

COMMENTS

Comment to “Calculation of the Dipole Moment for Polypeptides Using the Generalized Born-Electronegativity Equalization Method: Results in Vacuum and Continuum-Dielectric Solvent”

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In the past decades among the theoretical models devised for including polarization in molecular mechanics, those based on the electronegativity or chemical potential equalization¹ were found to be suitable for several reasons: transferability of the characteristic parameters² (typically atomic electronegativity and hardness), applicability to different thermodynamic states of the system, computational time saving, theoretical appealing (all electronegativity equalization models are based on the density functional theory,³ DFT).

Recently, Shimizu et al. used the electronegativity equalization methodology (EEM) in combination with the generalized Born method for calculating charges and dipole moments for a series of organic molecules and for polypeptides in vacuum and continuum-dielectric solvent.⁴ This model, called the generalized Born-electronegativity equalization method (GBEEM), was first proposed by the same authors in 2002.⁵ The GBEEM has been shown to be very promising for the calculation of the charge distribution of molecules in implicit solvent. However, we do believe, as also pointed out by Shimizu et al., that more reliable results could be generally obtained by implementing GBEEM with the explicit inclusion of the first-solvation-shell contribution. This should allow the local details of the solute–solvent interactions to be efficiently taken into account, certainly important when strong forces, e.g., hydrogen bonding, come into play.

A very important issue of the work of Shimizu et al.⁴ is the implementation of the EEM using the so-called constrained charge approximation (CCA) in order to overcome “a serious caveat of EEM that can limit its application for large molecules”. In fact it has been shown⁶ that several models based on EEM predict an incorrect dependence of the polarizability as a function of the molecular size, that is an exaggerated overestimate of the polarizability for large molecules. Shimizu et al. also showed this shortcoming of EEM by calculating the dipole moment of many isolated molecules classified in different organic functions. They found that the EEM dipole moments show an anomalous spiny pattern when plotted against PM3-CM1 dipole moments (see Figure 2 of ref 4). This pattern clearly results from the addition of methylene groups to the molecular structure, that is from an increase of the molecular size. The application of the CCA without providing a new EEM parametrization has been shown to reduce the overpolarization of EEM

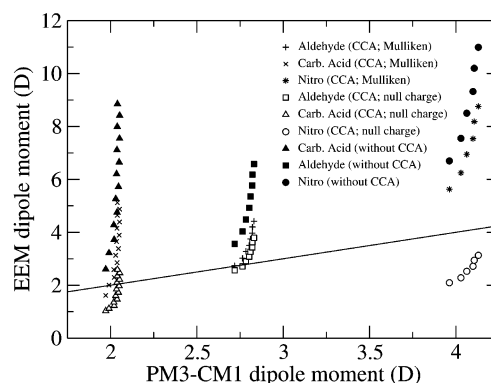


Figure 1. EEM versus PM3-CM1 dipole moments for some series of compounds (see legend). The continuous line represents the identity between EEM and PM3-CM1 dipole moments.

for the aldehyde, nitro, and carboxylic acid series, eliminating the aforementioned spiny pattern (see Figure 3 of ref 4).

Technically, the CCA consists of a partition of the molecule into more subsystems (ensembles of atoms of the molecule) where net charge is constrained to a fixed value with charge transfer among subsystems not allowed. The electronegativity is then equalized in each subsystem following the well-known EEM equations.⁴ In other words, the object molecule is broken into more pseudo-molecules interacting via EEM. In the case of the aldehyde, nitro, and carboxylic acid series,⁴ each molecule has been broken into two electrically neutral subsystems: the headgroup (–CHO, –NO₂, and –COOH) and the tail group (alkyl chain). For some polypeptides, also studied in ref 4, the single amino acids have been assumed as subsystems with null net charge. The approximation of null net charge for the –CHO, –NO₂, and –COOH groups has been adopted because it was also used in other molecular mechanics force fields (see discussion at page 4174 of ref 4). On the other hand, the CCA with null net charge is also supported by the results on the CM1 charge distribution⁷ obtained from semiempirical PM3 calculations. In fact, the absolute value of the net charge on the –CHO, –NO₂, and –COOH groups is found to be small, that is of the order of 10^{–3}, 10^{–2}, and 10^{–1} *e*, respectively. However, a different (non zero) net charge on the two subsystems could be chosen, in principle, on the basis of the Mulliken charges obtained from *ab initio* calculations. Using DFT at the B3LYP/6-31G(d,p) level, we found average Mulliken net charges of –0.035, –0.32, and –0.09 *e* for the groups –CHO, –NO₂, and –COOH, respectively. The dipole moments for the three series of compounds calculated using EEM combined to CCA with Mulliken net charges on the subsystems are reported in Figure 1 along with the dipole moments resulting from EEM combined to CCA with null net charge. In the figure, the results obtained by EEM without CCA are also reported. The reference dipole moments in Figure 1 (X axis) are those resulting from PM3-CM1 for consistency with the data of Shimizu et al. The EEM force field parameters used in this work are those labeled EEM-CM1 in Table 1 of ref 4. The differences between our results and those by Shimizu et al. (compare Figure 1 with Figure 3 of ref 4) are probably due to some differences in the

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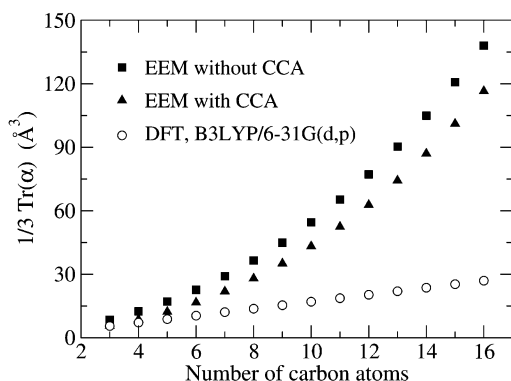


Figure 2. Average value of the diagonal elements of the polarizability tensor of all-trans carboxylic acids as a function of the number of carbon atoms. For the EEM with CCA, null net charge on the subsystems has been assumed.

molecular conformations.¹⁰ By inspection of Figure 1, we infer that the net charge on the subsystems, coming from the number and the type of atoms of the subsystems, is a determinant factor for reducing the overestimate of the dipole moment. In fact, a net charge of the order of 0.1 *e* (carboxylic acids) can even double the dipole moment with respect to the zero net charge assumption, whereas a net charge of 0.3 *e* (nitro compounds) increases the dipole moment by a factor three. A significant difference is also observed when a very small net charge is assumed (aldehydes). This result suggests that the application of EEM using CCA strongly depends on the chemical intuition and therefore the reliability of the obtained data should be verified in each single case. The model proposed in ref 4, and the CCA in particular, has been claimed “to treat the intrinsic problem of EEM in the prediction of molecular observables” (page 4177 of ref 4), by meaning as “intrinsic problem” the well-known overestimate of the polarizability for large molecules⁶ (see also discussion in the Introduction of ref 4). Although in some cases CCA can solve the polarizability catastrophe (see discussion below), the problem remains unsolved for aldehyde, nitro, and carboxylic acid series. This is well-evident in Figure 2, where the polarizability calculated by EEM with and without CCA and by ab initio method (DFT at the B3LYP/6-31G(d,p) level of theory) as a function of the number of carbon atoms is reported in the case of the carboxylic acid series. Similar results have been obtained for aldehyde and nitro compounds (data not shown). The nonlinear trend resulting from EEM (independent on the application of CCA) is typical of conjugated systems,⁶ and it was also observed for all-trans alkanes using a very similar EEM scheme.⁶ For each molecule, the largest contribution to the polarizability is given by the alkyl chain, because its size is very large with respect to that of the functional group. The EEM combined to the CCA with null net charge agrees slightly better with the ab initio data than the EEM without CCA (see Figure 2). Such a small improvement is due mainly to the lower dimensions of the subsystems defined for using CCA with respect to the full molecular size considered when CCA is not applied. This result shows that the correct reproduction of the dipole moment of an isolated molecule (with respect to experimental or ab initio data) by using CCA in the EEM does not imply necessarily a good reproduction of the polarizability. Some solutions to the EEM polarizability catastrophe have been proposed.^{2,6} In ref 6, a model where polarizability practically corresponds to a sum of “bond” polarizabilities has been devised. Such bonds are not necessarily covalent in nature but are intended only as pairs of atoms between which charge transfer can occur. In ref 2, to improve

the generality of the method (transferability of the EEM parameters), we suggested adding a term depending quadratically on the molecular induced dipole moment to the electrostatic energy. In principle, the effect of reducing the overpolarization could be also obtained using CCA. In this last case, however, care must be used for the choice of the dimensions of the various subsystems as well as to the type of atoms they contain. The entity of the subsystem size is not actually determined, but we believe that it should not exceed a few atoms (4–6). In this respect, we can confidently state that the subdivision of the alkyl chain of aldehydes, nitro compounds, and carboxylic acids in various subsystems (e.g., considering subsystems made of pairs of methylene groups) could reduce the overpolarization without affecting significantly the global dipole moment. Although polarizability is not determinant for reproducing the dipole moment of isolated molecules using EEM,¹¹ it is certainly important when intermolecular interactions occur. For example, the presence of charged groups in proteins can give rise to very strong local electric fields. In this case, polarizability plays a decisive role for having reliable induced dipole moments. To show this effect in the case of the all-trans decanoic acid, we have calculated its dipole moment induced by one external point charge (1 *e*) located at the end of the alkyl chain (about 3 Å away from the methyl group). We obtained induced dipole moments of 13.8, 11.8, and 2.9 D for EEM without CCA, EEM, with CCA (null net charge on the subsystems) and B3LYP/6-31G(d,p), respectively. The difference between the induced dipole moments with and without CCA is small, but both values strongly differ from the ab initio one. This finding is fully consistent with the polarizability behavior observed in Figure 2 and outlines the importance of a reliable modeling of the polarization for treating the intermolecular interactions. In conclusion, we can state that the use of CCA in the EEM does not imply necessarily a correct reproduction of the molecular polarizability. In any case, tests for considering external electric fields should be performed for evaluating the polarization response. In the case of proteins, where the presence of charged side chains is quite common, such tests become necessary.

The DFT and PM3 calculations reported in the present work were performed using the Gaussian 98⁸ and AMSOL⁹ programs, respectively.

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(10) Our data have been obtained using all-trans conformations for the alkyl chains (the atomic Cartesian coordinates are available upon request to the corresponding author).

(11) In the EEMs, the dipole moment of a molecule can be reproduced using many different sets of values for the atomic electronegativity and hardness. This means that a given dipole moment can be obtained independently on the value of the polarizability.