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Unraveling Interactions in Large Complex Systems Using Quantum Chemistry Interpretative Techniques and New Generation Polarizable Force Fields

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Abstract. In this contribution, following the results exposed at the Seventh International Conference of Computational Methods in Sciences and Engineering (ICCMSE 09), we present an overview of some available new techniques able to unravel interactions in large complex systems such as biomolecules, ions in solution, lanthanides and actinides complexes. We first focus our attention on Quantum Chemistry (QC) interpretative techniques introducing some Energy Decomposition Analysis (EDA) scheme such as the newly introduced fragment localized Single-CI DFT scheme. We then present the recently developed DEMEP analysis which is an extension of the topological analysis of the Electron Localization Function (ELF) to the computations of chemically intuitive local electrostatic moments. In a second part, we then discuss how such QC techniques can be used, following a “bottom-up” strategy in order to develop new generation polarizable force field based on distributed multipoles such as the AMOEBA and SIBFA (Sum of Interaction Between Fragments ab initio) procedure; or on electronic density as for the GEM (Gaussian electrostatic Model) method which is based on density fitting. Some applications are detailed.

Keywords: ELF, interpretative techniques, metals, cations, molecular mechanics, density fitting, multiscale approaches.

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INTRODUCTION

Modern quantum chemistry (QC) is now able to provide electronic structures on several hundreds of atoms through the used of Density Functional Theory. However, for very large systems of biological interest or systems containing several heavy atoms, QC techniques are still limited by their scaling. On the other hand, classical Molecular dynamics (MD) provides information to experimentalist as simulations are getting closer and closer to relevant timescales despite the fact that current molecular mechanics (MM) potentials have serious shortcomings. In this context, Anisotropic Polarizable Molecular Mechanics (APMM) procedures have been developed [1] and use advanced electrostatics. Indeed, such methods are directly designed following a “bottom up” strategy [1, 2] being uniquely grounded on ab initio quantum theory and therefore offer the possibility to access more quantitative MD results. We will first start by presenting the QC “interpretative” methods used for this development strategy. Then, we will detail some new MM models such as the SIBFA [1] and GEM [1, 3] approaches.

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QC INTERPRETATIVE TECHNIQUES: ELF AND EDA SCHEMES

The ELF function [4] can be interpreted as a measure of the Pauli repulsion in the atomic or molecular space and enables access to the probability of finding two same spin electrons: ELF is defined to have values restricted between 0 and 1 and can be interpreted as a signature of the electronic pair distribution but, in contrast to pair functions, it can be more easily calculated and interpreted. Once computed on a 3D grid from a given *ab initio* wave function, the ELF function can be partitioned into an intuitive chemical scheme [4b]. Indeed, core regions, denoted $C(X)$, can be determined for any atom. This is also the case for valence regions associated to lone pairs, denoted $V(X)$, and for chemical bonds ($V(X,Y)$). These ELF regions, the so-called basins (denoted Ω), match closely the domains of Gillespie's VSEPR (Valence Shell Electron Pair Repulsion) model. In addition to a visualization of the ELF isosurfaces, ELF offers the possibility to integrate the population (numbers of electrons) within a basin or to obtain local distributed electrostatic moments such as dipoles and quadrupoles (the so-called DEMEP analysis) [5]. That way, the Distributed Electrostatic Moments based on the ELF Partition (DEMEP) allows computing of local moments located at non-atomic centres such as lone pairs, σ bonds and π systems. Many applications of ELF have been performed over the years. Indeed, ELF has been shown to be a useful tool to understand the bonding in dicopper enzyme such as tyrosinase [6], in Zn(II)-metalloenzyme such as the Alcoholate Dehydrogenase (ADH) [7]. It has also been particularly suited for the understanding of the peculiar behaviour of Pb(II) $6s^2$ valence lone pair [8] which can be holo, hemi or bisdirected [8e] within a complex. The interested reader can find details about ELF and its applications to bioinorganic chemistry in a recent review paper [9].

Intermolecular Energy decomposition analyses (EDA) are key approaches to calibrate force fields. Indeed, they offer a direct evaluation of the physical components of the interaction energy, especially of the many-body induction, is a key issue for the development of polarizable models. EDA schemes such as Bagus' Constrained Space Orbital Variations (CSOV) [10], are generally limited to dimer interaction. The CSOV approach is particularly suited for MM calibration as it allows a correct computation of polarization and charge transfer energies and it can be performed at both DFT and MCSCF levels. EDA methods allowing the inclusion of electron correlation for multimolecule analysis did not exist until very recently, for the computation of large assemblies of molecules. We present here the methodology at the basis of a new potentially linear scaling local approach based on Fragment-localized Kohn-Sham orbitals via a Singles-CI procedure [11].

ANISOTROPIC MOLECULAR MECHANICS (APMM)

The presented QC interpretative techniques allow unravelling interactions in large systems. However, for realistic models encompassing thousands of atoms, these methods are not operational any more. Nevertheless, they can still provide data to design simplified models that remain accurate for the computation of many body effects. We review here some of these models.

The SIBFA intermolecular interaction energy is formulated as a sum of five contributions:

$$\Delta E_{\text{int}} = E_{\text{MTP}^*} + E_{\text{rep}^*} + E_{\text{pol}} + E_{\text{ct}} + E_{\text{disp}} + E_{\text{LF}} \quad (1)$$

denoting respectively the multipolar short-range, penetration corrected, electrostatic (E_{MTP^*}) [12], short-range repulsion (E_{rep^*}) [13], polarization (E_{pol}), charge-transfer (E_{ct}), dispersion (E_{disp}) and ligand-field (E_{LF}) contributions [14]. The analytical forms of these contributions are given in the original papers and we only recall here their essential features (see reference 1 and references therein). The SIBFA procedure has been recently successfully applied to ADH [7a], HIV-1 NCP7 nucleocapsid protein [15], Phosphomannose Isomerase (PMI) Zn(II)-enzyme [16] and to metallo-betalactames [17].

GEM [1, 3] follows the energetical scheme of the SIBFA approach but uses a different formalism for the computation its different contributions.

Indeed, GEM uses the formalism of the variational density fitting method [18], an approach which is usually devoted to a fast approximation of the Coulomb interaction.

This method relies on the use of an auxiliary Gaussian basis set (ABS) to fit the molecular electron density obtained from a relaxed one-electron density matrix using a linear combination of atomic orbitals.

Using the fitted electronic densities, it has been shown that it is possible to accurately compute the intermolecular Coulomb interaction energy (see Equation 3) from frozen monomer densities in the direct spirit of *ab initio* energy decomposition schemes. By using density fitting, both long-range multipolar and short-range penetration electrostatic energies (missing in a distributed multipole treatment) are included, the errors being relatively small compared to reference *ab initio* data using the same density matrices. All the required integrals

(electron-electron and electron-nuclear) were computed based on the McMurchie-Davidson recursions [19] enabling the use of higher angular moment Gaussian functions if required. It is important to point out that the formalism also enables an accurate representation of both electrostatic potentials and fields enabling a direct link between GEM and SIBFA through a multiscale approach. The GEM methodology has been recently successfully applied to water complexes [3] as first results on metals were shown for electrostatic and exchange-repulsion. We were able to compute polarization energies using GEM densities for both metal and water coupled to the SIBFA polarization scheme [1, 20]. The GEM approach offers a quasi-exact match of the ab initio polarization energy, even at very short-range when coupled to the SIBFA damping scheme. Of course as GEM requires the computations of integrals, one would like to be able to limit the approach to a subsystem like in QM/MM. The first multiscale SIBFA/GEM [21] and QM/GEM [3d] test computations have been performed and should lead us to a real integrated SIBFA/GEM/QM approach.

CONCLUSION

As we have seen, QC interpretative techniques can be applied to many systems, bringing new insights about the chemical physics of complex systems. For systems beyond the reach of quantum chemistry, APPM methods such as SIBFA and GEM can be applied to a vast range of molecules and metals, from transition metals to heavy metals. Indeed, present investigations are dealing with lanthanides and actinides complexes. The development of an integrated SIBFA-GEM multiscale scheme should enable use to perform computations on very large system with high accuracy. Such an interface with GEM which can itself be coupled to QM should give rise in the near future to a multilevel QM/GEM/SIBFA methodology since GEM offers a direct connection between multipoles and densities. Such ab initio based systematic procedure is currently applied [22] to refine other MM methods such as AMOEBA [23]. It should improve the gas phase fitting of parameter in order to be able to predict free energies of solvation of metal cations in water.

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