})_2NH$), as a function of its conformation. In a previous work [8], we have shown experimentally that DODA molecules spontaneously self-organize in plate-like structures in aqueous solution. This dynamics at the mesoscopic level was simulated with a functional Langevin model [9], and several features observed by electron microscopy could be qualitatively reproduced. However the crystalline-like ordering of the hydrocarbon tails was difficult to achieve, due to badly defined chain–chain correlations. Consequently, for a better understanding of the physical mechanisms underlying DODA self-association, we started to look at the electronic properties of the molecule, and more specifically partial charge distribution.

Our first objective was to investigate, using GAUSSIAN-98 [10], the net atomic charges of the molecule whose aliphatic chains were rendered almost perfectly linear through ab initio energy minimization at Hartree–Fock 6-31G(2d) level. We focused on the electrostatic potential (ESP)-derived charges using the Merz–Kollman–Singh scheme (MK population analysis), which fits the ESP to points selected on a set of concentric spheres around each atom [11,12]. We compared different levels of theory and basis sets, and confronted the gas phase results to the self-consistent reaction field (SCRF) ones (solvent modeled by a dielectric continuum), in order to best give account of the specific nature of the electronic distribution along the molecule.

Besides the completely stretched form (DODA-str), which served us as a reference, we then calculated the MK charges for two other conformations,

slightly twisted (DODA-tw1) and strongly twisted (DODA-tw2), leading to an important result with regard to the incidence of such large charge variations on intra and intermolecular interactions, dynamics and the notion of hydrophobicity itself. Furthermore we tried to relate these three DODA charge/conformation states to their free energy of hydration, using the Langevin Dipoles model of Warshel and Florian [13,14].

2. Calculation of charge distribution

2.1. Gas phase

Each structure was first drawn in the approximate conformation of interest using HYPERCHEM molecular modeling application. Bond lengths and angles were optimized running a BIO+ (CHARMM) molecular mechanics optimization, followed by a PM3 semi-empirical geometry optimization, using the Polak–Ribiere conjugate gradient algorithm to achieve convergence. In the case of the linearly drawn DODA, this ended up with a continuously slightly curved structure. From this starting conformation, cartesian coordinates were generated, and used as the input file for the charge determination, using GAUSSIAN-98 (G98) either on a PC (G98 Windows version (G98W), A7 revision) or at the IDRIS supercomputer facility (Orsay, France – G98 Unix version, A11.1 revision).

Ab initio computations were performed at the Hartree–Fock (HF) [15] level. A HF/6-31G(2d) gas phase energy minimization was carried out on each structure, with ‘tight’ convergence optimization criterium. This calculation was run using a Merz–Kollman–Singh procedure (MK) which fits the molecular ESP to the atomic charges. This approach for deriving net atomic charges for molecules was set up by Singh and Kollman [11] and Besler et al. [12]. As all our results are based on this method, let us briefly recall its principle. The ESP is determined quantum mechanically from the electron density matrix solved through the self-consistent field (SCF) procedure. It is calculated at points defined with the Connolly surface algorithm on a number of shells around each atom. A partial charge model is defined in agreement with specific

molecular properties (e.g. hydrogen bond energies in DNA [11], correspondence of the calculated and experimental dipole and quadrupole moments [16]). The potential corresponding to the set of model charges is then calculated, and through a Levenberg–Marquardt nonlinear optimization procedure, fitted to the quantum mechanical ESP. The charges are thus recalculated so as to best reproduce this potential.

2.2. Polarizing situation

The effect of polarization by the medium on charge distribution was checked by including solvent reaction field. Geometry inputs were the gas phase HF/6-31G(2d) ‘tight’ energy minimized structures. No further energy minimization was run during the self-consistent reaction field (SCRF) calculation done at the same level of theory. Indeed, geometrical variations between solvent and gas phase optimizations remain generally small. We compared two different SCRF methods, Onsager and Tomasi. Whereas in the Onsager model, the solute cavity in contact with the solvent field is spherical, in the Tomasi’s Polarizable Continuum Model (PCM), the cavity is defined as a series of interlocking spheres surrounding by default each group (in our case the heavy atom (HA) bound to its hydrogen(s)) [17]. We used the CPCM model, which performs a PCM calculation using the polarizable conductor calculation model [18] and gives good results in a water environment. Either $\epsilon = 78.39$ (water) or $\epsilon = 1.92$ (*n*-heptane) dielectric constants were input to define the polarizable dielectric continuum. The number of tesserae covering each sphere was 60. We checked the form of the cavity generated around DODA with the software `GEOMVIEW`. Unexpected irregularities appeared in the solvation cage for the twisted forms of DODA, in the form of aberrant peaks located at certain positions of the molecules. Only for DODA-str did we obtain perfect interlocking spheres profile. Thus we evaluated on DODA-str, using the CPCM model and at HF level of theory, MK charges dependence on two basis sets: the average level 6-31G(2d) versus the more complex 6-311+G(2d,p), in both solvents. With this last basis set,

tight optimization had to be switched on. The comparison with one quite standard (close to the 6-31G*) and one complex basis set was performed to test the sensitivity on the basis.

3. Free energies of solvation

To relate the different charge/conformation states of DODA to their influence on a macroscopic property, we calculated the corresponding hydration free energy ΔG using Langevin Dipoles (LD) solvation model [13,14]. The solvent is approximated by polarizable dipoles fixed on a cubic lattice. The solute is transferred from the gas phase to aqueous solution, at 298 K. The parameters used for calculating hydration free energies were given in [13] (program `CHEMSOL` [19]), but we increased the number of grids to 50 instead of 20. Gas phase HF/6-31G(2d) tight energy minimization cartesian coordinates with corresponding MK partial charges were data input. The calculation was performed for three conformations we named DODA-str, DODA-tw1 and 2 and, as a reference, the alkane of equal chain length: $\text{CH}_3(\text{CH}_2)_{35}\text{CH}_3$ (C37).

For DODA-str, the ΔG value issued from the LD model was compared to the values obtained by the method implemented in G98 in the Tomasi’s SCRF CPCM calculation (variational COSMO results) for water or *n*-heptane solvation, at 6-31G(2d) and 6-311+G(2d,p) levels.

4. Results

4.1. DODA-str

For the stretched DODA molecule, the HF energy minimization results in a structure which is all-antiperiplanar, i.e. transoid for every four successive carbons considered, and the nitrogen is aligned in the same way (Fig. 1). The total length of DODA-str (distance between the most distant H’s) is 47.59 Å.

Partial MK charges for DODA-str in CPCM polarized situation were compared for each given basis set, HF/6-31G(2d) and HF/6-311+G(2d,p), either in water or *n*-heptane dielectric media. Fig. 2

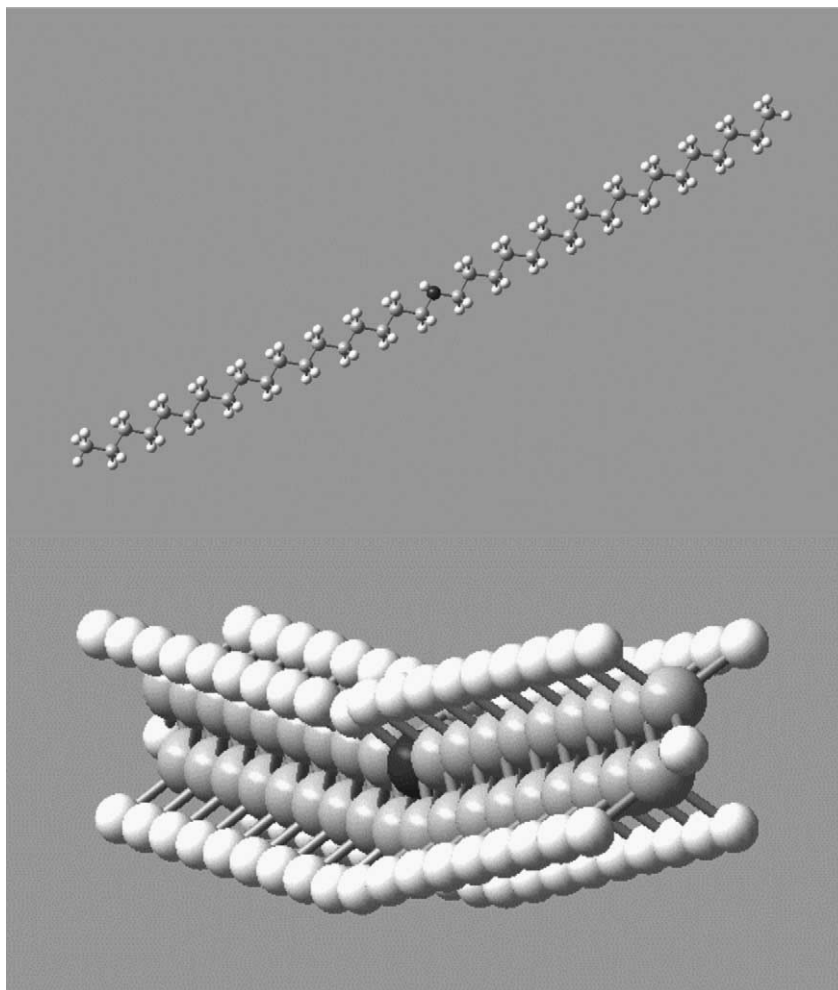


Fig. 1. Two different views of DODA-str (HF/6-31G(2d) tight energy minimization). In black: the nitrogen; in dark grey: the carbons; in light grey: the hydrogens.

illustrates these results in the case of water, for both HA's and H's. The main differences occur on the NH ($\Delta e^- (\text{N}) \approx 0.14$, $\Delta e^- (\text{H}) \approx 0.04$) and the first and fourth carbons near the nitrogen ($\Delta e^- \approx 0.05$ to 0.08). Δe^- vanishes for some of the last carbons, and increases to about $0.03 e^-$ for the terminal Cterm's. The amplitudes and differences of charges obtained in water with CPCM and Onsager's models (CPCM giving the most polarized charges) were about the same at HF/6-31G(2d) level of theory as for the CPCM ones obtained in water and n-heptane. For both HF/6-31G(2d) and HF/6-311+G(2d,p) basis sets, the

most noticeable differences between water and heptane again resided on the NH ($\Delta e^- (\text{N}) \approx 0.08$ and $0.12 e^-$ respectively) and the first carbon positions on each side of it (C α 's, ≈ 0.02 and $0.04 e^-$, resp.). One striking result is that the partial charge profiles are almost superimposable whatever the basis set or the method used. Note that when hydrogens are summed into HA's, their charges do not compensate the one on the HA they bind to, to the contrary to Mulliken charges for all carbons except C α 's (6-31G(2d) level), where the charge difference on the NH is caught up. Indeed, Mulliken charges are just arbitrary numbers (total

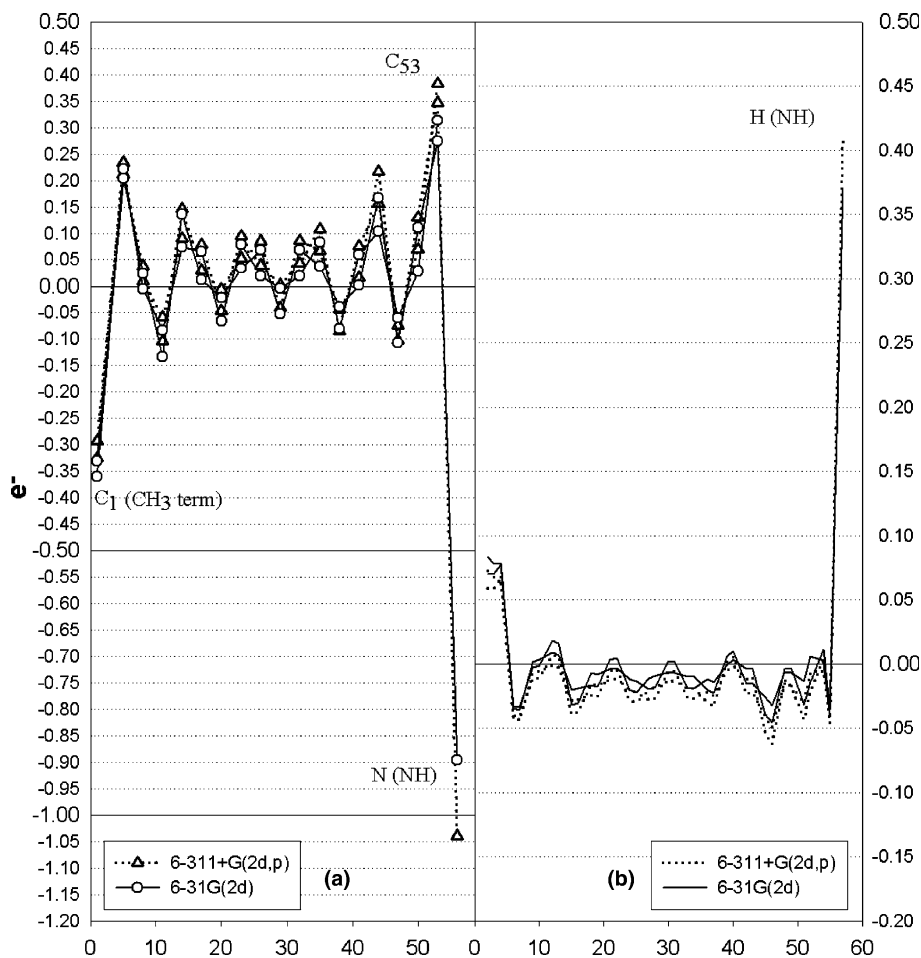


Fig. 2. DODA-str, HF/6-31G(2d) (solid lines/circles) vs. HF/6-311+G(2d,p) (dotted lines/triangles), water dielectric medium, CPCM polarized situation. X -axis: numbering follows DODA chain atoms, from left to right in each graph: (C₁H₂H₃H₄)(C₅H₆H₇)(C₈H₉H₁₀) ··· (C₅₃H₅₄H₅₅)N₅₆H₅₇, the two C18 chains being superimposed with same numbering. Y -axis: MK partial charges in units of electron charge, (a) for carbons and the nitrogen (HA's), and (b) for hydrogens.

charge partitioned so as to split negative charge among HA's and positive charge among H's), while MK charges really represent charge distribution at a few angströms distance from the molecule.

Two additional remarks can be done about these profiles: (i) the Cterm's bear a large negative charge of about $-(0.30-0.35) e^-$, with respect to the other carbons. This may be due to the sharing of one supplementary bond with a hydrogen, the carbon being electroattractive. For the other carbons, there might be inductive electronic effects occurring along the chain. (ii) Although one C₁₈

chain looks geometrically perfectly identical to the other one on each side of the nitrogen (Fig. 1), the MK partial charge distribution is slightly asymmetric. This discrepancy comes from a numerical problem in G98 (ESP grid placement), resulting in uncorrect symmetry determination (personal communication from K.M. Merz). But as the differences on the two C₁₈ chains were quite minor, DODA profiles could still be very well compared and qualitative conclusions drawn.

One calculation was performed on DODA-str on the gas phase HF/6-31G(2d) energy minimized ('tight') geometry, without further energy

minimization, at the B3LYP [20,21] level, a density functional theory (DFT)-based method allowing to take into account electron correlation effects [22]. We thus checked the validity of the HF charge distribution (data not shown). Except for the first carbons following the Cterm's, where the charges were equal, the B3LYP curve was found, for each position, only slightly above the corresponding HF one ($0.02 e^-$ in average for the carbons, about 0.04 for the Cterm's and 0.05 for the N). The situation was inversed for the hydrogens.

We can conclude from these results that the DODA-str molecule charge distribution is quasi insensitive to the presence of a solvent modelled in the form of a dielectric continuum (weak influence of the shape of the solvation cage and of the nature of the solvent). Induced polarization only affects the most polarizable NH group and the $C\alpha$'s, which compensate the charge on the nitrogen, except at 6-311+G(2d,p) level, where an overall distributed polarization effect is observed. In any case, the specific MK charges profile on the two C_{18} chains is unaltered, indicating that it may be related to an intrinsic property of the molecule.

An important feature of the DODA-str profile is the periodic oscillation of the charges, over about three carbons along the two aliphatic chains. It is not obvious to explain without considering the quantum behaviour of the electrons, and the superimposition of electronic stationary waves along this finite molecular system. Moreover, fluctuations have to depend upon the choice of the model charges and on the quality of the resulting ESP fit with the quantum mechanically calculated one.

We compared MK charges to other methods of population analysis (non ESP based): Mulliken and NBO (natural bond orbital [23]). Results for DODA-str are shown in Table 1, where we see that, as well for Mulliken as for NBO, the carbons along the two aliphatic chains wear about constant negative charges (-0.34 and -0.42 , resp.), strictly counterbalanced by the H's charges. With MK's method, all charges fluctuate around zero. Given these facts, we decided to proceed by focusing on the gas phase MK charges at HF/6-31G(2d) level of theory, with tight energy minimization for all the structures.

4.2. DODA-tw1 and 2

The HF energies of DODA-str, DODA-tw1 and DODA-tw2 are, respectively: -1461.43247 , -1461.42552 and -1461.41578 Hartree, i.e. an energy difference of 18.2 kJ mol^{-1} between DODA-str and DODA-tw1, and 25.6 kJ mol^{-1} between DODA-tw1 and 2. These differences are small: the probabilities for the molecule to be in one conformation or the other are close. In Fig. 3, molecular model views of DODA-tw1 and DODA-tw2 are the result of a tight gas phase HF/6-31G(2d) energy minimization. Whereas DODA-tw1 is only slightly deformed with regard to DODA-str, DODA-tw2 is much more twisted. These differences between the three conformations are reflected in their respective partial charge distributions (cf. Fig. 4a for HA's and 4b for hydrogens). We follow the atoms of the chain from the first to the last (starting from one Cterm), without superimposing the two C_{18} chains. For DODA-tw1,

Table 1

Comparison on DODA-str of partial charges obtained with MK, Mulliken and NBO population analysis models, gas phase, HF/6-31G(2d), tight optimization

Population analysis model	DODA-str charges (e^-)							
	HA's (a)				H's (b)			
	(i)	(ii)	(iii)	(iv)	(i)	(ii)	(iii)	(iv)
MK	-0.80	0.27 ± 0.03	-0.34 ± 0.02	(*)	0.32	-0.02 ± 0.03	0.08	(**)
Mulliken	-0.64	-0.17	-0.55	-0.34	0.33	0.16 ± 0.01	0.18	0.17
NBO	-0.73	-0.19	-0.63	-0.42	0.37	0.19 ± 0.02	0.21	0.21

(a) HA's; (b) H's. (i) nitrogen; (ii) $C\alpha$'s; (iii) Cterm's; (iv) other carbons (or H's corresponding to these positions, in (b)). For (ii)–(iv): mean values (Std Dev. < 0.01, otherwise indicated). (*) cf. Fig. 4a; (**) cf. Fig. 4b.

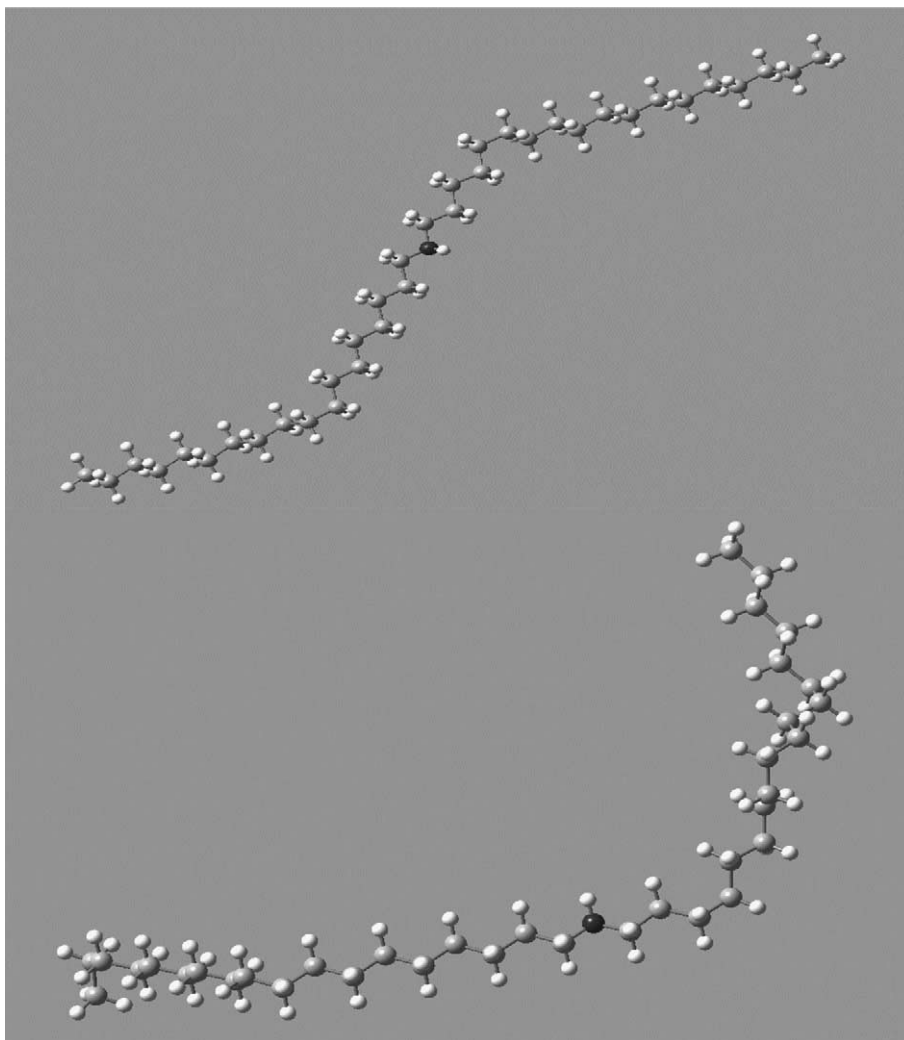


Fig. 3. DODA-tw1 (top) and DODA-tw2 (bottom) views after HF/6-31G(2d) tight energy minimization (see Fig. 1).

the fluctuations in the profile follow the ones of DODA-str quite well, with however a shift of the values which does not exceed $0.13 e^-$. For DODA-tw2, the distortion from DODA-str's profile is stronger and there are enormous fluctuations of the charges, with a progressive amplification on the right part from the Cterm to the nitrogen. Especially we see appear on the 6th carbon after the nitrogen a charge of about $-0.54 e^-$. This is corroborated by the hydrogens charge distribution, with highly charged H's on strongly charged carbons (e.g. 0.12, -0.08). As a reference, we compared these DODA-tw1 and 2 MK charges to

Mulliken ones. Despite slight fluctuations in the charge profiles of the carbon chains (not exceeding $\approx 0.02 e^-$), average values were exactly the same as for DODA-str (Table 1). Mulliken's method, to the contrary of MK, shows therefore to be quasi insensitive to the conformation.

4.3. ΔG of solvation

We report the results of the calculations of ΔG of hydration for DODA-str, DODA-tw1 and 2 and C37 by the LD method (Table 2, part (a)), together with ΔG 's of hydration and n-heptane solvation

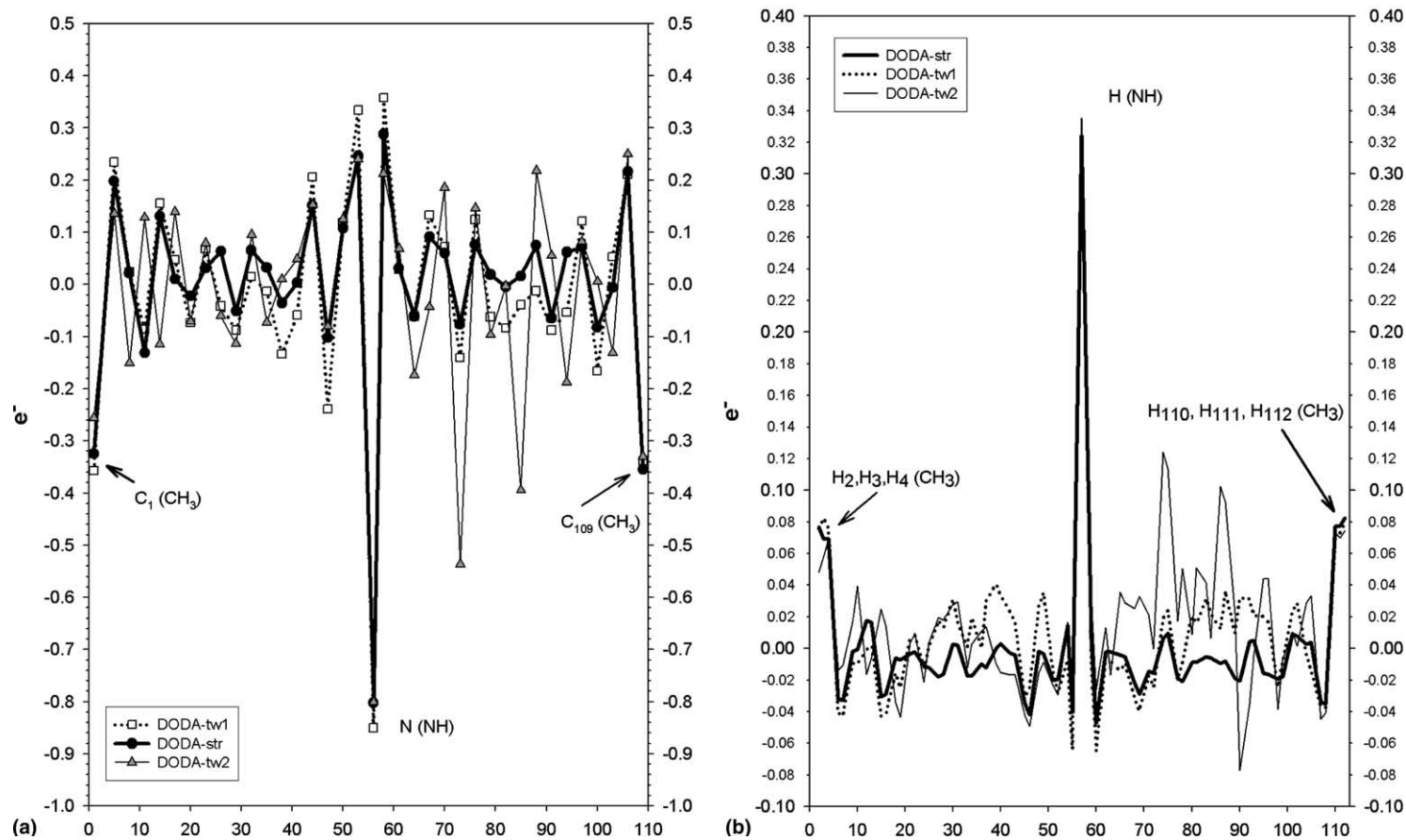


Fig. 4. (a) DODA-str (solid thick line/black circles) vs. DODA-tw1 (dotted line/white squares) and 2 (solid thin line/grey triangles), HF/6-31G(2d) MK charges. Heavy atoms. X-axis: atoms are numbered from one C-term to the other (hydrogens included in numbering): $C_1C_5C_8 \dots C_{53}N_{56}C_{58} \dots C_{103}C_{106}C_{109}$. (b) DODA-str vs. DODA-tw1 and 2: hydrogens (as in (a), without symbols). X-axis: $H_2H_3H_4$ of C_1 , H_6H_7 of $C_5 \dots$, $H_{54}H_{55}$ of C_{53} , H_{57} of N_{56} , $H_{59}H_{60}$ of $C_{58} \dots$, $H_{107}H_{108}$ of C_{106} , $H_{110}H_{111}H_{112}$ of C_{109} .

Table 2
 ΔG values in kJ mol^{-1}

(a)	Molecule	DODA-str	DODA-tw1	DODA-tw2	C37
	LD-water	15.48	15.15	14.77	22.13
(b)	COSMO	Water		<i>n</i> -heptane	
		HF/6-31G(2d)	HF/6-311 + G(2d,p)	HF/6-31G(2d)	HF/6-311 + G(2d,p)
	DODA-str	15.94	12.55	-48.45	-49.12

(a) LD model, $\Delta G(\text{water})$; (b) PCM model, $\Delta G(\text{water})$ and $\Delta G(\textit{n}\text{-heptane})$ for each basis set.

given in the CPCM calculations on DODA-str, at HF/6-31G(2d) and HF/6-311 + G(2d,p) levels (Table 2, part (b)). We see that the DODA-str values for ΔG of hydration given by the two models are close (15.48 vs. 15.94 kJ mol^{-1} at HF/6-31G(2d) level). In *n*-heptane, they are strongly negative, the solvation process being spontaneous, what is expected. An LD calculation on C37 gives a $\Delta G(\text{hydration})$ value of 22.13 kJ mol^{-1} , which is coherent because the polarized NH group is replaced by $-\text{CH}_2$. The LD values for DODA are slightly decreasing from the stretched to the tw2 conformation. Of course one would expect that the more charged (polarized) groups there are in the molecule, easier its hydration will be.

5. Discussion

Among all possible conformations with nearly the same energy, DODA-str may exist as such in crystalline state [24], or in solution as well as DODA-tw1 or DODA-tw2 only a minute fraction of time. An important consequence of the HF gas phase energy minimization on the stretched but slightly curved DODA resulting from the PM3 geometry optimization was the obtention of a perfect bilinearly stretched DODA. As can be seen in its specific charge distribution, this structure offers a chance for a theoretical understanding of its electronic properties. For the DODA-tw1 and 2 structures, the tight ab initio energy minimization led to a slight unfolding of the initially drawn and optimized PM3 structures. Nevertheless, in the same way this finely corrected for DODA-str bond lengths and valence and dihedral angles, this procedure guaranteed the twisted structures to be in a local energy minimum state for each given

conformation. Moreover, DODA-tw1 and 2 ended up with two conformations sufficiently different to see appear strong variations in their charge profiles.

We show that partial charge distributions, calculated either in gas phase or in a solvent modeled by a dielectric continuum, are very sensitive to the conformation of the aliphatic chains. Although one can be far from the situation of a true solvent medium composed of discrete molecules, these results are significant enough to allow us to extrapolate their incidence in a real medium. In particular, given the fact that in the twisted DODA molecules some parts of the chains become very charged (i.e. polar), as some others remain relatively uncharged (apolar), the solvent water will be a 'good' solvent for the former ones, and a 'bad' one for the latter. This changes the way we may apprehend long range interactions within such a polymer, based on the classical representation of repetitive hydrophobic units. Strong electrostatic interactions with water molecules may take place for the most charged methylene groups, with excluded volume effects, or to the contrary, facing sites with opposite partial charges may interact, bringing fragments closer, in a competitive way. Here the notion of hydrophobic interactions, depicted by the propensity of hydrophobic groups to regroup in order to avoid solvent interactions, appears simplistic and should be reconsidered in the light of these results. Thus, although the methylene repetitive units have the same chemical composition, they cannot be considered as physicochemically equivalent.

The oscillation of the charges along the chain may have a significant impact on the mesoscopic properties of the system. We have shown [8] that DODA molecules spontaneously form plates in

aqueous solution, some of them presenting a regular geometry, with clues in favor of a crystalline gel state of the lipids. Such behaviour is a purely collective property. However, the periodicity of the charge profile could be a driving force for the stabilization of the final arrangement of the DODA molecules within the plates. In a complementary work (to be published), we shall look at different dialkylamines and primary alkylamines, as well as alkanes, with different chain lengths allowing for rational comparison of the charge profiles between the molecules with DODA-str as a reference.

What we point out here through the hydration energy differences observed with the explicit LD model is that, although the differences are small from one conformation to the other, they are charge-dependent. In a hydrodynamic medium, thermal fluctuations are often strong enough to drive major conformational changes. It is likely that the strong differences in partial charge configuration as a function of the different conformations may trap the molecules in certain conformational states, through intra and/or intermolecular electrostatic interactions. Thus in a so-called ‘homogeneous’ solution, different favored subsets of populations may exist, whose free energy differences have to be expressed by taking into account the incidence of partial charge distribution. In the end, the knowledge of conformation-dependent charges may help understand solution properties better. For instance, it may allow to tackle the problem of the anomalous solvation of methyl-substituted amines [25,26] differently: the fact that $\text{CH}_3\text{-NH}_2$ is more water-soluble than NH_3 , and further increasing the number of methylene hydrophobic groups decreases the solubility by much less than expected, is still not understood.

A next step in this investigation would be to better model the aqueous environment by considering the closest surrounding of the DODA as formed by a few water molecules around the amine group, or elsewhere distributed along the molecule, or by using a hybrid QM/MM approach. Our observations also highlight the need for developing a polarizable model best suited for the description of long alkylamines. A serious effort by Jordan et al. [27] is to be mentioned, with an application to the study of N_2 .

In conclusion, we demonstrate for quite a large system the strong impact of conformation on atomic charge profile, in terms of partial charges. This shows to be an intrinsic property of the molecule, which would be naturally modulated in presence of explicit solvent molecules. The periodic behaviour of charges for DODA-str, and the increase of their amplitudes as the structure becomes random coil-like, was not expected. Moreover, the DODA-str optimized structure can be used to further rationally analyze and improve charge and polarization models. Our results should apply to the fields of polymer dynamics, properties of amines, of lipids (lipid–lipid/lipid–protein interactions in biological membranes structure and dynamics) and other domains where conformational electro-dynamics may be determinant, such as protein folding, nucleic acid properties and self-organizing molecular systems in general.

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