Howto prepare residues with RESP charges fitting for polarizable force fields in Amber 8

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This howto explains how you can prepare a residue with RESP charges fitting for polarizable force field simulations in Amber8. It takes into account corrections introduced by Cieplak and coworkers.

I. INTRODUCTION

This howto explains how you can prepare a residue with RESP charges fitting for polarizable force field simulations in Amber8. The procedure takes into account self-polarizability of molecule. It is based is based on :

- P. Cieplak, J. Caldwell, P. Kollman, J. Comput. Chem. 22 (2001) 1048.

- Ulf Ryde, How to run RESP calculation, http://www.teokem.lu.se/ ulf/Methods/resp.html

The latter document contains a very good and complete recipe for RESP fitting, however it requires one external program ('chengepot') to complete fitting procedure.

II. PREREQUISITIES

The procedure described here requires:

- Gaussian quantum-chemical package (or other program able to optimize your molecular structure and to produce ESP charges)

- Antechamber (part of Amber package)

- Sander (Amber's molecular dynamics program)

During the preparation of residues for non-polarizable simulations in Amber it is widely accepted to use HF/6-31G* to optimize geometry of desired molecule and get the charges distribution. It is known that at this level of quantum calculations the dipole moments are overestimated. However, in the molecular dynamics simulations with non-polarizable force field the exclusion of polarizability underestimates the dipole moments. Therefore it

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is accepted to balance this underestimation by the overestimated dipoles from Hartree-Fock calculations. In case of the polarizable force field simulations the polarizability is taken into account during calculations of the correct values of dipole moments. Therefore more sophisticated quantum methods, without the overestimation of dipoles, should be used. Usually it is either MP2 or DFT/B3LYP level of theory (with either cc-pvDZ or cc-pvTZ basis set). These methods do not overestimate dipole moments. However, as Cieplak and coworkerd showed, such procedure do not take under account self-polarization of molecule therefore the usage of residues prepared in this way leads to the incorrect intramolecular interaction energies.

The procedure presented here requires PDB file describing the structure of your molecule. The stucture can be unoptimized.

1. Use Antechamber to prepare Gaussian input file (based on your PDB file, eg. yyy.pdb):

```
antechamber -fi pdb -fo gcrt -i yyy.pdb \\
    -o yyy.inp -pf y
```

Additional options '-m' and '-nc' can be used to specify the multiplicity and the net charge of your molecule.

2. Edit the produced Gaussian input file entering desired calculation method and basis set and changing default options for charges analysis. Example line for B3LYP/cc-pvDZ calculations is shown here:

```
#b3lyp/cc-pvDZ SCF=Tight Test Pop=MK \\
    IOp(6/33=2,6/41=10,6/42=10) Opt nosymm
```

You can replace the method by MP2 or change basis set to cc-pvTZ but do not change other parameters unless you know what you are doing. Further information can be found in Ryde's document. See also the warning in step 4.

3. Run Gaussian to obtain an optimize structure and charge populations:

```
g03 < yyy.inp > yyy.gout
```

4. Now we need Antechamber to generate some files:

```
$antechamber -fi gout -fo prepi \\
  -i yyy.gout -o yyy.prepi \\
  -c resp -at gaff -rn yyy
```

In option '-rn' you should give three-letter symbol of the new residue (do not use capital letters). If you are not using GAFF force field set '-at amber'.

Warning! It can happen that for larger molecules the number of points in ESP file is too big (you will see a warning message generated by antechamber, then generated prepi file contains only dummy atoms and NEWPDB.PDB file is empty). In that case you have to go back to step 2 and decrease $6/42=10$ argument to $6/42=8$ or even $6/42=6$ (see Ryde's document). Sometimes you have to additionally decrease $6/41=10$ from 10 to either 8, 6 or 4. The minimal reasonable choice is $6/42=6$ and $6/41=4$. Sometimes it also happens that Antechamber cannot recognize at all atoms in your molecule and produces PREPI file with dummy atoms only. This may be solved by running a single-point calculation in Gaussian with optimized atomic coordinates (taken from the previous optimization run). And the output of this single-point run should be treated by Antechamber correctly.

5. You should check if the PREPI file generated by Antechamber correctly describes your molecule. Use 'xleap' program (part of the Amber package) to load and view PREPI file entering in 'xleap' the following commands:

```
> loadAmberPrep yyy.prepi
> edit yyy
```

Then select 'Display->Names' from the menu and inspect the displayed molecule checking if all atoms are placed and connected correctly.

6. We will need an ESP file generated by Antechamber as quantum mechanics ESP. Therefore:

```
$cp ANTECHAMBER.ESP esp.dat
```

The esp.dat file can be created without Antechamber but with espgen: ($espgen -i xxx.gout -i esp.dat). However, these two procedures give the same results and we will use other Antechamber's output files as well, so Antechamber is a good choice here).

7. We will also use Antechamber's resp input file. Therefore:

```
$cp ANTECHAMBER_RESP1.IN resp.in
```

8. Edit resp.in:

   (a) In 'cntrl' section set:
       - nmol = 1 (one molecule is described)
       - ihfree = 1 (hydrogen atoms not restrained)
       - qwt = 0.0000 (we are no fitting yet)
       - iqopt = 1 (reset initial charges and produce a new ones)

   (b) Take a look at last section. First line contains total charge and number of atoms. Each next line contains atomic number and integer controling resp fitting. All these integers should be now set to zero (as far as you don't have two or more atoms for which identical charges should be generated, if so set the integers for second, third etc. of them to n, where n is the number of first atom in the group).

9. Run resp program to retrieve charges values from ESP file:

```
$resp -O -i resp.in -o resp.out -e esp.dat
```

In the 'quot' file there are atomic charges extracted from the ESP file. The same values can be found in the 'resp.out' file, in section "Point Charges Before and After Optimization" in column q(opt) and in Gaussian optimization output file in section "Charges from ESP fit" (but you would have to find the last occurence of this section in this Gaussian file).

10. Edit atomic charges in 'yyy.prepi' file (last column for each atom), set atomic charges according to values from 'qout' file (or. easier. from 'resp.out'). Make sure the atom order in 'resp.out' file (check atomic numbers from the second column in the "Point Charges Before and After Optimization" section) is the same as in the 'yyy.prepi' file. If not, note the order of atoms in 'yyy.prepi', then reorder atoms in your original 'yyy.inp' input file to get the same order, and then start Gaussian again (i.e. repeat this procedure again starting from step 3).

11. If you are preparing the residue using GAFF force field, you have to check if there are missing parameters for your molecule. Therefore run:

```
$parmchk -f prepi -i yyy.prepi \\
  -o yyy.frcmod \\
  -p $AMBERHOME/dat/leap/parm/gaff.dat
```

This will generate 'yyy.frcmod' file. Look at it and see if there are missing parameters (if in each section there are only blank lines, all parameters were found in GAFF). In most cases parmchk suggests some values for missing parameters. Check them, if they look reasonable, you can just live them there. We will use the 'yyy.frcmod' file later.

12. We will use 'tleap' program (part of Amber package) to prepare input files for a test Sander run. First, you need the PDB file generated by Antechamber for optimized structure.

    ```
    $cp NEWPDB.PDB yyy_opt.pdb
    ```

    You have to remove values of atomic charges for atoms. Remove last column in the 'yyy_opt.pdb' file (only 3 columns of real numbers should left there). These charges are produced by an automatic resp fitting procedure and are not correct.

13. Run tleap:

    ```
    $tleap -s -f leaprc.gaff
    ```

    (in you want to use other force field than GAFF, use other '-f' option's value, for example '-f leaprc.ff02').

14. Run the following commands into tleap:

    ```
    > loadamberparams yyy.frcmod
    > loadAmberPrep yyy.prepi
    > model = loadpdb yyy_opt.pdb
    > check model
    > saveamberparmpol model yyy.prmtop yyy.prmcrd
    > quit
    ```

    The first command loads frcmod file for missing parameters of our molecule. Therefore 'check model' command should show no missing parameters.

    Check if tleap did not change atoms order (take a look at the atom symbols in the 'PRMTOP' file in the section 'FLAG ATOM_NAME').

    Now the 'yyy.prmtop' file contains parameters derived using ESP from Gaussian output and not calculated by an automatic Antechamber's resp fitting.

15. Prepare sander input file ('sander.in'). It should contain:

    ```
     Title line
      &cntrl
        irest=0, ntx=1,
        imin=1, maxcyc=1,
    ```

    ```
        ntc=1, ntf=1,
        cut=999.0,
        ntpr=100, ntwx=0, ntwv=0, ntwe=0,
        ipol=1, iesp=1,
        igb=0, ntb=0,
        scnb=2.0, scee=1.2
      &end
      &ewald
        indmeth=1
      &end
    ```

    Remember, sections tags, eg. '&cntrl', must be placed in the input file starting from 2nd column. The undocumented parameter 'iesp=1' forces Sander to use 'esp.dat' file and to write out two files: 'esp.induced' and 'esp.qm-induced' (second one containing esp_qm-esp_induced_dipole).

16. Run Sander:

    ```
    $sander -O -i sander.in -o sander.out \\
            -p yyy.prmtop -c yyy.prmcrd
    ```

17. Now we will iterate to get corrected charges. First we have to prepare a new resp input file:

    ```
    $cp resp.in resp_first_stage.in
    ```

18. Edit 'resp_first_stage.in':

    (a) in 'cntrl' section set:
        - nmol = 1 (one molecule)
        - ihfree = 1 (hydrogen atoms not restrained)
        - qwt = 0.0005 (now we want to make fitting)
        - iqopt = 2 (now we want resp to read initial charges from '-q qin' file)

    (b) Take a look at last section. First line contains total charge and number of atoms. Each next line contains atomic number and integer controling resp fitting. All these integers should be now set to zero (as far as you don't have two or more atoms for which identical charges should be generated, if so set the integers for second, third etc. of them to n, where n is the number of first atom in the group).

19. Copy old qout file to qin:

    ```
    $cp qout qin1
    ```

20. Run resp fitting:

```
$resp -O -i resp_first_stage.in \\
  -o resp2.out -q qin1 -t qout2 \\
  -e esp.qm-induced
```

21. Take a look at 'resp2.out', wheter charges are changed: q(init) vs. q(opt). If so, the repeating of the fitting is needed (see next steps).

22. Prepare tlep command file 'tleap.cmd' with the following lines:

```
logFile tleap.log
source leaprc.gaff
loadamberparams yyy.frcmod
loadAmberPrep yyy.prepi
model = loadpdb yyy_opt.pdb
check model
saveamberparmpol model yyy.prmtop yyy.prmcrd
quit
```

23. Start the repeating procedure:

    (a) Edit 'yyy.prepi' (like in step 10) entering corrected values for charges taken from 'qout2' file (or, easier, from 'resp2.out').

    (b) Run tleap:

    ```
    $tleap -s -f tleap.cmd
    ```

    (c) Run Sander

    ```
    $sander -O -i sander.in -o sander.out \\
      -p yyy.prmtop -c yyy.prmcrd
    ```

    (d) Prepare input file with charges for resp (base on the previous values):

    ```
    $cp quot2 qin2
    ```

    (e) Run resp:

    ```
    $resp -O -i resp_first_stage.in \\
      -o resp3.out -q qin2 -t qout3 \\
      -e esp.qm-induced
    ```

    (f) Take a look at 'resp3.out' file wheter charges are changed: q(init) vs. q(opt). If so, repeat fitting, starting from step 23a but changing number of iteration in filenames in step 23a, 23d, 23e and 23f.

24. If in your molecule there are polar hydrogens bound to the same atoms, you may want to constrain them to have the same charge and run resp once more (eg. like in step 23e but only once now). Then copy the corrected charge values to yyy.prepi file.

25. If in your molecule there are carbons with more than one hydrogen, fix the charges for all atoms except of these carbons and 'their' hydrogens (i.e. edit resp_first_stage.in putting -1 values in the second column for all fixed-charge atoms), constrain charges on these hydrogens to be equal, change qwt to qwt=0.01 in resp input file and run resp once more (but only once). Then copy the corrected charge values to yyy.prepi file.

26. Already finished! Insert charges from last respXX.out or qoutXX to 'yyy.prepi' Check if the order of atoms is the same! This 'yyy.prepi' containes partial charges corrected to the self-polarization and can be used (together with 'yyy.frcmod' if non-standard parameters were needed, see step 11).