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 ITP Adjuster 1.0.

Nr	Type	resnr	resid	Atom	cgnr	Charge	Mass	Nr	Type	resnr	resid	Atom	cgnr	Charge	Mass
1	CR1	1	FOL	C15	1	0.022	12.0110	1	CR1	1	FOL	C15	1	0.113688	12.0110
2	HC	1	FOL	H15	1	0.058	1.0080	2	HC	1	FOL	H15	1	0.091572	1.0080
3	NR	1	FOL	N3	1	-0.434	14.0067	3	NR	1	FOL	N3	1	-0.504841	14.0067
4	C	1	FOL	C16	1	0.335	12.0110	4	C	1	FOL	C16	1	0.798970	12.0110
5	NR	1	FOL	N6	1	-0.434	14.0067	5	NR	1	FOL	N6	1	-0.821446	14.0067
6	C	1	FOL	C19	1	0.453	12.0110	6	C	1	FOL	C19	1	0.946175	12.0110
7	NT	1	FOL	N7	2	0.082	14.0067	7	NT	1	FOL	N7	2	-0.931989	14.0067
8	H	1	FOL	H72	2	0.027	1.0080	8	H	1	FOL	H72	2	0.414024	1.0080
9	H	1	FOL	H71	2	0.027	1.0080	9	H	1	FOL	H71	2	0.433222	1.0080
10	NR	1	FOL	N5	2	0.061	14.0067	10	NR	1	FOL	N5	2	-0.786769	14.0067
11	H	1	FOL	H53	2	0.027	1.0080	11	H	1	FOL	H53	2	0.414871	1.0080
12	C	1	FOL	C18	2	0.294	12.0110	12	C	1	FOL	C18	2	0.698881	12.0110
13	O	1	FOL	O4	2	-0.676	15.9994	13	O	1	FOL	O4	2	-0.485705	15.9994
14	C	1	FOL	C17	2	0.158	12.0110	14	C	1	FOL	C17	2	-0.275218	12.0110
15	NR	1	FOL	N4	3	-0.619	14.0067	15	NR	1	FOL	N4	3	-0.194434	14.0067
16	C	1	FOL	C14	3	0.127	12.0110	16	C	1	FOL	C14	3	0.172175	12.0110
17	CH2	1	FOL	C13	3	0.161	14.0270	17	CH2	1	FOL	C13	3	0.134163	14.0270
18	N	1	FOL	N2	3	0.127	14.0067	18	N	1	FOL	N2	3	-0.476189	14.0067
19	H	1	FOL	H22	3	0.021	1.0080	19	H	1	FOL	H22	3	0.222443	1.0080
20	C	1	FOL	C3	3	0.127	12.0110	20	C	1	FOL	C3	3	0.404365	12.0110
21	CR1	1	FOL	C4	3	0.015	12.0110	21	CR1	1	FOL	C4	3	-0.305799	12.0110
22	HC	1	FOL	H4	3	0.041	1.0080	22	HC	1	FOL	H4	3	0.156776	1.0080
23	CR1	1	FOL	C5	4	0.000	12.0110	23	CR1	1	FOL	C5	4	-0.091238	12.0110
24	HC	1	FOL	H51	4	0.000	1.0080	24	HC	1	FOL	H51	4	0.118576	1.0080
25	CR1	1	FOL	C2	4	0.000	12.0110	25	CR1	1	FOL	C2	4	-0.334445	12.0110
26	HC	1	FOL	H21	4	0.000	1.0080	26	HC	1	FOL	H21	4	0.172869	1.0080
27	CR1	1	FOL	C1	4	0.000	12.0110	27	CR1	1	FOL	C1	4	-0.022017	12.0110
28	HC	1	FOL	H11	4	0.000	1.0080	28	HC	1	FOL	H11	4	0.106113	1.0080
29	C	1	FOL	C6	4	0.000	12.0110	29	C	1	FOL	C6	4	-0.147662	12.0110
30	C	1	FOL	C7	5	0.429	12.0110	30	C	1	FOL	C7	5	0.566722	12.0110
31	O	1	FOL	O1	5	-0.612	15.9994	31	O	1	FOL	O1	5	-0.487695	15.9994
32	N	1	FOL	N1	5	0.176	14.0067	32	N	1	FOL	N1	5	-0.654534	14.0067
33	H	1	FOL	H12	5	0.030	1.0080	33	H	1	FOL	H12	5	0.322800	1.0080
34	CH1	1	FOL	C8	5	0.229	13.0190	34	CH1	1	FOL	C8	5	0.290274	13.0190
35	C	1	FOL	C12	5	0.428	12.0110	35	C	1	FOL	C12	5	0.640657	12.0110
36	O	1	FOL	O3	5	-0.612	15.9994	36	O	1	FOL	O3	5	-0.499644	15.9994
37	OA	1	FOL	O6	5	-0.149	15.9994	37	OA	1	FOL	O6	5	-0.637158	15.9994
38	H	1	FOL	H6	5	0.081	1.0080	38	H	1	FOL	H6	5	0.456952	1.0080
39	CH2	1	FOL	C9	6	0.198	14.0270	39	CH2	1	FOL	C9	6	0.004713	14.0270
40	CH2	1	FOL	C10	6	0.198	14.0270	40	CH2	1	FOL	C10	6	-0.014129	14.0270
41	C	1	FOL	C11	6	0.384	12.0110	41	C	1	FOL	C11	6	0.703747	12.0110
42	O	1	FOL	O2	6	-0.685	15.9994	42	O	1	FOL	O2	6	-0.512801	15.9994
43	OA	1	FOL	O5	6	-0.167	15.9994	43	OA	1	FOL	O5	6	-0.633904	15.9994
44	H	1	FOL	H52	6	0.072	1.0080	44	H	1	FOL	H52	6	0.432867	1.0080

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

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

TABLE 2: *.itp files of cystein before (left) and after (right) applying ITP Adjuster 1.0.

Nr	Type	resnr	resid	Atom	cgnr	Charge	Mass	Nr	Type	resnr	resid	Atom	cgnr	Charge	Mass
1	OA	1	CYS	O2	1	-0.180	15.9994	1	OA	1	CYS	O2	1	-0.553855	15.9994
2	H	1	CYS	H22	1	0.057	1.0080	2	H	1	CYS	H22	1	0.366426	1.0080
3	C	1	CYS	C3	1	0.372	12.0110	3	C	1	CYS	C3	1	0.638891	12.0110
4	O	1	CYS	O1	1	-0.693	15.9994	4	O	1	CYS	O1	1	-0.478926	15.9994
5	CH1	1	CYS	C2	1	0.175	13.0190	5	CH1	1	CYS	C2	1	0.098300	13.0190
6	NT	1	CYS	N1	1	0.066	14.0067	6	NT	1	CYS	N1	1	-0.630975	14.0067
7	H	1	CYS	H16	1	0.012	1.0080	7	H	1	CYS	H16	1	0.282228	1.0080
8	H	1	CYS	H15	1	0.012	1.0080	8	H	1	CYS	H15	1	0.282036	1.0080
9	CH2	1	CYS	C1	1	0.153	14.0270	9	CH2	1	CYS	C1	1	-0.101843	14.0270
10	S	1	CYS	S1	1	0.077	32.0600	10	S	1	CYS	S1	1	0.049643	32.0600
11	H	1	CYS	H13	1	-0.051	1.0080	11	H	1	CYS	H13	1	0.048076	1.0080

FIGURE 1: The ITP Adjuster interface.

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.

TABLE 3: *.itp files of ATP before (left) and after (right) applying ITP Adjuster 1.0.

Nr	Type	resnr	resid	Atom	cgnr	Charge	Mass	Nr	Type	resnr	resid	Atom	cgnr	Charge	Mass
1	OA	1	ATP	O12	1	-0.256	15.9994	1	OA	1	ATP	O12	1	-0.674862	15.9994
2	H	1	ATP	H12	1	0.001	1.0080	2	H	1	ATP	H12	1	0.395648	1.0080
3	P	1	ATP	P3	1	1.081	30.9738	3	P	1	ATP	P3	1	1.542343	30.9738
4	OA	1	ATP	O13	1	-0.256	15.9994	4	OA	1	ATP	O13	1	-0.731008	15.9994
5	H	1	ATP	H13	1	0.001	1.0080	5	H	1	ATP	H13	1	0.418396	1.0080
6	OM	1	ATP	O7	1	-0.151	15.9994	6	OM	1	ATP	O7	1	-0.606703	15.9994
7	OA	1	ATP	O6	1	0.246	15.9994	7	OA	1	ATP	O6	1	-0.781970	15.9994
8	P	1	ATP	P2	1	1.081	30.9738	8	P	1	ATP	P2	1	1.666306	30.9738
9	OA	1	ATP	O11	1	-0.256	15.9994	9	OA	1	ATP	O11	1	-0.709606	15.9994
10	H	1	ATP	H11	1	0.001	1.0080	10	H	1	ATP	H11	1	0.430751	1.0080
11	OM	1	ATP	O5	2	0.000	15.9994	11	OM	1	ATP	O5	2	-0.656411	15.9994
12	OA	1	ATP	O4	3	-0.191	15.9994	12	OA	1	ATP	O4	3	-0.836197	15.9994
13	P	1	ATP	P1	3	1.389	30.9738	13	P	1	ATP	P1	3	1.661303	30.9738
14	OA	1	ATP	O10	3	-0.199	15.9994	14	OA	1	ATP	O10	3	-0.668092	15.9994
15	H	1	ATP	H93	3	0.001	1.0080	15	H	1	ATP	H93	3	0.410779	1.0080
16	OM	1	ATP	O3	4	-0.177	15.9994	16	OM	1	ATP	O3	4	-0.641581	15.9994
17	OA	1	ATP	O2	4	-0.289	15.9994	17	OA	1	ATP	O2	4	-0.604805	15.9994
18	CH2	1	ATP	C10	4	-0.062	12.0110	18	CH2	1	ATP	C10	4	0.301881	12.0110
19	CH1	1	ATP	C9	4	0.093	12.0110	19	CH1	1	ATP	C9	4	0.289979	12.0110
20	OA	1	ATP	O1	4	-0.289	15.9994	20	OA	1	ATP	O1	4	-0.515384	15.9994
21	CH1	1	ATP	C8	4	0.024	12.0110	21	CH1	1	ATP	C8	4	0.189925	12.0110
22	OA	1	ATP	O8	4	-0.301	15.9994	22	OA	1	ATP	O8	4	-0.558061	15.9994
23	H	1	ATP	H82	4	0.001	1.0080	23	H	1	ATP	H82	4	0.358163	1.0080
24	CH1	1	ATP	C7	5	0.047	12.0110	24	CH1	1	ATP	C7	5	0.186587	12.0110
25	OA	1	ATP	O9	5	0.261	15.9994	25	OA	1	ATP	O9	5	-0.541491	15.9994
26	H	1	ATP	H92	5	0.001	1.0080	26	H	1	ATP	H92	5	0.370706	1.0080
27	CH1	1	ATP	C6	5	0.126	12.0110	27	CH1	1	ATP	C6	5	0.578117	12.0110
28	NR	1	ATP	N3	5	0.169	14.0067	28	NR	1	ATP	N3	5	-0.804205	14.0067
29	CR1	1	ATP	C5	5	-0.059	12.0110	29	CR1	1	ATP	C5	5	0.257766	12.0110
30	HC	1	ATP	H51	5	-0.023	1.0080	30	HC	1	ATP	H51	5	0.276650	1.0080
31	NR	1	ATP	N4	6	-0.499	14.0067	31	NR	1	ATP	N4	6	-0.572949	14.0067
32	C	1	ATP	C3	6	0.096	12.0110	32	C	1	ATP	C3	6	0.176370	12.0110
33	C	1	ATP	C4	6	0.247	12.0110	33	C	1	ATP	C4	6	0.666733	12.0110
34	NR	1	ATP	N2	6	-0.512	14.0067	34	NR	1	ATP	N2	6	-0.611459	14.0067
35	CR1	1	ATP	C1	6	-0.048	12.0110	35	CR1	1	ATP	C1	6	0.210905	12.0110
36	HC	1	ATP	H1	6	-0.019	1.0080	36	HC	1	ATP	H1	6	0.220957	1.0080
37	NR	1	ATP	N1	6	-0.512	14.0067	37	NR	1	ATP	N1	6	-0.605878	14.0067
38	C	1	ATP	C2	6	0.247	12.0110	38	C	1	ATP	C2	6	0.640460	12.0110
39	NT	1	ATP	N5	7	0.031	14.0270	39	NT	1	ATP	N5	7	-0.794455	14.0270
40	H	1	ATP	H53	7	-0.016	1.0080	40	H	1	ATP	H53	7	0.327604	1.0080
41	H	1	ATP	H52	7	-0.015	1.0080	41	H	1	ATP	H52	7	0.336786	1.0080

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

FIGURE 2: Structures of some molecules tested with ATP adjuster 1.0.

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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