

Force field generation for a bioinorganic complex: the 'broken symmetry' approach

Tutorial by:

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This tutorial is related to characterizing the spin state of a bioinorganic complex with metal centers, which are antiferromagnetically coupled using the broken symmetry approach.^[1-3] Once fully identified the minimum obtained after geometry optimization is involved in force field generation.

The quantum mechanics (QM) Gaussian program version 2009 is selected during the input submission procedure using the web interface: one has to register and use her/his private account: See <http://q4md-forcefieldtools.org/REDServer-Development/faq.php#3>

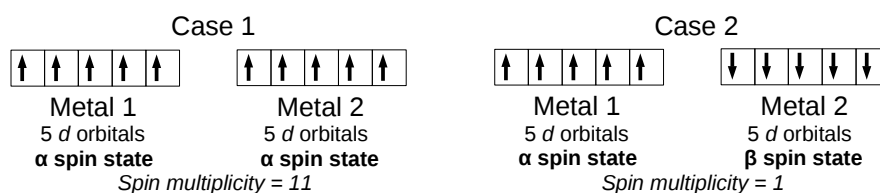
1- General pieces of information

Read first the tutorial related to the Complex mode.

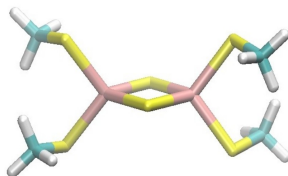
<http://q4md-forcefieldtools.org/Tutorial/Tutorial-4-demo21.pdf>

Metal centers, which are antiferromagnetically coupled

In the broken symmetry approach two metal centers with an antiferromagnetic coupling are represented with spins in the α and β -states. A lower energy value is obtained for the singlet (Case 2, figure below) compared to the corresponding multiplet (Case 1, figure below). For this purpose the use of molecular fragments, within the Gaussian 2009 program was implemented in the PyRED program. This approach allows the control of the input spin states for the different regions of the complex, and specifying the α and β -states.



Comparison between the 11-et (Case 1) and singlet (Case 2) spin states for a bioinorganic complex containing two antiferromagnetically coupled Fe(III) ions (see a corresponding structure below).



Ferric iron atoms are represented in pink color, sulfur atoms in yellow and carbon atoms in cyan. The two antiferromagnetically coupled Fe(III) atoms are separated by a distance of ~ 3 angstroms.

2- Generate the force field for the multiplet

Let us first prepare a *Project.config* and a *System.config* files to characterize the multiplet state using the Complex mode (the bioinorganic complex reported in the page 1 of this tutorial is used as an example). Simply directly apply the tutorial related to using the Complex mode to generate a force field for a bioinorganic complex (see <http://q4md-forcefieldtools.org/Tutorial/Tutorial-4-demo21.pdf>).

The *Project.config* file:

```
# No intra-mcc is requested; one is interested here in characterizing the
# spin state of the molecule; not in inserting the corresponding fragment
# within the protein (to be inserted back within a protein the  $\alpha$ -carbon
# and three hydrogen atoms could be added to design a capping group for
# each cysteine residue in the thiolate form).
# No geometry constraint is needed for geometry optimization in this case
MOLECULE1-TITLE      = 11-et_di_Fe(III)_complex
# The total charge and spin multiplicity of the complex
MOLECULE1-SPINMULT   = 11 # There are 10 single electrons in the  $\alpha$ -state
MOLECULE1-TOTCHARGE  = -2 # i. e.  $2*3 + 2*(-2) + 4*(-1)$ 
MOLECULE1-ATMREORDR  = OFF
MOLECULE1-CALCONNECT = ON
```

The *System.config* file:

```
# To save some cpu time
OPT_Calc      = On2
MEPCHR_Calc   = On
MOD_GAUSSIAN_JOB = Complex
Freq_Calc     = Off
# Let us first use two stage charge fitting instead of one or three
CHR_TYP       = RESP-X1
# The cluster on which R.E.D. Server Dev. is installed can handle such a
# triple- $\zeta$  basis set for this molecular size - just be patient.
METHOD_OPTCALC = OPBE
BASSET_OPTCALC = cc-pVTZ
METHOD_MEPCALC = OPBE
BASSET_MEPCALC = cc-pVTZ
```

Create the archive file with the PDB input file, and upload that archive to run a PyRED job.

3- Generate the force field for the singlet

The use of molecular fragments, within the Gaussian 2009 program allows the definition of input spin states for different regions of the complex, and in the present case specifying the α and β -states of the metal centers. This approach can also be used to input different spin multiplicities of different atoms, which can lead to an energy minimum if the provided input electronic configuration along with the spin state corresponds to a correct hypothesis.

Let us prepare a *Project.config* and a *System.config* files to characterize the singlet state based on the broken symmetry approach using the Complex mode (the bioinorganic complex reported in the page 1 of this tutorial is used as an example).

It is important to underline here that the singlet generated using the broken symmetry is different than the 'regular' singlet that would result in an unrealistic electronic state.

The *Project.config* file:

```
MOLECULE1-TITLE      = Singlet_di_Fe(III)_complex__broken symmetry
# Define the spin multiplicity and total charge of the whole molecule
MOLECULE1-SPINMULT   = 1
MOLECULE1-TOTCHARGE  = -2
MOLECULE1-ATMREORDR  = OFF
MOLECULE1-CALCONNECT = ON
# Now let us define the fragments of the different regions of the molecule
#   to specify that one Fe(III) is in the  $\alpha$ -state and the other in the  $\beta$ -state
# ALL THE ATOMS OF THE MOLECULE HAVE TO BELONG TO A FRAGMENT
# The first atom of the molecule is the Fe(III) in the  $\alpha$ -state
#   the total charge and spin multiplicity of this atom equals 3 and 6 ( $\alpha$ -state)
MOLECULE1-FRGBRKSVM = 3 6 | 1
# The second atom of the molecule is the Fe(III) in the  $\beta$ -state
#   the total charge and spin multiplicity equal 3 and -6 ( $\beta$ -state)
MOLECULE1-FRGBRKSVM = 3 -6 | 2
# The third atom of the molecule is the first S2- atom
#   the total charge and spin multiplicity of this atom equal -2 and 1 (singlet)
MOLECULE1-FRGBRKSVM = -2 1 | 3
# The fourth atom of the molecule is the second S2- atom
MOLECULE1-FRGBRKSVM = -2 1 | 4
# The four last fragments are related to the four methylthiolate groups
#   the total charge and spin multiplicity of this atom group equal -1 and 1
MOLECULE1-FRGBRKSVM = -1 1 | 5 6 7 8 9
MOLECULE1-FRGBRKSVM = -1 1 | 10 11 12 13 14
MOLECULE1-FRGBRKSVM = -1 1 | 15 16 17 18 19
MOLECULE1-FRGBRKSVM = -1 1 | 20 21 22 23 24
```

The *System.config* file is identical to that constructed when generating the force field for the multiplet.

Create the archive file with the PDB input file, and upload that archive to run a PyRED job.

4- Compare the two PyRED jobs

A lower energy value is found for the singlet obtained with the broken symmetry approach compared to the multiplet.

RESP charge values are affected by the broken symmetry approach.

Specific force field parameters can be provided in the *frmod.user* file in a second job by using the 'Re_Fit' mode (see the tutorial at <http://q4md-forcefieldtools.org/Tutorial/Tutorial-4-demo1.pdf>).

5- Using the force field generated by PyRED within the AmberTools

The force field generated by PyRED can be found in the following sub-directories:

- The *force field libraries* are available in the *MO1_m1* or in the *MO1_MM* sub-directory (the *mol3* file format is the default; see <http://q4md-forcefieldtools.org/Tutorial/leap-mol3.php>) if the number of PDB input file(s) equals one, or is strictly greater than one, respectively.
- The *force field parameter files* are available in the *Data-Default-Proj* sub-directory.

Three files are generated:

- the *frcmod.known* file lists the known force field parameters determined by PyRED based on the atom types assigned to the input molecules,
- the *frcmod.corespondence* file lists the force field parameters, which were determined by analogy to the existing ones,
- the *frcmod.unknown* file lists the force field parameters, which remains unknown.

The 'Re_Fit' mode can be used to provide a *frcmod.user* input file in agreement with the atom types assigned by PyRED, or after update of these atom types (see the MOLECULE1-ATMTYPE keyword):

See <http://q4md-forcefieldtools.org/Tutorial/Tutorial-4-demo1.pdf>

- The *leaprc.q4mdfft* script available in the *Data-Default-Proj* sub-directory allows the direct use of the force field generated by PyRED within the LEaP program (see the Amber tools at <http://ambermd.org/#AmberTools>):

```
# Extract the PXXXX.tar.bz2 R.E.D. Server Dev./PyRED job after download
tar -jxvf PXXXX.tar.bz2
cd PXXXX/Data-R.E.D.Server/Data-Default-Proj
# Edit to update the LEaP script and extend its use
gedit leaprc.q4mdfft &
# Run the LEaP program:
# see http://q4md-forcefieldtools.org/REDServer-Development/images/PyRED.gif
xleap -f leaprc.q4mdfft
```

References

- [1] L. Noodleman, J. G. Norman Jr, *J. Chem. Phys.* 1979, 70, 4903.
- [2] L. Noodleman, *J. Chem. Phys.* 1981, 74, 5737.
- [3] L. Noodleman, E. R. Davidson, *Chem. Phys.* 1986, 109, 131.

Last update of this tutorial: November 30th, 2014.