Supporting Information

MCPB.py: A Python Based Metal Center Parameter Builder

*Pengfei Li and Kenneth M. Merz, Jr.**

AUTHOR ADDRESS

Department of Chemistry,

Department of Biochemistry and Molecular Biology

Michigan State University,

East Lansing, Michigan 48824-1322

E-mail: kmerz1@gmail.com

Table of Contents

Full References of AMBER 2015 and Gaussian 03

AMBER 2015

Case, D. A.; Berryman, J. T.; Betz, R. M.; Cerutti, D. S.; Cheatham III, T. E.; Darden, T. A.; Duke, R. E.; Giese, T. J.; Gohlke, H.; Goetz, A. W.; Homeyer, N.; Izadi, S.; Janowski, P.; Kaus, J.; Kovalenko, A.; Lee, T. S.; LeGrand, S.; Li, P.; Luchko, T.; Luo, R.; Madej, B.; Merz Jr, K. M.; Monard, G.; Needham, P.; Nguyen, H.; Nguyen, H. T.; Omelyan, I.; Onufriev, A.; Roe, D. R.; Roitberg, A.; Salomon-Ferrer, R.; Simmerling, C. L.; Smith, W.; Swails, J.; Walker, R. C.; Wang, J.; Wolf, R. M.; Wu, X.; York, D. M.; Kollman, P. A. *AMBER 2015*, University of California, San Francisco: 2015.

Gaussian 03

Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; J. A. Montgomery, J.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision E. 01*, Gaussian Inc.: Wallingford, CT, 2004.

Examples

In what follows we delineate two sample examples. Yet one more parameterization example for 1 zinc ion, 3 HIS residues and 1 MNS ligand in the metal site can be found as an AMBER tutorial: http://ambermd.org/tutorials/advanced/tutorial20/mcpbpy.htm.

Example 1

Our first example is from PDB entry: 1E67, which is a zinc containing azurin protein from Pseudomonas aeruginosa which has a resolution of 2.14 Å.[1] The protein is a tetramer where each monomer contains 128 amino acid residues, has a metal site with four residues bound to the central zinc ion: two HIS residues and one CYS residue which have sidechain atoms coordinated to the zinc ion, along with a GLY residue which has its backbone oxygen bound to the zinc ion. Here we only treat chain A (see Figure S1) as an example– the generated parameters are applicable to the other chains. First we prepare the system by using H++ web server[2] to add hydrogen atoms (note: users need to add the zinc ion into the final PDB file and modify the residues which bind to the zinc ion manually because to H++ will delete the metal ions and water molecules, and ignore them when adding the hydrogen atoms). Following this we use the following input file to generate the necessary files for small, standard, and large models.

In order to keep the example straightforward there are only a few variables in the MCPB.py input file (see Figure S2). For more complicated cases users can consult the

manual for the details concerning all of the available options. Here we specify the PDB file name we are using (after the original_pdb variable name), the group name of the system (the default group name is "MOL" while here it is 1E67), the bond cut off value between the ligand and metal ion (here it is 2.7 Å and the default is 2.8 - sometimes adjustment of this value is needed to specify which residue is bound to the metal ion), the atom IDs of the central ions in the metal site of the PDB file (here we only have one number because it is a single center metal site), the mol2 file of the zinc ion in which we specify its atom type as "ZN" with a charge of 2.00 for the zinc residue (with residue name as "ZN" for consistency with the PDB file, which gives the zinc ion a residue name "ZN" and atom name "ZN").

Figure S3 lists the commands used during the MCPB.py modeling procedure. First we use the command: *"MCPB.py –i 1E67.in –s 1"*, which generates the small, standard and large models of the ion metal coordination sphere. In the fingerprint file for the standard model (see the files supplied in SI), there is atom type specification for each atom in the residues bound to the metal site (*i.e.,* residues which are bound to central metal ion), and the linkage information between metal ion and its ligating atoms. The third and fifth columns of atom information show the original and new atom types, respectively. The –s 1 flag tells the program to assign the atom types for the central metal ion and the metal bound atoms automatically (importantly each one is assigned differently). Users can change the atom types and/or linkage information manually based on their own preferences (*e.g.* by treating some of the bound atoms identically).

With all the files in hand we then use the small model to calculate the force constants and the large model to calculate the Merz-Kollman charges[3] by using Gaussian03,[4] Gaussian09[5] or GAMESS-US.[6] By default MCPB.py treats the output files as being from Gaussian03. If Gaussian09 or GAMESS-US is being used, users need to add "software_version g09" or "software_version gms" as a line in the input file before performing the second and third steps. Users can also modify the QM input files based on their own needs, *i.e.* changing the number of CPUs, memory usage, level of theory *etc.* Here we used the B3LYP/6-31G* level of theory to perform the Gaussian calculations of example 1.

For the force constant determination there are two substeps: the first substep is QM geometry optimization (line 2 in Figure S3) and the second substep (line 3 in Figure S3) is the evaluation of the Cartesian Hessian matrix. The Cartesian Hessian matrix, which will be used by the Seminario method to obtain force constants, was stored by Gaussian03 in the Gaussian binary chk file (the chk file should be converted to a fchk file using the *formchk* command). Alternatively, this matrix could be in a GAMESS-US log file (if using GAMESS-US) after the second QM calculation substep. The internal force constants (based on the Z-matrix method) are also stored in the Gaussian log file, while Z-matrix method is not supported using the GAMESS-US software in the current version of MCPB.py. For the Merz-Kollman population analysis of the large model, there is only one calculation performed (line 5 in Figure 3), in which the van der Waals (VDW) radii for metal ions are taken from the recent work of Li *et al*.[7]

After performing the QM calculations we can use *"MCPB.py –i 1E67.in –s 2"* to generate the final force constant parameters using the Seminario method. The resultant metal ion related bond and angle parameters have the "Created by Seminario method using MCPB.py" comment in the end of the line (see Figure S4). We observe see that the generated parameters are in a physically meaningful range: the bond and angle force constants are all lower than 100 (AMBER parameter files use the unit of kcal/mol•Å^2 for the bond force constants and kcal/mol•Rad^2 for the angle force constants). Following this step we use the *"MCPB.py –i 1E67.in –s 3"* command to perform a RESP charge fit for the large model and generate the mol2 files for the metal site residues. From the RESP fit we obtain a charge on the zinc ion of ~0.5 e, which represents a strong electron transfer effect from the ligands to the zinc ion inside the complex. This is consistent with previous work from Merz et al.,[8] which observed that refitting the charge of the metal site, besides simply assigning a +2 charge to zinc ion, is needed to accurately mimic the metal site charge distribution. Finally, we use the *"MCPB.py –I 1E67.in –s 4"* command to generate the PDB file with the renamed metal site residues and the leap source file for the system. Afterwards, the topology and coordinate files can be created using the *"tleap –s –f 1E67_tleap.in > 1E67_tleap.out"* command. With all files in hand we can perform minimization and MD simulations using AMBER, or transfer the topology and coordinate files to another format if desired (see Figure 1 in the main text). In this example, we used pmemd.MPI from AMBER 14[9] to perform energy minimization, the MD heating up procedure and subsequent equilibration. For the production MD simulations pmemd.cuda[10, 11] from AMBER 14[9] was used.

Except the parameters obtained from MCPB.py, we used the AMBER ff14SB force field to model the protein system. The protein structure was solvated in a rectangular TIP3P[12] water box (with size ~67Å×57 Å ×65 Å and 5549 waters) with water molecule at least ~1.5 Å away from the protein surface. No ions were added because the system was neutral. Next four minimization steps were performed. 1000 steps of steepest descent minimization and 1000 steps of conjugated gradient minimization were performed for the first three stages. The first stage involved a 200 kcal/mol•Å^2 restraint on the protein system, the second stage used a 200 kcal/mol•Å^2 restraint on the heavy atoms in the protein system, while the third stage used a 200 kcal/mol•Å^2 restraint on the backbone N, CA, C atoms in the protein system. Finally, in the fourth stage of minimization no restraints were imposed for 2000 steps of steepest descent minimization followed by 3000 steps of conjugated gradient minimization. Next 1ns of thermalization was performed to heat the system from 0 K to 298.15 K in the NVT ensemble, followed by another 1 ns simulation to equilibrate the system at 298.15 K in the NVT ensemble. After this step a 1 ns simulation was carried at 298.15 K and 1 atmosphere of pressure in the NPT ensemble to correct the density of the system. Finally, 20 ns of production sampling was performed at 298.15 K in NVT ensemble with snapshots stored every 10 ps. In total, 2000 frames were collected for the final RMSD analyses. The Langevin algorithm was used to control the temperature with a collision frequency of 1.0 ps^{-1} while the Berendsen barostat[13] was employed to control the pressure with a relaxation time of 1.0 ps. SHAKE[14] was used to constrain the bonds between hydrogen and heavy atoms and a specific three-point algorithm[15] was used for the water molecules.

Figure S5 shows the RMSD values of the protein backbone atoms N, CA, C and the heavy atoms in the metal site over 2000 snapshots across 20 ns of sampling. The RMSD values of the heavy atoms in the metal site are fluctuating around 0.3 Å while the RMSD values of the whole protein backbone N, CA, C atoms are ~1.0 Å. These results indicate that the metal site structure was well conserved during the simulation, thereby, further validating the parameterization accomplished by MCPB.py.

Example 2

Os^{2+} complexes are attracting interest due to their special electronic properties.[16] Here we treat the $Os[(phen)_3]^{2+}$ system as an example to prove the ability of MCPB.py to parameterize an organometallic compound. In the present work we use the structure of the $Os[(phen)_3]^{2+}$ complex from residue 1 in the Cambridge Structural Database (CSD) entry: FAJYAR01 (see Figure S6), from the work of Demadis *et al*.[16] The content of the input file for MCPB.py to build the complex is shown in Figure S7. The commands used for processing the MCPB.py construction are shown in Figure S8.

We employed the B3LYP/SDD level of theory to do the quantum mechanical (QM) calculation. The VDW radius of Os^{2+} during the Merz-Kollman charge calculation was treated as 1.56 Å and was obtained from the VDW parameters for "Os6+6" atom type from the universal force field (UFF).[17] The final bond and angle parameters obtained are shown in Figure S9.

The molecular mechanics (MM) minimization and normal mode analysis was carried out using the nucleic acid builder (NAB) module in AmberTools15.[18] The minimization was performed in the gas phase with two steps with a cutoff of 100 Å. The first step used the conjugate gradient minimization algorithm. Its converge criteria was set to an RMS of the energy gradient of 5×10^{-5} kcal/mol with a maximum 20000 steps. The second step used the Newton-Raphson algorithm with a convergence criteria of 2×10^{-12} kcal/mol over 200 steps. Afterwards the normal mode analysis was performed.

We have calculated the RMSD values between each pair of CSD, QM optimized and MM optimized structures (see Table S1). We can see that in general the RMSD values are relative small (less than 0.4 Å). Note that the CSD structure is from a crystal, with two PF_6^- anions and 1/2 water molecule for each $Os[(phen)_3]^{2+}$ complex while the QM optimization and MM minimization were all performed in the gas phase for the independent Os complex.

We performed the linear fitting of the QM and MM calculated normal modes. The R^2 value of the fitting is ~0.99, which is reasonable. Meanwhile, we also compared the normal modes calculated based on QM and MM methods in Figure S10, with the normal mode numbers along the X axis, while the QM and MM calculated frequencies are on the Y axis. Generally the agreement is good with the exception of some medium (around 1500 cm^{-1}) and higher (around 3200 cm^{-1}) frequencies. This may due to the force constants of hydrogen containing bonds in GAFF, as shown in the work regarding parameterization of zinc complexes by Lin and Wang.[19] Lin and Wang also showed that

improvement could be obtained after tuning these parameters: Moreover, they noted that hydrogen containing bonds are usually constrained using SHAKE,[14] so there would only be a small impact if these parameters were fully optimized or not.

Tables and Figures

Table S1. The RMSD values between the CSD, QM optimized and MM minimized structures.[a]

	CSD structure	QM optimized	MM minimized
CSD structure	--	0.280(0.219)	0.377(0.327)
QM optimized	0.280(0.219)	--	0.201(0.193)
MM minimized	0.377(0.327)	0.201(0.193)	--

[a]Unit is Å. The value out of the bracket is for all atoms while the value inside the bracket is just for heavy atoms. The CSD structure is from the first residue in entry: FAJYAR01.

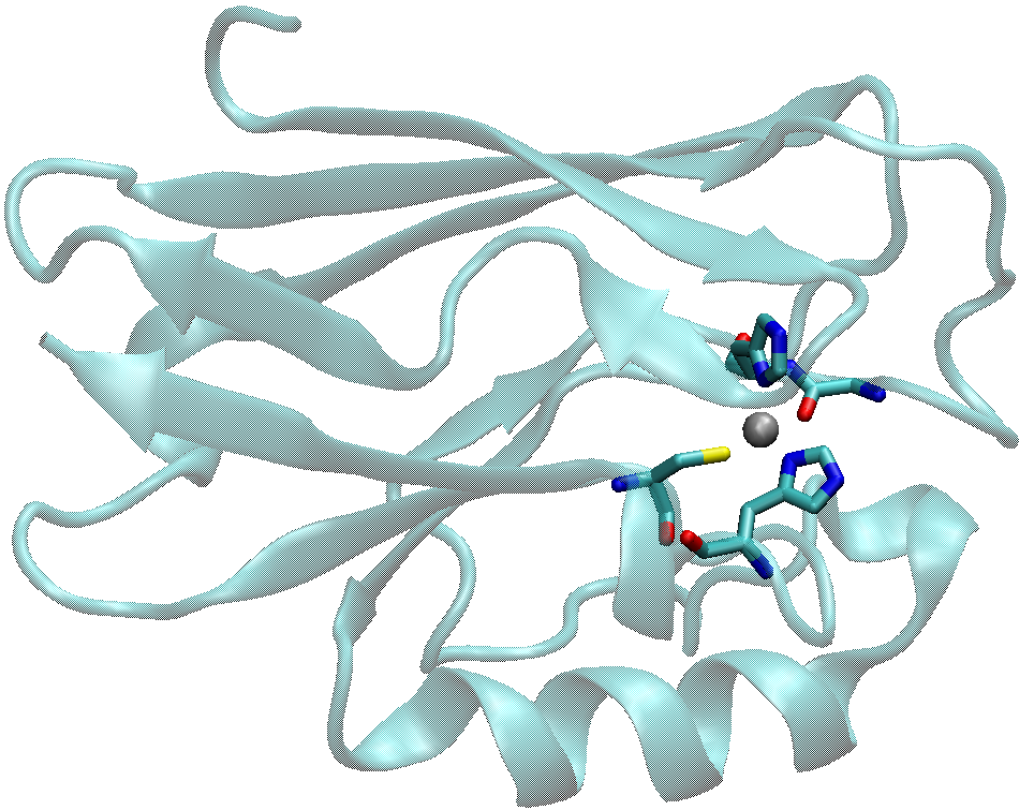

Figure S1. Structure of chain A from PDB entry 1E67 with the zinc ion represented by VDW sphere and the metal site residues indicated by sticks. This figure was made by VMD.[20]

```
original_pdb 1E67_fixed_H.pdb
group_name 1E67
cut_off 2.7
ion_ids 1931
ion_mol2files ZN.mol2
```

Figure S2. Input file content for the construction of the metal site found in chain A of PDB entry 1E67 using MCPB.py.

```
MCPB.py -i 1E67.in -s 1
g03 < 1E67_small_opt.com > 1E67_small_opt.log
g03 < 1E67_small_fc.com > 1E67_small_fc.log
formchk 1E67_small_opt.chk
g03 < 1E67_large_mk.com > 1E67_large_mk.log
MCPB.py -i 1E67.in -s 2
MCPB.py -i 1E67.in -s 3
MCPB.py -i 1E67.in -s 4
tleap -s -f 1E67_tleap.in > 1E67_tleap.out
```

Figure S3. Commands used for the construction of the metal site found in chain A of PDB entry 1E67 using MCPB.py. The second to the fifth lines are for QM calculations using Gaussian03, while the last line is to build the topology and coordinate files using tleap.

```
BOND
Y1-M1   27.1    2.0672      Created by Seminario method using MCPB.py
Y2-M1   61.8    2.0539      Created by Seminario method using MCPB.py
Y3-M1   96.5    2.2398      Created by Seminario method using MCPB.py
Y4-M1   70.6    2.0312      Created by Seminario method using MCPB.py
C -Y1  570.0    1.229       JCC,7,(1986),230; AA,CYT,GUA,THY,URA
CC-Y2  410.0    1.394       JCC,7,(1986),230; HIS
CC-Y4  410.0    1.394       JCC,7,(1986),230; HIS
CT-Y3  237.0    1.810       changed from 222.0 based on methanethiol nmodes
Y2-CR  488.0    1.335       JCC,7,(1986),230; HIS
Y4-CR  488.0    1.335       JCC,7,(1986),230; HIS

ANGL
C -Y1-M1    17.95     137.78    Created by Seminario method using MCPB.py
CC-Y2-M1    53.19     129.51    Created by Seminario method using MCPB.py
CC-Y4-M1    62.23     127.49    Created by Seminario method using MCPB.py
CT-Y3-M1    82.67     103.87    Created by Seminario method using MCPB.py
M1-Y2-CR    47.72     123.07    Created by Seminario method using MCPB.py
M1-Y4-CR    65.46     124.24    Created by Seminario method using MCPB.py
Y1-M1-Y2    35.60      93.07    Created by Seminario method using MCPB.py
Y1-M1-Y3    16.02     117.34    Created by Seminario method using MCPB.py
Y1-M1-Y4    41.15      94.09    Created by Seminario method using MCPB.py
Y2-M1-Y3    34.92     120.93    Created by Seminario method using MCPB.py
Y2-M1-Y4    32.58     107.73    Created by Seminario method using MCPB.py
Y3-M1-Y4    19.26     118.04    Created by Seminario method using MCPB.py
CC-Y2-CR    70.0      117.00    AA his
CC-Y4-CR    70.0      117.00    AA his
CT-CC-Y2    70.0      120.00    AA his
CT-CC-Y4    70.0      120.00    AA his
CW-CC-Y2    70.0      120.00    AA his
CW-CC-Y4    70.0      120.00    AA his
CX-C -Y1    80.0      120.40    (was CT-C-O)
CX-CT-Y3    50.0      108.60    AA cys (was CT-CT-SH)
N -C -Y1    80.0      122.90    AA general
Y2-CR-H5    50.0      120.00    AA his
Y2-CR-NA    70.0      120.00    AA his
Y3-CT-H1    50.0      109.50    AA cyx     changed based on NMA nmodes
Y4-CR-H5    50.0      120.00    AA his
Y4-CR-NA    70.0      120.00    AA his
```

Figure S4. Bond parameters (above) and angle parameters (below) for metal site chain A from the1E67 PDB structure. Here M1 is the atom type of the zinc ion, Y1, Y2, Y3, Y4 are the atom types for the four atoms bound to the zinc ion, which are the GLY45 backbone oxygen atom, the δ nitrogen atom in HIE46, the sidechain sulfur atom in CYM112 and the δ nitrogen atom in HIE117, respectively. Here HIE and CYM are "AMBER style" residue names: HIE means a HIS residue which has the ε nitrogen protonated, CYM indicates a CYS residue which is negatively charged (*i.e.* with a CH_2S^- sidechain group).

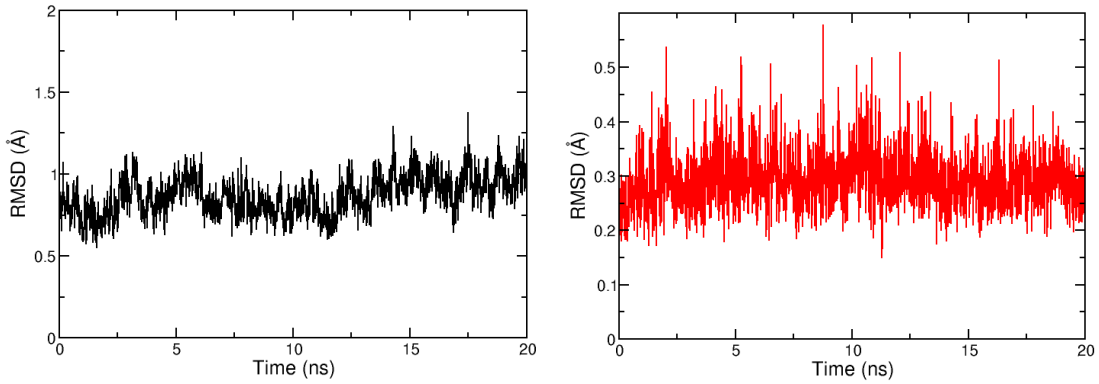

Figure S5. RMSD values of the protein backbone N, CA and C atoms (left) and the heavy atoms in the metal site (right) over 20 ns. The RMSD values were calculated using CPPTRAJ.[21]

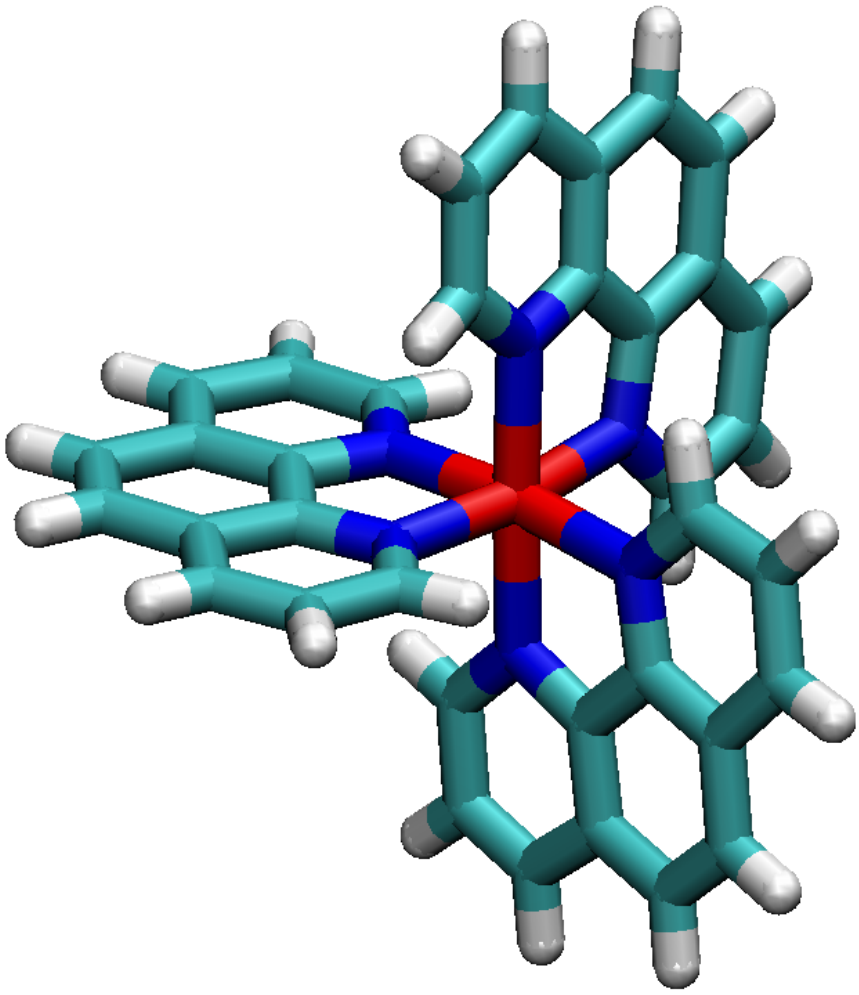

Figure S6. Structure of residue 1 from CSD entry FAJYAR01. This figure was made using VMD.[20]

```
original_pdb FAJYAR01.pdb
group_name FAJYAR01
ion_ids 1
ion_mol2files OS.mol2
naa_mol2files RES.mol2
frcmod_files RES.frcmod
```

Figure S7. Input file content for the construction of the metal site found in residue 1 of CSD entry FAJYAR01 using MCPB.py.

```
MCPB.py -i FAJYAR01.in -s 1
g03 < FAJYAR01_small_opt.com > FAJYAR01_small_opt.log
g03 < FAJYAR01_small_fc.com > FAJYAR01_small_fc.log
formchk FAJYAR01_small_opt.chk
g03 < FAJYAR01_large_mk.com > FAJYAR01_large_mk.log
MCPB.py -i FAJYAR01.in -s 2
MCPB.py -i FAJYAR01.in -s 3
MCPB.py -i FAJYAR01.in -s 4
tleap -s -f FAJYAR01_tleap.in > FAJYAR01_tleap.out
```

Figure S8. Commands used for the construction of the metal site found in residue 1 of CSD entry FAJYAR01 using MCPB.py. The second to the fifth lines are for QM calculations using Gaussian03, while the last line is to build the topology and coordinate files using tleap.

```
BOND
M1-Y1   80.2    2.1026      Created by Seminario method using MCPB.py
M1-Y2   76.1    2.1020      Created by Seminario method using MCPB.py
M1-Y3   81.4    2.1024      Created by Seminario method using MCPB.py
M1-Y4   78.6    2.1025      Created by Seminario method using MCPB.py
M1-Y5   76.4    2.1024      Created by Seminario method using MCPB.py
M1-Y6   77.5    2.1024      Created by Seminario method using MCPB.py
Y1-ca  483.1    1.3420       SOURCE3     104    0.0076
Y3-ca  483.1    1.3420       SOURCE3     104    0.0076
Y5-ca  483.1    1.3420       SOURCE3     104    0.0076
ca-Y2  483.1    1.3420       SOURCE3     104    0.0076
ca-Y4  483.1    1.3420       SOURCE3     104    0.0076
ca-Y6  483.1    1.3420       SOURCE3     104    0.0076

ANGL
M1-Y1-ca   144.27     121.08    Created by Seminario method using MCPB.py
M1-Y2-ca   144.88     121.08    Created by Seminario method using MCPB.py
M1-Y3-ca   146.06     121.08    Created by Seminario method using MCPB.py
M1-Y4-ca   145.17     121.08    Created by Seminario method using MCPB.py
M1-Y5-ca   142.46     121.08    Created by Seminario method using MCPB.py
M1-Y6-ca   151.58     121.08    Created by Seminario method using MCPB.py
Y2-M1-Y1   197.44      78.94    Created by Seminario method using MCPB.py
Y3-M1-Y1   153.76      96.01    Created by Seminario method using MCPB.py
Y3-M1-Y2   219.58     173.03    Created by Seminario method using MCPB.py
Y4-M1-Y1   140.45      89.31    Created by Seminario method using MCPB.py
Y4-M1-Y2   152.39      96.09    Created by Seminario method using MCPB.py
Y4-M1-Y3   200.41      78.93    Created by Seminario method using MCPB.py
Y5-M1-Y1   157.32      96.03    Created by Seminario method using MCPB.py
Y5-M1-Y2   138.66      89.37    Created by Seminario method using MCPB.py
Y5-M1-Y3   155.74      95.99    Created by Seminario method using MCPB.py
Y5-M1-Y4   220.28     173.01    Created by Seminario method using MCPB.py
Y6-M1-Y1   217.79     173.01    Created by Seminario method using MCPB.py
Y6-M1-Y2   147.77      96.04    Created by Seminario method using MCPB.py
Y6-M1-Y3   134.31      89.38    Created by Seminario method using MCPB.py
Y6-M1-Y4   152.07      96.10    Created by Seminario method using MCPB.py
Y6-M1-Y5   194.35      78.94    Created by Seminario method using MCPB.py
Y1-ca-ca   69.16      122.63    SOURCE3           83    1.1249
Y1-ca-h4   51.82      115.94    SOURCE3           52    0.7370
Y3-ca-ca   69.16      122.63    SOURCE3           83    1.1249
Y3-ca-h4   51.82      115.94    SOURCE3           52    0.7370
Y5-ca-ca   69.16      122.63    SOURCE3           83    1.1249
Y5-ca-h4   51.82      115.94    SOURCE3           52    0.7370
ca-Y1-ca   68.59      115.86    SOURCE3           46    1.1645
ca-Y2-ca   68.59      115.86    SOURCE3           46    1.1645
ca-Y3-ca   68.59      115.86    SOURCE3           46    1.1645
ca-Y4-ca   68.59      115.86    SOURCE3           46    1.1645
ca-Y5-ca   68.59      115.86    SOURCE3           46    1.1645
ca-Y6-ca   68.59      115.86    SOURCE3           46    1.1645
ca-ca-Y2   69.16      122.63    SOURCE3           83    1.1249
ca-ca-Y4   69.16      122.63    SOURCE3           83    1.1249
ca-ca-Y6   69.16      122.63    SOURCE3           83    1.1249
h4-ca-Y2   51.82      115.94    SOURCE3           52    0.7370
h4-ca-Y4   51.82      115.94    SOURCE3           52    0.7370
h4-ca-Y6   51.82      115.94    SOURCE3           52    0.7370
```

Figure S9. Bond parameters (above) and angle parameters (below) for the metal site of residue 1 from FAJYAR01. Here M1 is the atom type of the Os^{2+} ion, while Y1 to Y6 are the atom types for the six bound N atoms.

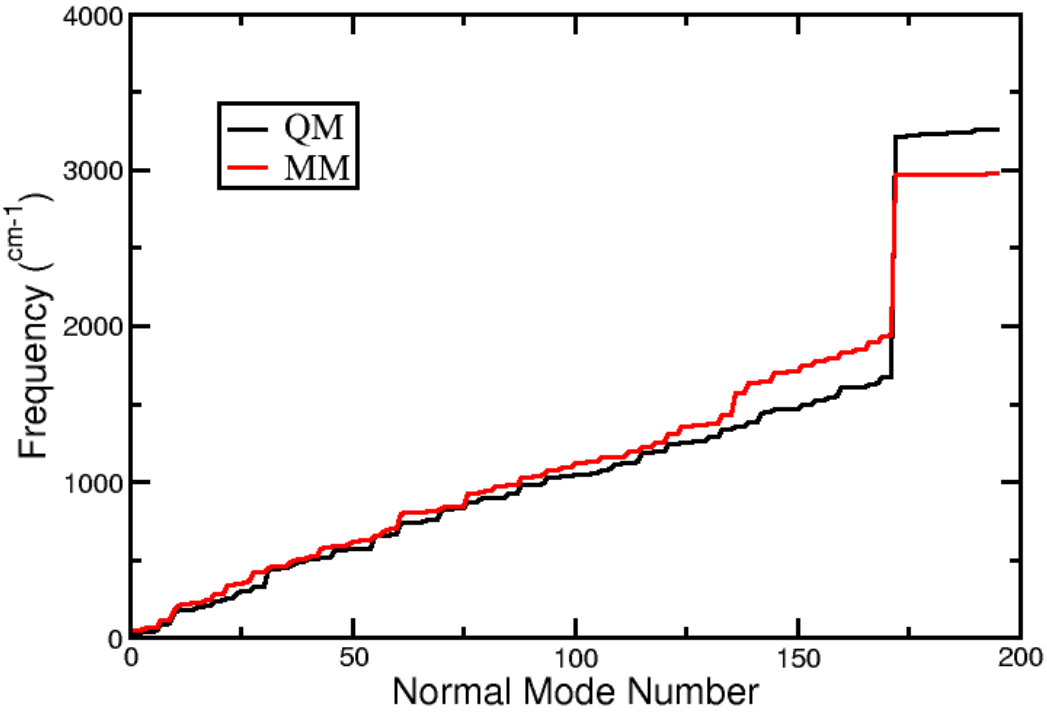

Figure S10. Comparison of QM and MM calculated normal modes.

References

1. Nar, H.; Huber, R.; Messerschmidt, A.; Filippou, A. C.; Barth, M.; Jaquinod, M.; van de Kamp, M.; Canters, G. W., Characterization and crystal structure of zinc azurin, a by-product of heterologous expression in Escherichia coli of Pseudomonas aeruginosa copper azurin. *Eur. J. Biochem.* **1992**, 205, 1123-1129.
2. Gordon, J. C.; Myers, J. B.; Folta, T.; Shoja, V.; Heath, L. S.; Onufriev, A., H++: a server for estimating pKas and adding missing hydrogens to macromolecules. *Nucleic Acids Res.* **2005**, 33, W368-W371.
3. Besler, B. H.; Merz Jr, K. M.; Kollman, P. A., Atomic charges derived from semiempirical methods. *J. Comput. Chem.* **1990**, 11, 431-439.
4. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; J. A. Montgomery, J.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision E. 01*, Gaussian Inc.: Wallingford, CT, 2004.
5. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision C. 01*, Gaussian Inc.: Wallingford, CT, 2009.
6. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S., General atomic and molecular electronic structure system. *J. Comput. Chem.* **1993**, 14, 1347-1363.

7. Li, P.; Roberts, B. P.; Chakravorty, D. K.; Merz Jr, K. M., Rational Design of Particle Mesh Ewald Compatible Lennard-Jones Parameters for +2 Metal Cations in Explicit Solvent. *J. Chem. Theory Comput.* **2013**, 9, 2733-2748.
8. Merz Jr, K. M., Carbon dioxide binding to human carbonic anhydrase II. *J. Am. Chem. Soc.* **1991**, 113, 406-411.
9. Case, D. A.; Babin, V.; Berryman, J. T.; Betz, R. M.; Cai, Q.; Cerutti, D. S.; Cheatham III, T. E.; Darden, T. A.; Duke, R. E.; Gohlke, H.; Goetz, A. W.; Gusarov, S.; Homeyer, N.; Janowski, P.; Kaus, J.; Kolossváry, I.; Kovalenko, A.; Lee, T. S.; LeGrand, S.; Luchko, T.; Luo, R.; Madej, B.; Merz Jr, K. M.; Paesani, F.; Roe, D. R.; Roitberg, A.; Sagui, C.; Salomon-Ferrer, R.; Seabra, G.; Simmerling, C. L.; Smith, W.; Swails, J.; Walker, R. C.; Wang, J.; Wolf, R. M.; Wu, X.; Kollman, P. A. *AMBER 14*, University of California, San Francisco: 2014.
10. Götz, A. W.; Williamson, M. J.; Xu, D.; Poole, D.; Le Grand, S.; Walker, R. C., Routine microsecond molecular dynamics simulations with AMBER on GPUs. 1. Generalized born. *J. Chem. Theory Comput.* **2012**, 8, 1542-1555.
11. Salomon-Ferrer, R.; Götz, A. W.; Poole, D.; Le Grand, S.; Walker, R. C., Routine Microsecond Molecular Dynamics Simulations with AMBER on GPUs. 2. Explicit Solvent Particle Mesh Ewald. *J. Chem. Theory Comput.* **2013**, 9, 3878-3888.
12. Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L., Comparison of simple potential functions for simulating liquid water. *J. Chem. Phys.* **1983**, 79, 926-935.
13. Berendsen, H. J.; Postma, J. P. M.; van Gunsteren, W. F.; DiNola, A.; Haak, J., Molecular dynamics with coupling to an external bath. *J. Chem. Phys.* **1984**, 81, 3684-3690.
14. Ryckaert, J.-P.; Ciccotti, G.; Berendsen, H. J., Numerical integration of the cartesian equations of motion of a system with constraints: molecular dynamics of n-alkanes. *J. Comput. Phys.* **1977**, 23, 327-341.
15. Miyamoto, S.; Kollman, P. A., SETTLE: an analytical version of the SHAKE and RATTLE algorithm for rigid water models. *J. Comput. Chem.* **1992**, 13, 952-962.
16. Demadis, K. D.; Dattelbaum, D. M.; Kober, E. M.; Concepcion, J. J.; Paul, J. J.; Meyer, T. J.; White, P. S., Vibrational and structural mapping of [Os(bpy)3]3+/2+ and [Os(phen)3]3+/2+. *Inorg. Chim. Acta* **2007**, 360, 1143-1153.
17. Rappé, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard III, W. A.; Skiff, W. M., UFF, a full periodic table force field for molecular mechanics and molecular dynamics simulations. *J. Am. Chem. Soc.* **1992**, 114, 10024-10035.
18. Case, D. A.; Berryman, J. T.; Betz, R. M.; Cerutti, D. S.; Cheatham III, T. E.; Darden, T. A.; Duke, R. E.; Giese, T. J.; Gohlke, H.; Goetz, A. W.; Homeyer, N.; Izadi, S.; Janowski, P.; Kaus, J.; Kovalenko, A.; Lee, T. S.; LeGrand, S.; Li, P.; Luchko, T.; Luo, R.; Madej, B.; Merz Jr, K. M.; Monard, G.; Needham, P.; Nguyen, H.; Nguyen, H. T.; Omelyan, I.; Onufriev, A.; Roe, D. R.; Roitberg, A.; Salomon-Ferrer, R.; Simmerling, C. L.; Smith, W.; Swails, J.; Walker, R. C.; Wang, J.; Wolf, R. M.; Wu, X.; York, D. M.; Kollman, P. A. *AMBER 2015*, University of California, San Francisco: 2015.
19. Lin, F.; Wang, R., Systematic derivation of AMBER force field parameters applicable to zinc-containing systems. *J. Chem. Theory Comput.* **2010**, 6, 1852-1870.
20. Humphrey, W.; Dalke, A.; Schulten, K., VMD: visual molecular dynamics. *J. Mol. Graphics* **1996**, 14, 33-38.

21. Roe, D. R.; Cheatham III, T. E., PTRAJ and CPPTRAJ: software for processing and analysis of molecular dynamics trajectory data. *J. Chem. Theory Comput.* **2013**, 9, 3084-3095.