Research Article

ITP Adjuster 1.0: A New Utility Program to Adjust Charges in the Topology Files Generated by the PRODRG Server

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The suitable computation of accurate atomic charges for the GROMACS topology *.itp files of small molecules, generated in the PRODRG server, has been a tricky task nowadays because it does not calculate atomic charges using an ab initio method. Usually additional steps of structure optimization and charges calculation, followed by a tedious manual replacement of atomic charges in the *.itp file, are needed. In order to assist this task, we report here the ITP Adjuster 1.0, a utility program developed to perform the replacement of the PRODRG charges in the *.itp files of small molecules by ab initio charges.

1. Introduction

The GROMACS package [1] is extensively used for energy minimizations (EM) and molecular dynamics (MD) simulations of biomolecules such as proteins, nucleic acids, peptides, and drugs [2–11]. The input topology files used by GROMACS [1] for small molecules (*.itp files) may be generated by the server PRODRG [12]. However, these files must be adjusted for MD due to the charge group concepts adopted by PRODRG [12].

The topology files preparation for performing EM and MD simulations with GROMACS [1] is very important in investigations of biological processes involving drug interactions with their molecular targets. The force fields available for biomolecules in the literature [13–16] are generally based on macromolecules, such as proteins and nucleic acids, making the preparation of consistent and reliable topology files for small ordinary molecules a challenging task. The PRODRG server [12] is a reliable tool for quickly generating topologies and coordinates of ligands in protein-ligand complexes, using the empirical GROMOS96 force field [14], from a variety of different input files. This tool has been used in several studies and a wide range of knowledge areas [17–25]. This server works with the concept of charge groups, which is defined as a group of bonded atoms that sums an integer total charge. Lemkul et al. [26] investigated the quality of topologies generated by the PRODRG server [12] for small molecules for the GROMOS96 43A1 force field [14] and described their functional groups. Their results show that the atomic partial charges are critically incompatible with the GROMOS force fields. Furthermore, when we use the PRODRG [12] parameters, the behavior of the system is notably different than the one observed using the GROMOS parameters. Thus, they suggest a more consistent strategy for the calculation of partial atomic charges, avoiding the deviation of behavior in the system.

Several computer programs are available for structure optimization and charge calculations using quantum chemical calculations [27–29]. The Frisch et al. software [30] has been reported as the most standard for quantum chemical calculations of small molecules [31–33]. Thus, the ITP adjuster 1.0 was built to make the interface of Frisch et al.
Table 1: *.itp files of folic acid before (left) and after (right) applying TPA adjuster 1.0.

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[30] with the GROMACS package [1]. However, it may also be easily modified to work with different quantum chemical software.

There are several problems to adjust the output files of PRODRG [12] based on Frisch et al. [30] output files (*.out files): (i) the manual edition of the topology charges is an exhausting, tedious, and time-demanding assignment and, so, very susceptible to mistakes; (ii) PRODRG [12] uses a charge group concept, differently from Frisch et al. [30] and any other quantum chemical softwares; (iii) the numbering of hydrogen atoms in the *.itp files is incompatible with the output files from quantum chemical softwares; (iv) the bonds
information in the Frisch et al. [30] output files may have some inconsistencies, such as hydrogen atoms bonded to two different atoms.

The ITP Adjuster 1.0 (Figure 1) performs a quick and safe edition of the *.itp files considering the charge calculations from Frisch et al. [30] using Mulliken or Chelpg (Charges from Electrostatic Potentials) charges. It handles charges of up to six decimal places. At the end of the execution, a message box will inform the total charge of the molecule in the edited *.itp file, which may be used as a guide to detect inconsistencies between the *.itp and *.out files.

2. Materials and Methods

2.1. Considerations for Using ITP Adjuster. Some requirements for using the ITP Adjuster 1.0 are important to guarantee its proper installation and use, as discussed below.

ITP Adjuster 1.0 needs the Microsoft .Net Framework 4 or later installed for running properly. The authors recommend the Frisch et al. [30] calculations and PRODRG server [12] topology generation. It is highly desirable to have a *.pdb file with numbered atom names before submitting it to the PRODRG server [12]. It guarantees the correspondence of the atom names between the *.out and the final *.itp files. ITP Adjuster 1.0 also has a functionality named “PDB Adjustment,” which verifies a *.pdb file and, if necessary, numbers the atom names.

The hydrogen charges are based on the information of bonds presented in the Frisch et al. [30] output files, which is necessary to provide an *.itp file which is compatible with the *.out file indicated. An usual mistake occurs when the PRODRG server [12] removes hydrogen atoms from oxygen and nitrogen atoms or adds hydrogen atoms that do not exist in the *.out file. In these cases, the user must use the ADDHYD, DELHYD, PATCH, or a combination of these commands in the PRODRG server [12] in order to correct these inconsistencies before using ITP Adjuster 1.0. Not performing this strategy leads to unreliable final *.itp files and meaningless total charges.

3. Results and Discussion

3.1. Validating ITP Adjuster 1.0. We validated the ITP Adjuster 1.0 with the three common molecules in biological systems: folic acid, adenosine-5′-triphosphate (ATP), and cystein. Structures of these molecules are shown in Figure 2. First we built their 3D structures in the *.pdb format using Gauss View 4.0 and Frisch et al. [30] and submitted them to energy minimization with Frisch et al. [30] using the algorithm B3LYP/3-21G with charge chelpg, in order to generate their *.out files. Besides, the *.itp files of each molecule were generated at the PRODRG server [12]. The *.out and *.itp files were then loaded into the ITP Adjuster 1.0 to change the charges of the *.itp files generated by the PRODRG server [12] by using ab initio charges of the *.out files from Frisch et al. [30]. The results are presented in Tables 1, 2, and 3. As it can be seen, the ITP Adjuster 1.0 was able to recognize the atoms in each file. It properly adjusted the charges without modifying the positions of the atoms. The ITP Adjuster 1.0 was also tested against several other small molecules (data not shown) and, without exception, it was able to adjust charges accordingly.
4. Conclusion

We reported here the development of the ITP Adjuster 1.0, a utility program built to adjust ab initio charges into *.itp files generated by the PRODRG server [12]. This utility program is already in use in our laboratory and proved to be very accurate in the interface of Frisch et al. [30] and GROMACS [1], providing a friendly user interface and a quick way
to generate suitable topology files to perform EM and MD calculations with the GROMACS package [1].

This utility program is available free of charge by request at lmm@puc-rio.br.

Conflict of Interests

All the authors declare that there is no conflict of interests related to the publishing of this paper on the Journal of Chemistry or any direct financial relation with the trademarks mentioned in the paper.

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