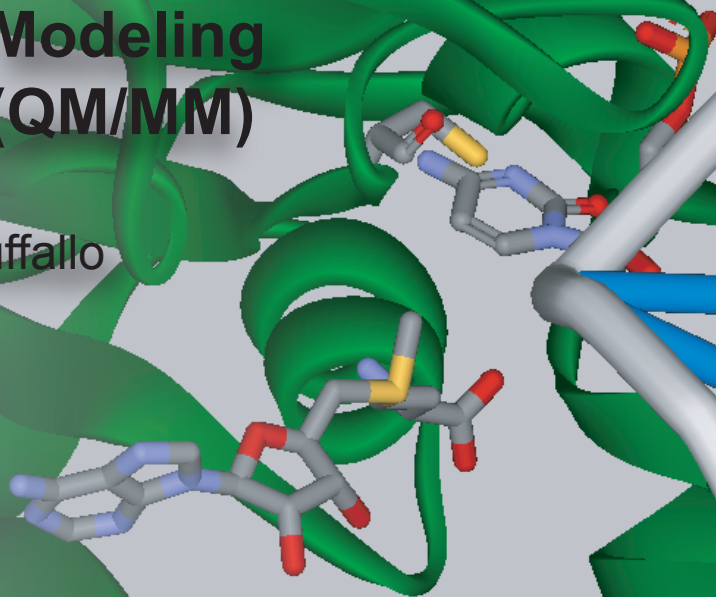


Marek  
Freindorf

## Molecular Modeling Examples (QM/MM)

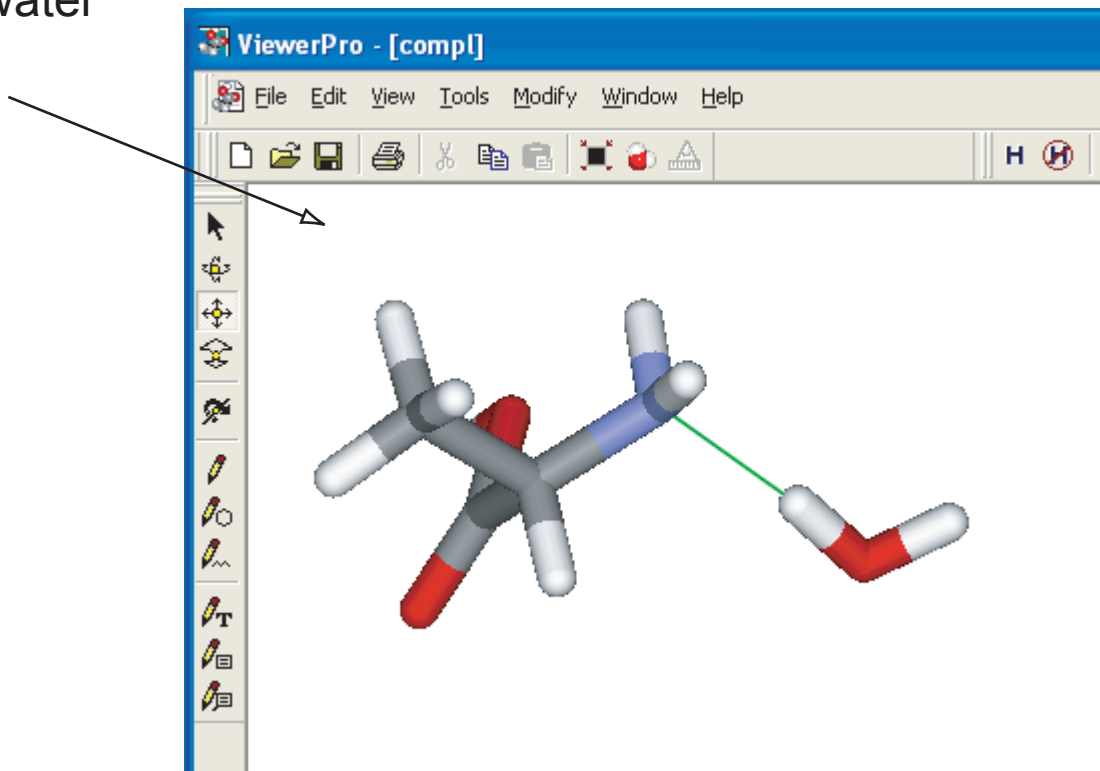
University at Buffalo  
April 2007



# QM/MM calculations of alanine water dimer

---

Geometry optimization  
of the alanine water  
dimer

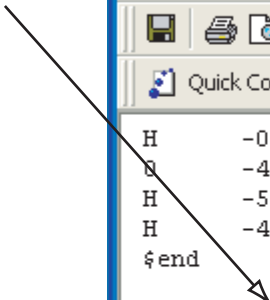




# QM/MM calculations of alanine water dimer

---

Technical details of  
the QM calculations



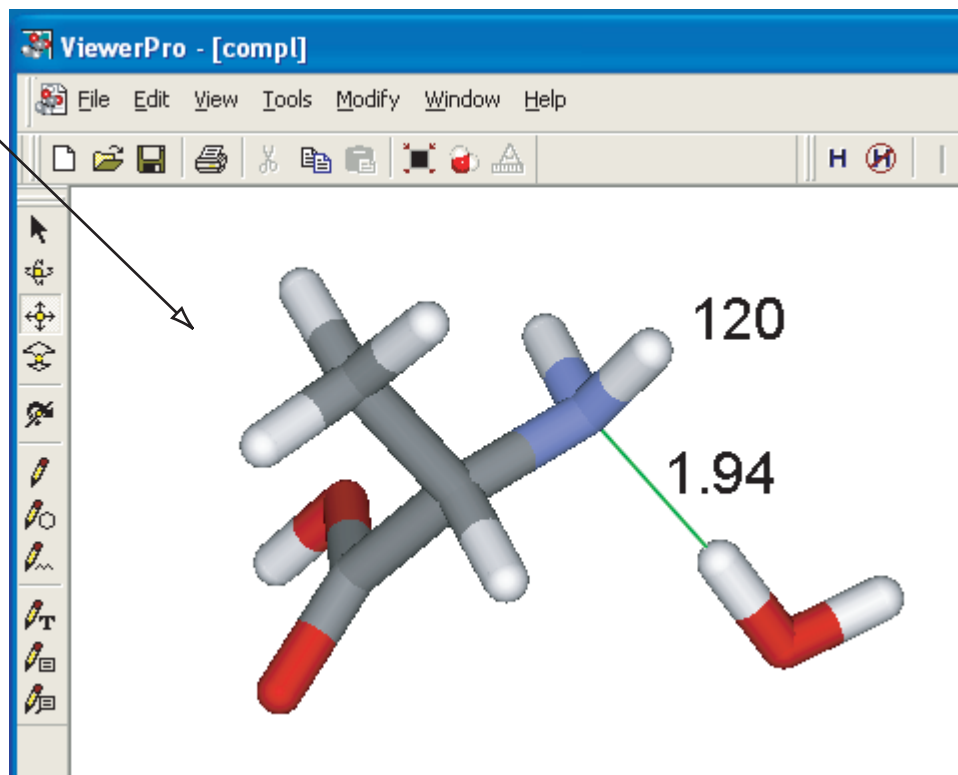
```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles
H      -0.596  -1.696   0.014
O      -4.590  -1.334  -1.499
H      -5.486  -1.630  -1.167
H      -4.201  -0.668  -0.863
$end

$rem
jobtype          opt
exchange         b3lyp
basis            6-31+G*
mem_static       128
mem_total       2000
$end
```

# QM/MM calculations of alanine water dimer

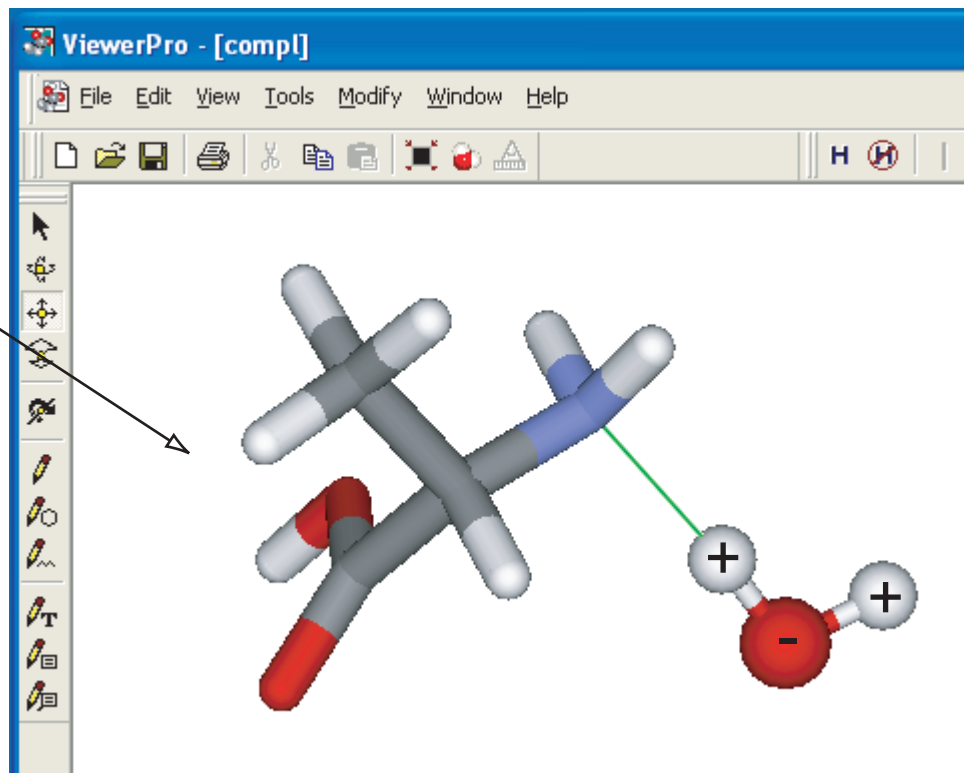
---

Final structure after  
QM geometry  
optimization



# QM/MM calculations of alanine water dimer

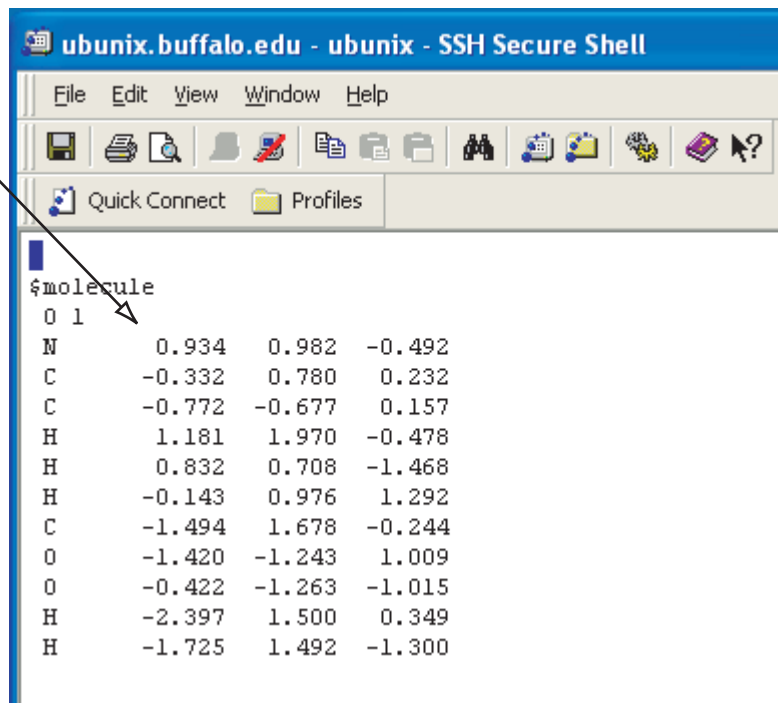
Geometry  
optimization of  
alanine in the  
presence of the  
fixed MM atoms  
of water



# QM/MM calculations of alanine water dimer

---

Cartesian coordinates  
of the alanine only



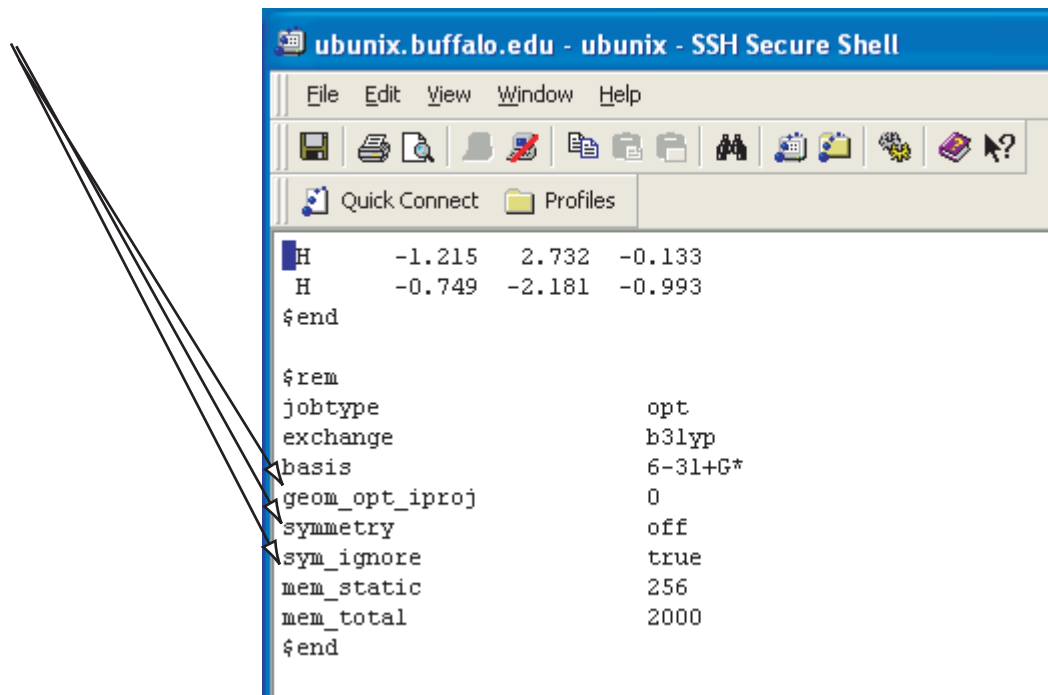
```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons: Save, Print, Find, etc.]
Quick Connect Profiles

$ molecule
O 1
N      0.934    0.982   -0.492
C     -0.332    0.780    0.232
C     -0.772   -0.677    0.157
H      1.181    1.970   -0.478
H      0.832    0.708   -1.468
H     -0.143    0.976    1.292
C     -1.494    1.678   -0.244
O     -1.420   -1.243    1.009
O     -0.422   -1.263   -1.015
H     -2.397    1.500    0.349
H     -1.725    1.492   -1.300
```

# QM/MM calculations of alanine water dimer

---

Additional commands  
of the QM calculations



```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

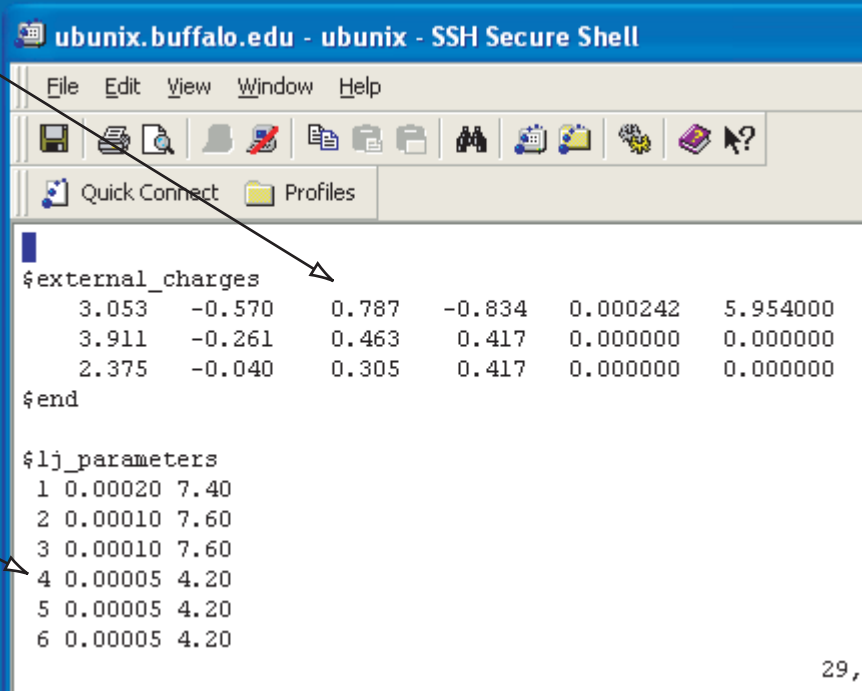
H      -1.215   2.732  -0.133
H      -0.749  -2.181  -0.993
$end

$rem
jobtype                opt
exchange               b3lyp
basis                  6-31+G*
geom_opt_iproj         0
symmetry               off
sym_ignore             true
mem_static             256
mem_total              2000
$end
```

# QM/MM calculations of alanine water dimer

MM atoms are represented by point charges and vdW spheres

vdW spheres of the QM atoms



```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

$external_charges
  3.053   -0.570   0.787   -0.834   0.000242   5.954000
  3.911   -0.261   0.463    0.417   0.000000   0.000000
  2.375   -0.040   0.305    0.417   0.000000   0.000000
$end

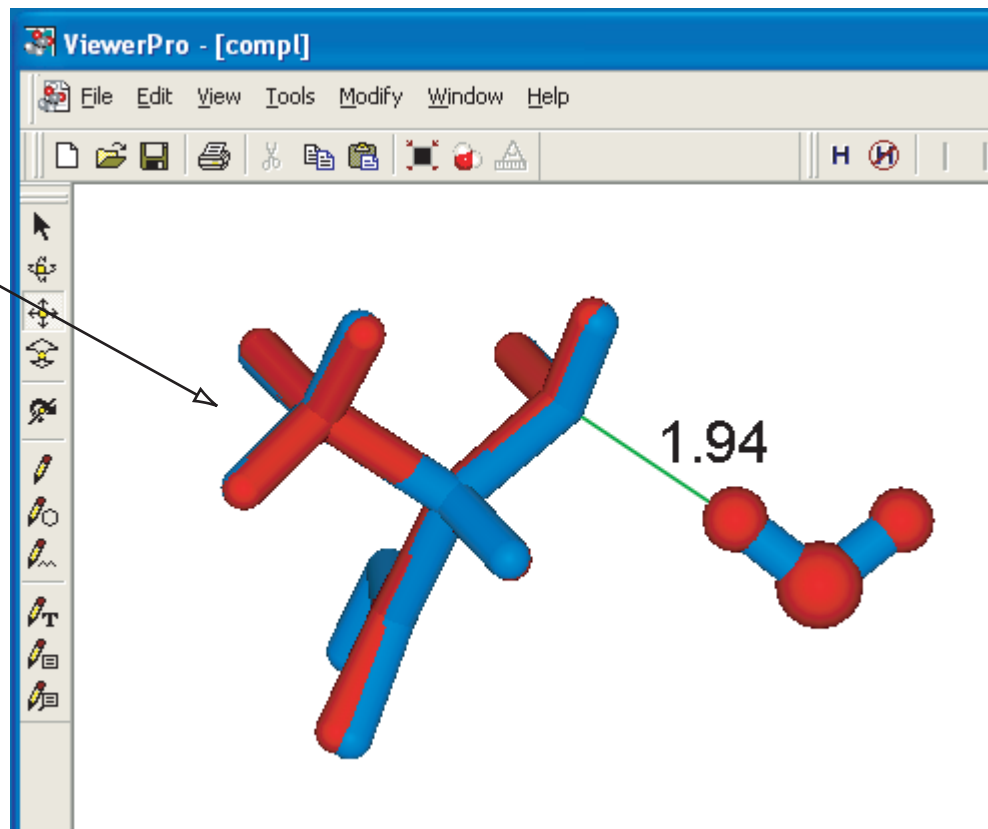
$lj_parameters
  1 0.00020 7.40
  2 0.00010 7.60
  3 0.00010 7.60
  4 0.00005 4.20
  5 0.00005 4.20
  6 0.00005 4.20
```

29,



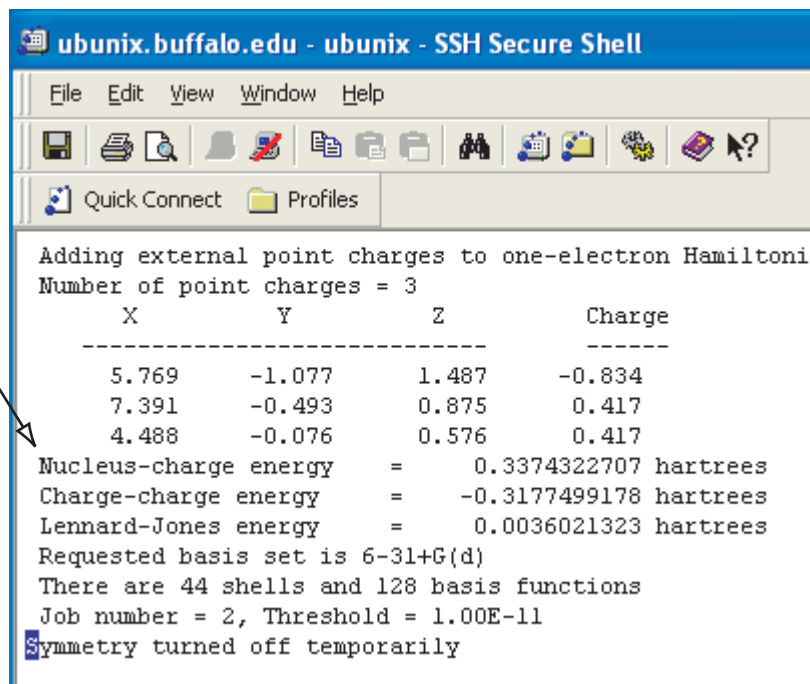
# QM/MM calculations of alanine water dimer

Final QM/MM  
geometry (red)  
of alanine,  
compared  
with full QM  
geometry of the  
dimer (blue)



# QM/MM calculations of alanine water dimer

Energy components in  
the QM/MM  
calculations

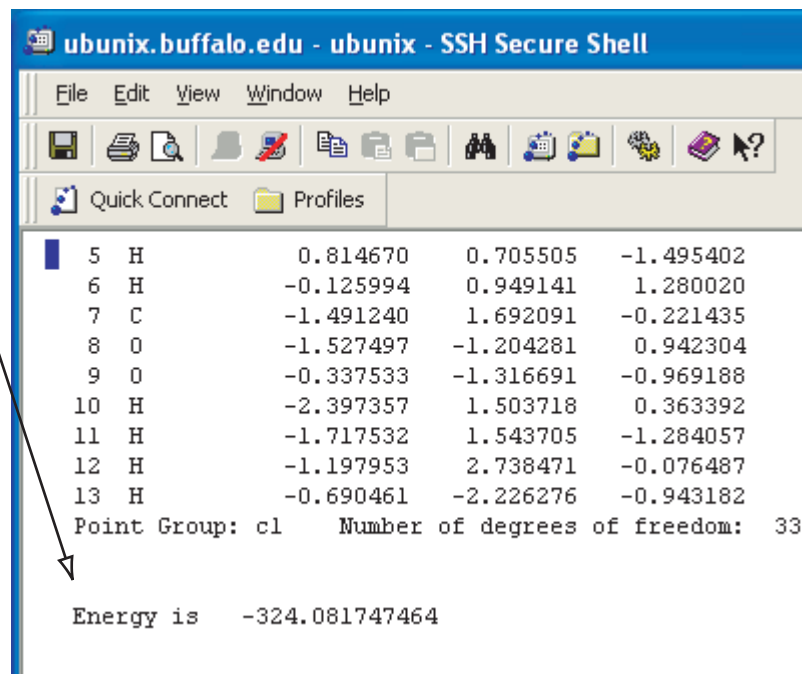


```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

Adding external point charges to one-electron Hamiltonian
Number of point charges = 3
      X           Y           Z           Charge
-----
      5.769      -1.077        1.487       -0.834
      7.391      -0.493        0.875        0.417
      4.488      -0.076        0.576        0.417
Nucleus-charge energy = 0.3374322707 hartrees
Charge-charge energy = -0.3177499178 hartrees
Lennard-Jones energy = 0.0036021323 hartrees
Requested basis set is 6-31+G(d)
There are 44 shells and 128 basis functions
Job number = 2, Threshold = 1.00E-11
Symmetry turned off temporarily
```

# QM/MM calculations of alanine water dimer

Final total energy of  
QM alanine, calculated  
in the presence of MM



```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons: Save, Print, Find, etc.]
Quick Connect Profiles

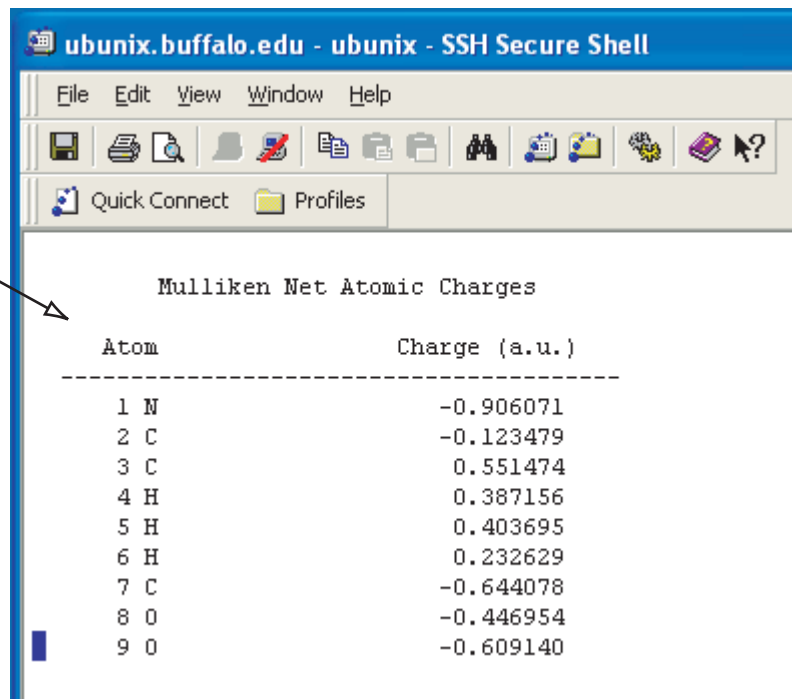
5 H      0.814670    0.705505   -1.495402
6 H      -0.125994    0.949141    1.280020
7 C      -1.491240    1.692091   -0.221435
8 O      -1.527497   -1.204281    0.942304
9 O      -0.337533   -1.316691   -0.969188
10 H     -2.397357    1.503718    0.363392
11 H     -1.717532    1.543705   -1.284057
12 H     -1.197953    2.738471   -0.076487
13 H     -0.690461   -2.226276   -0.943182
Point Group: cl      Number of degrees of freedom: 33

Energy is  -324.081747464
```

# QM/MM calculations of alanine water dimer

---

Atomic charges of QM  
alanine with the  
presence of MM water  
molecule



ubunix.buffalo.edu - ubunix - SSH Secure Shell

File Edit View Window Help

Quick Connect Profiles

Mulliken Net Atomic Charges

Atom	Charge (a.u.)
1 N	-0.906071
2 C	-0.123479
3 C	0.551474
4 H	0.387156
5 H	0.403695
6 H	0.232629
7 C	-0.644078
8 O	-0.446954
9 O	-0.609140

# QM/MM calculations of alanine water dimer

Dipole moment of  
QM alanine with the  
presence of MM  
water molecule

```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

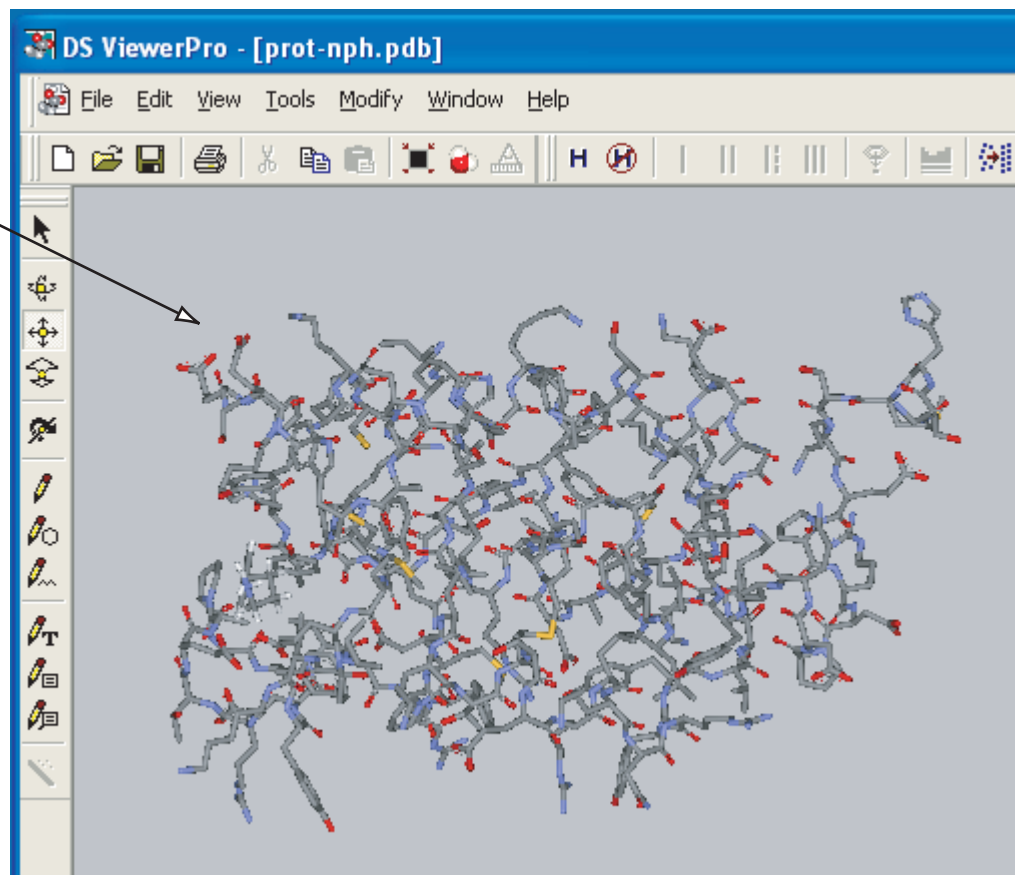
Sum of atomic charges =      0.000000

-----
                        Cartesian Multipole Moments
-----
Charge (ESU x 10^10)
      0.0000
Dipole Moment (Debye)
  X      -0.5216      Y      1.4518      Z      -1.7819
  Tot      2.3569
Quadrupole Moments (Debye-Ang)
  XX      -42.3210      XY      -0.9557      YY      -29.6882
  XZ      2.9255      YZ      2.9890      ZZ      -37.0901
Octapole Moments (Debye-Ang^2)
                                           3679,5
```

# QM/MM calculations of active site of PCAF

---

Experimental  
structure of the  
PCAF protein  
with a ligand

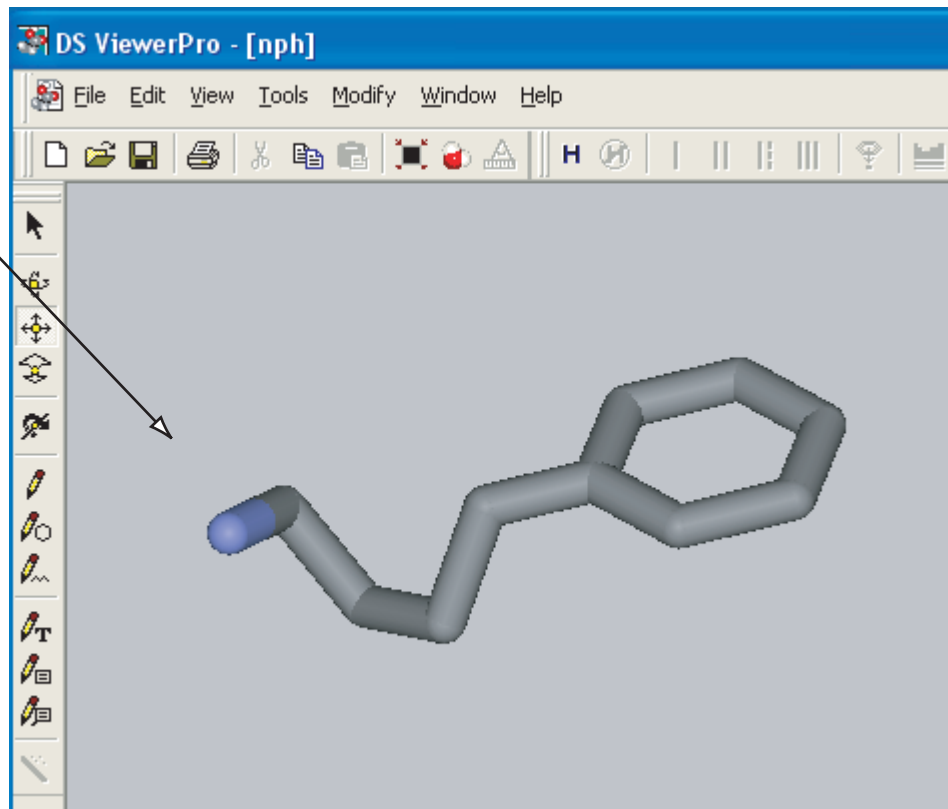




# QM/MM calculations of active site of PCAF

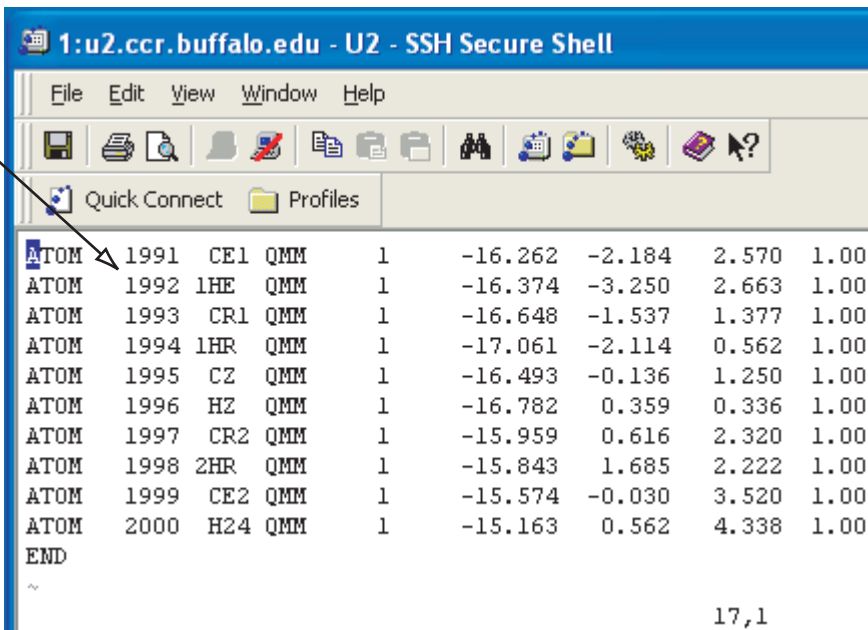
---

The ligand of  
the PCAF  
protein



# QM/MM calculations of active site of PCAF

PDB file of the ligand,  
should have the  
residue name: QMM



1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell

File Edit View Window Help

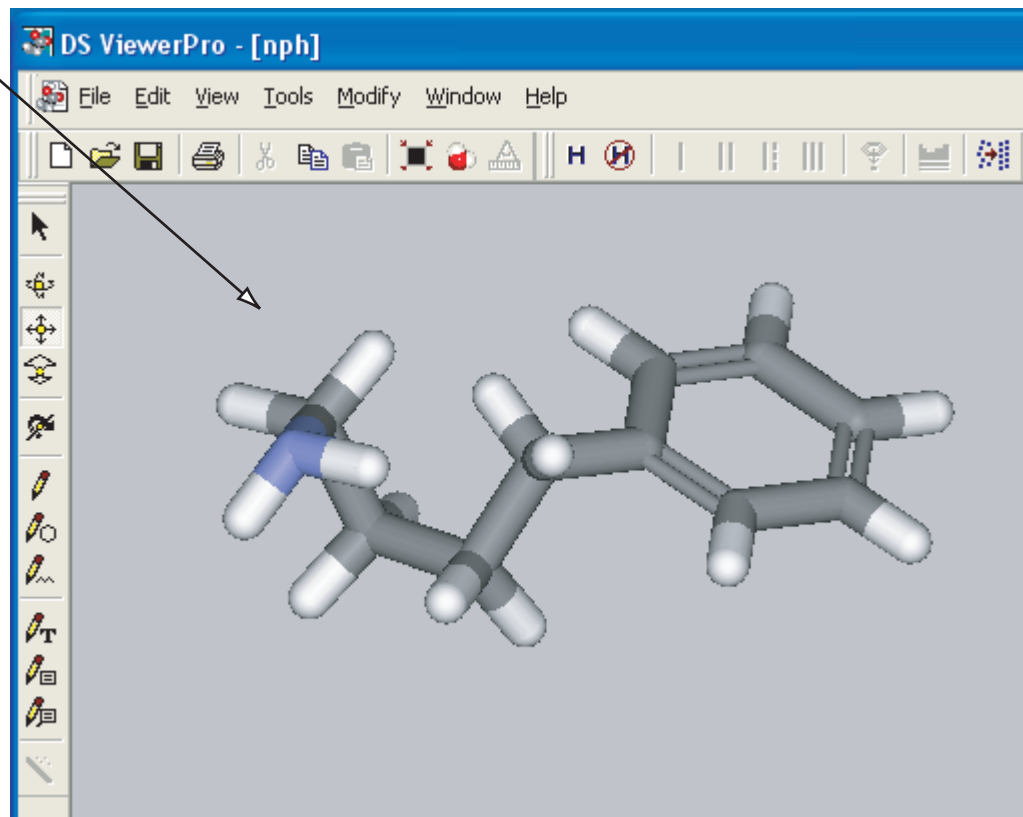
Quick Connect Profiles

ATOM	1991	CE1	QMM	1	-16.262	-2.184	2.570	1.00
ATOM	1992	1HE	QMM	1	-16.374	-3.250	2.663	1.00
ATOM	1993	CR1	QMM	1	-16.648	-1.537	1.377	1.00
ATOM	1994	1HR	QMM	1	-17.061	-2.114	0.562	1.00
ATOM	1995	CZ	QMM	1	-16.493	-0.136	1.250	1.00
ATOM	1996	HZ	QMM	1	-16.782	0.359	0.336	1.00
ATOM	1997	CR2	QMM	1	-15.959	0.616	2.320	1.00
ATOM	1998	2HR	QMM	1	-15.843	1.685	2.222	1.00
ATOM	1999	CE2	QMM	1	-15.574	-0.030	3.520	1.00
ATOM	2000	H24	QMM	1	-15.163	0.562	4.338	1.00
END								
~								
17,1								

# QM/MM calculations of active site of PCAF

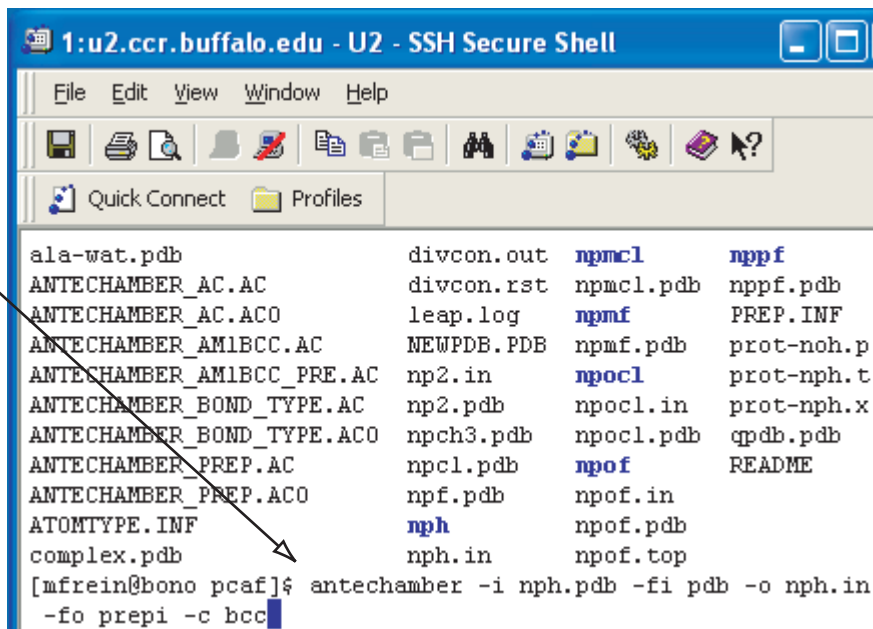
---

The ligand with  
hydrogen atoms



# QM/MM calculations of active site of PCAF

Antechamber  
program creating  
the preparations  
file of the ligand

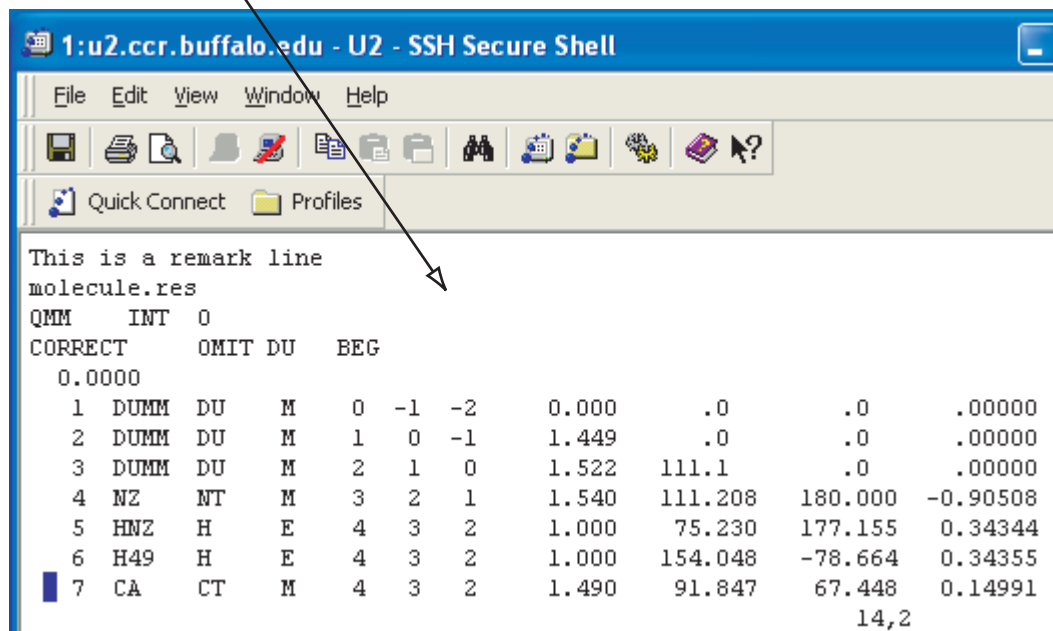


The screenshot shows an SSH Secure Shell window titled "1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell". The window displays a file directory with various files and folders. A file named "complex.pdb" is highlighted. Below the directory listing, a command is being executed in the terminal:

```
[mfrein@bono pcaf]$ antechamber -i nph.pdb -fi pdb -o nph.in  
-fo prepi -c bcc
```

# QM/MM calculations of active site of PCAF

The preparation file, generated by the "antechamber" program



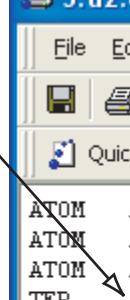
```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

This is a remark line
molecule.res
QMM      INT  0
CORRECT      OMIT DU      BEG
0.0000
  1  DUMM  DU      M      0 -1 -2      0.000      .0      .0      .00000
  2  DUMM  DU      M      1  0 -1      1.449      .0      .0      .00000
  3  DUMM  DU      M      2  1  0      1.522     111.1      .0      .00000
  4  NZ     NT      M      3  2  1      1.540     111.208    180.000    -0.90508
  5  HNZ    H       E      4  3  2      1.000      75.230    177.155     0.34344
  6  H49    H       E      4  3  2      1.000     154.048    -78.664     0.34355
  7  CA     CT      M      4  3  2      1.490      91.847     67.448     0.14991
                                     14,2
```

# QM/MM calculations of active site of PCAF

---

Merging the pdb  
structure of the ligand  
with the pdb structure  
of the protein



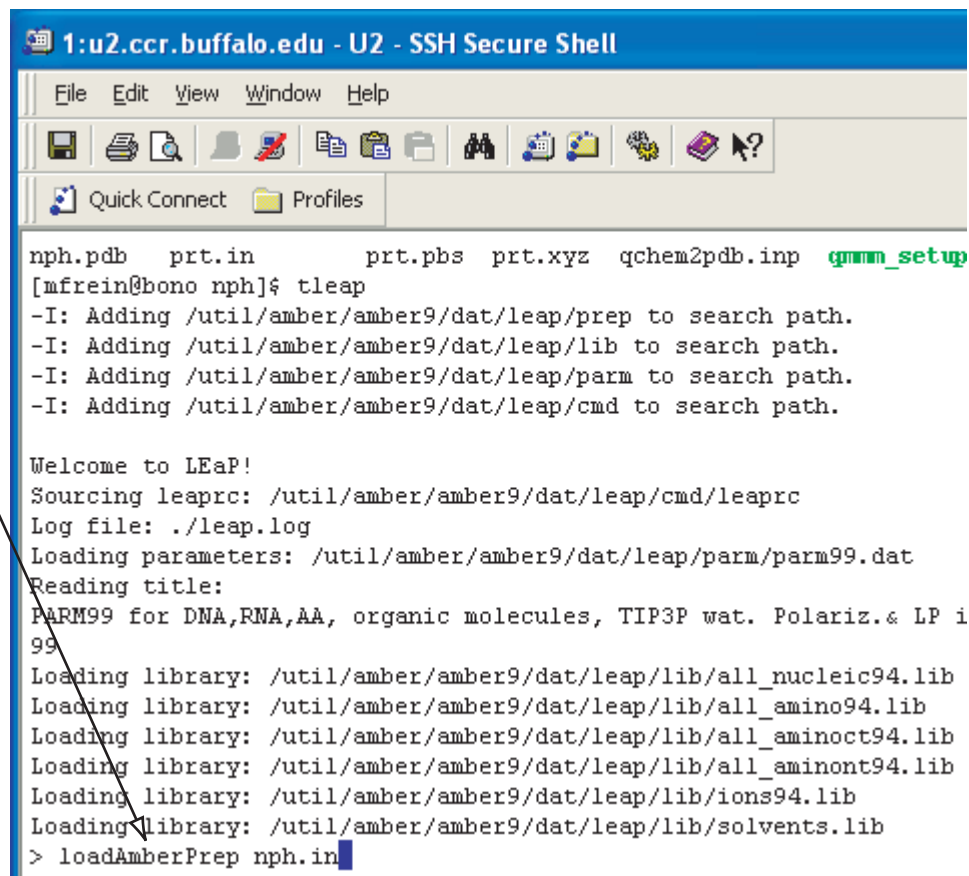
3:u2.ccr.buffalo.edu - u2 - SSH Secure Shell

File	Edit	View	Window	Help			
Quick Connect	Profiles						
ATOM	1972	C	LYS	118	7.881	8.370	-11.203
ATOM	1973	O	LYS	118	8.299	7.263	-11.535
ATOM	1974	OXT	LYS	118	7.795	9.254	-12.053
TER							
ATOM	1975	NZ	QMM	119	-14.748	-3.998	7.037
ATOM	1976	HNZ	QMM	119	-15.003	-3.032	6.989
ATOM	1977	H49	QMM	119	-13.849	-4.084	7.466
ATOM	1978	CA	QMM	119	-14.700	-4.569	5.662
ATOM	1979	1HA	QMM	119	-14.426	-5.611	5.703
ATOM	1980	2HA	QMM	119	-15.653	-4.450	5.169
ATOM	1981	CB	QMM	119	-13.616	-3.760	4.941
ATOM	1982	1HB	QMM	119	-13.592	-4.045	3.896
ATOM	1983	2HB	QMM	119	-12.657	-3.972	5.389



# QM/MM calculations of active site of PCAF

The "tleap"  
program reading  
the preparation  
file



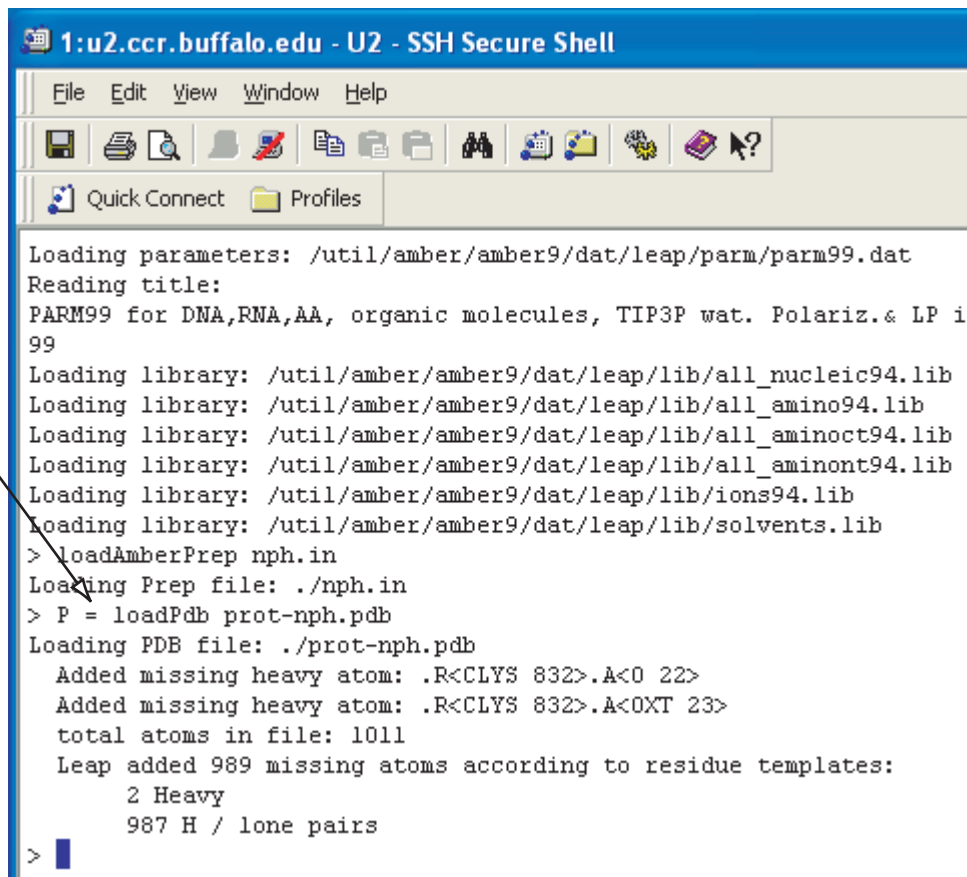
```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

nph.pdb prt.in prt.pbs prt.xyz qchem2pdb.inp gmmm_setup
[mfrein@bono nph]$ tleap
-I: Adding /util/amber/amber9/dat/leap/prep to search path.
-I: Adding /util/amber/amber9/dat/leap/lib to search path.
-I: Adding /util/amber/amber9/dat/leap/parm to search path.
-I: Adding /util/amber/amber9/dat/leap/cmd to search path.

Welcome to LEaP!
Sourcing leaprc: /util/amber/amber9/dat/leap/cmd/leaprc
Log file: ./leap.log
Loading parameters: /util/amber/amber9/dat/leap/parm/parm99.dat
Reading title:
PARM99 for DNA, RNA, AA, organic molecules, TIP3P wat. Polariz. & LP i
99
Loading library: /util/amber/amber9/dat/leap/lib/all_nucleic94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_amino94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc94.lib
Loading library: /util/amber/amber9/dat/leap/lib/ions94.lib
Loading library: /util/amber/amber9/dat/leap/lib/solvents.lib
> loadAmberPrep nph.in
```

# QM/MM calculations of active site of PCAF

The "tleap"  
program reading  
the PDB file of  
the protein and  
the ligand

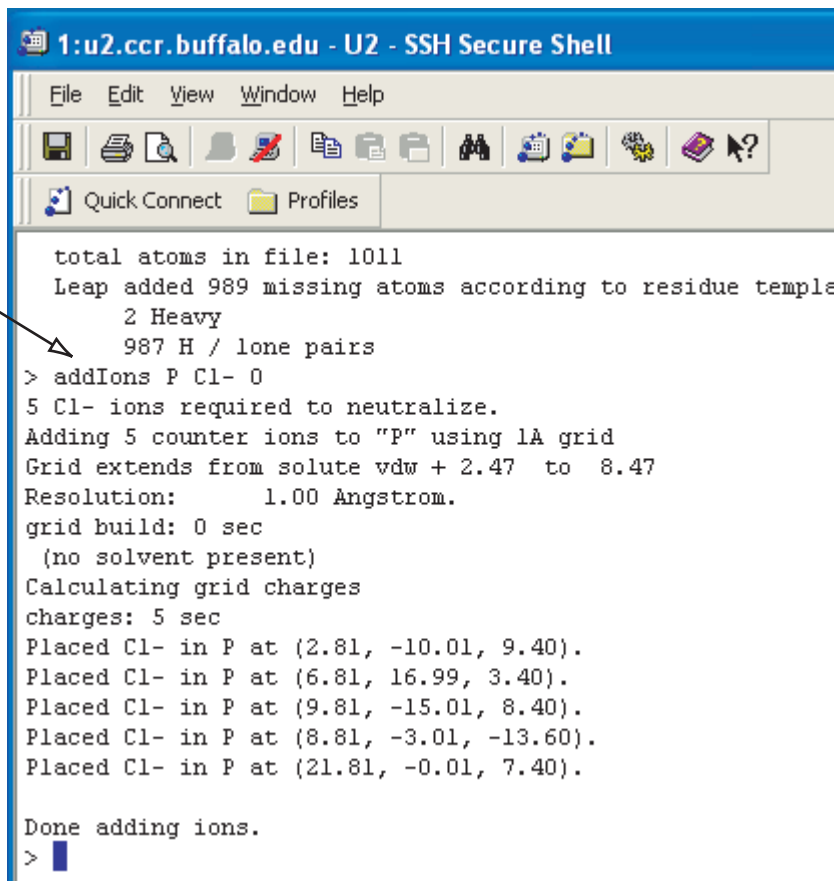


```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles
Loading parameters: /util/amber/amber9/dat/leap/parm/parm99.dat
Reading title:
PARM99 for DNA,RNA,AA, organic molecules, TIP3P wat. Polariz.& LP i
99
Loading library: /util/amber/amber9/dat/leap/lib/all_nucleic94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_amino94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminont94.lib
Loading library: /util/amber/amber9/dat/leap/lib/ions94.lib
Loading library: /util/amber/amber9/dat/leap/lib/solvents.lib
> loadAmberPrep nph.in
Loading Prep file: ./nph.in
> P = loadPdb prot-nph.pdb
Loading PDB file: ./prot-nph.pdb
  Added missing heavy atom: .R<CLYS 832>.A<O 22>
  Added missing heavy atom: .R<CLYS 832>.A<OXT 23>
  total atoms in file: 1011
  Leap added 989 missing atoms according to residue templates:
    2 Heavy
   987 H / lone pairs
>
```

# QM/MM calculations of active site of PCAF

---

The "tleap" program  
adding Chlorine anions  
for neutralization



```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

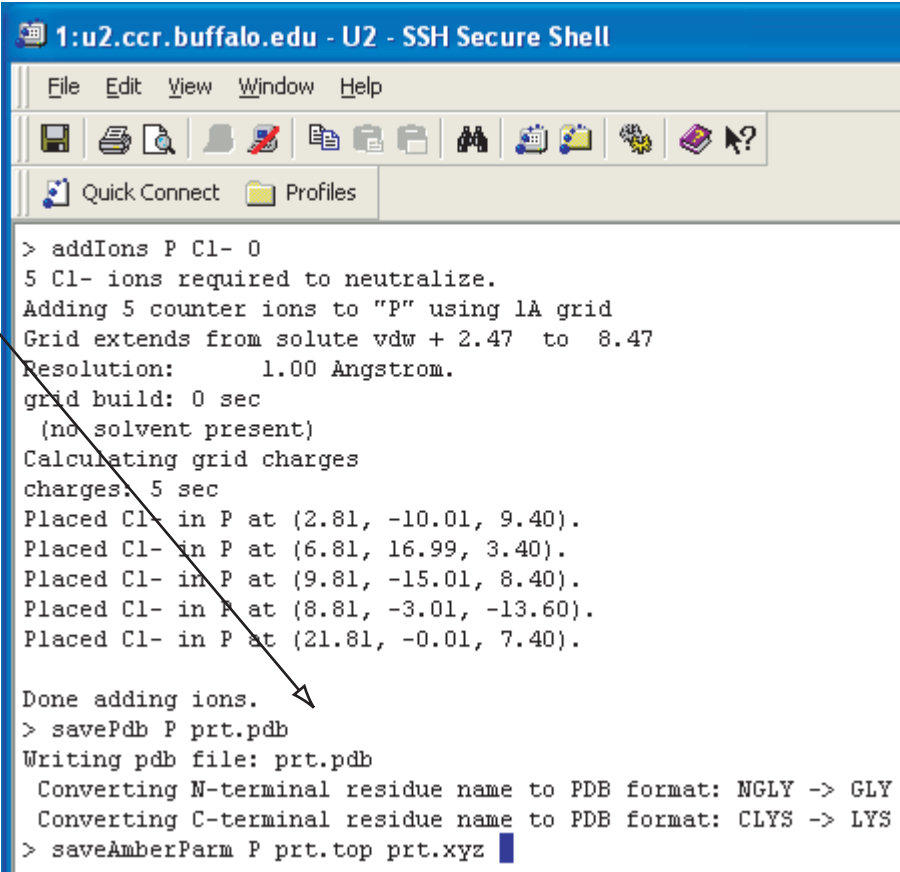
total atoms in file: 1011
Leap added 989 missing atoms according to residue template
  2 Heavy
  987 H / lone pairs
> addIons P Cl- 0
5 Cl- ions required to neutralize.
Adding 5 counter ions to "P" using 1A grid
Grid extends from solute vdw + 2.47 to 8.47
Resolution: 1.00 Angstrom.
grid build: 0 sec
(no solvent present)
Calculating grid charges
charges: 5 sec
Placed Cl- in P at (2.81, -10.01, 9.40).
Placed Cl- in P at (6.81, 16.99, 3.40).
Placed Cl- in P at (9.81, -15.01, 8.40).
Placed Cl- in P at (8.81, -3.01, -13.60).
Placed Cl- in P at (21.81, -0.01, 7.40).

Done adding ions.
> 
```

# QM/MM calculations of active site of PCAF

---

The "tleap" program  
saving the PDB file,  
the topology file and  
the coordinates file

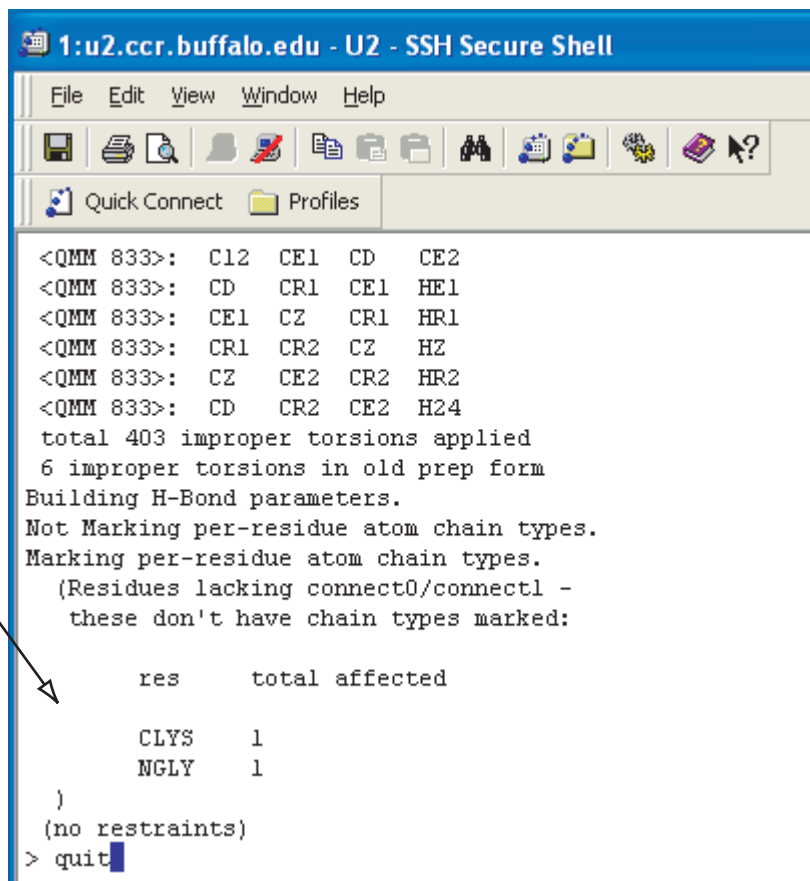


```
> addIons P Cl- 0
5 Cl- ions required to neutralize.
Adding 5 counter ions to "P" using 1A grid
Grid extends from solute vdw + 2.47 to 8.47
Resolution:      1.00 Angstrom.
grid build: 0 sec
(no solvent present)
Calculating grid charges
charges: 5 sec
Placed Cl- in P at (2.81, -10.01, 9.40).
Placed Cl- in P at (6.81, 16.99, 3.40).
Placed Cl- in P at (9.81, -15.01, 8.40).
Placed Cl- in P at (8.81, -3.01, -13.60).
Placed Cl- in P at (21.81, -0.01, 7.40).

Done adding ions.
> savePdb P prt.pdb
Writing pdb file: prt.pdb
Converting N-terminal residue name to PDB format: NGLY -> GLY
Converting C-terminal residue name to PDB format: CLYS -> LYS
> saveAmberParm P prt.top prt.xyz
```

# QM/MM calculations of active site of PCAF

Quitting the "tleap" program



```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

<QMM 833>: C12 CE1 CD CE2
<QMM 833>: CD CR1 CE1 HE1
<QMM 833>: CE1 CZ CR1 HR1
<QMM 833>: CR1 CR2 CZ HZ
<QMM 833>: CZ CE2 CR2 HR2
<QMM 833>: CD CR2 CE2 H24
total 403 improper torsions applied
6 improper torsions in old prep form
Building H-Bond parameters.
Not Marking per-residue atom chain types.
Marking per-residue atom chain types.
(Residues lacking connect0/connect1 -
these don't have chain types marked:

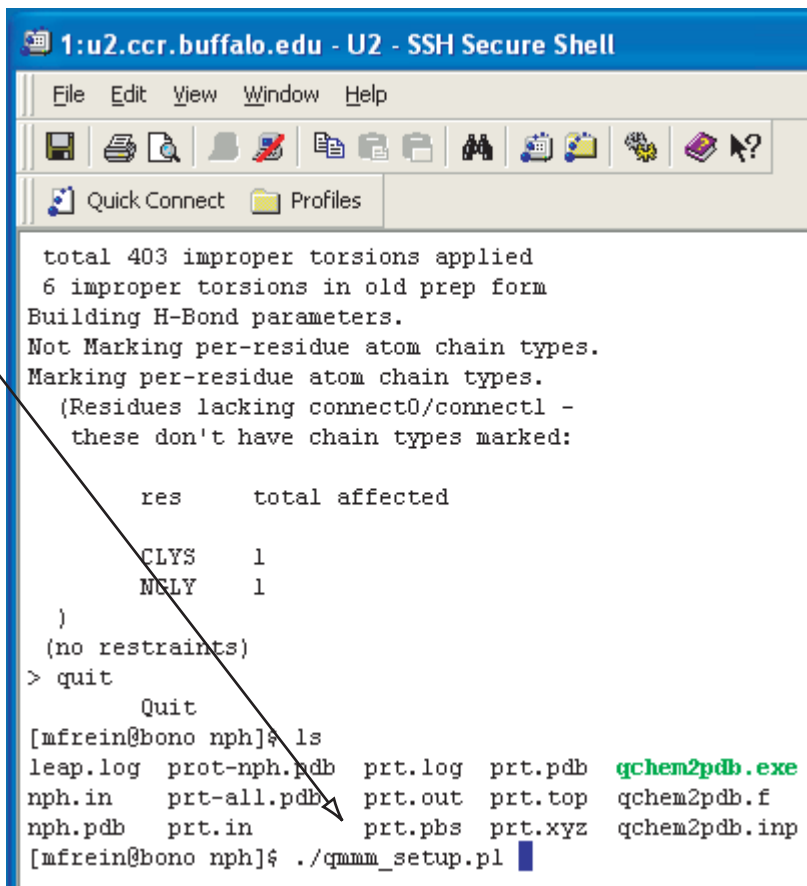
    res      total affected

    CLYS      1
    NGLY      1

)
(no restraints)
> quit
```

# QM/MM calculations of active site of PCAF

Running the "perl"  
script generating the  
input file for the  
QM/MM calculations



```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

total 403 improper torsions applied
6 improper torsions in old prep form
Building H-Bond parameters.
Not Marking per-residue atom chain types.
Marking per-residue atom chain types.
(Residues lacking connect0/connect1 -
these don't have chain types marked:

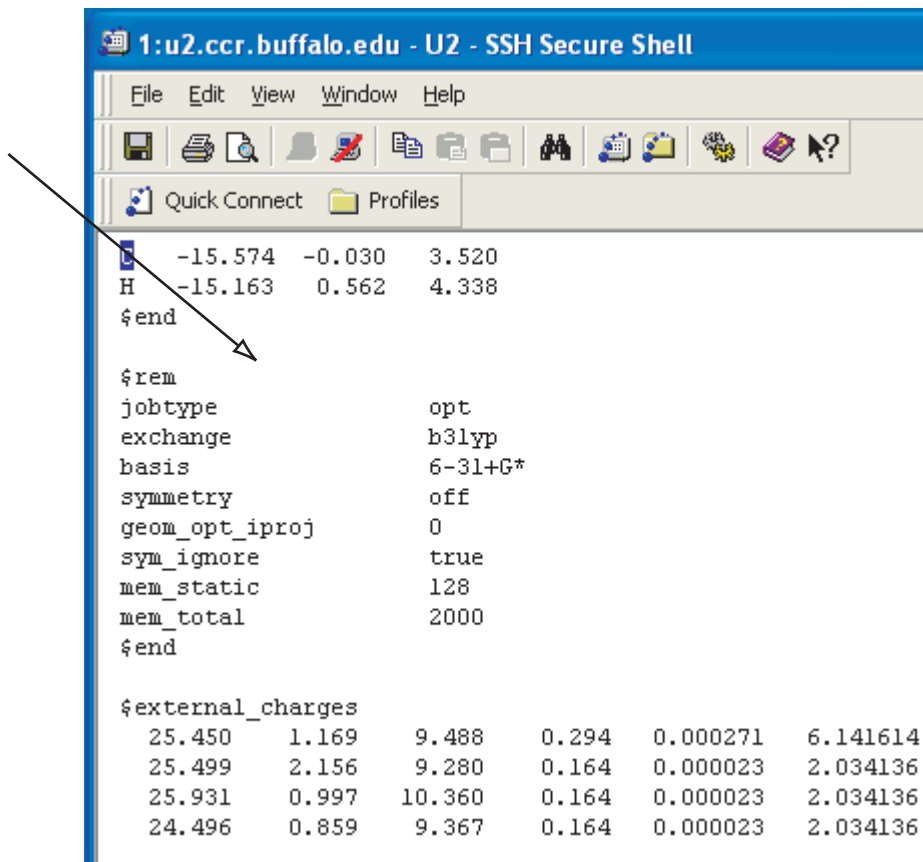
      res      total affected
      CLYS      1
      NSLY      1
)
(no restraints)
> quit
Quit
[mfrein@bono nph]$ ls
leap.log  prt-nph.pdb  prt.log  prt.pdb  qchem2pdb.exe
nph.in    prt-all.pdb  prt.out  prt.top  qchem2pdb.f
nph.pdb   prt.in       prt.pbs  prt.xyz  qchem2pdb.inp
[mfrein@bono nph]$ ./qmmm_setup.pl
```



# QM/MM calculations of active site of PCAF

---

The input file for the  
QM/MM calculations



```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

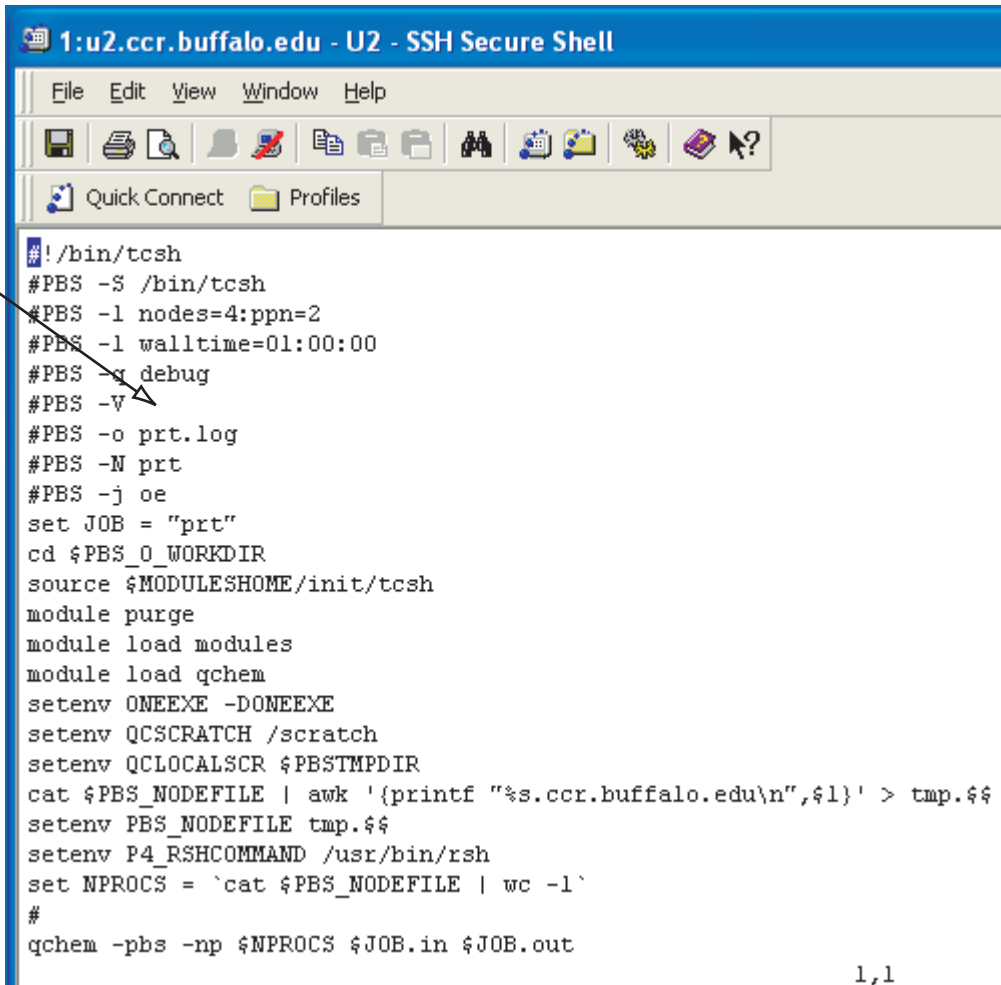
[Blue Icon] -15.574 -0.030 3.520
H -15.163 0.562 4.338
$end

$rem
jobtype opt
exchange b3lyp
basis 6-31+G*
symmetry off
geom_opt_iproj 0
sym_ignore true
mem_static 128
mem_total 2000
$end

$external_charges
25.450 1.169 9.488 0.294 0.000271 6.141614
25.499 2.156 9.280 0.164 0.000023 2.034136
25.931 0.997 10.360 0.164 0.000023 2.034136
24.496 0.859 9.367 0.164 0.000023 2.034136
```

# QM/MM calculations of active site of PCAF

The PBS script for the QM/MM calculations



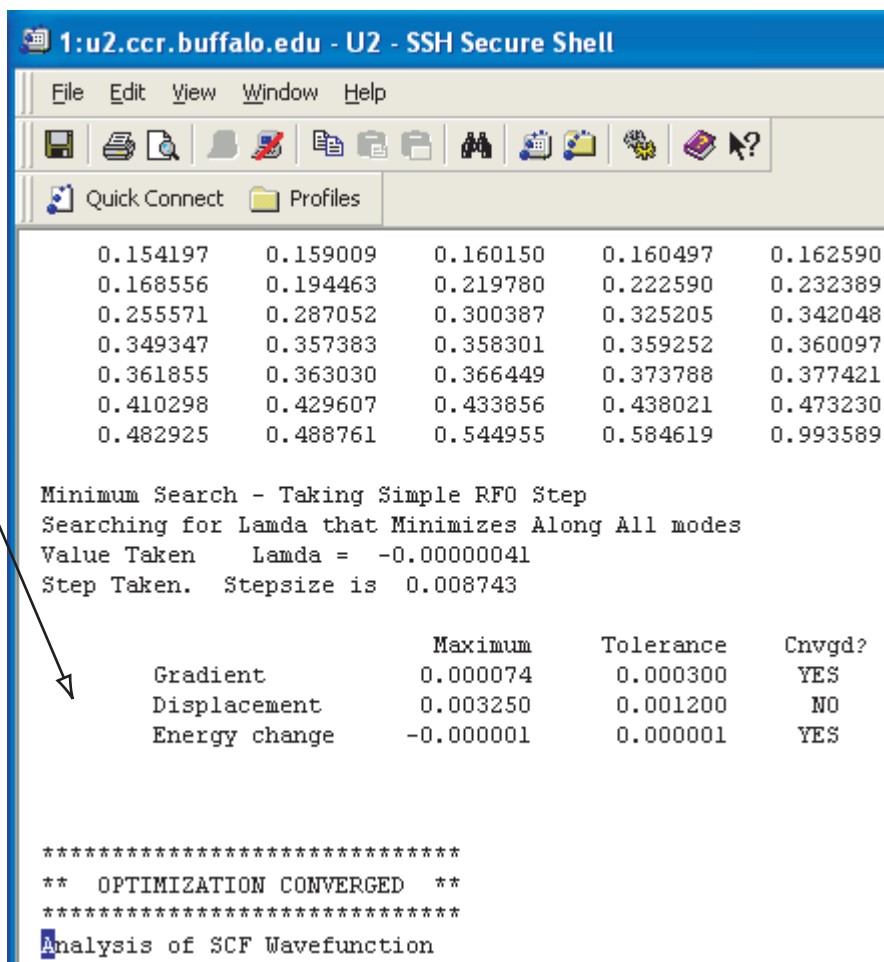
The screenshot shows an SSH terminal window titled "1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell". The terminal displays a PBS script for QM/MM calculations. The script starts with a shebang line and various PBS directives. An arrow from the text "The PBS script for the QM/MM calculations" points to the "#PBS -q debug" line. The script sets the job name to "prt", sets the working directory to the PBS work directory, and loads the necessary modules. It then sets environment variables for the scratch directory, local scratch directory, nodefile, and rsh command. Finally, it sets the number of processors and runs the qchem command.

```
#!/bin/tcsh
#PBS -S /bin/tcsh
#PBS -l nodes=4:ppn=2
#PBS -l walltime=01:00:00
#PBS -q debug
#PBS -V
#PBS -o prt.log
#PBS -N prt
#PBS -j oe
set JOB = "prt"
cd $PBS_O_WORKDIR
source $MODULESHOME/init/tcsh
module purge
module load modules
module load qchem
setenv ONEEXE -DONEEXE
setenv QCSCRATCH /scratch
setenv QCLOCALSCR $PBSTMPDIR
cat $PBS_NODEFILE | awk '{printf "%s.ccr.buffalo.edu\n", $1}' > tmp.$$
setenv PBS_NODEFILE tmp.$$
setenv P4_RSHCOMMAND /usr/bin/rsh
set NPROCS = `cat $PBS_NODEFILE | wc -l`
#
qchem -pbs -np $NPROCS $JOB.in $JOB.out
```

1,1

# QM/MM calculations of active site of PCAF

Final results of the  
QM/MM calculations



```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

0.154197 0.159009 0.160150 0.160497 0.162590
0.168556 0.194463 0.219780 0.222590 0.232389
0.255571 0.287052 0.300387 0.325205 0.342048
0.349347 0.357383 0.358301 0.359252 0.360097
0.361855 0.363030 0.366449 0.373788 0.377421
0.410298 0.429607 0.433856 0.438021 0.473230
0.482925 0.488761 0.544955 0.584619 0.993589

Minimum Search - Taking Simple RFO Step
Searching for Lamda that Minimizes Along All modes
Value Taken Lamda = -0.00000041
Step Taken. Stepsize is 0.008743

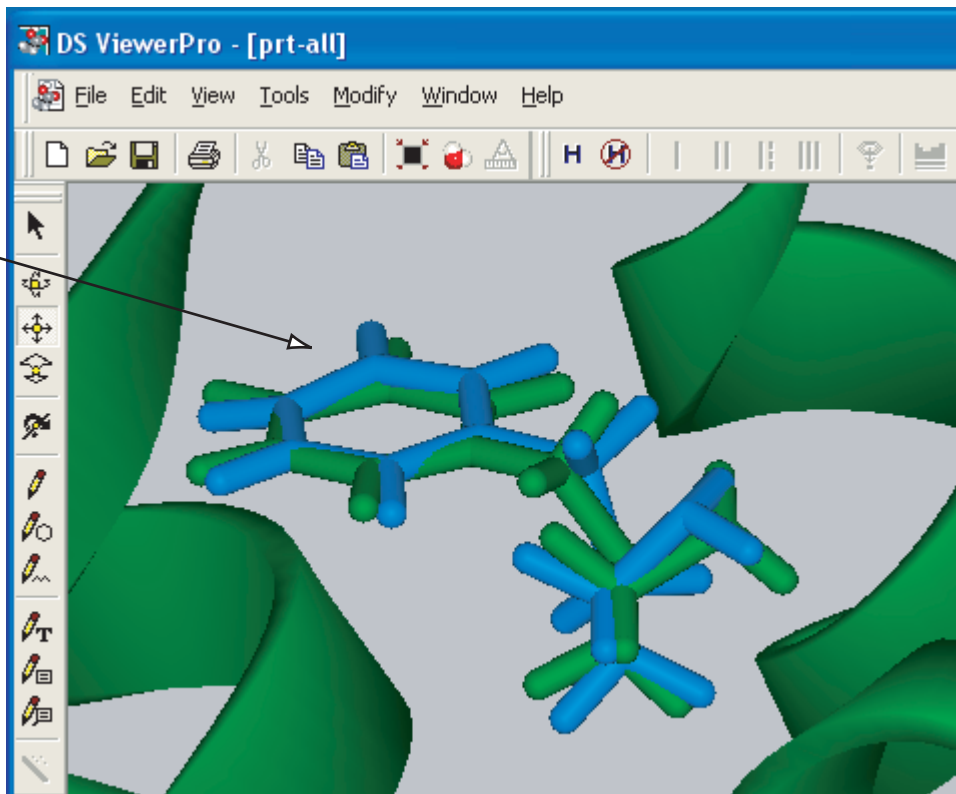
      Maximum      Tolerance      Cnvgd?
Gradient      0.000074      0.000300      YES
Displacement  0.003250      0.001200      NO
Energy change -0.000001      0.000001      YES

*****
**  OPTIMIZATION CONVERGED  **
*****
Analysis of SCF Wavefunction
```

# QM/MM calculations of active site of PCAF

---

The optimal  
calculated geometry  
of the ligand (blue)  
compared with the  
initial experimental  
geometry of the  
ligand (green)



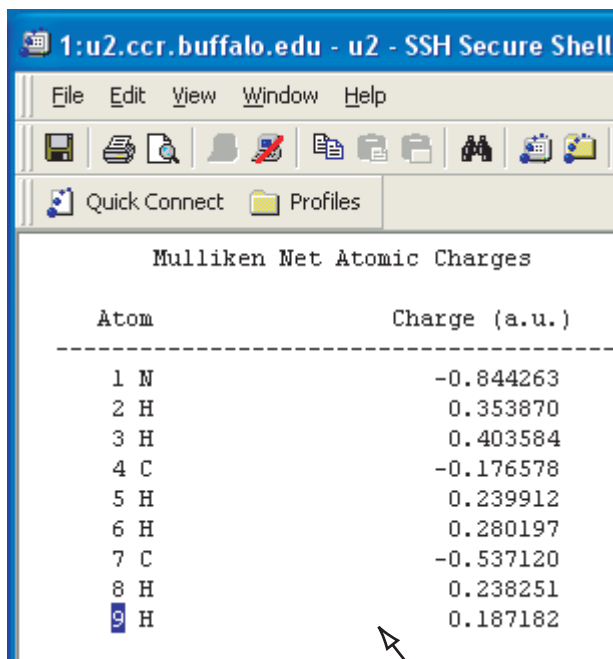
# QM/MM calculations of active site of PCAF

1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell			
File Edit View Window Help			
Quick Connect Profiles			
19	C	-16.610121	-1.606909
20	H	-16.922682	-2.270889
21	C	-16.547519	-0.259033
22	H	-16.653603	0.071960
23	C	-16.241352	0.640167
24	H	-16.181249	1.696333
25	C	-15.817746	0.153650
26	H	-15.476860	0.862122
Point Group: c1 Number of degrees			
Energy is -502.786817363			

1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell			
File Edit View Window Help			
Quick Connect Profiles			
19	C	-16.547087	-1.743349
20	H	-16.937066	-2.450811
21	C	-16.184951	-0.454614
22	H	-16.293020	-0.151007
23	C	-15.688043	0.445105
24	H	-15.408151	1.452416
25	C	-15.556632	0.055855
26	H	-15.178574	0.768353
Point Group: c1 Number of degrees			
Energy is -444.862055503			

Total energy of the ligand in the protein  
(left) and in the gas phase (right)

# QM/MM calculations of active site of PCAF



1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell

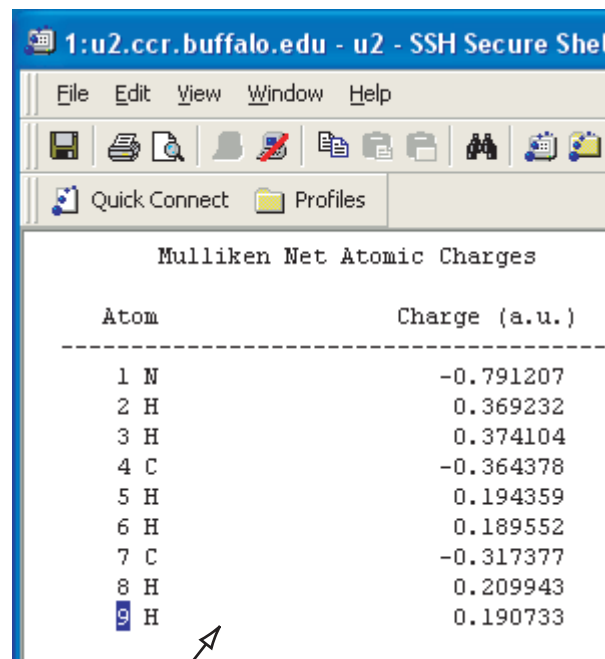
File Edit View Window Help

Quick Connect Profiles

Mulliken Net Atomic Charges

Atom	Charge (a.u.)
1 N	-0.844263
2 H	0.353870
3 H	0.403584
4 C	-0.176578
5 H	0.239912
6 H	0.280197
7 C	-0.537120
8 H	0.238251
9 H	0.187182

Arrows from the caption point to the '9 H' row and the 'Charge (a.u.)' column header.



1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell

File Edit View Window Help

Quick Connect Profiles

Mulliken Net Atomic Charges

Atom	Charge (a.u.)
1 N	-0.791207
2 H	0.369232
3 H	0.374104
4 C	-0.364378
5 H	0.194359
6 H	0.189552
7 C	-0.317377
8 H	0.209943
9 H	0.190733

Arrows from the caption point to the '9 H' row and the 'Charge (a.u.)' column header.

Atomic charges of the ligand in the protein  
(left) and in the gas phase (right)

# QM/MM calculations of active site of PCAF

1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell

File	Edit	View	Window	Help
Quick Connect Profiles				
25	C	-0.407188		
26	H	0.151745		
-----				
Sum of atomic charges =		0.000000		
-----				
Cartesian Multipole Moments				
-----				
Charge (ESU x 10 <sup>10</sup> )				
0.0000				
Dipole Moment (Debye)				
X	2.2011	Y	-2.6519	
Tot	3.4491			

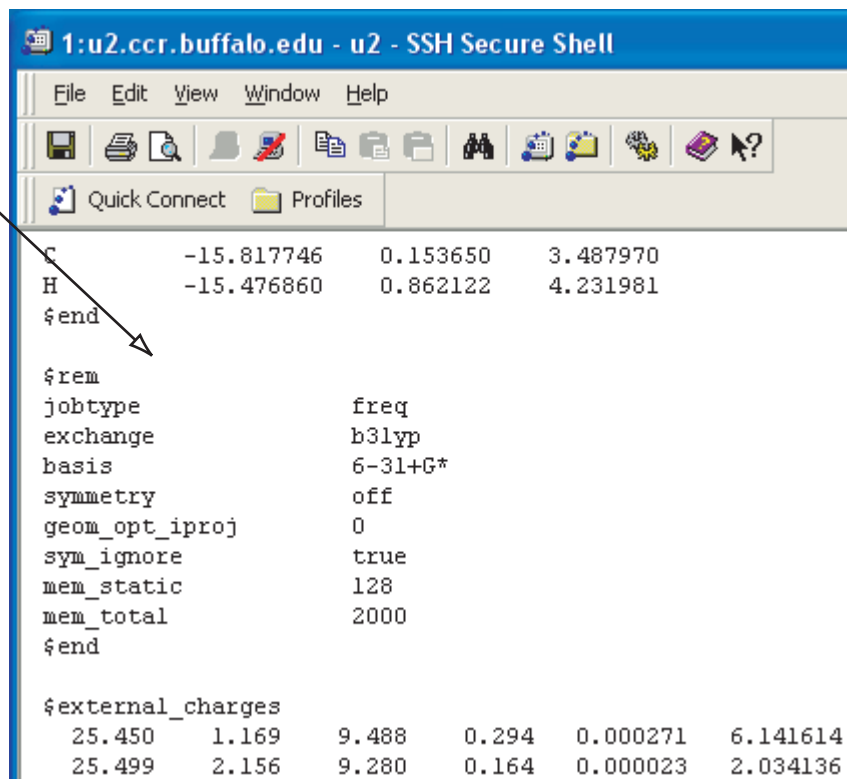
1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell

File	Edit	View	Window	Help
Quick Connect Profiles				
25	C	-0.083434		
26	H	0.173589		
-----				
Sum of atomic charges =		0.000000		
-----				
Cartesian Multipole Moments				
-----				
Charge (ESU x 10 <sup>10</sup> )				
0.0000				
Dipole Moment (Debye)				
X	0.7860	Y	1.2670	
Tot	1.4934			

Dipole moment of the ligand in the protein  
(left) and in the gas phase (right)

# QM/MM calculations of active site of PCAF

Molecular oscillation  
calculations of the ligand  
inside the protein



```
1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell
File Edit View Window Help
[Icons: Save, Print, Find, etc.]
Quick Connect Profiles

C      -15.817746    0.153650    3.487970
H      -15.476860    0.862122    4.231981
$end

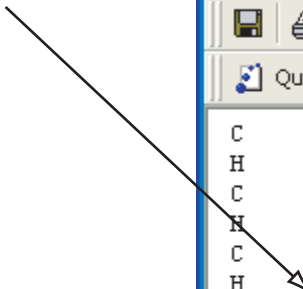
$rem
jobtype          freq
exchange         b3lyp
basis            6-31+G*
symmetry         off
geom_opt_iproj   0
sym_ignore       true
mem_static       128
mem_total        2000
$end

$external_charges
  25.450    1.169    9.488    0.294    0.000271    6.141614
  25.499    2.156    9.280    0.164    0.000023    2.034136
```



# QM/MM calculations of active site of PCAF

Final results of the  
oscillation hessian  
calculations



1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell

C	0.001	-0.007	0.003	0.000	0.000	0.000
H	-0.003	0.052	-0.010	0.000	-0.001	0.000
C	-0.023	-0.051	-0.058	0.000	0.000	0.000
H	0.279	0.658	0.691	0.000	0.000	0.000
C	-0.001	0.002	-0.007	0.000	0.000	0.000
H	0.007	-0.020	0.053	0.000	0.000	0.000
C	0.000	0.000	0.000	0.000	0.000	0.000
H	-0.001	-0.008	-0.001	0.000	0.000	0.000
C	0.000	0.000	0.000	0.000	0.000	0.000
H	-0.003	-0.007	-0.008	0.000	0.000	0.000

STANDARD THERMODYNAMIC QUANTITIES AT 298.18 K AND

This Molecule has 0 Imaginary Frequencies  
Zero point vibrational energy: 150.925 kcal/mol

# QM/MM calculations of active site of PCAF

1:u2.ccr.buffalo.edu - u2 - SSH Sec

File	Edit	View	Window	Help
Quick Connect	Profiles			

Mode:	70		
Frequency:	3390.46		
Force Cnst:	7.3244		
Red. Mass:	1.0814		
IR Active:	YES		
IR Intens:	56.915		
Raman Active:	YES		
	X	Y	Z
N	0.000	0.000	0.000
H	0.000	0.000	0.000
H	0.001	0.000	0.001
C	0.000	0.000	0.001
H	0.000	0.001	0.001

2:u2.ccr.buffalo.edu - u2 - SSH Sec

File	Edit	View	Window	Help
Quick Connect	Profiles			

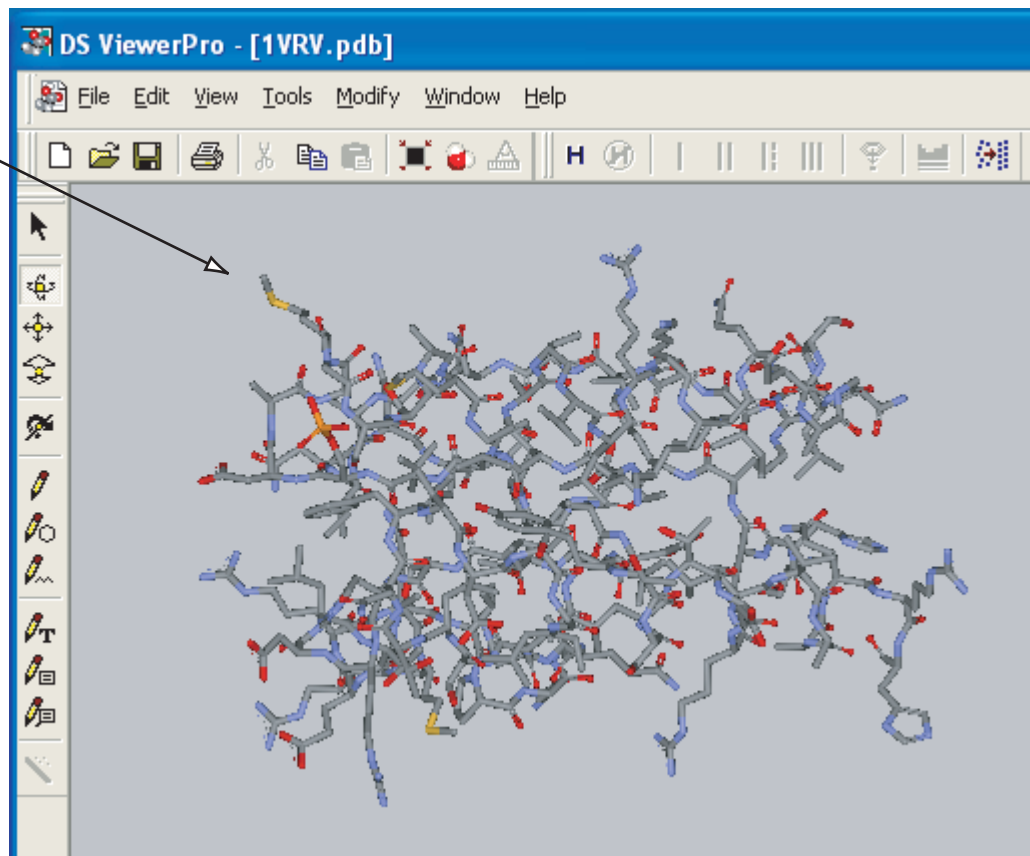
Mode:	70		
Frequency:	3670.06		
Force Cnst:	8.3844		
Red. Mass:	1.0565		
IR Active:	YES		
IR Intens:	45.085		
Raman Active:	YES		
	X	Y	Z
N	0.002	0.002	0.003
H	0.003	0.002	0.003
H	0.002	0.001	0.002
C	0.000	0.000	0.003
H	0.003	-0.009	0.002

High frequency oscillations of the ligand in the protein (left) and in the gas phase (right)

# QM/MM calculations of active site of mannitol enzyme

---

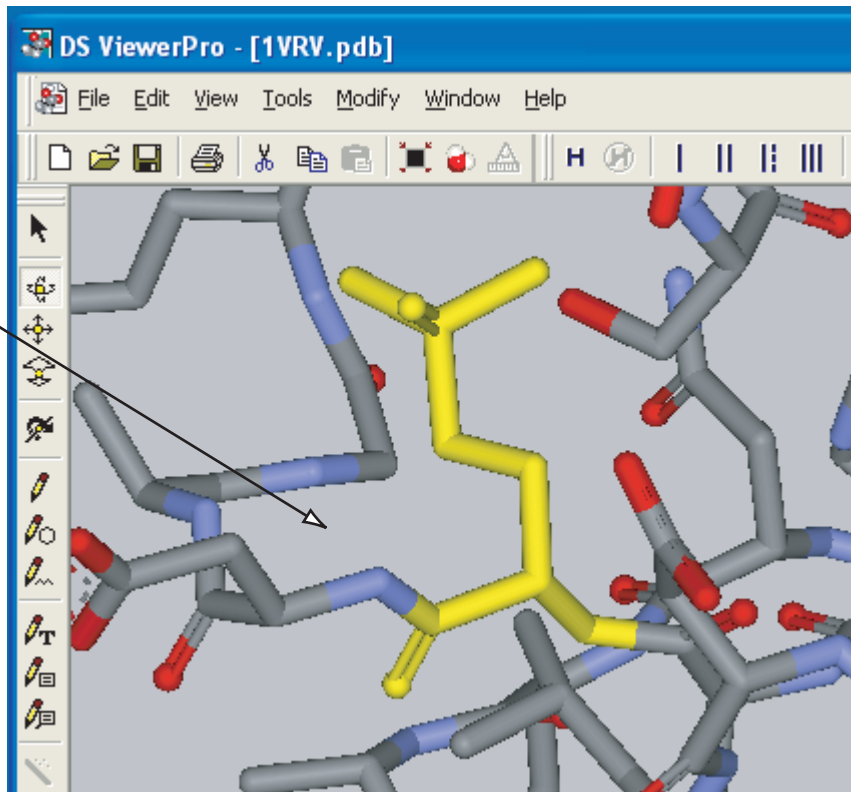
Experimental  
structure of the  
mannitol enzyme



# QM/MM calculations of active site of mannitol enzyme

---

The active site of the enzyme, which is connected by two chemical bonds with the protein backbone

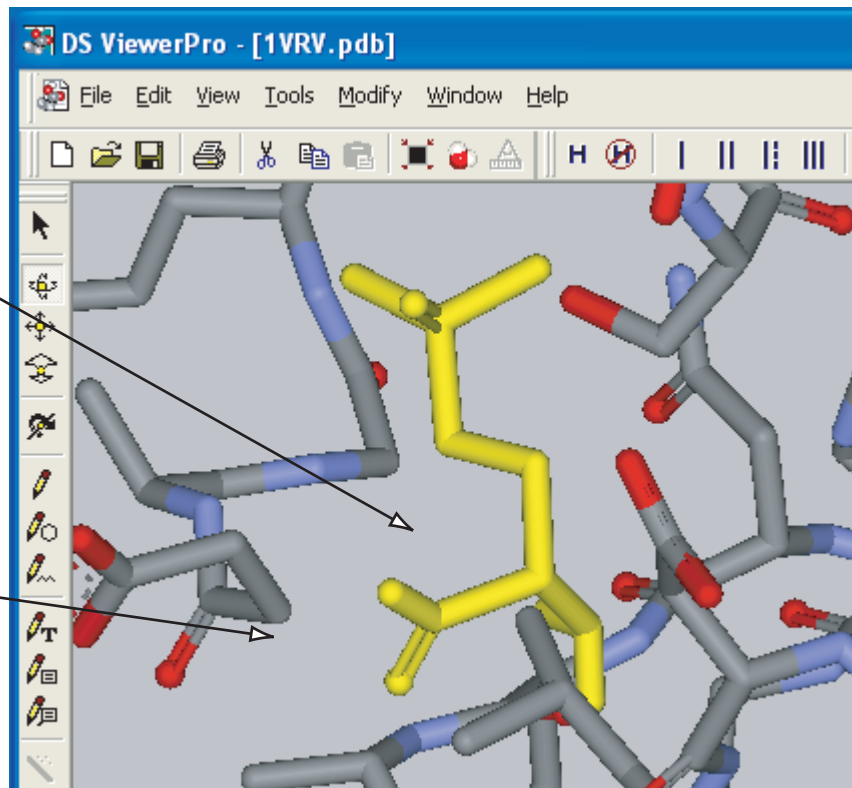


# QM/MM calculations of active site of mannitol enzyme

---

Two chemical bonds have been cut, and free chemical valences of the active site have been filled out by hydrogens

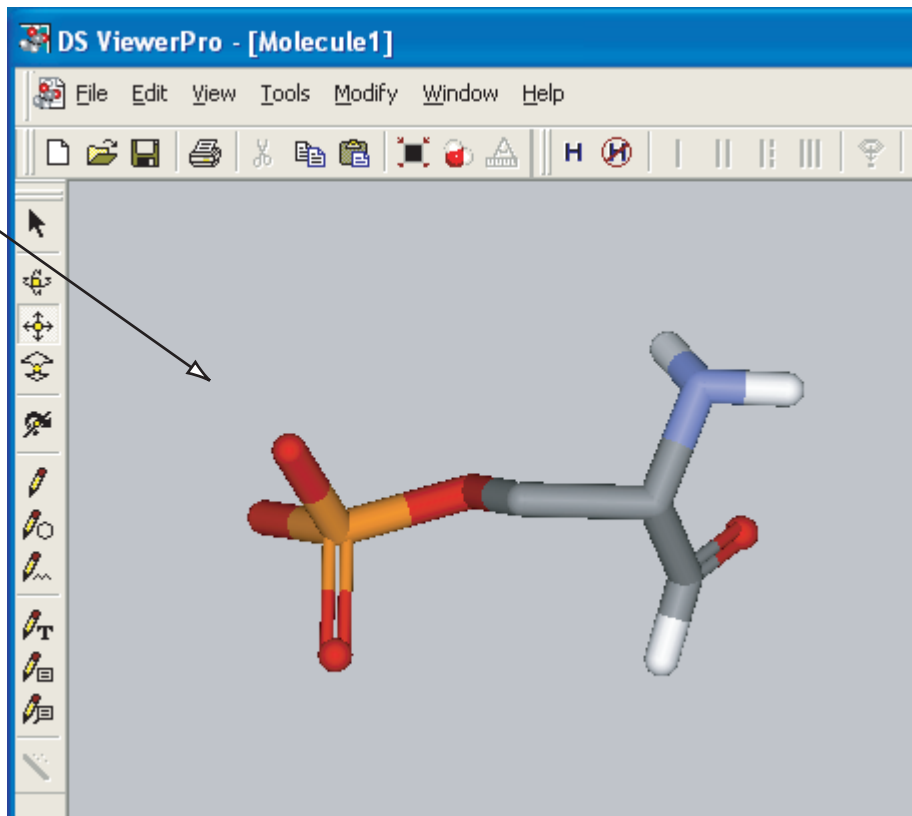
Heavy atoms from both sides of the backbone have been removed



# QM/MM calculations of active site of mannitol enzyme

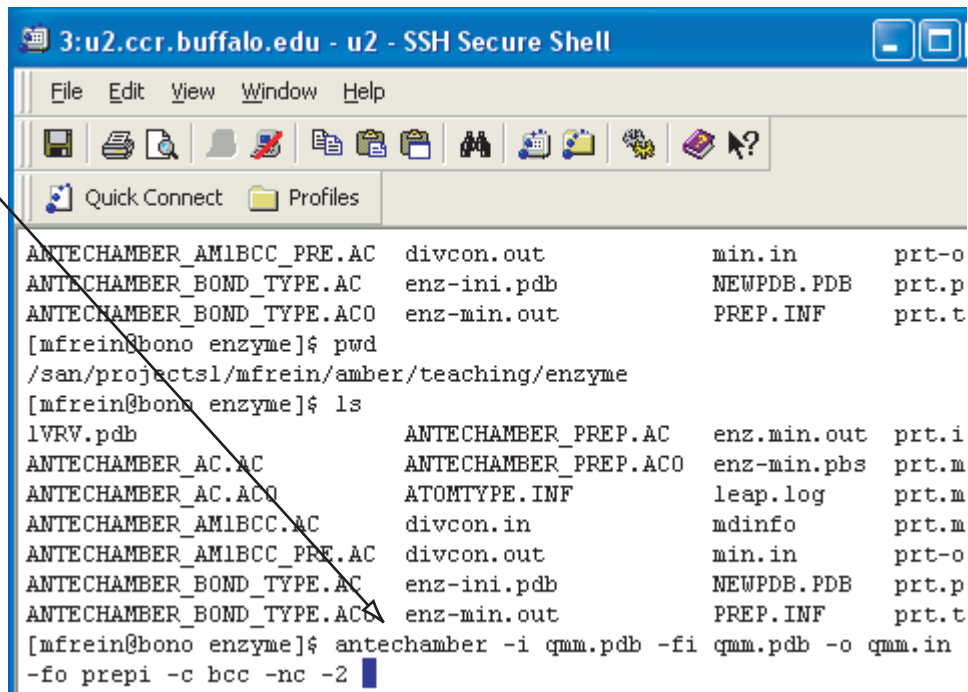
---

The active site of the enzyme has been temporary separated from the protein structure



# QM/MM calculations of active site of mannitol enzyme

The "antechamber" program has been used to generate the preparation file of the active site



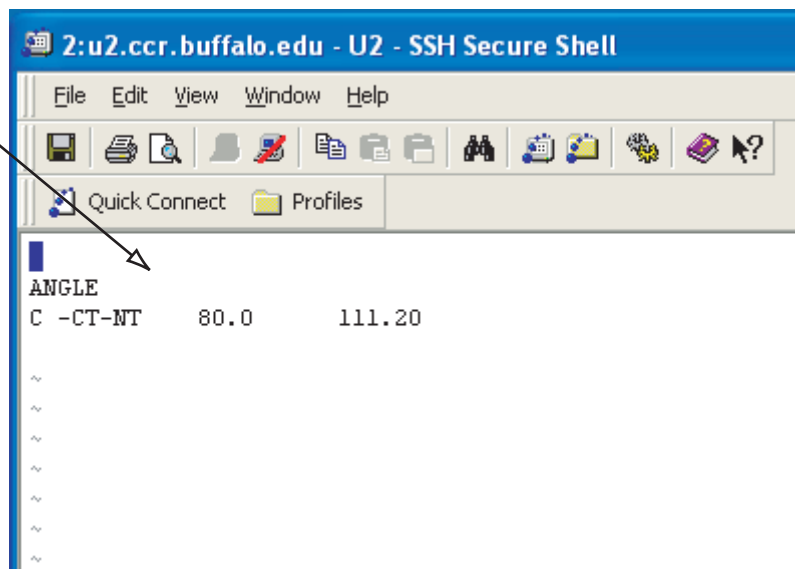
The screenshot shows a terminal window titled "3:u2.ccr.buffalo.edu - u2 - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons. The terminal displays the following commands and output:

```
[mfrein@bono enzyme]$ pwd
/san/projects1/mfrein/amber/teaching/enzyme
[mfrein@bono enzyme]$ ls
lvrv.pdb          ANTECHAMBER_PREP.AC  enz.min.out  prt.i
ANTECHAMBER_AC.AC ANTECHAMBER_PREP.ACO enz-min.pbs  prt.m
ANTECHAMBER_AC.ACO ATOMTYPE.INFO        leap.log     prt.m
ANTECHAMBER_AM1BCC.AC  divcon.in            mdinfo       prt.m
ANTECHAMBER_AM1BCC_PRE.AC  divcon.out          min.in       prt-o
ANTECHAMBER_BOND_TYPE.AC  enz-ini.pdb          NEWPDB.PDB  prt.p
ANTECHAMBER_BOND_TYPE.ACO enz-min.out           PREP.INFO   prt.t
[mfrein@bono enzyme]$ antechamber -i qmm.pdb -fi qmm.pdb -o qmm.in
-fs prep -c bcc -nc -2
```

# QM/MM calculations of active site of mannitol enzyme

---

Missing parameters  
of the active site  
have been included  
in the parameter file

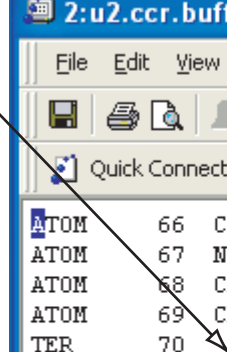




# QM/MM calculations of active site of mannitol enzyme

---

The new pdb structure of the active site has been merged with the protein structure

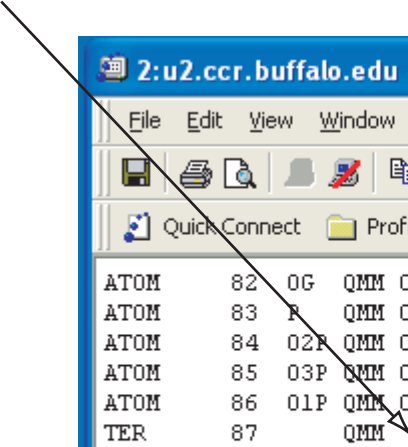


2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell

File	Edit	View	Window	Help			
Quick Connect	Profiles						
ATOM	66	CG2	VAL	A 382	112.510	6.877	-16.248
ATOM	67	N	ALA	A 383	111.745	2.288	-16.184
ATOM	68	CA	ALA	A 383	111.135	1.040	-15.738
ATOM	69	CB	ALA	A 383	111.354	-0.043	-16.783
TER	70		ALA	383			
ATOM	71	O	QMM	C 1	109.869	-2.599	-13.011
ATOM	72	C	QMM	C 1	110.642	-2.124	-12.178
ATOM	73	HC	QMM	C 1	110.834	-2.630	-11.337
ATOM	74	CA	QMM	C 1	111.310	-0.773	-12.414
ATOM	75	N	QMM	C 1	110.907	-0.240	-13.709
ATOM	76	HT1	QMM	C 1	109.914	-0.124	-13.728
ATOM	77	HT2	QMM	C 1	111.182	-0.874	-14.431

# QM/MM calculations of active site of mannitol enzyme

The main backbone of the protein has been divided into three chains



2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell

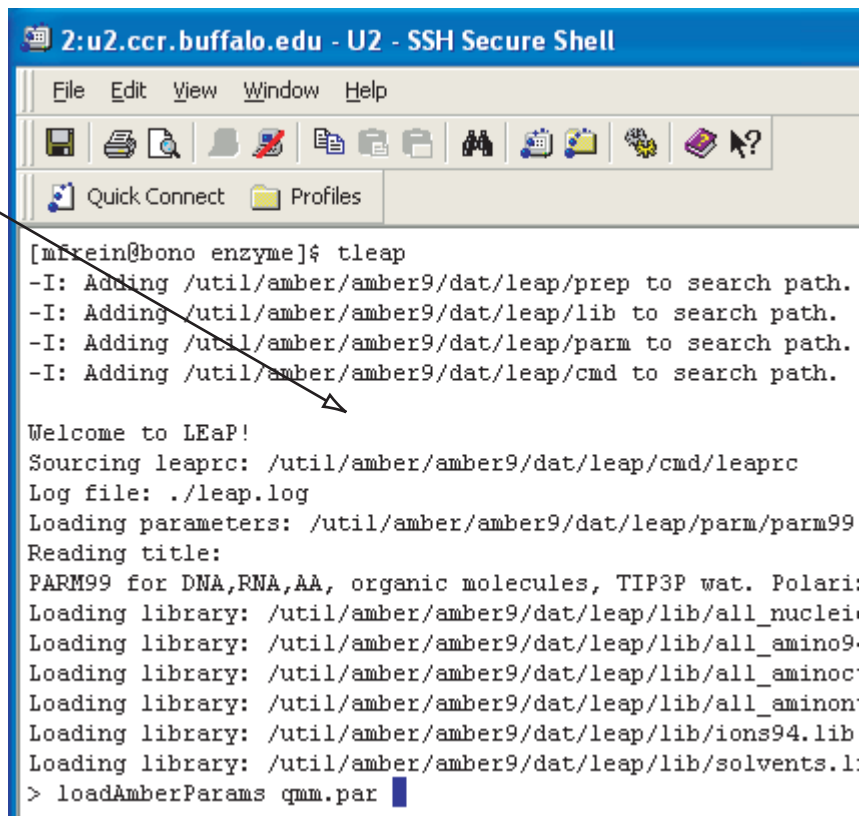
File Edit View Window Help

Quick Connect Profiles

ATOM	82	OG	QMM	C	1	109.531	-0.054	-10.974
ATOM	83	P	QMM	C	1	109.460	0.686	-9.516
ATOM	84	O2P	QMM	C	1	108.027	0.659	-9.009
ATOM	85	O3P	QMM	C	1	110.355	-0.038	-8.521
ATOM	86	O1P	QMM	C	1	109.916	2.129	-9.652
TER	87		QMM		1			
ATOM	88	CA	ASP	B	385	110.303	-4.004	-10.664
ATOM	89	C	ASP	B	385	108.793	-3.949	-10.804
ATOM	90	O	ASP	B	385	108.198	-4.718	-11.560
ATOM	91	CB	ASP	B	385	110.668	-4.362	-9.225
ATOM	92	CG	ASP	B	385	110.023	-5.689	-8.837
ATOM	93	OD1	ASP	B	385	109.198	-6.167	-9.596

# QM/MM calculations of active site of mannitol enzyme

The "tleap" program has been used to generate the topology and PDB file of the enzyme with the modified active site



```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

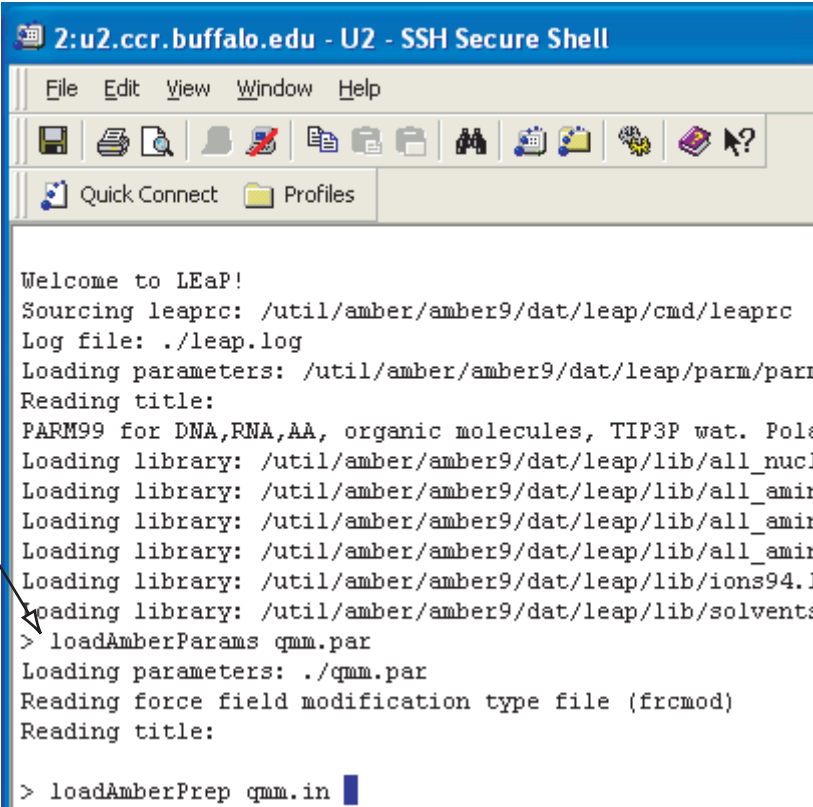
[mfrein@bono enzyme]$ tleap
-I: Adding /util/amber/amber9/dat/leap/parm to search path.
-I: Adding /util/amber/amber9/dat/leap/lib to search path.
-I: Adding /util/amber/amber9/dat/leap/parm to search path.
-I: Adding /util/amber/amber9/dat/leap/cmd to search path.

Welcome to LEaP!
Sourcing leaprc: /util/amber/amber9/dat/leap/cmd/leaprc
Log file: ./leap.log
Loading parameters: /util/amber/amber9/dat/leap/parm/parm99
Reading title:
PARM99 for DNA, RNA, AA, organic molecules, TIP3P wat. Polari:
Loading library: /util/amber/amber9/dat/leap/lib/all_nuclei
Loading library: /util/amber/amber9/dat/leap/lib/all_aminos
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc
Loading library: /util/amber/amber9/dat/leap/lib/all_aminon
Loading library: /util/amber/amber9/dat/leap/lib/ions94.lib
Loading library: /util/amber/amber9/dat/leap/lib/solvents.1
> loadAmberParams qmm.par
```

# QM/MM calculations of active site of mannitol enzyme

---

First the parameter and the preparation files of the active site have been loaded

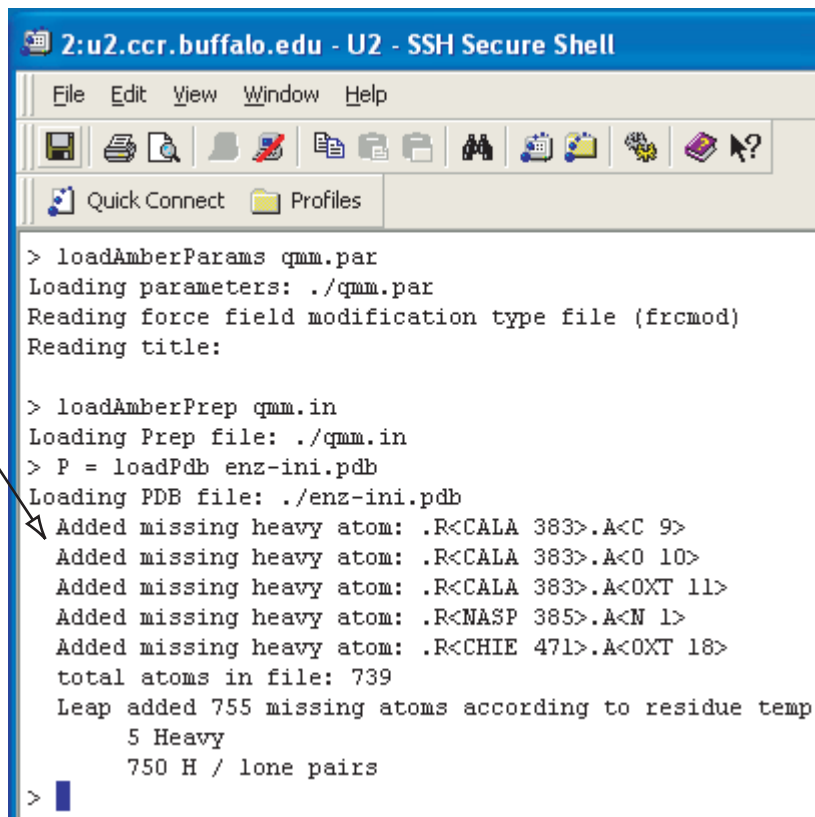


```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

Welcome to LEaP!
Sourcing leaprc: /util/amber/amber9/dat/leap/cmd/leaprc
Log file: ./leap.log
Loading parameters: /util/amber/amber9/dat/leap/parm/parm
Reading title:
PARM99 for DNA,RNA,AA, organic molecules, TIP3P wat. Pols
Loading library: /util/amber/amber9/dat/leap/lib/all_nucl
Loading library: /util/amber/amber9/dat/leap/lib/all_amir
Loading library: /util/amber/amber9/dat/leap/lib/all_amir
Loading library: /util/amber/amber9/dat/leap/lib/all_amir
Loading library: /util/amber/amber9/dat/leap/lib/ions94.l
Loading library: /util/amber/amber9/dat/leap/lib/solvents
> loadAmberParams qmm.par
Loading parameters: ./qmm.par
Reading force field modification type file (frcmod)
Reading title:
> loadAmberPrep qmm.in
```

# QM/MM calculations of active site of mannitol enzyme

After loading the PDB file of the system, the program generated additional atoms



```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

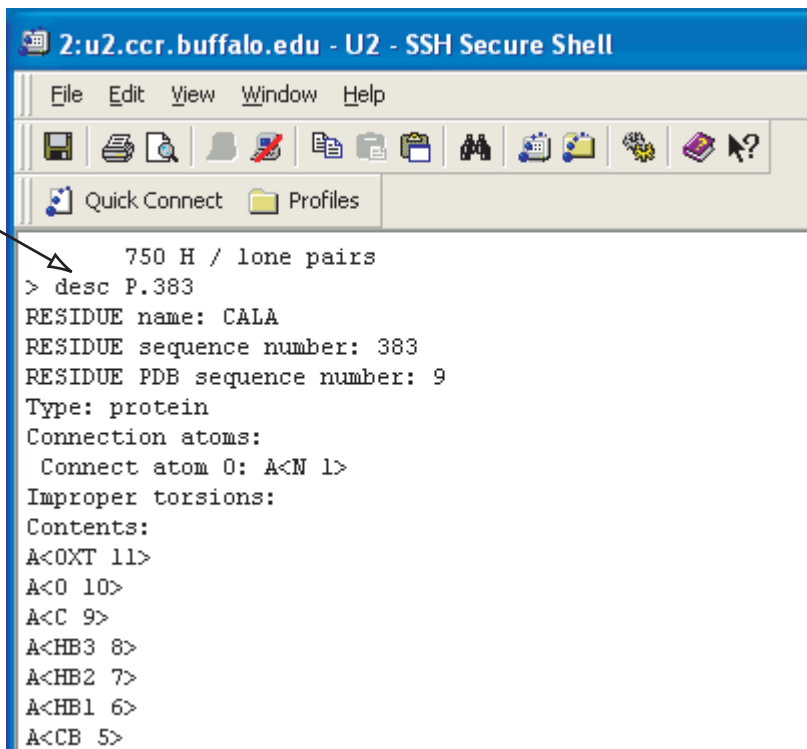
> loadAmberParams qmm.par
Loading parameters: ./qmm.par
Reading force field modification type file (frcmod)
Reading title:

> loadAmberPrep qmm.in
Loading Prep file: ./qmm.in
> P = loadPdb enz-ini.pdb
Loading PDB file: ./enz-ini.pdb
Added missing heavy atom: .R<CALA 383>.A<C 9>
Added missing heavy atom: .R<CALA 383>.A<O 10>
Added missing heavy atom: .R<CALA 383>.A<OXT 11>
Added missing heavy atom: .R<NASP 385>.A<N 1>
Added missing heavy atom: .R<CHIE 471>.A<OXT 18>
total atoms in file: 739
Leap added 755 missing atoms according to residue temp
5 Heavy
750 H / lone pairs
>
```

# QM/MM calculations of active site of mannitol enzyme

---

The "desc" command has been used for description of the ALA residue



The screenshot shows a terminal window titled "2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons. The terminal output shows the command "> desc P.383" and its results:

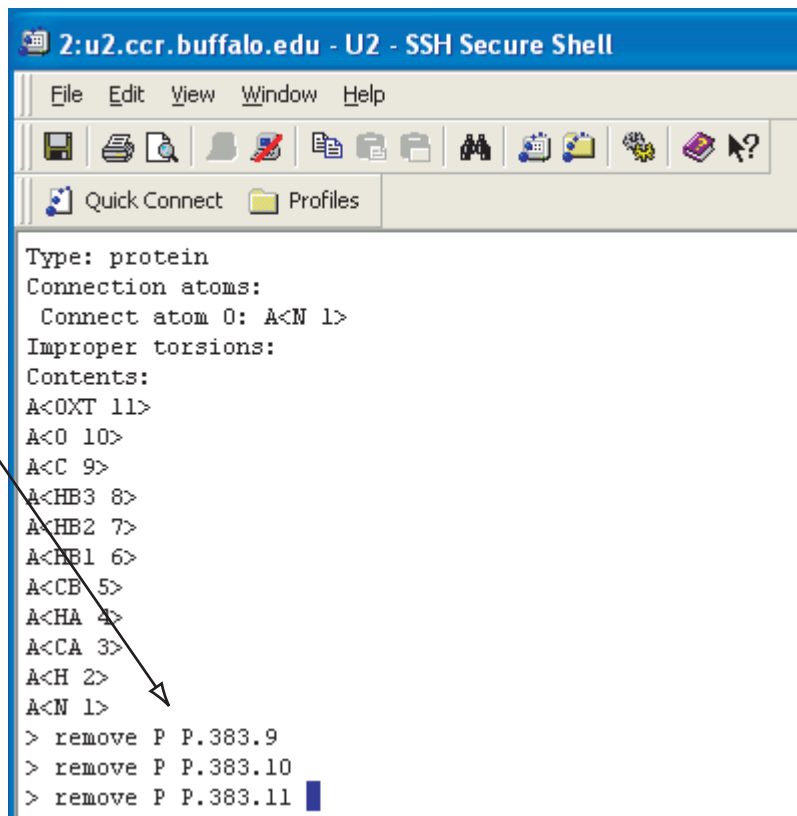
```
750 H / lone pairs
> desc P.383
RESIDUE name: CALA
RESIDUE sequence number: 383
RESIDUE PDB sequence number: 9
Type: protein
Connection atoms:
  Connect atom 0: A<N 1>
Improper torsions:
Contents:
A<OXT 11>
A<O 10>
A<C 9>
A<HB3 8>
A<HB2 7>
A<HB1 6>
A<CB 5>
```

An arrow from the text "The 'desc' command has been used for description of the ALA residue" points to the "desc P.383" command in the terminal output.

# QM/MM calculations of active site of mannitol enzyme

---

The "remove" command has been used to delete atoms between the protein and the active site



```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

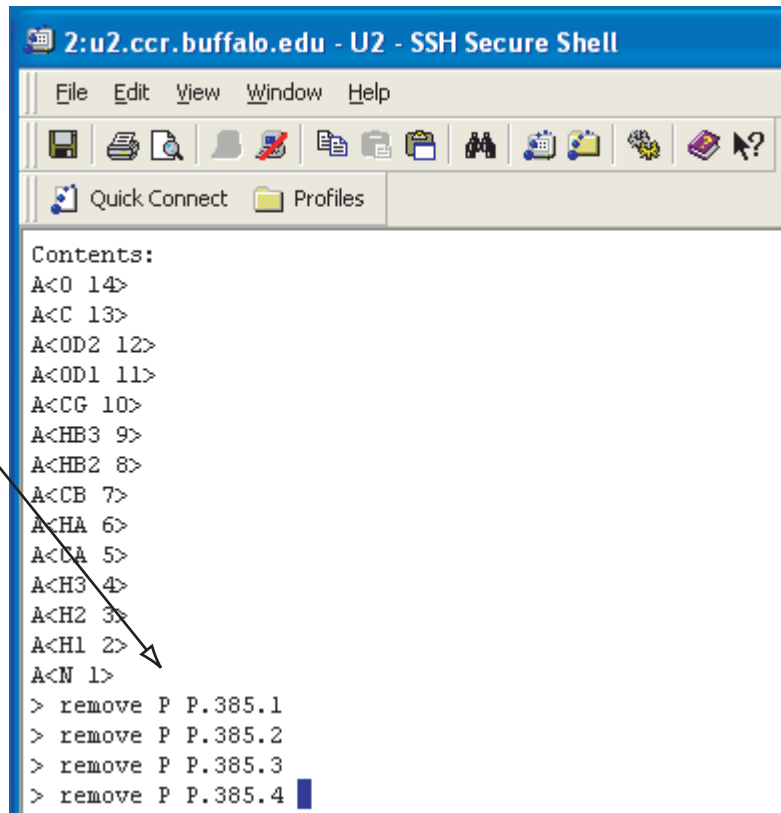
Type: protein
Connection atoms:
  Connect atom 0: A<N 1>
Improper torsions:
Contents:
A<OXT 11>
A<O 10>
A<C 9>
A<HB3 8>
A<HB2 7>
A<HB1 6>
A<CB 5>
A<HA 4>
A<CA 3>
A<H 2>
A<N 1>
> remove P P.383.9
> remove P P.383.10
> remove P P.383.11
```

An arrow points from the text "The 'remove' command has been used to delete atoms between the protein and the active site" to the 'remove' commands in the terminal window.

# QM/MM calculations of active site of mannitol enzyme

---

In the similar way, protein atoms from the other side of the active site have been removed



```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

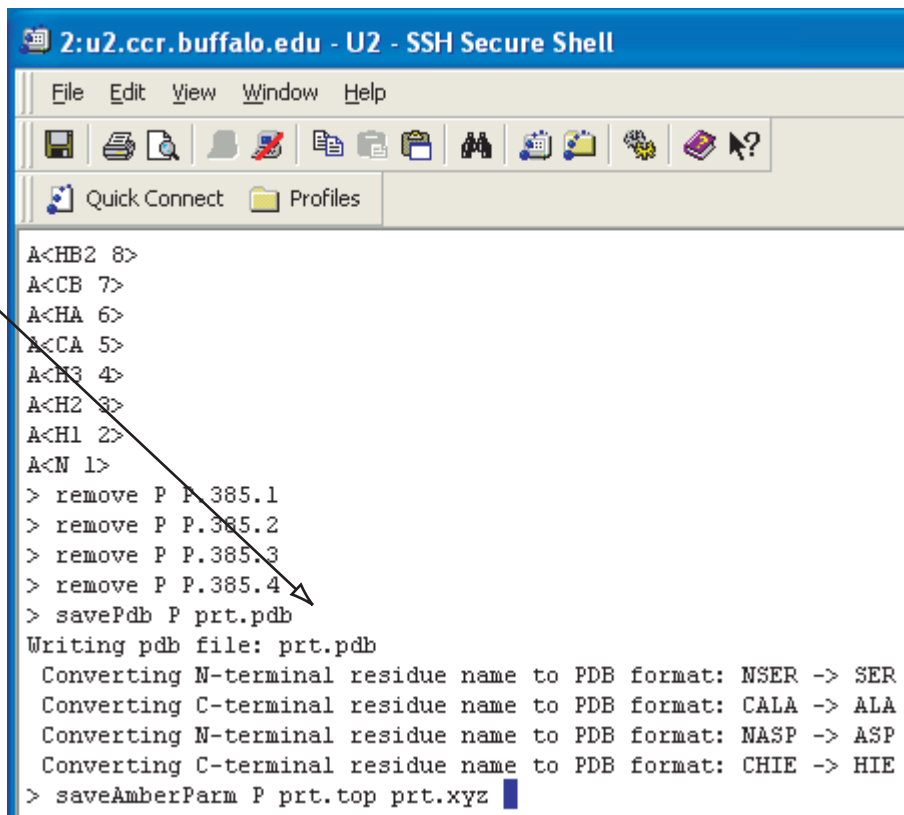
Contents:
A<O 14>
A<C 13>
A<OD2 12>
A<OD1 11>
A<CG 10>
A<HB3 9>
A<HB2 8>
A<CB 7>
A<HA 6>
A<OA 5>
A<H3 4>
A<H2 3>
A<H1 2>
A<N 1>
> remove P P.385.1
> remove P P.385.2
> remove P P.385.3
> remove P P.385.4
```



# QM/MM calculations of active site of mannitol enzyme

---

The PDB file, the topology file and the coordinates file have been saved



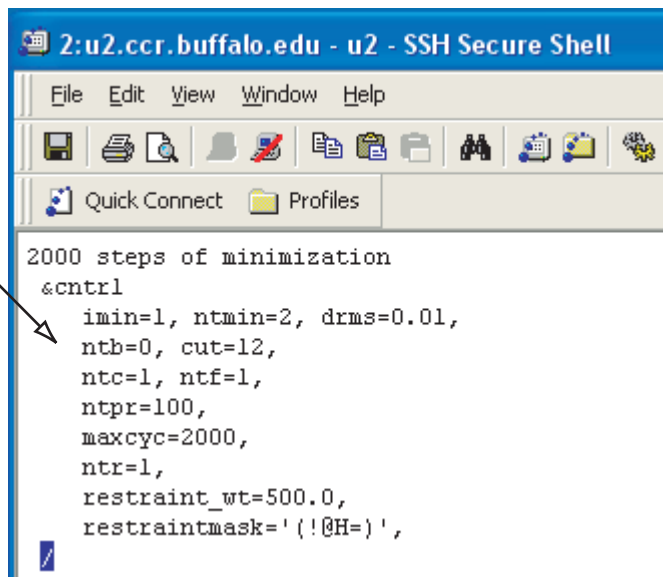
```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

A<HB2 8>
A<CB 7>
A<HA 6>
A<CA 5>
A<H3 4>
A<H2 3>
A<H1 2>
A<N 1>
> remove P P.385.1
> remove P P.385.2
> remove P P.385.3
> remove P P.385.4
> savePdb P prt.pdb
Writing pdb file: prt.pdb
  Converting N-terminal residue name to PDB format: NSER -> SER
  Converting C-terminal residue name to PDB format: CALA -> ALA
  Converting N-terminal residue name to PDB format: NASP -> ASP
  Converting C-terminal residue name to PDB format: CHIE -> HIE
> saveAmberParm P prt.top prt.xyz
```

# QM/MM calculations of active site of mannitol enzyme

---

The input file for  
minimization of all  
hydrogens



The image shows a terminal window titled "2:u2.ccr.buffalo.edu - u2 - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons. The main area of the terminal displays the following text:

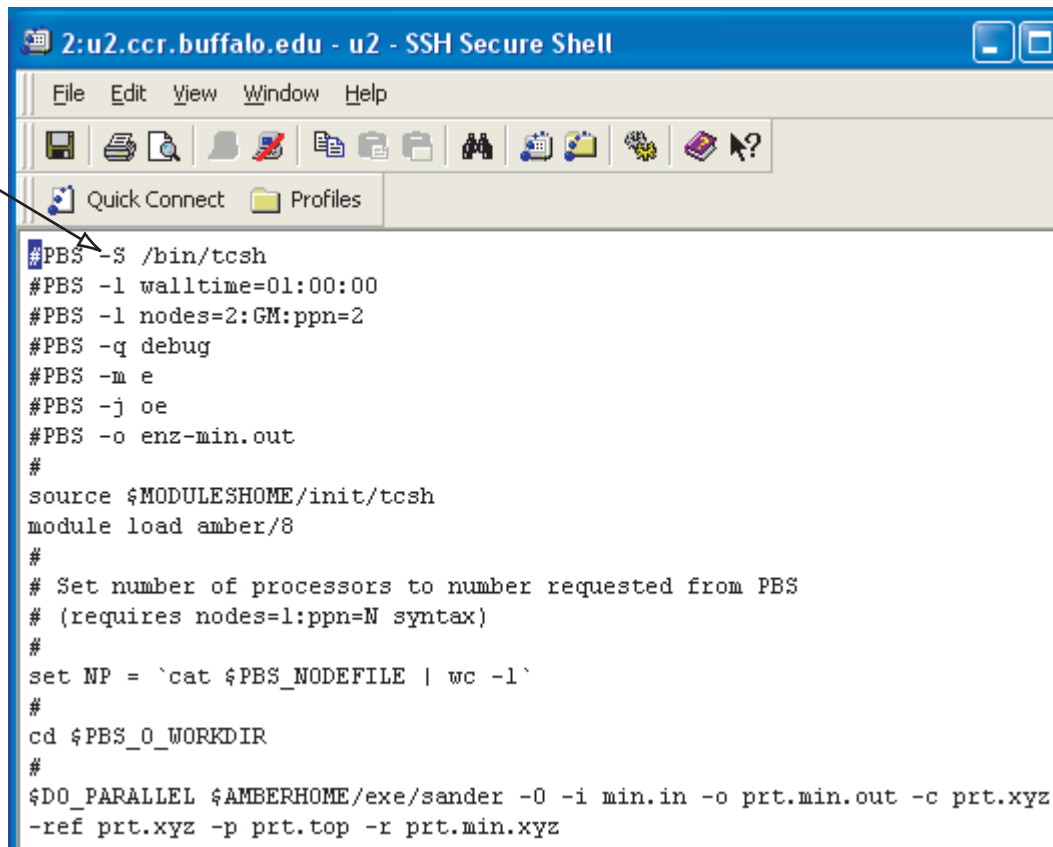
```
2000 steps of minimization
&cntrl
  imin=1, ntmin=2, drms=0.01,
  nth=0, cut=12,
  ntc=1, ntf=1,
  ntpr=100,
  maxcyc=2000,
  ntr=1,
  restraint_wt=500.0,
  restraintmask='(!@H=)',
```

An arrow points from the text "The input file for minimization of all hydrogens" to the line "restraintmask='(!@H=)'," in the terminal output.

# QM/MM calculations of active site of mannitol enzyme

---

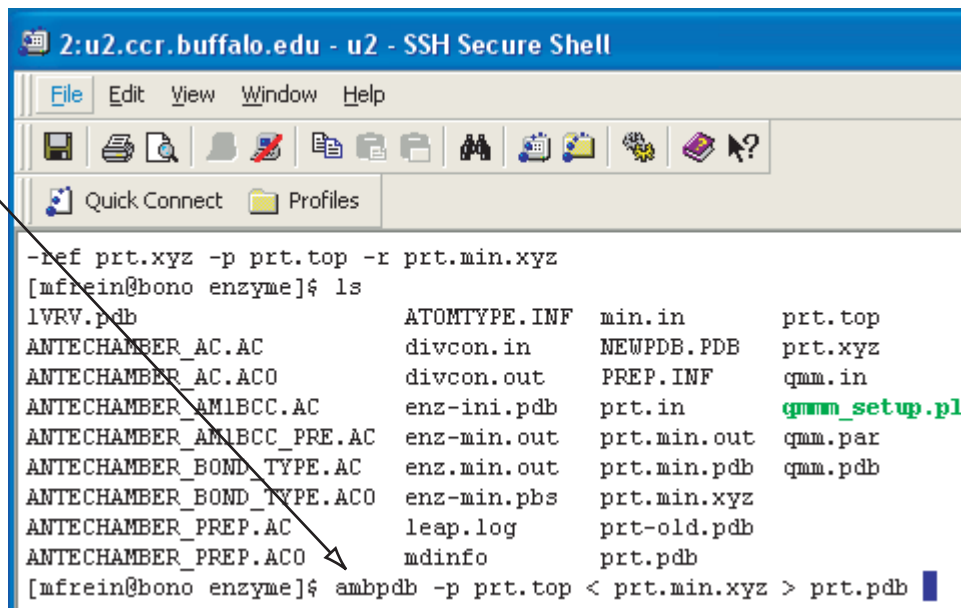
The pbs  
script for  
minimization

A screenshot of an SSH Secure Shell window titled "2:u2.ccr.buffalo.edu - u2 - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons for file operations and system functions. The main area of the window displays a PBS script for minimization. The script starts with "#PBS -S /bin/tcsh" and includes various PBS directives like "#PBS -l walltime=01:00:00", "#PBS -l nodes=2:GM:ppn=2", "#PBS -q debug", "#PBS -m e", "#PBS -j oe", and "#PBS -o enz-min.out". It then sources the tcsh module, loads the amber/8 module, and sets the number of processors (NP) based on the PBS nodefile. Finally, it runs the sander program with specific input and output files for minimization. An arrow points from the text "The pbs script for minimization" to the first line of the script, "#PBS -S /bin/tcsh".

```
#PBS -S /bin/tcsh
#PBS -l walltime=01:00:00
#PBS -l nodes=2:GM:ppn=2
#PBS -q debug
#PBS -m e
#PBS -j oe
#PBS -o enz-min.out
#
source $MODULESHOME/init/tcsh
module load amber/8
#
# Set number of processors to number requested from PBS
# (requires nodes=1:ppn=N syntax)
#
set NP = `cat $PBS_NODEFILE | wc -l`
#
cd $PBS_O_WORKDIR
#
$DO_PARALLEL $AMBERHOME/exe/sander -O -i min.in -o prt.min.out -c prt.xyz
-ref prt.xyz -p prt.top -r prt.min.xyz
```

# QM/MM calculations of active site of mannitol enzyme

Generating the  
pdb file from  
the minimized  
protein  
coordinates

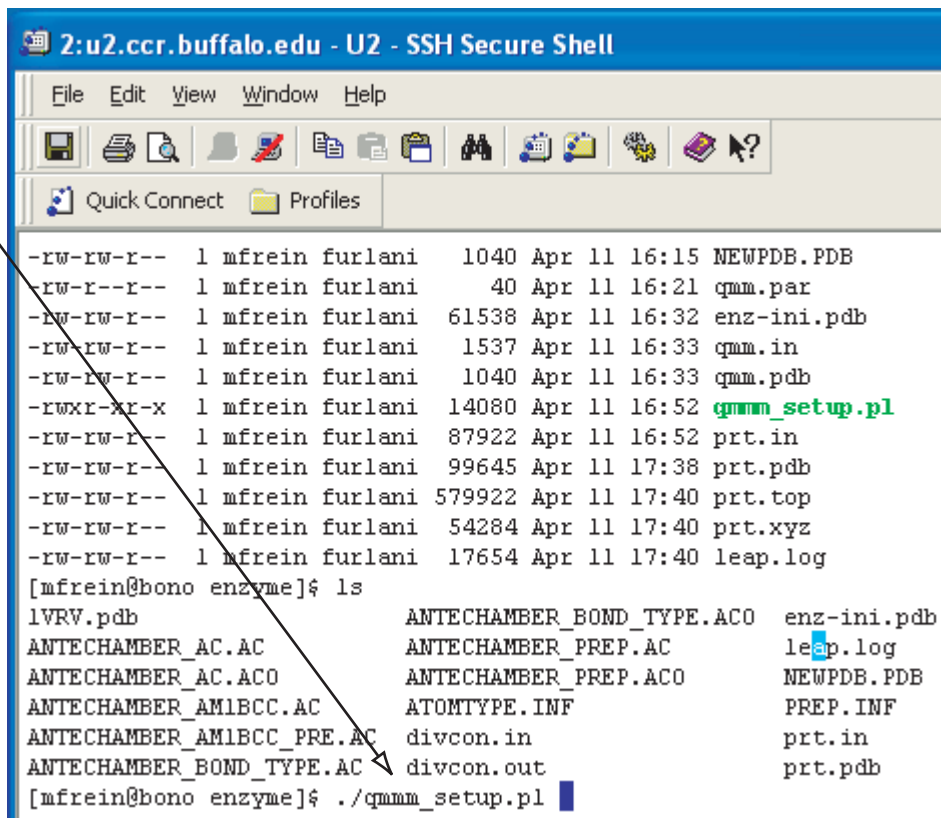


The screenshot shows a terminal window titled "2:u2.ccr.buffalo.edu - u2 - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons. The terminal content shows a user prompt "[mfrein@bono enzyme]" followed by a command "ls" which lists several files. An arrow points from the text "Generating the pdb file from the minimized protein coordinates" to the file "prtd.pdb" in the list. Below the list, the user enters the command "ambpdb -p prt.top < prt.min.xyz > prt.pdb".

```
-ref prt.xyz -p prt.top -r prt.min.xyz
[mfrein@bono enzyme]$ ls
lvrv.pdb          ATOMTYPE.INF    min.in          prt.top
ANTECHAMBER_AC.AC  divcon.in       NEWPDB.PDB     prt.xyz
ANTECHAMBER_AC.ACO  divcon.out      PREP.INF       qmm.in
ANTECHAMBER_AMBCC.AC  enz-ini.pdb    prt.in         qmm_setup.pl
ANTECHAMBER_AMBCC_PRE.AC  enz-min.out   prt.min.out    qmm.par
ANTECHAMBER_BOND_TYPE.AC  enz.min.out   prt.min.pdb    qmm.pdb
ANTECHAMBER_BOND_TYPE.ACO  enz-min.pbs   prt.min.xyz
ANTECHAMBER_PREP.AC    leap.log        prt-old.pdb
ANTECHAMBER_PREP.ACO    mdinfo         prt.pdb
[mfrein@bono enzyme]$ ambpdb -p prt.top < prt.min.xyz > prt.pdb
```

# QM/MM calculations of active site of mannitol enzyme

The "qmm\_setup" perl script has been used to create the q-chem input file for the QM/MM calculations



The screenshot shows an SSH Secure Shell window titled "2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell". The window has a menu bar (File, Edit, View, Window, Help) and a toolbar with various icons. Below the toolbar, there is a "Quick Connect" section and a "Profiles" section. The main area displays a file listing for the user "mfrein" on the host "bono" in the directory "enzyme". The listing shows files with permissions, user, group, size, date, time, and filename. The file "qmm\_setup.pl" is highlighted in green. Below the listing, the user enters the command "ls" and the output shows a list of files including "lvr.pdb", "ANTECHAMBER\_AC.AC", "ANTECHAMBER\_AC.ACO", "ANTECHAMBER\_AM1BCC.AC", "ANTECHAMBER\_AM1BCC\_PRE.AC", "ANTECHAMBER\_BOND\_TYPE.AC", "ANTECHAMBER\_BOND\_TYPE.ACO", "ANTECHAMBER\_PREP.AC", "ANTECHAMBER\_PREP.ACO", "ATOMTYPE.INF", "divcon.in", "divcon.out", "enz-ini.pdb", "leap.log", "NEWPDB.PDB", "PREP.INF", "prt.in", and "prt.pdb". The user then enters the command "./qmm\_setup.pl" and the prompt returns.

```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

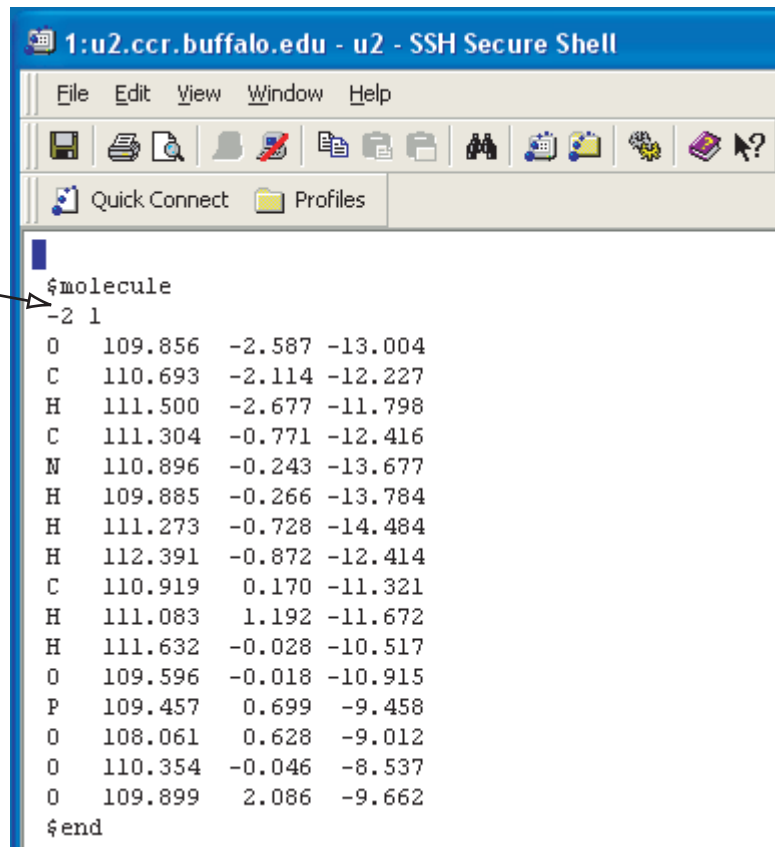
-rw-rw-r-- 1 mfrein furlani 1040 Apr 11 16:15 NEWPDB.PDB
-rw-r--r-- 1 mfrein furlani 40 Apr 11 16:21 qmm.par
-rw-rw-r-- 1 mfrein furlani 61538 Apr 11 16:32 enz-ini.pdb
-rw-rw-r-- 1 mfrein furlani 1537 Apr 11 16:33 qmm.in
-rw-rw-r-- 1 mfrein furlani 1040 Apr 11 16:33 qmm.pdb
-rwxr-xr-x 1 mfrein furlani 14080 Apr 11 16:52 qmm_setup.pl
-rw-rw-r-- 1 mfrein furlani 87922 Apr 11 16:52 prt.in
-rw-rw-r-- 1 mfrein furlani 99645 Apr 11 17:38 prt.pdb
-rw-rw-r-- 1 mfrein furlani 579922 Apr 11 17:40 prt.top
-rw-rw-r-- 1 mfrein furlani 54284 Apr 11 17:40 prt.xyz
-rw-rw-r-- 1 mfrein furlani 17654 Apr 11 17:40 leap.log
[mfrein@bono enzyme]$ ls
lvr.pdb ANTECHAMBER_BOND_TYPE.ACO enz-ini.pdb
ANTECHAMBER_AC.AC ANTECHAMBER_PREP.AC leap.log
ANTECHAMBER_AC.ACO ANTECHAMBER_PREP.ACO NEWPDB.PDB
ANTECHAMBER_AM1BCC.AC ATOMTYPE.INF PREP.INF
ANTECHAMBER_AM1BCC_PRE.AC divcon.in prt.in
ANTECHAMBER_BOND_TYPE.AC divcon.out prt.pdb
[mfrein@bono enzyme]$ ./qmm_setup.pl
```

# QM/MM calculations of active site of mannitol enzyme

---

The q-chem input file  
for the QM/MM  
calculations

The charge of the  
molecule should be  
changed



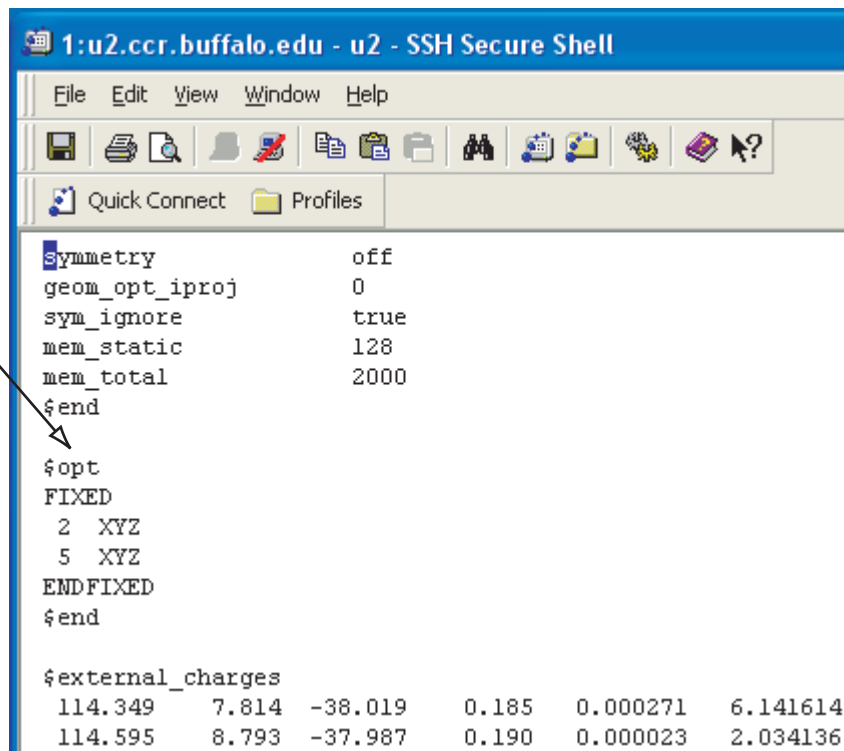
```
1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

$
$molecule
-2 1
O 109.856 -2.587 -13.004
C 110.693 -2.114 -12.227
H 111.500 -2.677 -11.798
C 111.304 -0.771 -12.416
N 110.896 -0.243 -13.677
H 109.885 -0.266 -13.784
H 111.273 -0.728 -14.484
H 112.391 -0.872 -12.414
C 110.919 0.170 -11.321
H 111.083 1.192 -11.672
H 111.632 -0.028 -10.517
O 109.596 -0.018 -10.915
P 109.457 0.699 -9.458
O 108.061 0.628 -9.012
O 110.354 -0.046 -8.537
O 109.899 2.086 -9.662
$end
```

# QM/MM calculations of active site of mannitol enzyme

---

The calculations with  
the fixed position of  
two atoms of the  
ligand



```
1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

Symmetry                off
geom_opt_iproj           0
sym_ignore               true
mem_static               128
mem_total                2000
$end


$opt
FIXED
  2 XYZ
  5 XYZ
ENDFIXED
$end

$external_charges
  114.349    7.814   -38.019    0.185    0.000271    6.141614
  114.595    8.793   -37.987    0.190    0.000023    2.034136
```

# QM/MM calculations of active site of mannitol enzyme

---

The geometry optimization in cartesian coordinates



```
1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell
File Edit View Window Help
[Icons: Save, Print, Find, Copy, Paste, Undo, Redo, Open, Save, Print, Run, Stop, Help, etc.]
Quick Connect Profiles

** GEOMETRY OPTIMIZATION IN CARTESIAN COORDINATES **
Searching for a Minimum

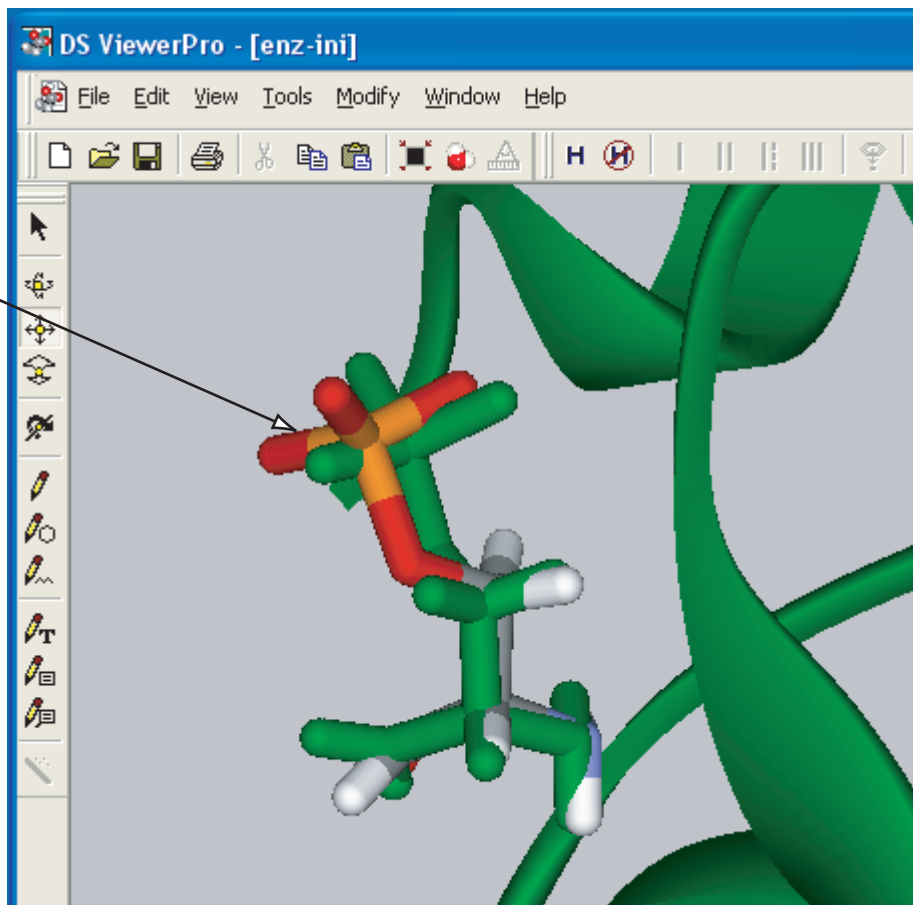
Optimization Cycle: 2

Coordinates (Angstroms)
ATOM      X      Y      Z
1  O      109.495264 -2.390898 -12.977885
2  C      110.497056 -2.072015 -12.352940
3  H      111.299990 -2.783072 -12.074005
4  C      111.063689 -0.649136 -12.498148
5  N      110.762056 -0.188015 -13.883940
6  H      109.779143 -0.342128 -14.102014
7  H      111.320974 -0.786927 -14.475974
8  H      112.156043 -0.795988 -12.440994
```



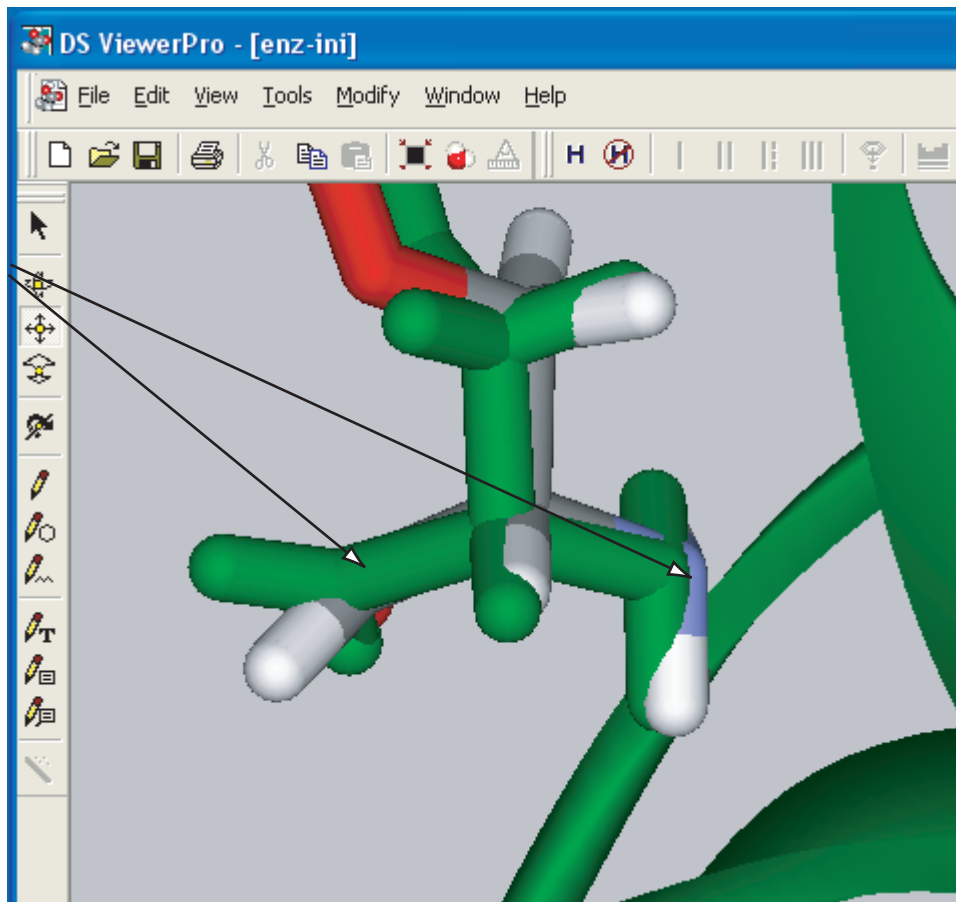
# QM/MM calculations of active site of mannitol enzyme

The calculated optimal geometry and the initial experimental geometry (green) of the ligand in the protein



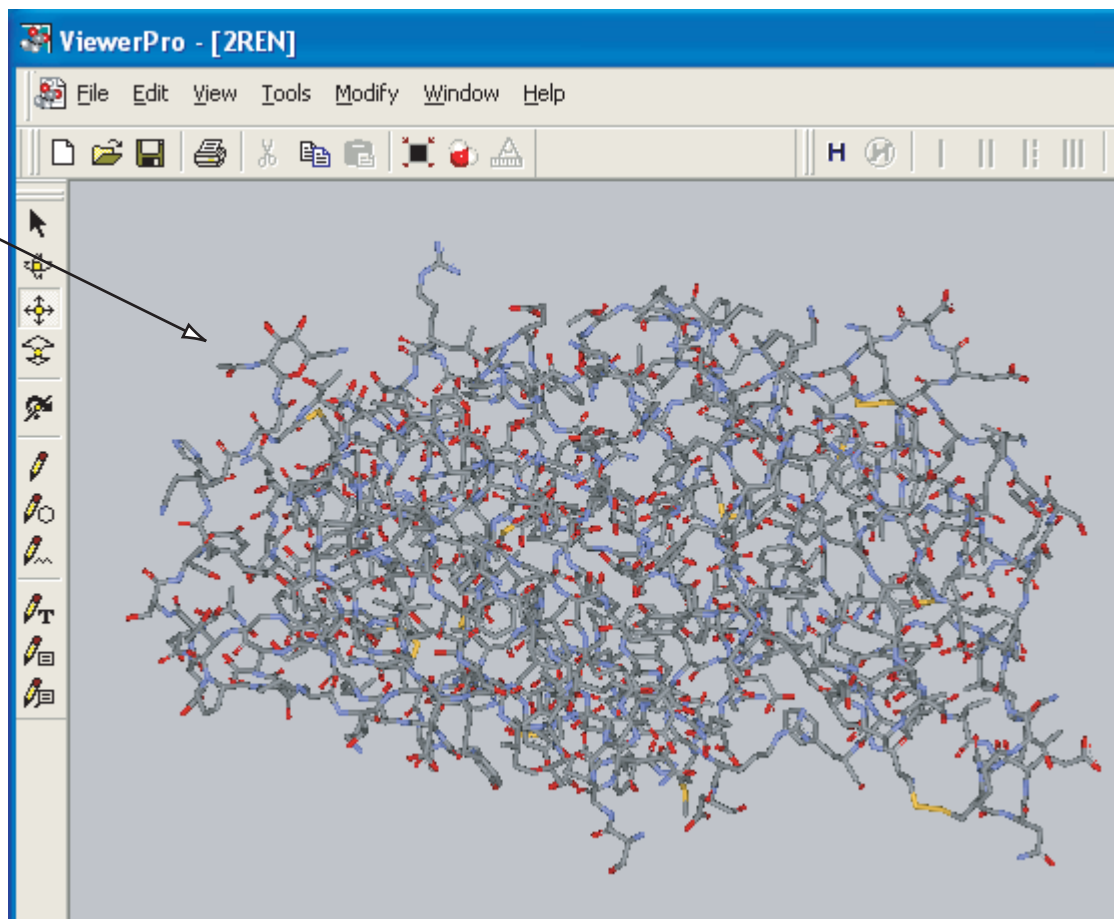
# QM/MM calculations of active site of mannitol enzyme

The fixed atoms used  
in the calculations



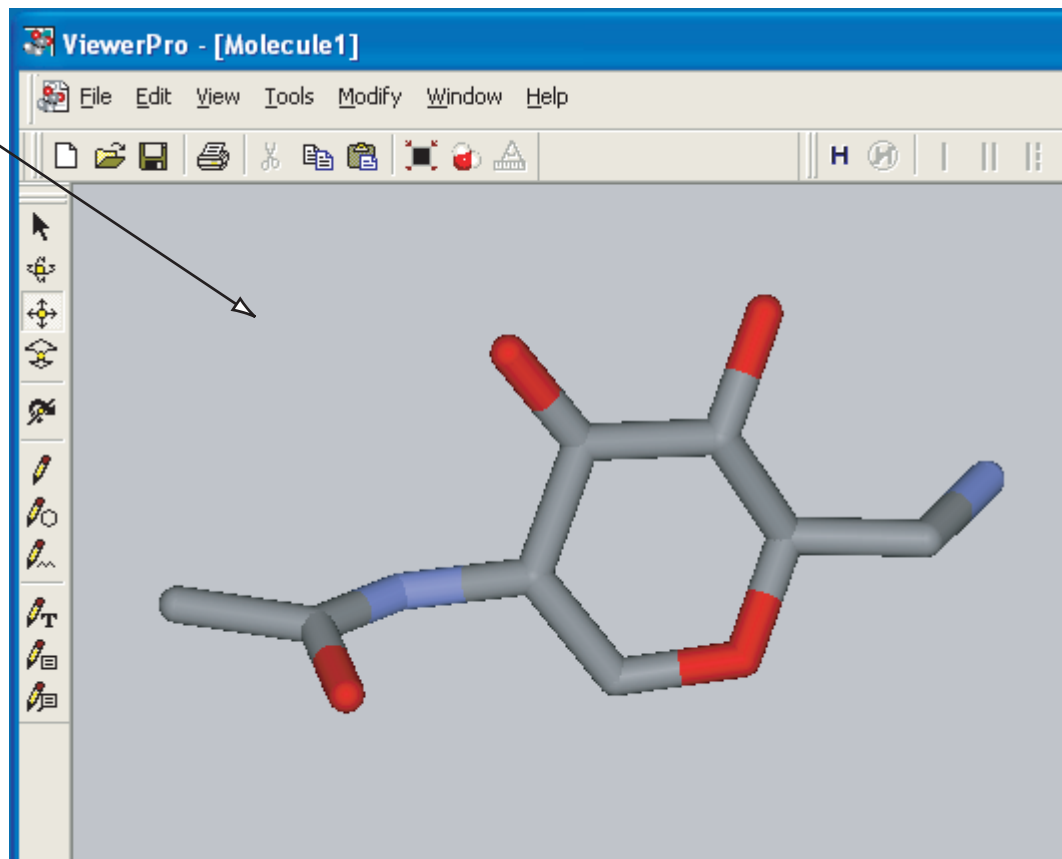
# QM/MM calculations of chemical reaction in renin protein

Experimental  
structure of  
the renin  
protein



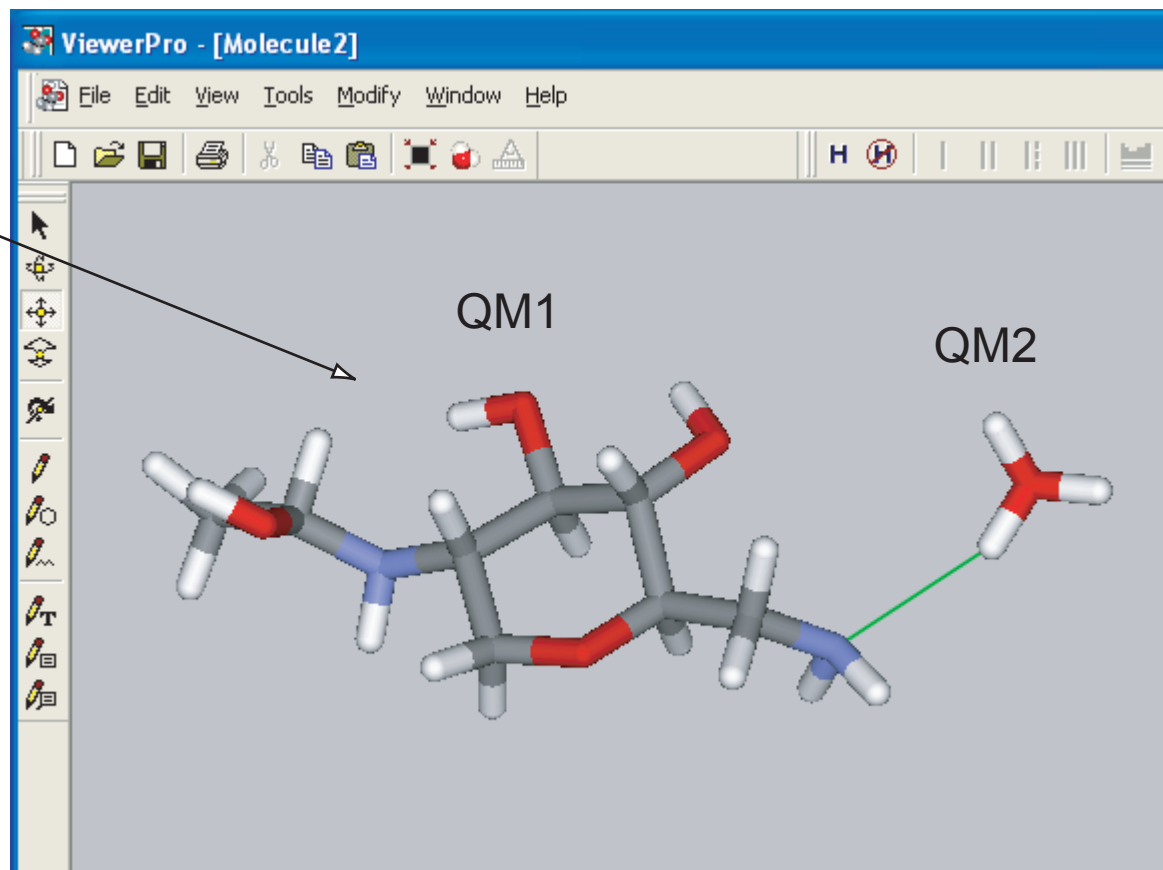
# QM/MM calculations of chemical reaction in renin protein

The active site  
of the renin  
protein



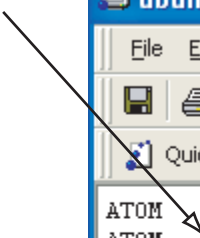
# QM/MM calculations of chemical reaction in renin protein

The  
protonation  
reaction of  
the renin  
ligand



# QM/MM calculations of chemical reaction in renin protein

The pdb file of  
the renin ligand

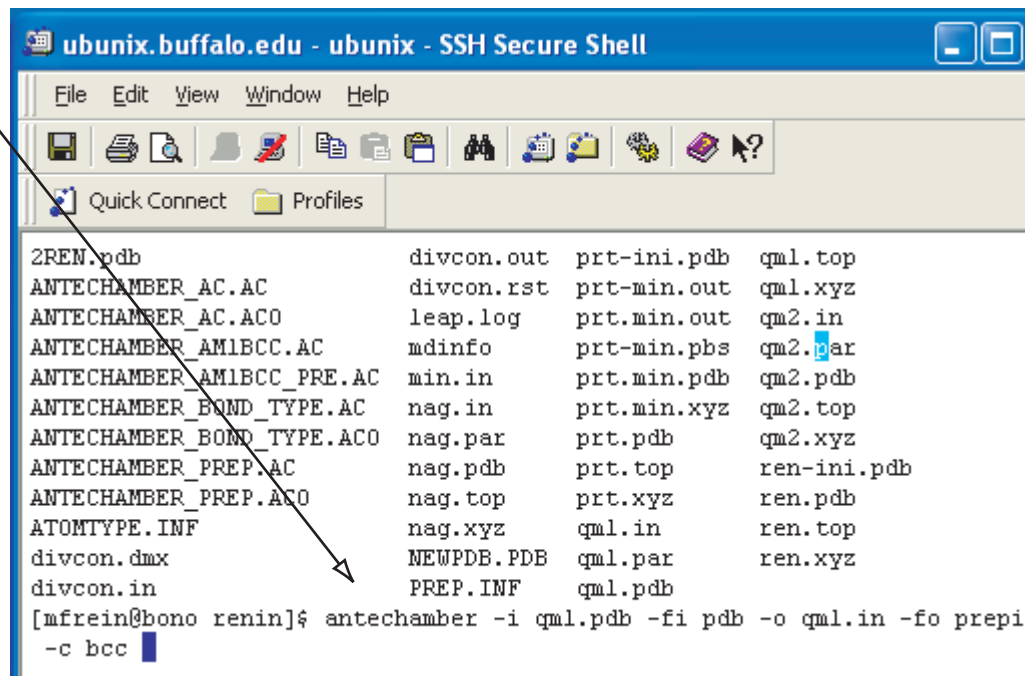


ubunix.buffalo.edu - ubunix - SSH Secure Shell

ATOM	1	C8	QM1	1	-5.298	48.721	-22.000	-0.127460
ATOM	2	H47	QM1	1	-6.043	49.385	-21.939	0.040320
ATOM	3	H49	QM1	1	-5.672	47.795	-21.951	0.050070
ATOM	4	H51	QM1	1	-4.816	48.841	-22.868	0.058810
ATOM	5	C7	QM1	1	-4.327	48.939	-20.845	0.368400
ATOM	6	O7	QM1	1	-4.679	49.644	-19.866	-0.643760
ATOM	7	H61	QM1	1	-4.898	50.568	-20.181	0.411800
ATOM	8	H45	QM1	1	-3.800	49.745	-21.116	0.055680
ATOM	9	N2	QM1	1	-3.248	48.107	-20.786	-0.821880
ATOM	10	H53	QM1	1	-3.573	47.225	-20.446	0.374780
ATOM	11	C2	QM1	1	-2.098	48.505	-19.941	0.111620
ATOM	12	H33	QM1	1	-2.289	49.434	-19.623	0.082490
ATOM	13	C1	QM1	1	-1.968	47.708	-18.702	0.112710
ATOM	14	H29	QM1	1	-2.671	48.035	-18.071	0.082360
ATOM	15	H31	QM1	1	-2.155	46.757	-18.947	0.033930
ATOM	16	O5	QM1	1	-0.785	47.717	-18.017	-0.402500

# QM/MM calculations of chemical reaction in renin protein

Generating the  
preparation file  
for the ligand

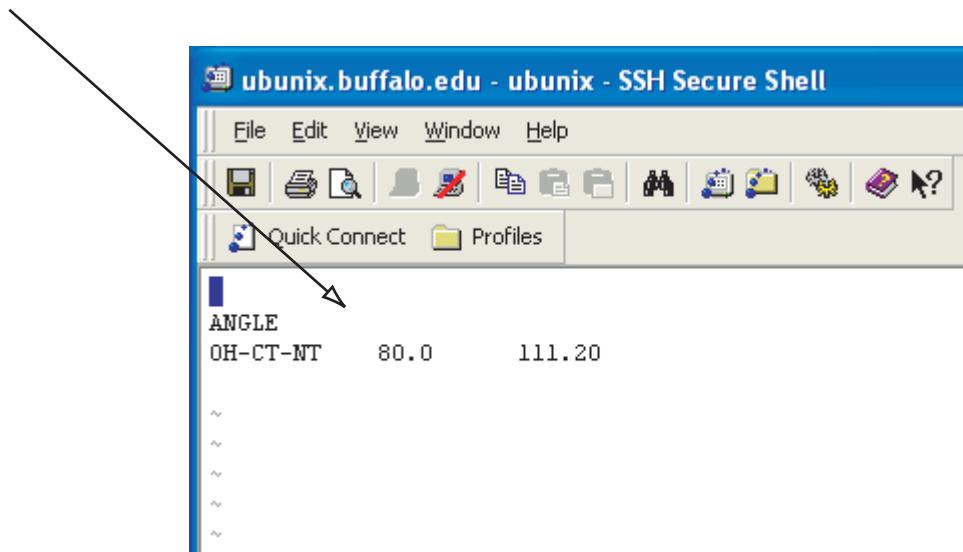


The screenshot shows a terminal window titled "ubunix.buffalo.edu - ubunix - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons. The main area of the terminal displays a directory listing of files in a grid format. The files include protein-related files like "2REN.pdb", "ANTECHAMBER\_AC.AC", and "ANTECHAMBER\_AM1BCC.AC", as well as calculation-related files like "divcon.out", "prtm-ini.pdb", and "qm1.top". At the bottom of the terminal, a command is being executed: `[mfrein@bono renin]$ antechamber -i qm1.pdb -fi pdb -o qm1.in -fo prep -c bcc`. An arrow from the text "Generating the preparation file for the ligand" points to the `qm1.pdb` file in the listing.

```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles
2REN.pdb divcon.out prtm-ini.pdb qm1.top
ANTECHAMBER_AC.AC divcon.rst prtm-min.out qm1.xyz
ANTECHAMBER_AC.ACO leap.log prtm.min.out qm2.in
ANTECHAMBER_AM1BCC.AC mdinfo prtm-min.pbs qm2.par
ANTECHAMBER_AM1BCC_PRE.AC min.in prtm.min.pdb qm2.pdb
ANTECHAMBER_BOND_TYPE.AC nag.in prtm.min.xyz qm2.top
ANTECHAMBER_BOND_TYPE.ACO nag.par prtm.pdb qm2.xyz
ANTECHAMBER_PREP.AC nag.pdb prtm.top ren-ini.pdb
ANTECHAMBER_PREP.ACO nag.top prtm.xyz ren.pdb
ATOMTYPE.INF nag.xyz qm1.in ren.top
divcon.dmx NEWPDB.PDB qm1.par ren.xyz
divcon.in PREP.INF qm1.pdb
[mfrein@bono renin]$ antechamber -i qm1.pdb -fi pdb -o qm1.in -fo prep
-c bcc
```

# QM/MM calculations of chemical reaction in renin protein

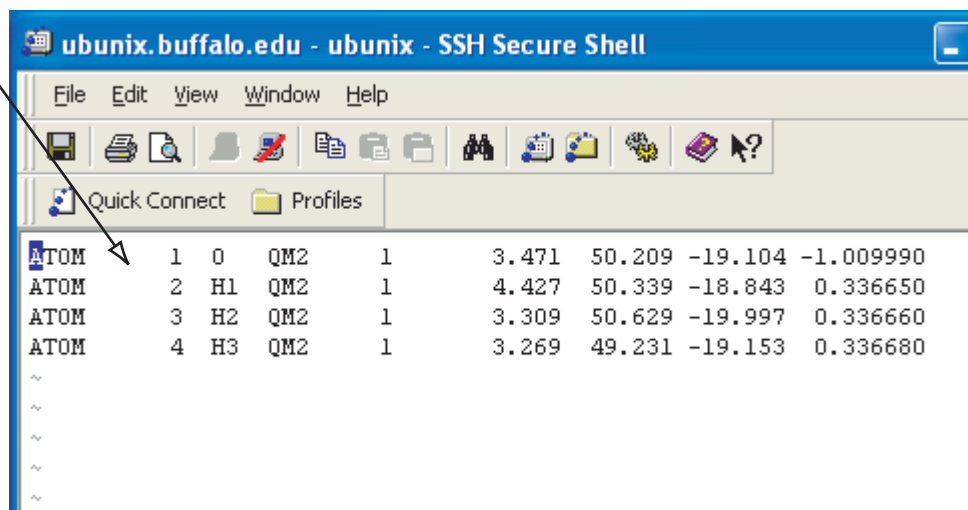
The parameter file of  
the ligand





# QM/MM calculations of chemical reaction in renin protein

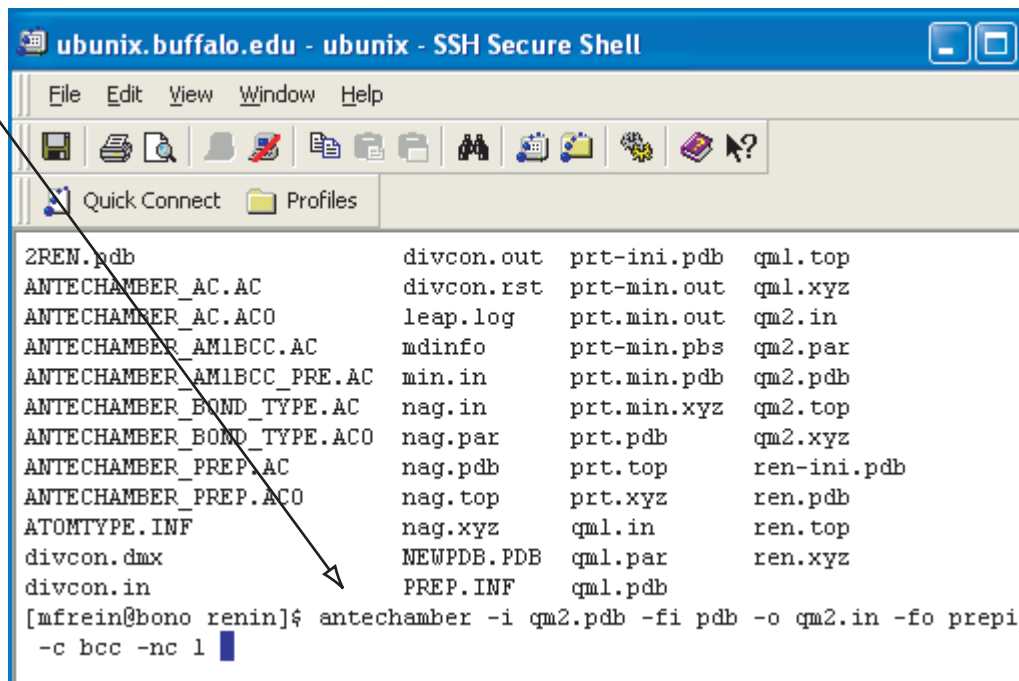
The pdb file of  
the substrat of  
the reaction



```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles
ATOM 1 O QM2 1 3.471 50.209 -19.104 -1.009990
ATOM 2 H1 QM2 1 4.427 50.339 -18.843 0.336650
ATOM 3 H2 QM2 1 3.309 50.629 -19.997 0.336660
ATOM 4 H3 QM2 1 3.269 49.231 -19.153 0.336680
~
~
~
~
~
```

# QM/MM calculations of chemical reaction in renin protein

Generating the  
preparation file  
for the substrat

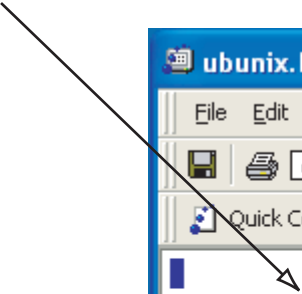


```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons: Save, Print, Find, Copy, Paste, Undo, Redo, Home, Up, Down, Left, Right, Search, Help]
Quick Connect Profiles

2REN.pdb          divcon.out      prt-ini.pdb    qm1.top
ANTECHAMBER_AC.AC divcon.rst      prt-min.out    qm1.xyz
ANTECHAMBER_AC.ACO leap.log        prt.min.out    qm2.in
ANTECHAMBER_AM1BCC.AC mdinfo          prt-min.pbs    qm2.par
ANTECHAMBER_AM1BCC_PRE.AC min.in          prt.min.pdb    qm2.pdb
ANTECHAMBER_BOND_TYPE.AC nag.in          prt.min.xyz    qm2.top
ANTECHAMBER_BOND_TYPE.ACO nag.par         prt.pdb        qm2.xyz
ANTECHAMBER_PREP.AC  nag.pdb        prt.top        ren-ini.pdb
ANTECHAMBER_PREP.ACO nag.top         prt.xyz        ren.pdb
ATOMTYPE.INF        nag.xyz        qm1.in         ren.top
divcon.dmx          NEWPDB.PDB     qm1.par        ren.xyz
divcon.in           PREP.INF       qm1.pdb
[mfrein@bono renin]$ antechamber -i qm2.pdb -fi pdb -o qm2.in -fo prepi
-c bcc -nc 1
```

# QM/MM calculations of chemical reaction in renin protein

The parameter file  
of the substrat

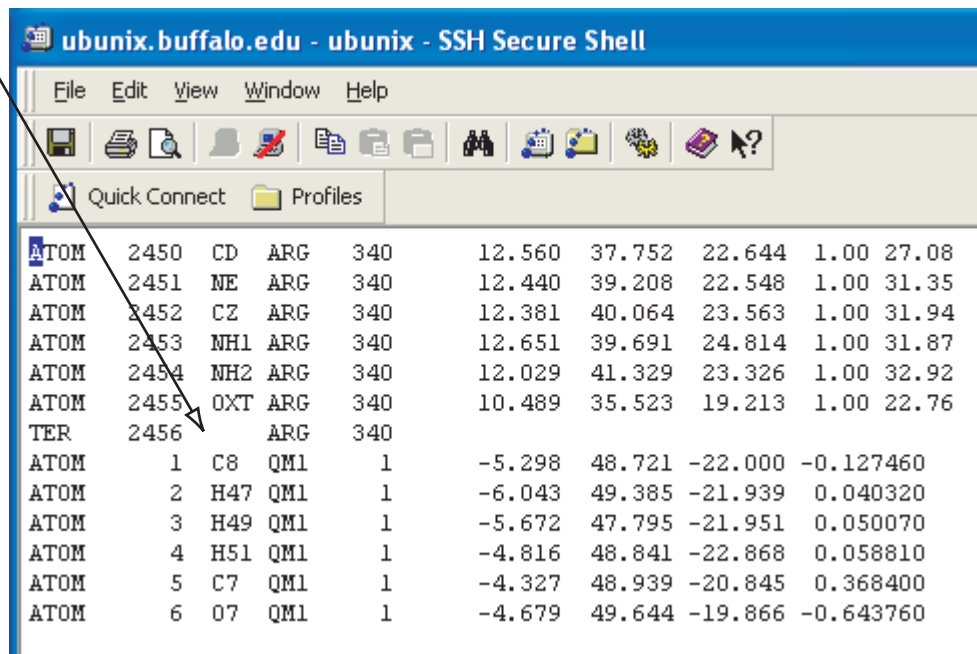


```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons: Save, Print, Find, etc.]
Quick Connect Profiles

ANGLE
HO-OH-HO      80.0      109.00
~
~
~
~
~
```

# QM/MM calculations of chemical reaction in renin protein

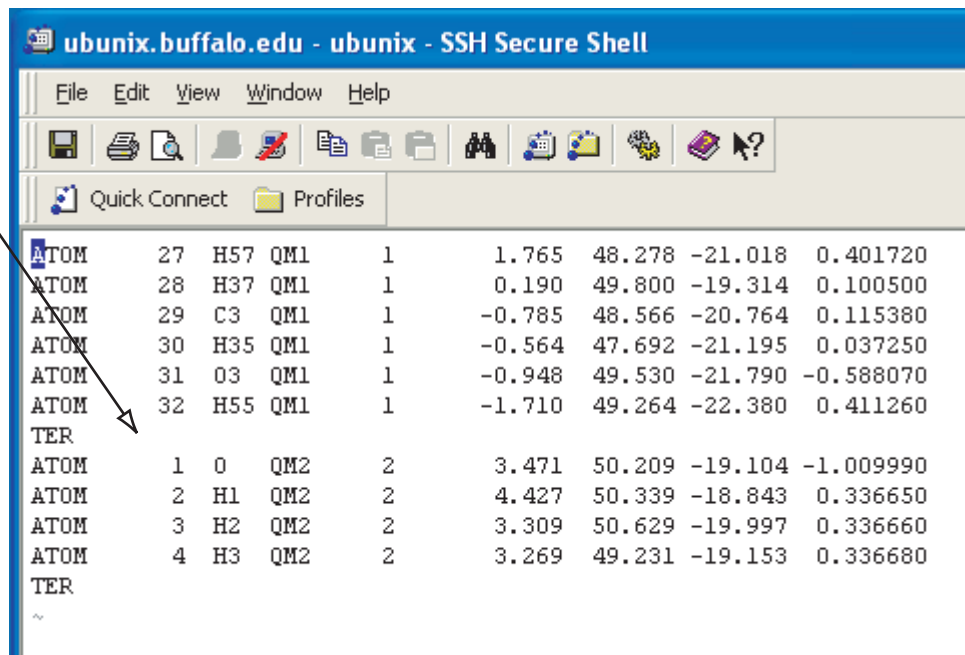
Merging the ligand  
pdb file with the  
protein structure



ATOM	2450	CD	ARG	340	12.560	37.752	22.644	1.00	27.08
ATOM	2451	NE	ARG	340	12.440	39.208	22.548	1.00	31.35
ATOM	2452	CZ	ARG	340	12.381	40.064	23.563	1.00	31.94
ATOM	2453	NH1	ARG	340	12.651	39.691	24.814	1.00	31.87
ATOM	2454	NH2	ARG	340	12.029	41.329	23.326	1.00	32.92
ATOM	2455	OXT	ARG	340	10.489	35.523	19.213	1.00	22.76
TER	2456		ARG	340					
ATOM	1	C8	QM1	1	-5.298	48.721	-22.000	-0.127460	
ATOM	2	H47	QM1	1	-6.043	49.385	-21.939	0.040320	
ATOM	3	H49	QM1	1	-5.672	47.795	-21.951	0.050070	
ATOM	4	H51	QM1	1	-4.816	48.841	-22.868	0.058810	
ATOM	5	C7	QM1	1	-4.327	48.939	-20.845	0.368400	
ATOM	6	O7	QM1	1	-4.679	49.644	-19.866	-0.643760	

# QM/MM calculations of chemical reaction in renin protein

Merging the  
substrat pdb file  
with the protein  
structure



ubunix.buffalo.edu - ubunix - SSH Secure Shell

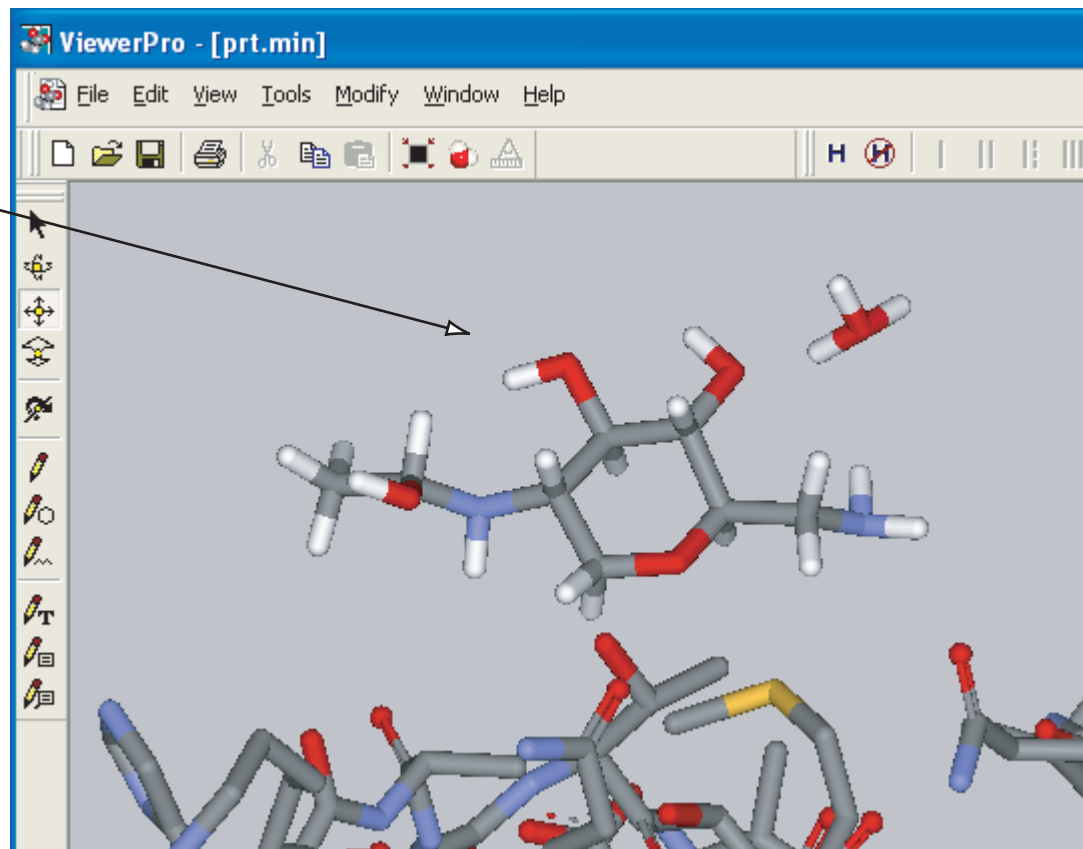
File Edit View Window Help

Quick Connect Profiles

ATOM	27	H57	QM1	1	1.765	48.278	-21.018	0.401720
ATOM	28	H37	QM1	1	0.190	49.800	-19.314	0.100500
ATOM	29	C3	QM1	1	-0.785	48.566	-20.764	0.115380
ATOM	30	H35	QM1	1	-0.564	47.692	-21.195	0.037250
ATOM	31	O3	QM1	1	-0.948	49.530	-21.790	-0.588070
ATOM	32	H55	QM1	1	-1.710	49.264	-22.380	0.411260
TER								
ATOM	1	O	QM2	2	3.471	50.209	-19.104	-1.009990
ATOM	2	H1	QM2	2	4.427	50.339	-18.843	0.336650
ATOM	3	H2	QM2	2	3.309	50.629	-19.997	0.336660
ATOM	4	H3	QM2	2	3.269	49.231	-19.153	0.336680
TER								
~								

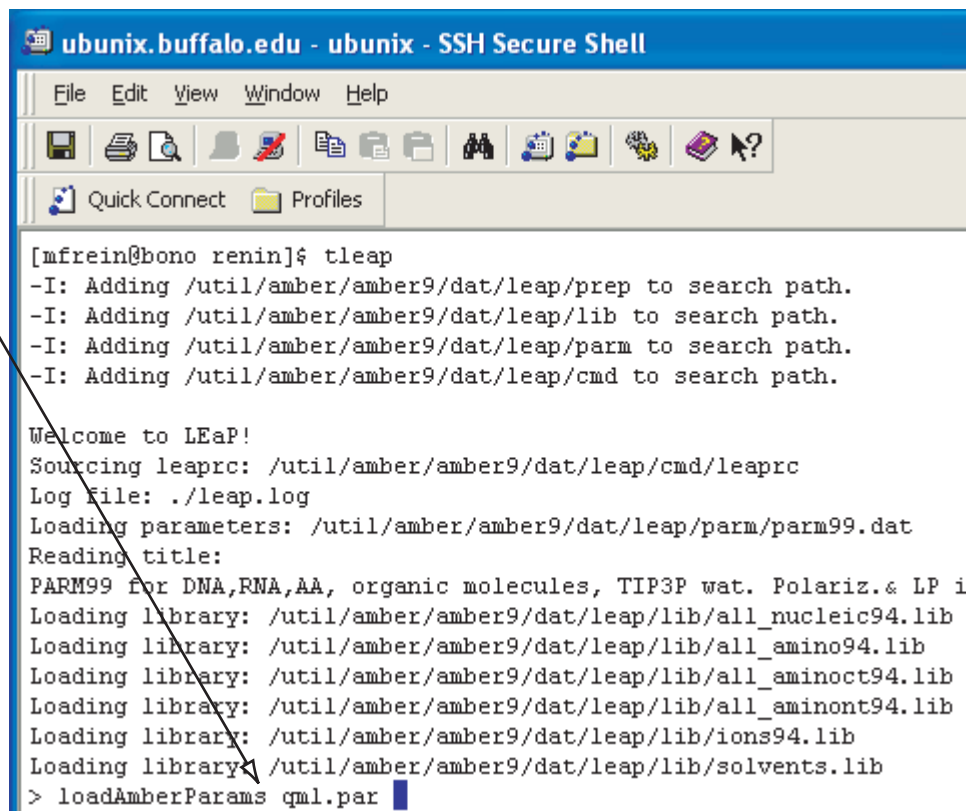
# QM/MM calculations of chemical reaction in renin protein

The initial pdb  
file of the  
protein with  
the ligand and  
the substrat



# QM/MM calculations of chemical reaction in renin protein

Loading the  
parameter file of  
the ligand in the  
"tleap" program



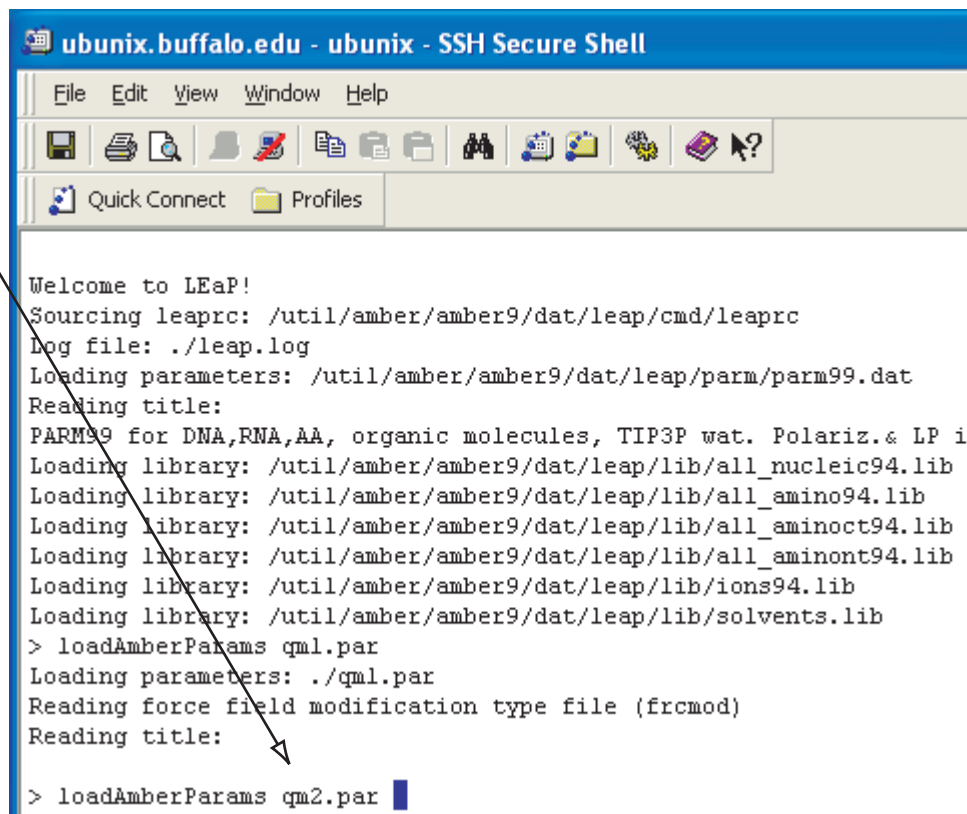
```
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File Edit View Window Help
Quick Connect Profiles

[mfrein@bono renin]$ tleap
-I: Adding /util/amber/amber9/dat/leap/prep to search path.
-I: Adding /util/amber/amber9/dat/leap/lib to search path.
-I: Adding /util/amber/amber9/dat/leap/parm to search path.
-I: Adding /util/amber/amber9/dat/leap/cmd to search path.

Welcome to LEaP!
Sourcing leaprc: /util/amber/amber9/dat/leap/cmd/leaprc
Log file: ./leap.log
Loading parameters: /util/amber/amber9/dat/leap/parm/parm99.dat
Reading title:
PARM99 for DNA, RNA, AA, organic molecules, TIP3P wat. Polariz. & LP i
Loading library: /util/amber/amber9/dat/leap/lib/all_nucleic94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_amino94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminont94.lib
Loading library: /util/amber/amber9/dat/leap/lib/ions94.lib
Loading library: /util/amber/amber9/dat/leap/lib/solvents.lib
> loadAmberParams qml.par
```

# QM/MM calculations of chemical reaction in renin protein

Loading the  
parameter file of  
the substrat in the  
"tleap" program



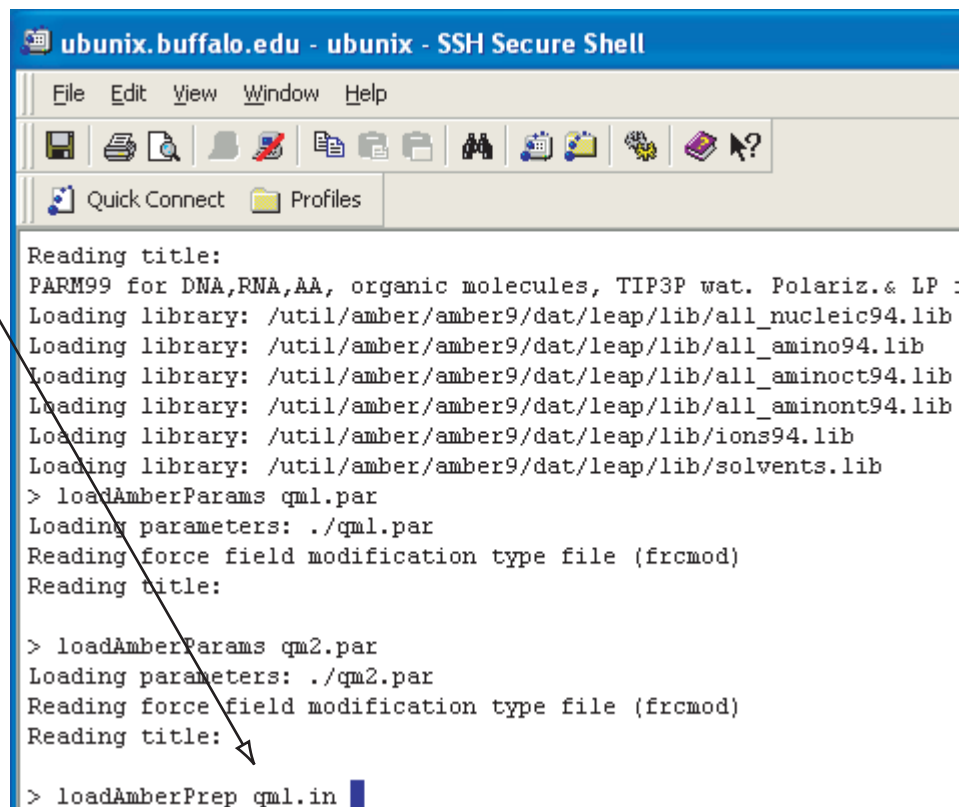
```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

Welcome to LEaP!
Sourcing leaprc: /util/amber/amber9/dat/leap/cmd/leaprc
log file: ./leap.log
Loading parameters: /util/amber/amber9/dat/leap/parm/parm99.dat
Reading title:
PARM99 for DNA,RNA,AA, organic molecules, TIP3P wat. Polariz.& LP i
Loading library: /util/amber/amber9/dat/leap/lib/all_nucleic94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_amino94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminont94.lib
Loading library: /util/amber/amber9/dat/leap/lib/ions94.lib
Loading library: /util/amber/amber9/dat/leap/lib/solvents.lib
> loadAmberParams qm1.par
Loading parameters: ./qm1.par
Reading force field modification type file (frcmod)
Reading title:
> loadAmberParams qm2.par
```



# QM/MM calculations of chemical reaction in renin protein

Loading the  
preparation file of  
the ligand in the  
"tleap" program



```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

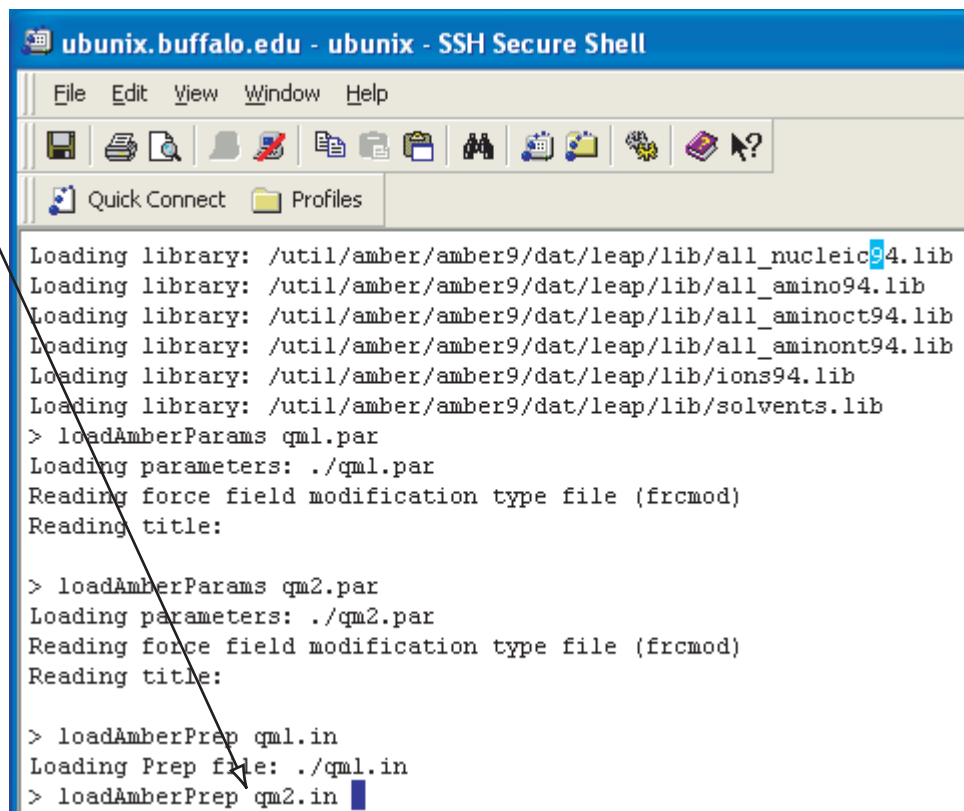
Reading title:
PARM99 for DNA,RNA,AA, organic molecules, TIP3P wat. Polariz.& LP :
Loading library: /util/amber/amber9/dat/leap/lib/all_nucleic94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_amino94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminont94.lib
Loading library: /util/amber/amber9/dat/leap/lib/ions94.lib
Loading library: /util/amber/amber9/dat/leap/lib/solvents.lib
> loadAmberParams qm1.par
Loading parameters: ./qm1.par
Reading force field modification type file (frcmod)
Reading title:

> loadAmberParams qm2.par
Loading parameters: ./qm2.par
Reading force field modification type file (frcmod)
Reading title:

> loadAmberPrep qm1.in
```

# QM/MM calculations of chemical reaction in renin protein

Loading the  
preparation file of  
the substrat in the  
"tleap" program



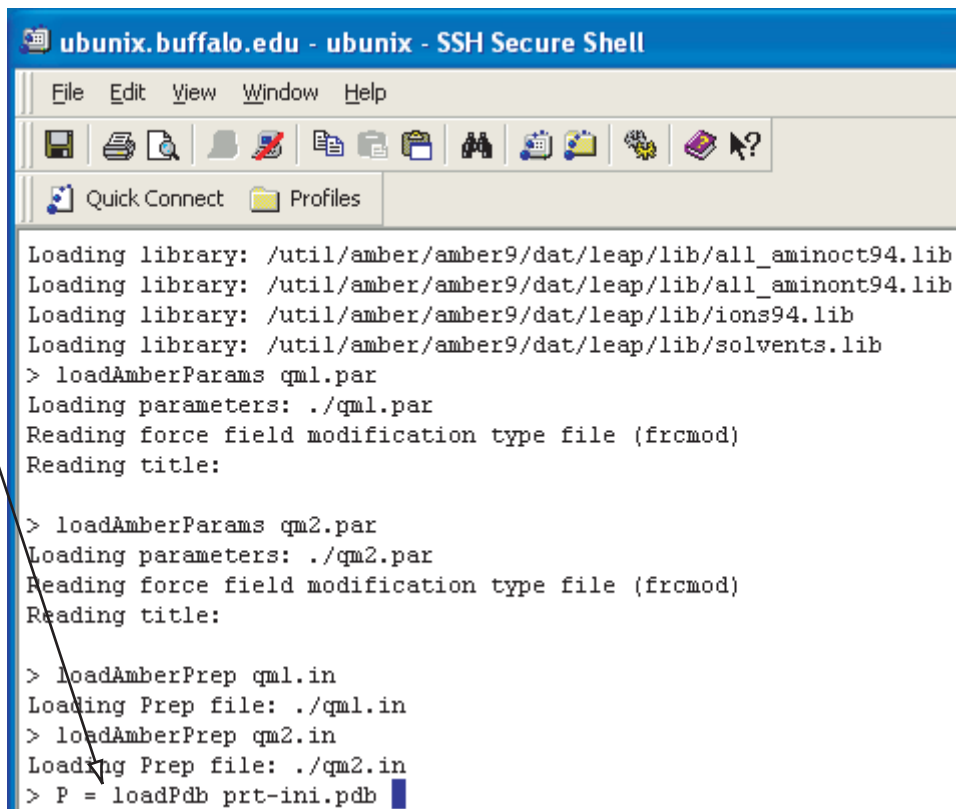
```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
Loading library: /util/amber/amber9/dat/leap/lib/all_nucleic94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_amino94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminont94.lib
Loading library: /util/amber/amber9/dat/leap/lib/ions94.lib
Loading library: /util/amber/amber9/dat/leap/lib/solvents.lib
> loadAmberParams qm1.par
Loading parameters: ./qm1.par
Reading force field modification type file (frcmod)
Reading title:

> loadAmberParams qm2.par
Loading parameters: ./qm2.par
Reading force field modification type file (frcmod)
Reading title:

> loadAmberPrep qm1.in
Loading Prep file: ./qm1.in
> loadAmberPrep qm2.in
```

# QM/MM calculations of chemical reaction in renin protein

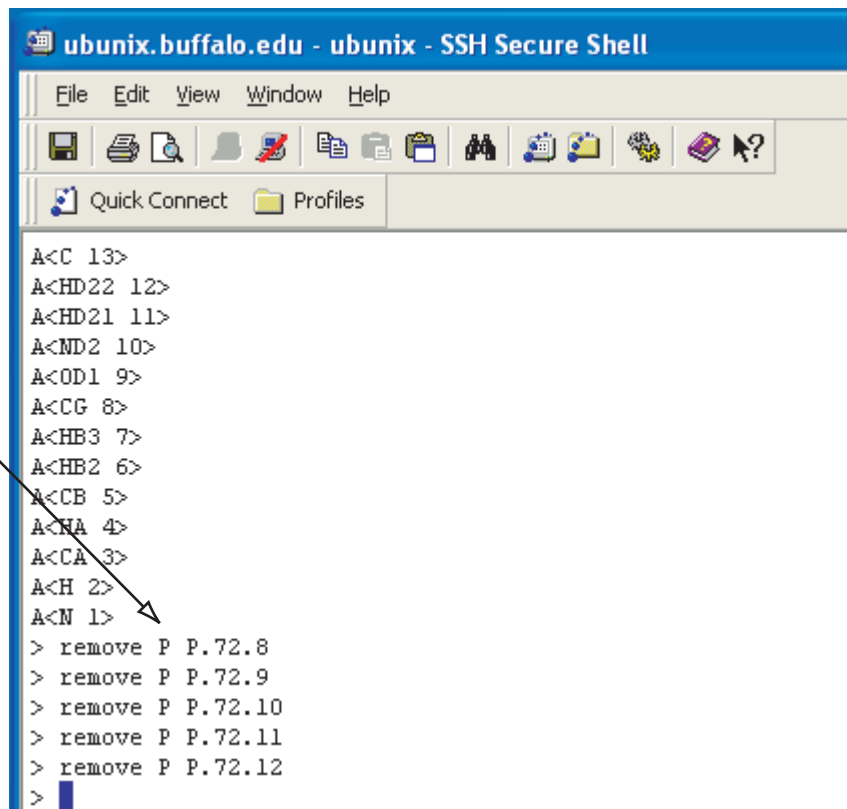
Loading the pdb file  
of the protein, the  
ligand and the  
substrat in the  
"tleap" program



```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc94.lib
Loading library: /util/amber/amber9/dat/leap/lib/all_aminont94.lib
Loading library: /util/amber/amber9/dat/leap/lib/ions94.lib
Loading library: /util/amber/amber9/dat/leap/lib/solvents.lib
> loadAmberParams qm1.par
Loading parameters: ./qm1.par
Reading force field modification type file (frcmod)
Reading title:
> loadAmberParams qm2.par
Loading parameters: ./qm2.par
Reading force field modification type file (frcmod)
Reading title:
> loadAmberPrep qm1.in
Loading Prep file: ./qm1.in
> loadAmberPrep qm2.in
Loading Prep file: ./qm2.in
> P = loadPdb prt-ini.pdb
```

# QM/MM calculations of chemical reaction in renin protein

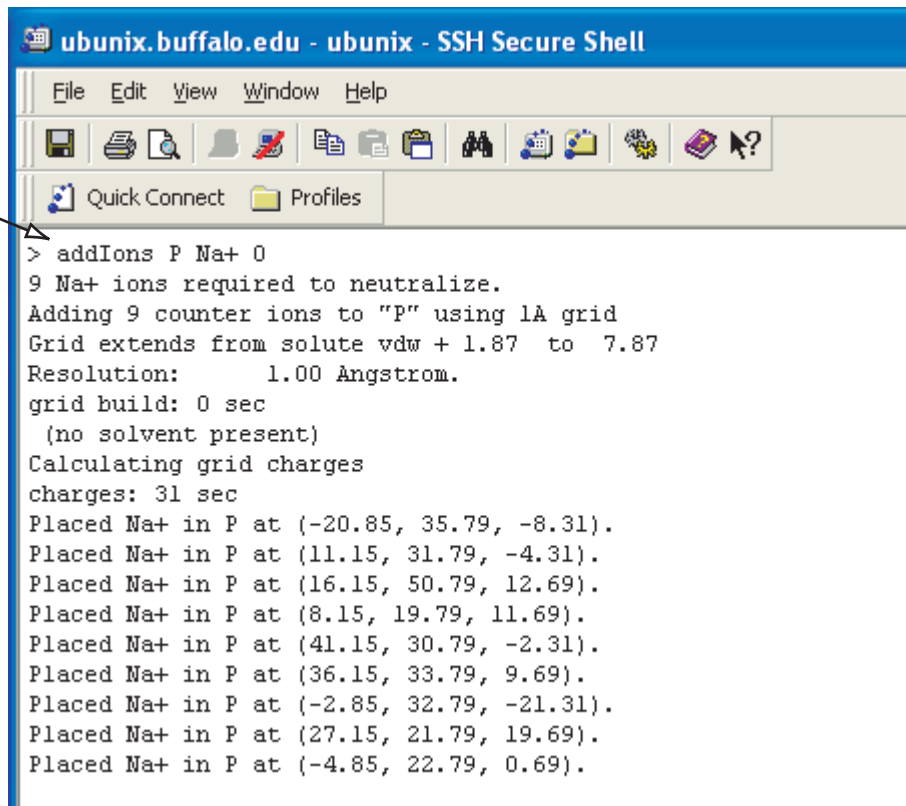
Removing atoms of  
the protein which  
are too close to the  
ligand



```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles
A<C 13>
A<HD22 12>
A<HD21 11>
A<ND2 10>
A<OD1 9>
A<CG 8>
A<HB3 7>
A<HB2 6>
A<CB 5>
A<NA 4>
A<CA 3>
A<H 2>
A<N 1>
> remove P P.72.8
> remove P P.72.9
> remove P P.72.10
> remove P P.72.11
> remove P P.72.12
>
```

# QM/MM calculations of chemical reaction in renin protein

Adding sodium cations ( $\text{Na}^+$ ) to neutralize the protein system

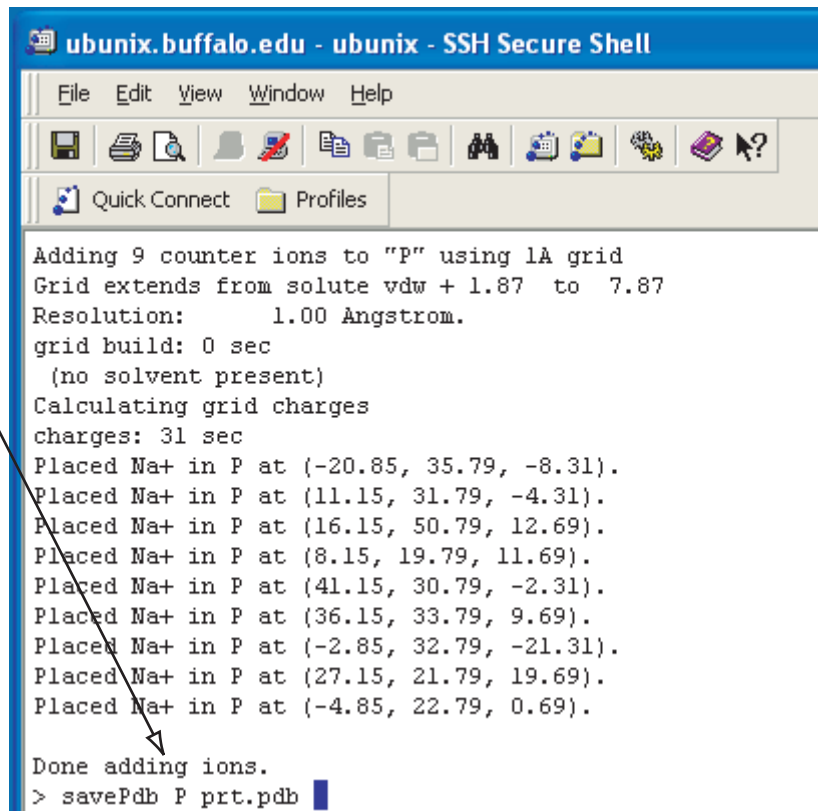


```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons: Save, Print, Find, Copy, Paste, Undo, Redo, Home, Recent, Favorites, Run, Stop, Help]
Quick Connect Profiles

> addIons P Na+ 0
9 Na+ ions required to neutralize.
Adding 9 counter ions to "P" using 1A grid
Grid extends from solute vdw + 1.87 to 7.87
Resolution: 1.00 Angstrom.
grid build: 0 sec
(no solvent present)
Calculating grid charges
charges: 31 sec
Placed Na+ in P at (-20.85, 35.79, -8.31).
Placed Na+ in P at (11.15, 31.79, -4.31).
Placed Na+ in P at (16.15, 50.79, 12.69).
Placed Na+ in P at (8.15, 19.79, 11.69).
Placed Na+ in P at (41.15, 30.79, -2.31).
Placed Na+ in P at (36.15, 33.79, 9.69).
Placed Na+ in P at (-2.85, 32.79, -21.31).
Placed Na+ in P at (27.15, 21.79, 19.69).
Placed Na+ in P at (-4.85, 22.79, 0.69).
```

# QM/MM calculations of chemical reaction in renin protein

Saving the pdb file of  
the protein system



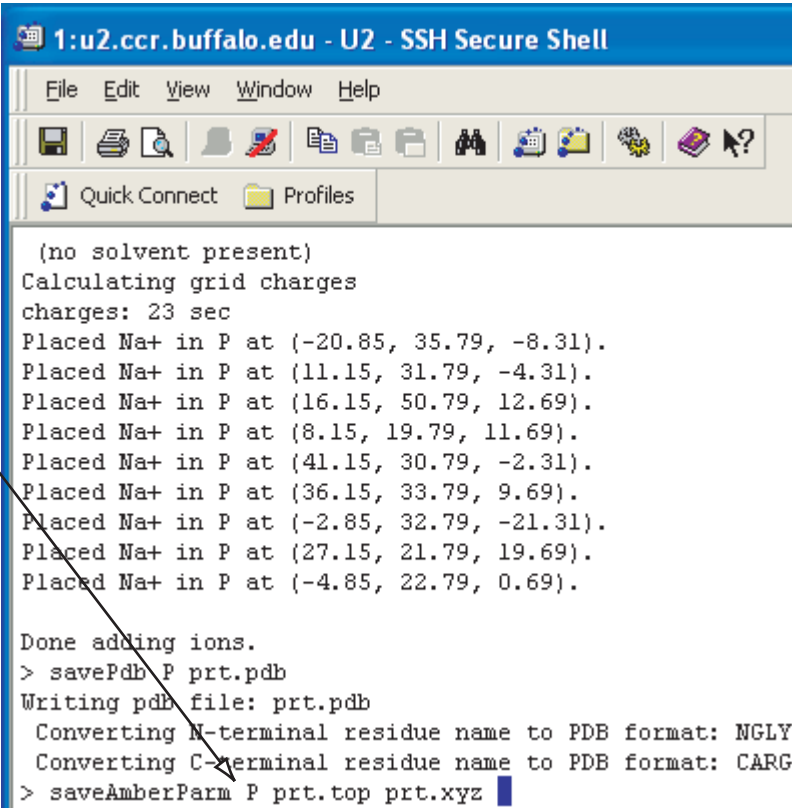
```
ubunix.buffalo.edu - ubunix - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

Adding 9 counter ions to "P" using 1A grid
Grid extends from solute vdw + 1.87 to 7.87
Resolution:      1.00 Angstrom.
grid build: 0 sec
(no solvent present)
Calculating grid charges
charges: 31 sec
Placed Na+ in P at (-20.85, 35.79, -8.31).
Placed Na+ in P at (11.15, 31.79, -4.31).
Placed Na+ in P at (16.15, 50.79, 12.69).
Placed Na+ in P at (8.15, 19.79, 11.69).
Placed Na+ in P at (41.15, 30.79, -2.31).
Placed Na+ in P at (36.15, 33.79, 9.69).
Placed Na+ in P at (-2.85, 32.79, -21.31).
Placed Na+ in P at (27.15, 21.79, 19.69).
Placed Na+ in P at (-4.85, 22.79, 0.69).

Done adding ions.
> savePdb P prt.pdb
```

# QM/MM calculations of chemical reaction in renin protein

Saving the topology  
and the coordinates  
files



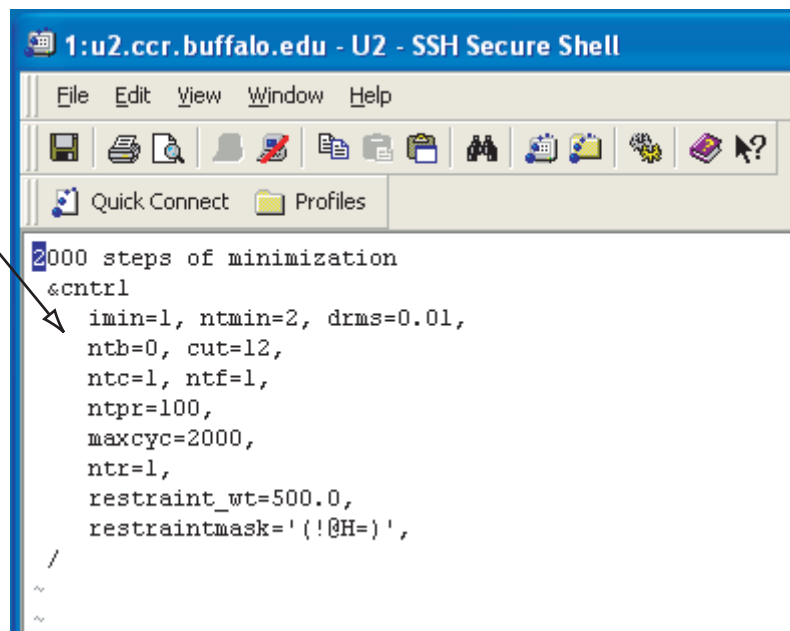
```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons: Save, Print, Find, etc.]
Quick Connect Profiles

(no solvent present)
Calculating grid charges
charges: 23 sec
Placed Na+ in P at (-20.85, 35.79, -8.31).
Placed Na+ in P at (11.15, 31.79, -4.31).
Placed Na+ in P at (16.15, 50.79, 12.69).
Placed Na+ in P at (8.15, 19.79, 11.69).
Placed Na+ in P at (41.15, 30.79, -2.31).
Placed Na+ in P at (36.15, 33.79, 9.69).
Placed Na+ in P at (-2.85, 32.79, -21.31).
Placed Na+ in P at (27.15, 21.79, 19.69).
Placed Na+ in P at (-4.85, 22.79, 0.69).

Done adding ions.
> savePdb P prt.pdb
Writing pdb file: prt.pdb
  Converting N-terminal residue name to PDB format: NGLY
  Converting C-terminal residue name to PDB format: CARG
> saveAmberParm P prt.top prt.xyz
```

# QM/MM calculations of chemical reaction in renin protein

The input file for the minimization of the protein system



The screenshot shows a terminal window titled "1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons. The main area of the window displays a text file with the following content:

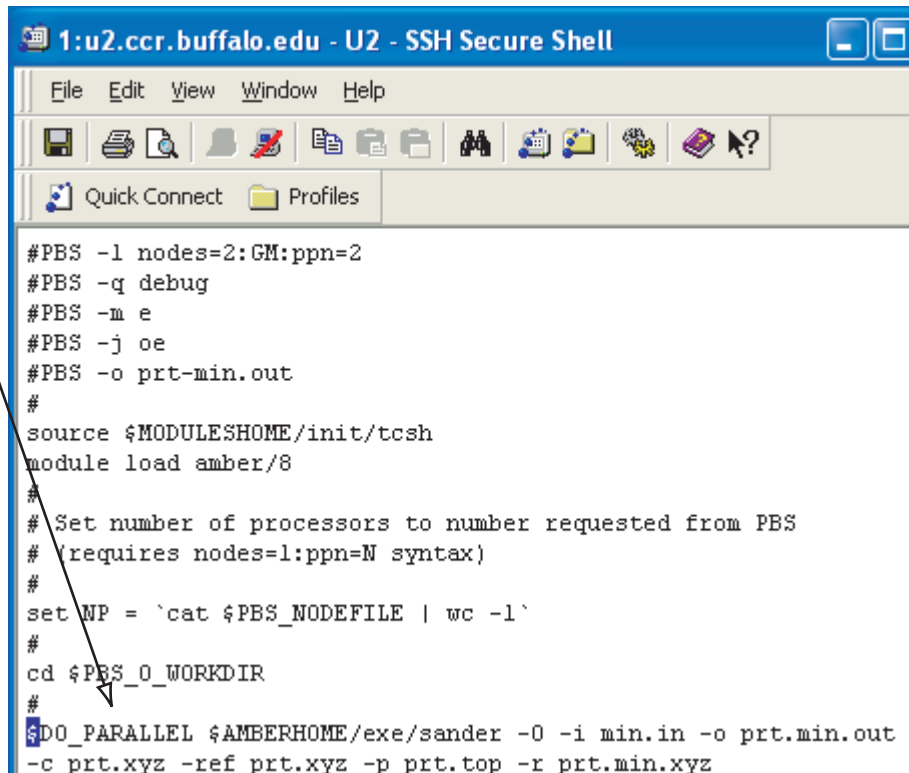
```
2000 steps of minimization
&cntrl
  imin=1, ntmin=2, drms=0.01,
  ntb=0, cut=12,
  ntc=1, ntf=1,
  ntpr=100,
  maxcyc=2000,
  ntr=1,
  restraint_wt=500.0,
  restraintmask='(!@H=)',
/
~
~
```

An arrow points from the text "The input file for the minimization of the protein system" to the line "imin=1, ntmin=2, drms=0.01," in the terminal output.



# QM/MM calculations of chemical reaction in renin protein

The pbs script for  
the minimization

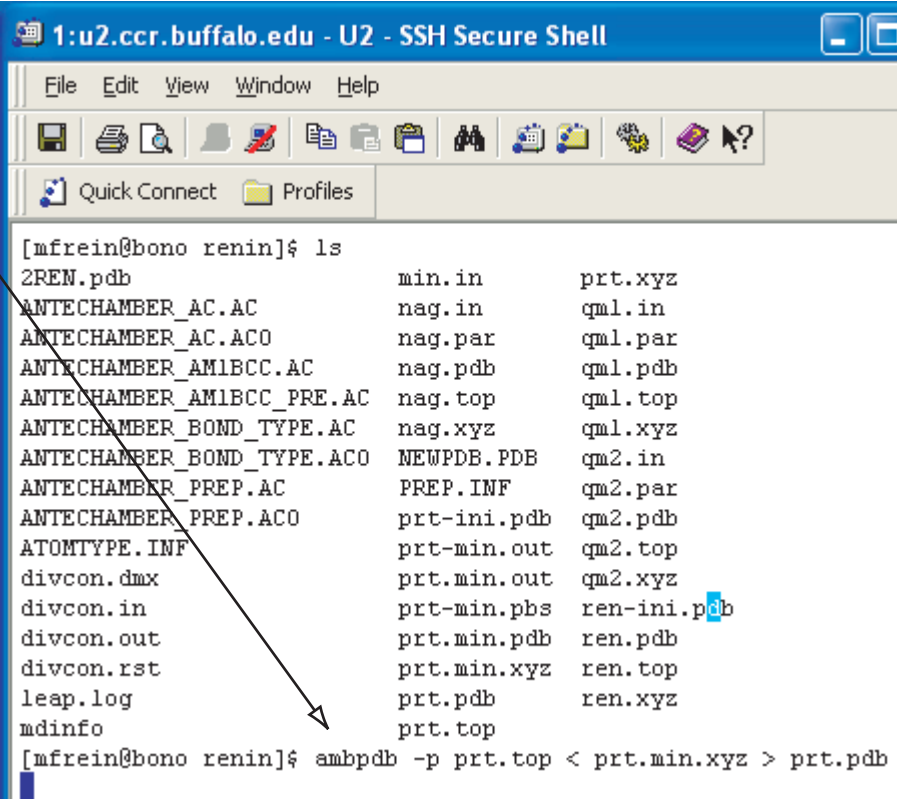


```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

#PBS -l nodes=2:GM:ppn=2
#PBS -q debug
#PBS -m e
#PBS -j oe
#PBS -o prt-min.out
#
source $MODULESHOME/init/tcsh
module load amber/8
#
# Set number of processors to number requested from PBS
# (requires nodes=1:ppn=N syntax)
#
set NP = `cat $PBS_NODEFILE | wc -l`
#
cd $PBS_O_WORKDIR
#
$DO_PARALLEL $AMBERHOME/exe/sander -O -i min.in -o prt.min.out
-c prt.xyz -ref prt.xyz -p prt.top -r prt.min.xyz
```

# QM/MM calculations of chemical reaction in renin protein

Generating the pdb  
file of the minimized  
protein structure



The screenshot shows a terminal window titled "1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons. The terminal content shows a directory listing command and its output:

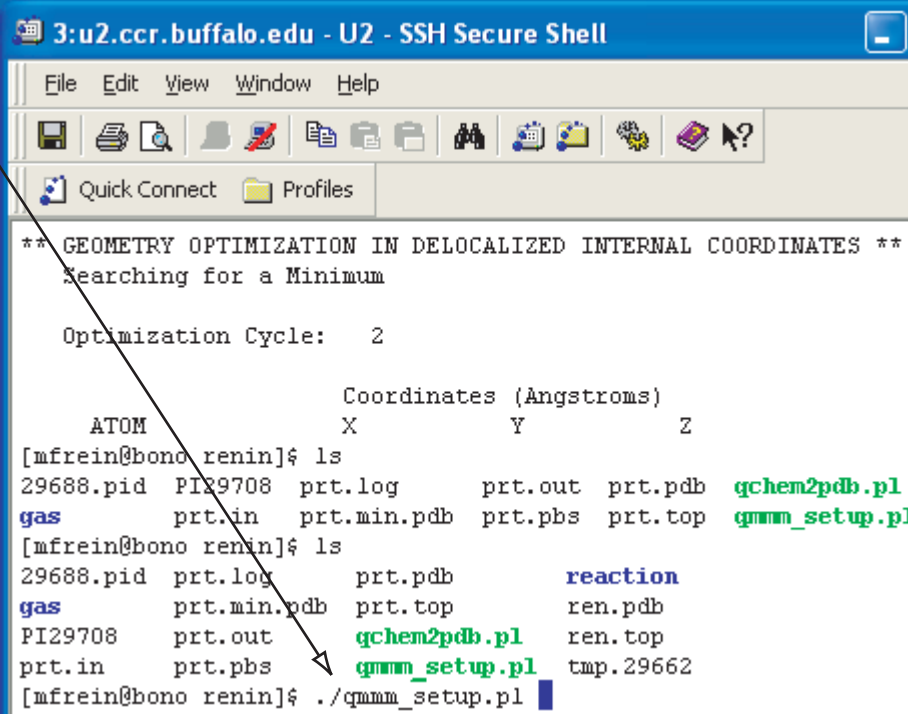
```
[mfrein@bono renin]$ ls
2REN.pdb                min.in                  prt.xyz
ANTECHAMBER_AC.AC       nag.in                  qml.in
ANTECHAMBER_AC.ACO      nag.par                 qml.par
ANTECHAMBER_AM1BCC.AC   nag.pdb                 qml.pdb
ANTECHAMBER_AM1BCC_PRE.AC nag.top                 qml.top
ANTECHAMBER_BOND_TYPE.AC nag.xyz                 qml.xyz
ANTECHAMBER_BOND_TYPE.ACO NEWPDB.PDB              qm2.in
ANTECHAMBER_PREP.AC     PREP.INF                qm2.par
ANTECHAMBER_PREP.ACO    prt-ini.pdb             qm2.pdb
ATOMTYPE.INF            prt-min.out             qm2.top
divcon.dmx              prt.min.out             qm2.xyz
divcon.in               prt-min.pbs             ren-ini.pdb
divcon.out              prt.min.pdb             ren.pdb
divcon.rst              prt.min.xyz             ren.top
leap.log                prt.pdb                 ren.xyz
mdinfo                  prt.top
[mfrein@bono renin]$ ambpdb -p prt.top < prt.min.xyz > prt.pdb
```

An arrow points from the text "Generating the pdb file of the minimized protein structure" to the file "prt.pdb" in the directory listing.

# QM/MM calculations of chemical reaction in renin protein

Creating the q-chem  
input file for the  
QM/MM calculations

The script assumes  
that the topology file  
has a name "prt.top",  
the pdb file has a  
name "prt.pdb", and  
the QM molecules  
have residue names  
with the "QM"  
keyword



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

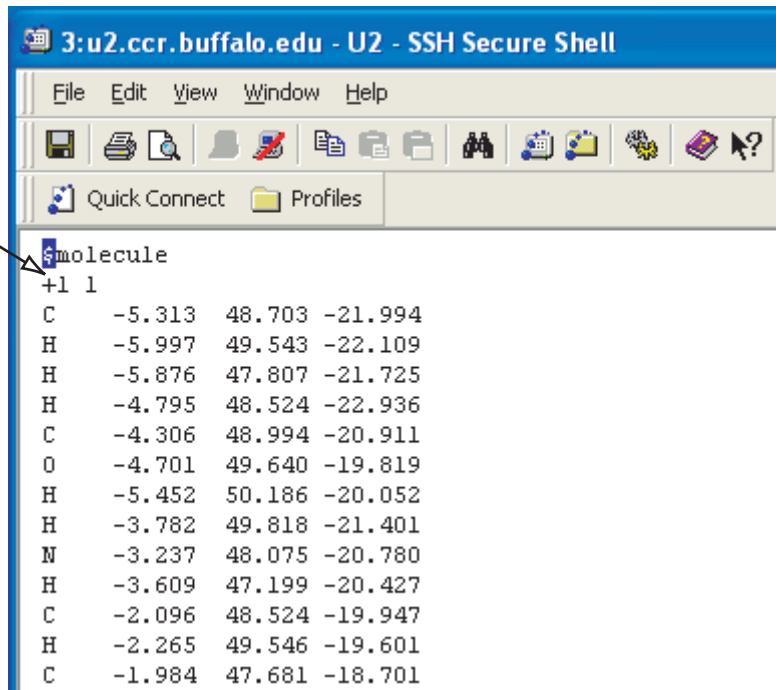
** GEOMETRY OPTIMIZATION IN DELOCALIZED INTERNAL COORDINATES **
Searching for a Minimum

Optimization Cycle: 2

Coordinates (Angstroms)
ATOM      X      Y      Z
[mfrein@bono renin]$ ls
29688.pid  PI29708  prt.log   prt.out   prt.pdb   qchem2pdb.pl
gas        prt.in    prt.min.pdb prt.pbs    prt.top   qmmm_setup.pl
[mfrein@bono renin]$ ls
29688.pid  prt.log   prt.pdb   reaction
gas        prt.min.pdb prt.top    ren.pdb
PI29708    prt.out   qchem2pdb.pl ren.top
prt.in     prt.pbs   qmmm_setup.pl tmp.29662
[mfrein@bono renin]$ ./qmmm_setup.pl
```

# QM/MM calculations of chemical reaction in renin protein

The input file of the q-chem program, the charge of the molecule is "+1"

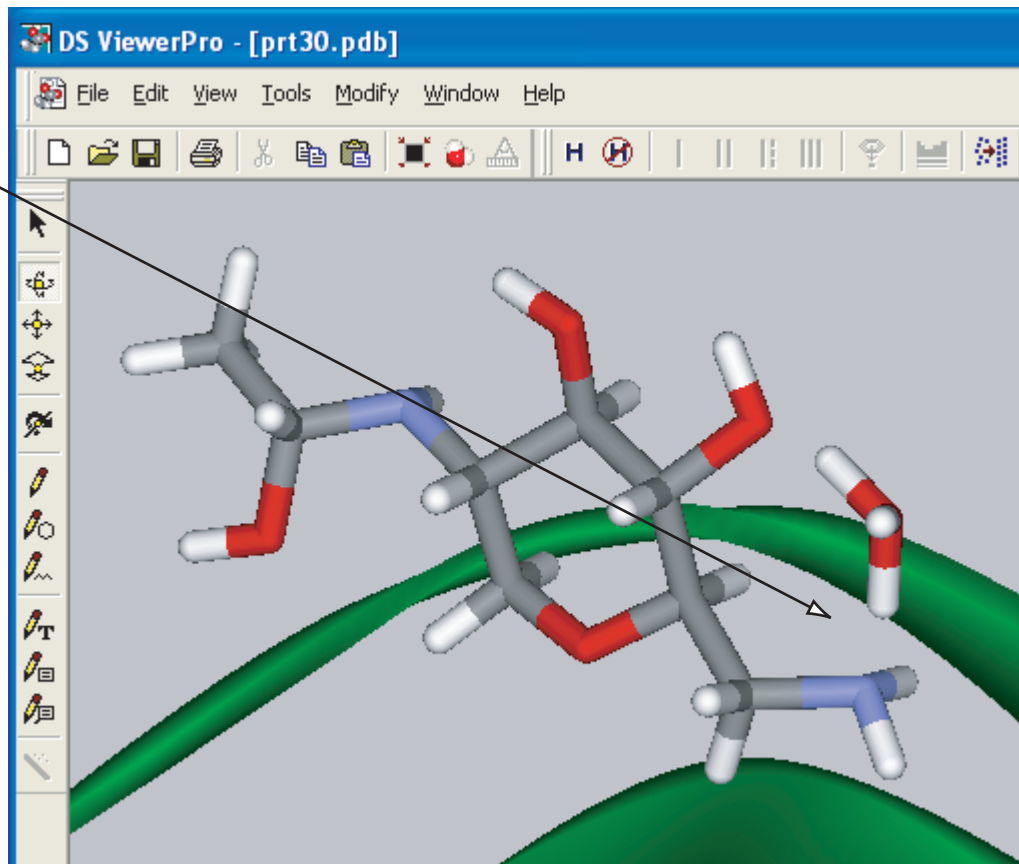


```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles
molecule
+1 1
C -5.313 48.703 -21.994
H -5.997 49.543 -22.109
H -5.876 47.807 -21.725
H -4.795 48.524 -22.936
C -4.306 48.994 -20.911
O -4.701 49.640 -19.819
H -5.452 50.186 -20.052
H -3.782 49.818 -21.401
N -3.237 48.075 -20.780
H -3.609 47.199 -20.427
C -2.096 48.524 -19.947
H -2.265 49.546 -19.601
C -1.984 47.681 -18.701
```

# QM/MM calculations of chemical reaction in renin protein

There are two  
reaction  
coordinates:

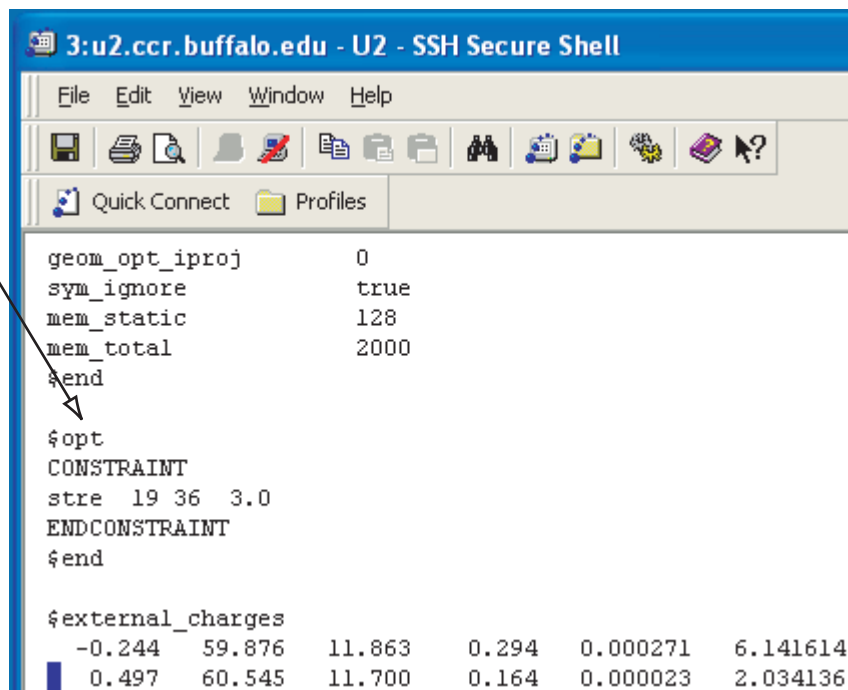
N-H distance  
O-H distance



# QM/MM calculations of chemical reaction in renin protein

The calculations for  
the reactants valley

N-H distance  
constrained



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

geom_opt_iproj      0
sym_ignore          true
mem_static          128
mem_total           2000
$end

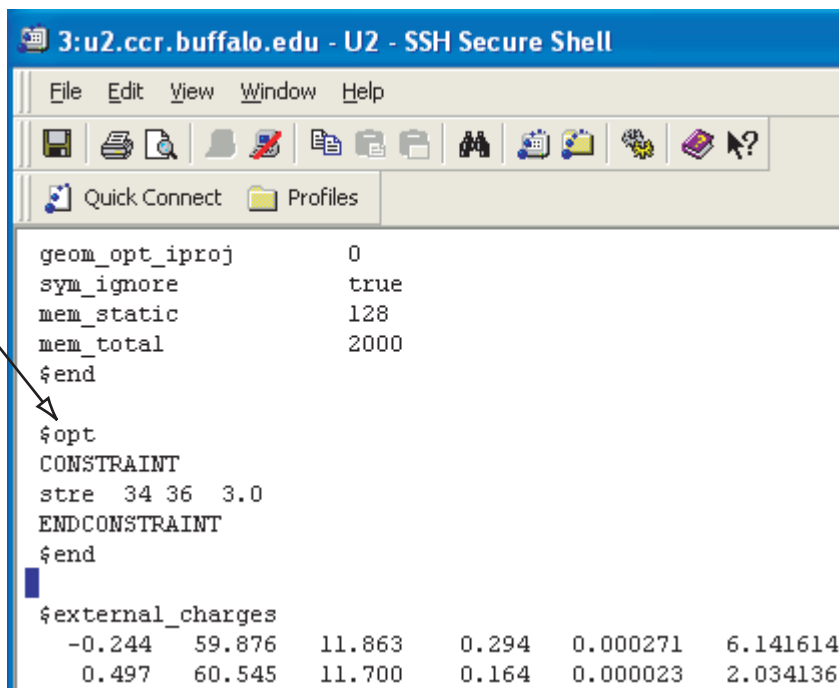
$opt
CONSTRAINT
stre 19 36 3.0
ENDCONSTRAINT
$end

$external_charges
-0.244  59.876  11.863  0.294  0.000271  6.141614
0.497   60.545  11.700  0.164  0.000023  2.034136
```

# QM/MM calculations of chemical reaction in renin protein

The calculations for  
the products valley

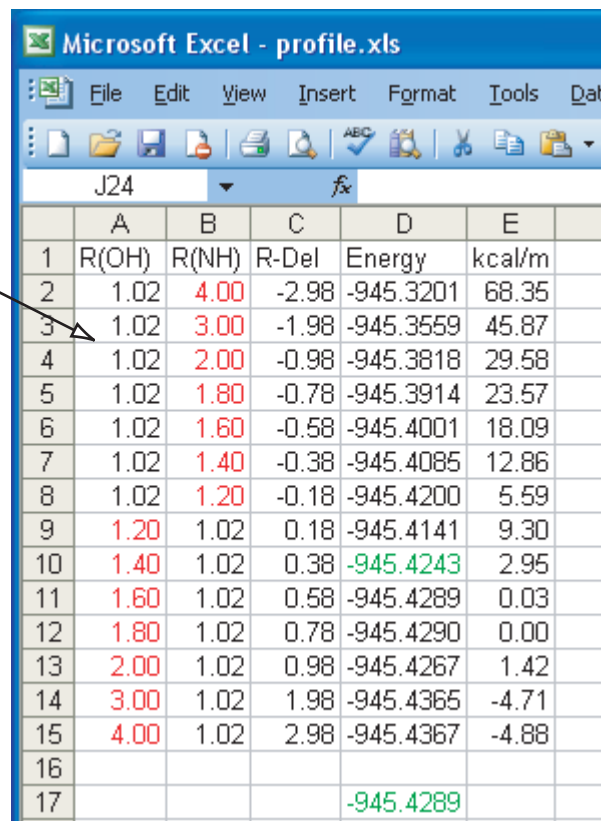
O-H distance  
constrained



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles
geom_opt_iproj      0
sym_ignore          true
mem_static          128
mem_total           2000
$end
$opt
CONSTRAINT
stre 34 36 3.0
ENDCONSTRAINT
$end
$external_charges
-0.244  59.876  11.863  0.294  0.000271  6.141614
 0.497  60.545  11.700  0.164  0.000023  2.034136
```

# QM/MM calculations of chemical reaction in renin protein

The energy of the QM systems as the function of the reaction coordinate in the protein



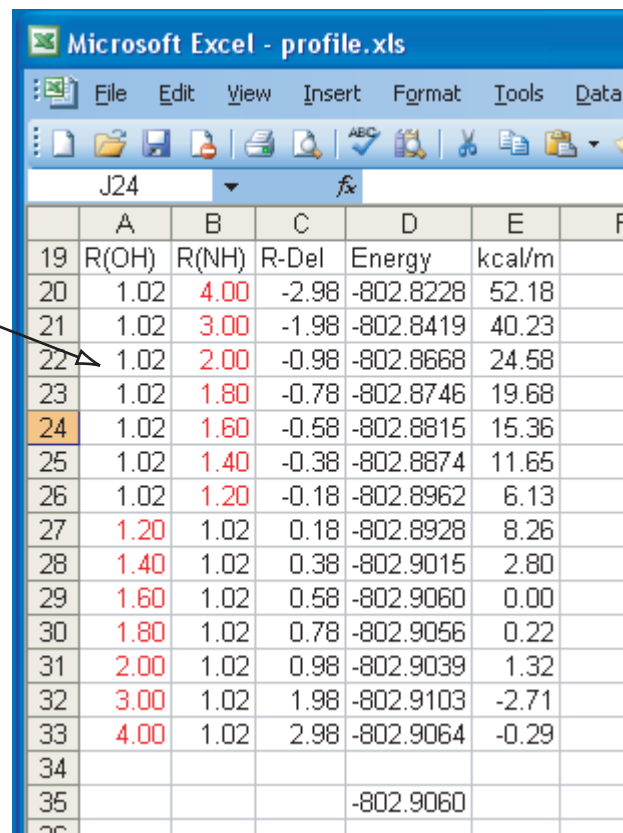
Microsoft Excel - profile.xls

	A	B	C	D	E
1	R(OH)	R(NH)	R-Del	Energy	kcal/m
2	1.02	4.00	-2.98	-945.3201	68.35
3	1.02	3.00	-1.98	-945.3559	45.87
4	1.02	2.00	-0.98	-945.3818	29.58
5	1.02	1.80	-0.78	-945.3914	23.57
6	1.02	1.60	-0.58	-945.4001	18.09
7	1.02	1.40	-0.38	-945.4085	12.86
8	1.02	1.20	-0.18	-945.4200	5.59
9	1.20	1.02	0.18	-945.4141	9.30
10	1.40	1.02	0.38	-945.4243	2.95
11	1.60	1.02	0.58	-945.4289	0.03
12	1.80	1.02	0.78	-945.4290	0.00
13	2.00	1.02	0.98	-945.4267	1.42
14	3.00	1.02	1.98	-945.4365	-4.71
15	4.00	1.02	2.98	-945.4367	-4.88
16					
17				-945.4289	



# QM/MM calculations of chemical reaction in renin protein

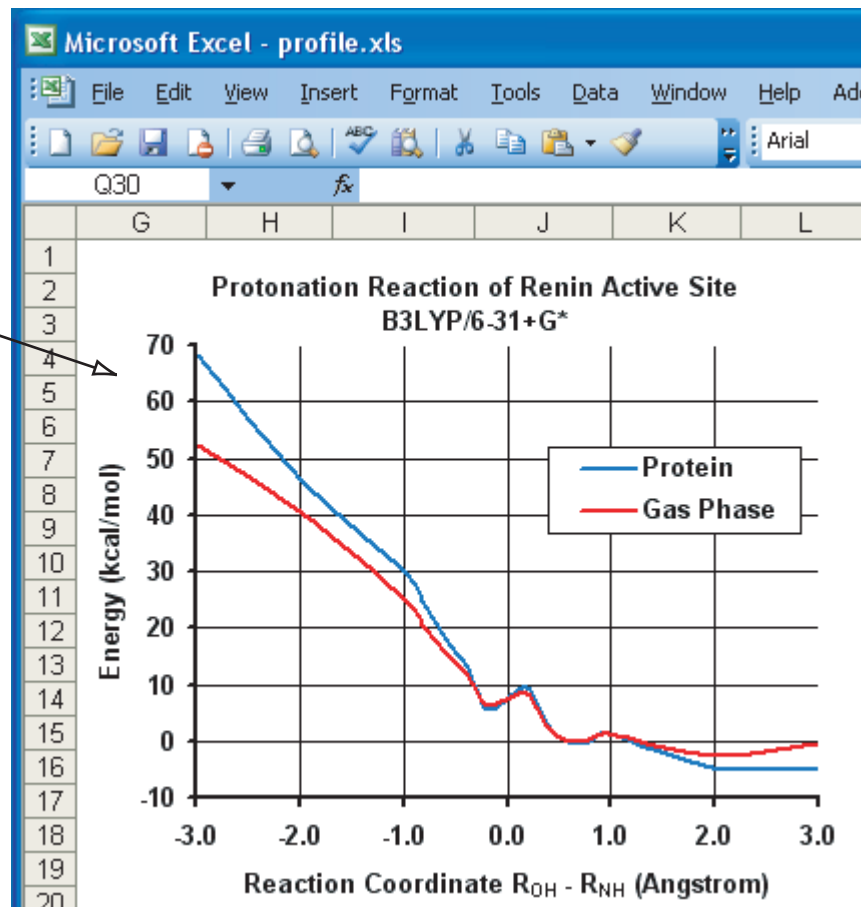
The energy of the QM systems as the function of the reaction coordinate in the gas phase



	A	B	C	D	E	F
19	R(OH)	R(NH)	R-Del	Energy	kcal/m	
20	1.02	4.00	-2.98	-802.8228	52.18	
21	1.02	3.00	-1.98	-802.8419	40.23	
22	1.02	2.00	-0.98	-802.8668	24.58	
23	1.02	1.80	-0.78	-802.8746	19.68	
24	1.02	1.60	-0.58	-802.8815	15.36	
25	1.02	1.40	-0.38	-802.8874	11.65	
26	1.02	1.20	-0.18	-802.8962	6.13	
27	1.20	1.02	0.18	-802.8928	8.26	
28	1.40	1.02	0.38	-802.9015	2.80	
29	1.60	1.02	0.58	-802.9060	0.00	
30	1.80	1.02	0.78	-802.9056	0.22	
31	2.00	1.02	0.98	-802.9039	1.32	
32	3.00	1.02	1.98	-802.9103	-2.71	
33	4.00	1.02	2.98	-802.9064	-0.29	
34						
35				-802.9060		
36						

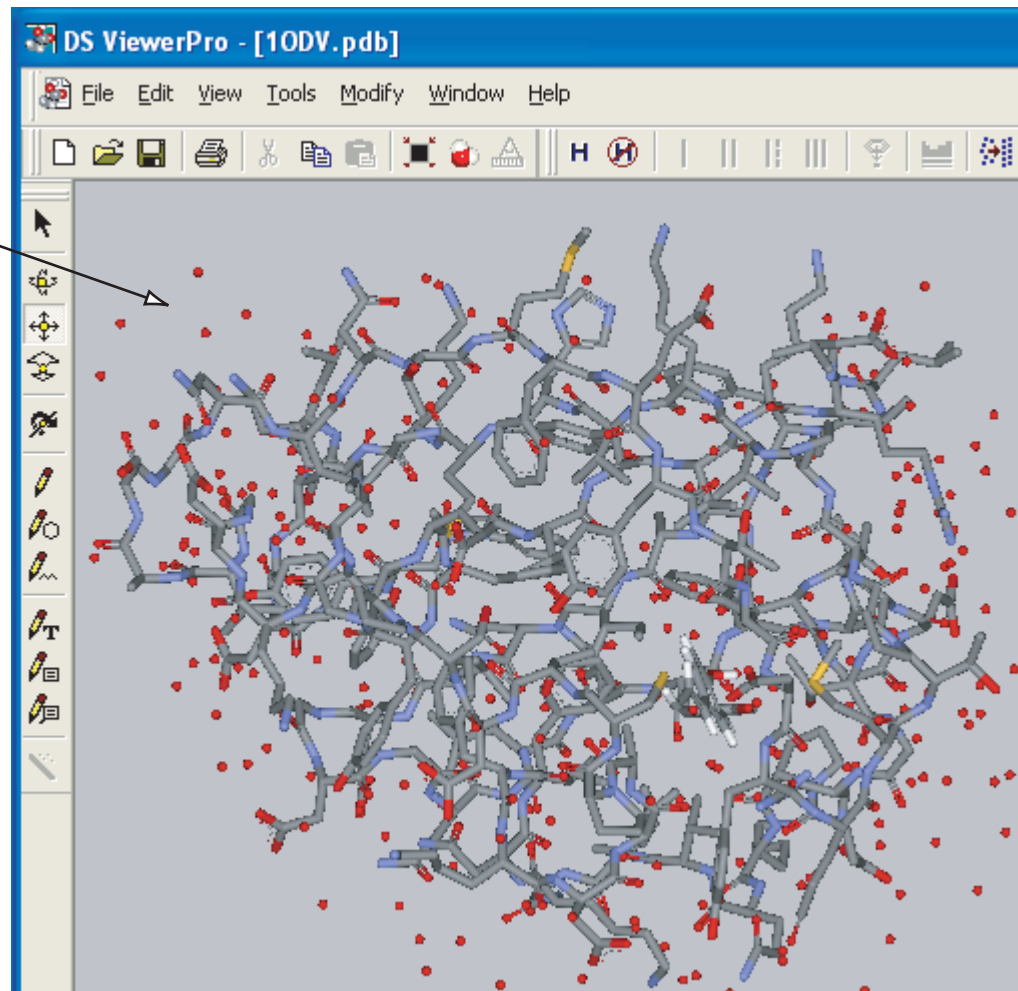
# QM/MM calculations of chemical reaction in renin protein

The final results of the reaction profile calculations in the protein and in the gas phase



# QM/MM electronic excitations in yellow protein

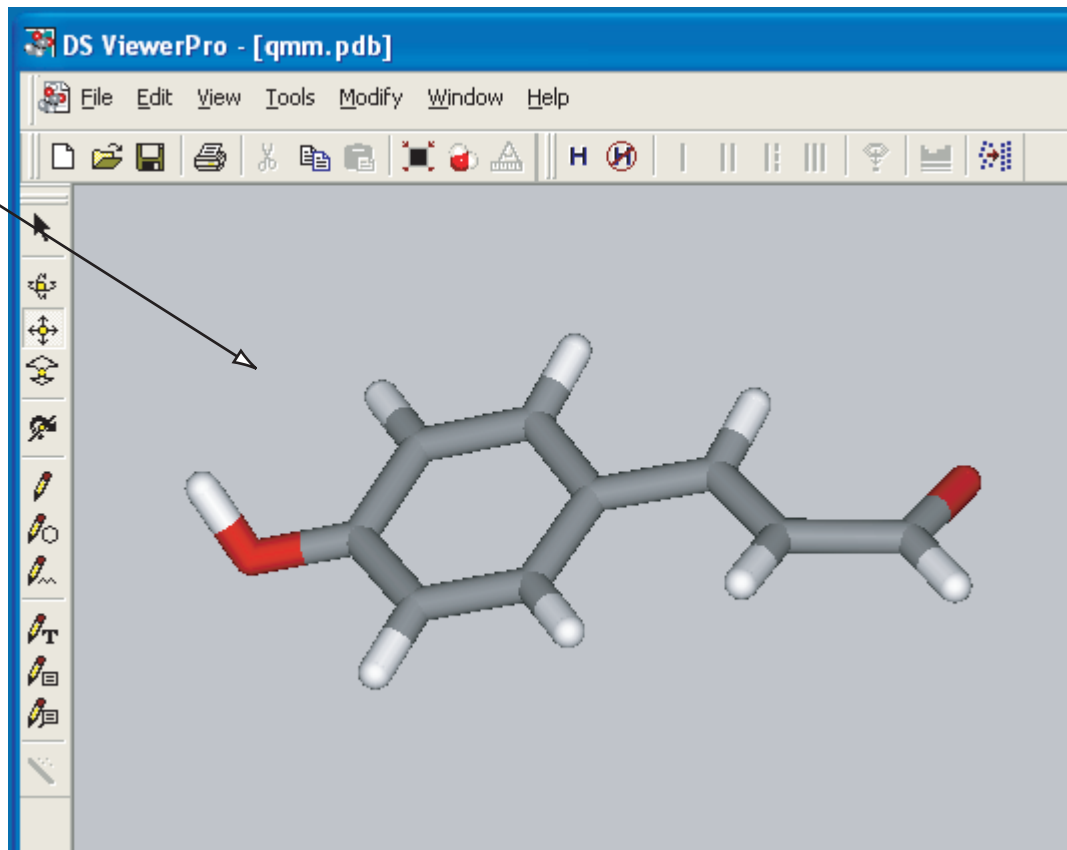
Experimental  
structure of the  
yellow protein



# QM/MM electronic excitations in yellow protein

---

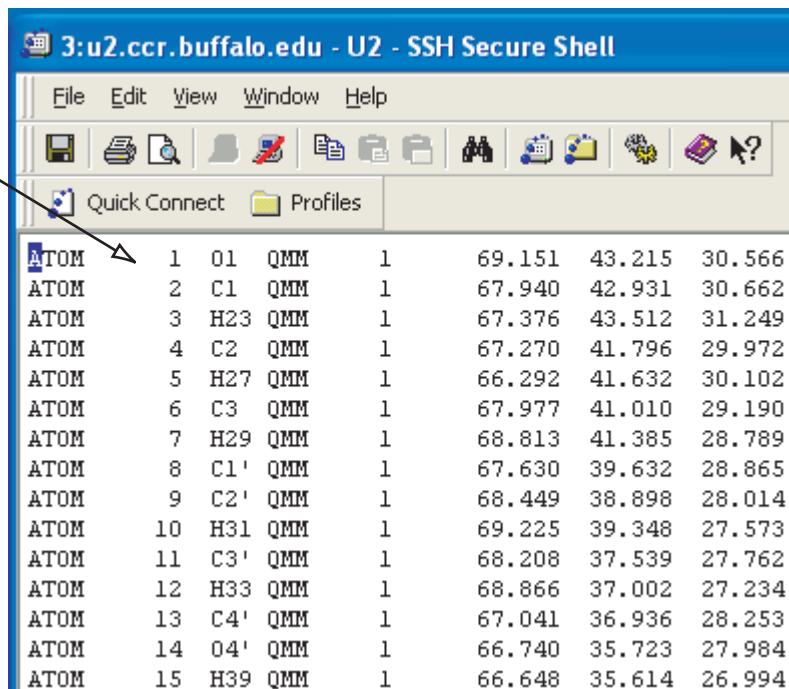
The active site  
of the yellow  
protein



# QM/MM electronic excitations in yellow protein

---

The pdb file of the  
ligand



3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell

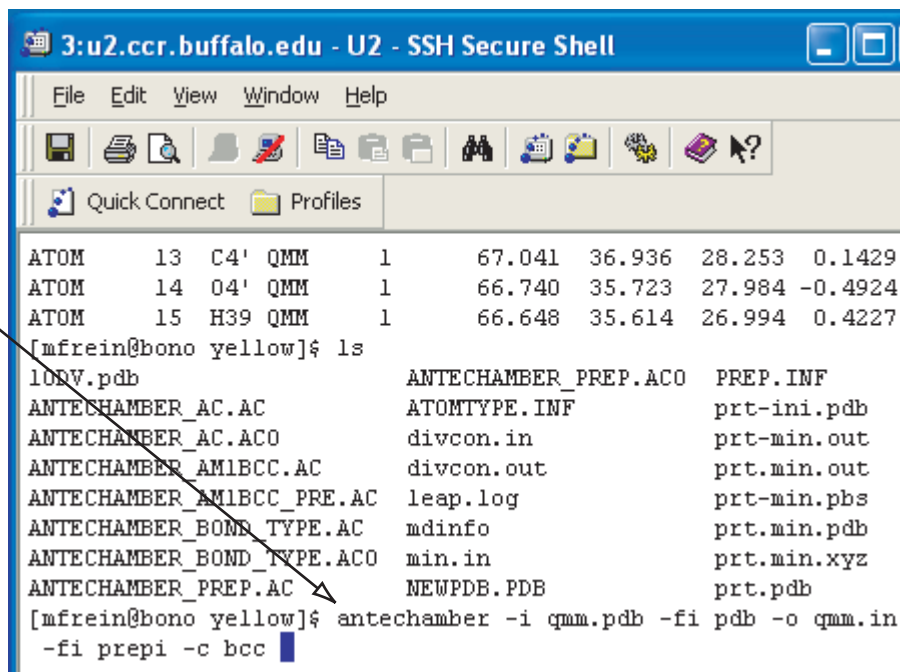
File Edit View Window Help

Quick Connect Profiles

ATOM	1	O1	QMM	1	69.151	43.215	30.566
ATOM	2	C1	QMM	1	67.940	42.931	30.662
ATOM	3	H23	QMM	1	67.376	43.512	31.249
ATOM	4	C2	QMM	1	67.270	41.796	29.972
ATOM	5	H27	QMM	1	66.292	41.632	30.102
ATOM	6	C3	QMM	1	67.977	41.010	29.190
ATOM	7	H29	QMM	1	68.813	41.385	28.789
ATOM	8	C1'	QMM	1	67.630	39.632	28.865
ATOM	9	C2'	QMM	1	68.449	38.898	28.014
ATOM	10	H31	QMM	1	69.225	39.348	27.573
ATOM	11	C3'	QMM	1	68.208	37.539	27.762
ATOM	12	H33	QMM	1	68.866	37.002	27.234
ATOM	13	C4'	QMM	1	67.041	36.936	28.253
ATOM	14	O4'	QMM	1	66.740	35.723	27.984
ATOM	15	H39	QMM	1	66.648	35.614	26.994

# QM/MM electronic excitations in yellow protein

Creating the preparation file of the ligand, using the "antechamber" program



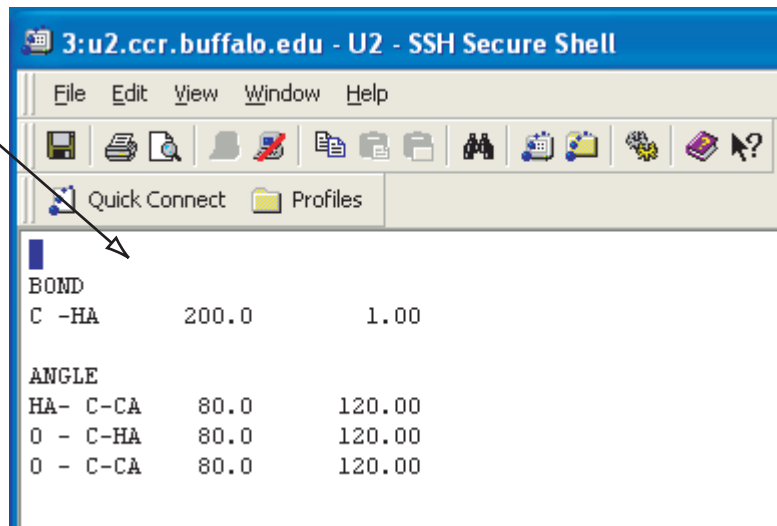
```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

ATOM      13  C4'  QMM      1      67.041  36.936  28.253  0.1429
ATOM      14  O4'  QMM      1      66.740  35.723  27.984 -0.4924
ATOM      15  H39  QMM      1      66.648  35.614  26.994  0.4227
[mfrein@bono yellow]$ ls
100V.pdb          ANTECHAMBER_PREP.ACO  PREP.INF
ANTECHAMBER_AC.AC  ATOMTYPE.INF         prt-ini.pdb
ANTECHAMBER_AC.ACO  divcon.in            prt-min.out
ANTECHAMBER_AM1BCC.AC  divcon.out          prt.min.out
ANTECHAMBER_AM1BCC_PRE.AC  leap.log            prt-min.pbs
ANTECHAMBER_BOND_TYPE.AC  mdinfo              prt.min.pdb
ANTECHAMBER_BOND_TYPE.ACO  min.in              prt.min.xyz
ANTECHAMBER_PREP.AC      NEWPDB.PDB          prt.pdb
[mfrein@bono yellow]$ antechamber -i qmm.pdb -fi pdb -o qmm.in
                        -fi prepi -c bcc
```

# QM/MM electronic excitations in yellow protein

---

Creating the parameter  
file of the ligand



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles
BOND
C -HA      200.0      1.00

ANGLE
HA- C-CA   80.0      120.00
O - C-HA   80.0      120.00
O - C-CA   80.0      120.00
```















# QM/MM electronic excitations in yellow protein



---

Merging the pdb  
structure of the ligand  
with the structure of  
the protein

3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell

FileEditViewWindowHelp



 Quick Connect Profiles

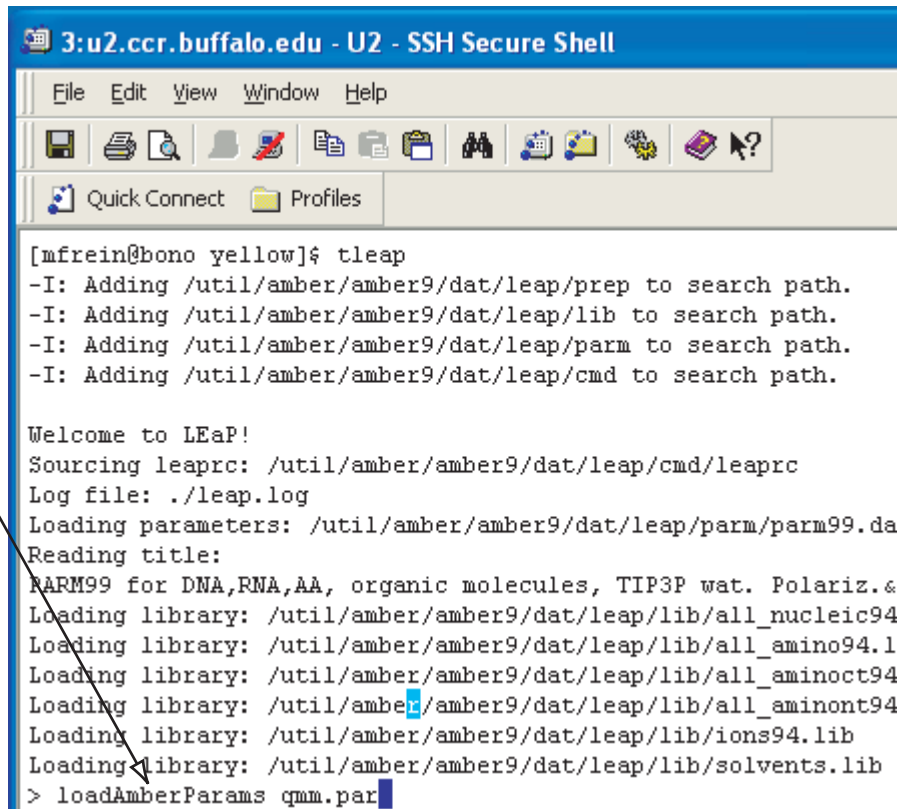
ATOM	784	CB	VAL B 125	53.328	43.051	26.402
ATOM	785	CG1	VAL B 125	53.814	42.542	27.739
ATOM	786	CG2	VAL B 125	54.204	44.201	25.910
ATOM	787	OXT	VAL B 125	52.104	43.483	23.893
TER	788		VAL B 125			
ATOM	1	O1	QMM 1	69.151	43.215	30.566
ATOM	2	C1	QMM 1	67.940	42.931	30.662
ATOM	3	H23	QMM 1	67.376	43.512	31.249
ATOM	4	C2	QMM 1	67.270	41.796	29.972
ATOM	5	H27	QMM 1	66.292	41.632	30.102
ATOM	6	C3	QMM 1	67.977	41.010	29.190
ATOM	7	H29	QMM 1	68.813	41.385	28.789
ATOM	8	C1'	QMM 1	67.630	39.632	28.865



# QM/MM electronic excitations in yellow protein

---

Running the "tleap" program, loading the parameter file of the ligand



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

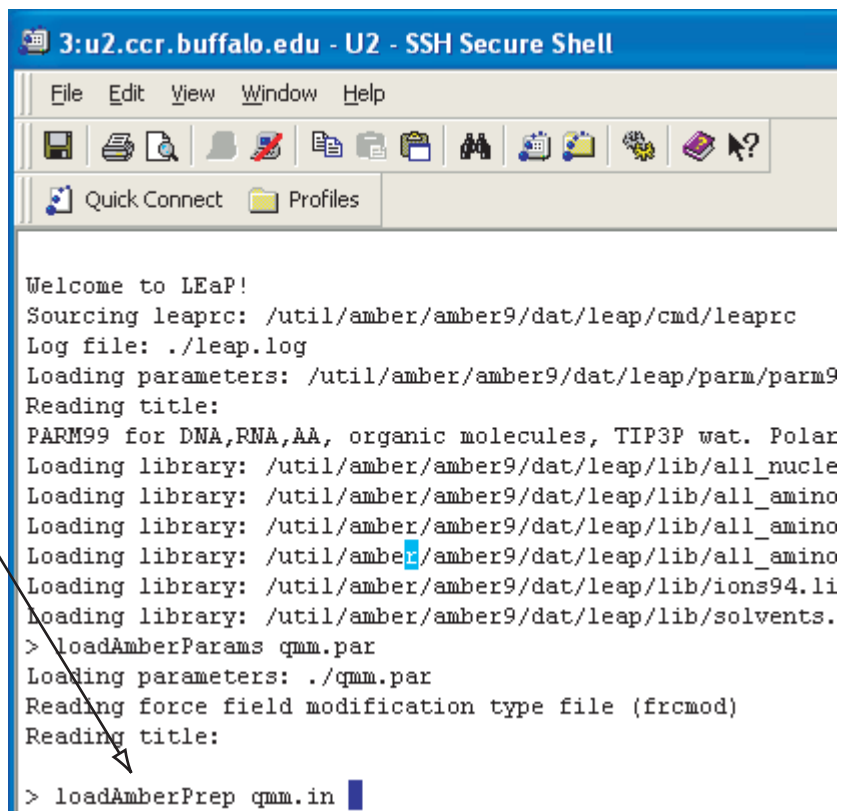
[mfrein@bono yellow]$ tleap
-I: Adding /util/amber/amber9/dat/leap/prep to search path.
-I: Adding /util/amber/amber9/dat/leap/lib to search path.
-I: Adding /util/amber/amber9/dat/leap/parm to search path.
-I: Adding /util/amber/amber9/dat/leap/cmd to search path.

Welcome to LEaP!
Sourcing leaprc: /util/amber/amber9/dat/leap/cmd/leaprc
Log file: ./leap.log
Loading parameters: /util/amber/amber9/dat/leap/parm/parm99.da
Reading title:
PARM99 for DNA, RNA, AA, organic molecules, TIP3P wat. Polariz.&
Loading library: /util/amber/amber9/dat/leap/lib/all_nucleic94
Loading library: /util/amber/amber9/dat/leap/lib/all_amino94.1
Loading library: /util/amber/amber9/dat/leap/lib/all_aminoc94
Loading library: /util/amber/amber9/dat/leap/lib/all_aminont94
Loading library: /util/amber/amber9/dat/leap/lib/ions94.lib
Loading library: /util/amber/amber9/dat/leap/lib/solvents.lib
> loadAmberParams qmm.par
```

# QM/MM electronic excitations in yellow protein

---

Loading the  
preparation file of  
the ligand

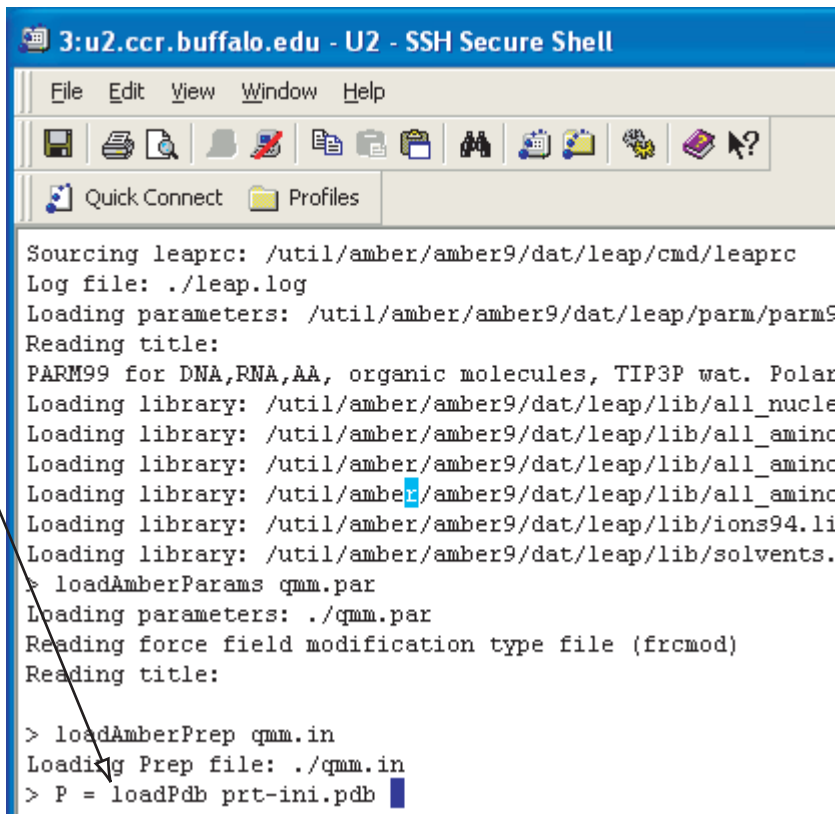


```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Welcome to LEaP!
Sourcing leaprc: /util/amber/amber9/dat/leap/cmd/leaprc
Log file: ./leap.log
Loading parameters: /util/amber/amber9/dat/leap/parm/parm9
Reading title:
PARM99 for DNA,RNA,AA, organic molecules, TIP3P wat. Polar
Loading library: /util/amber/amber9/dat/leap/lib/all_nucle
Loading library: /util/amber/amber9/dat/leap/lib/all_amino
Loading library: /util/amber/amber9/dat/leap/lib/all_amino
Loading library: /util/amber/amber9/dat/leap/lib/all_amino
Loading library: /util/amber/amber9/dat/leap/lib/ions94.li
Loading library: /util/amber/amber9/dat/leap/lib/solvents.
> loadAmberParams qmm.par
Loading parameters: ./qmm.par
Reading force field modification type file (frcmod)
Reading title:
> loadAmberPrep qmm.in
```

# QM/MM electronic excitations in yellow protein

---

Loading the pdb  
file of the protein  
and the ligand



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons: Save, Print, Find, etc.]
Quick Connect Profiles

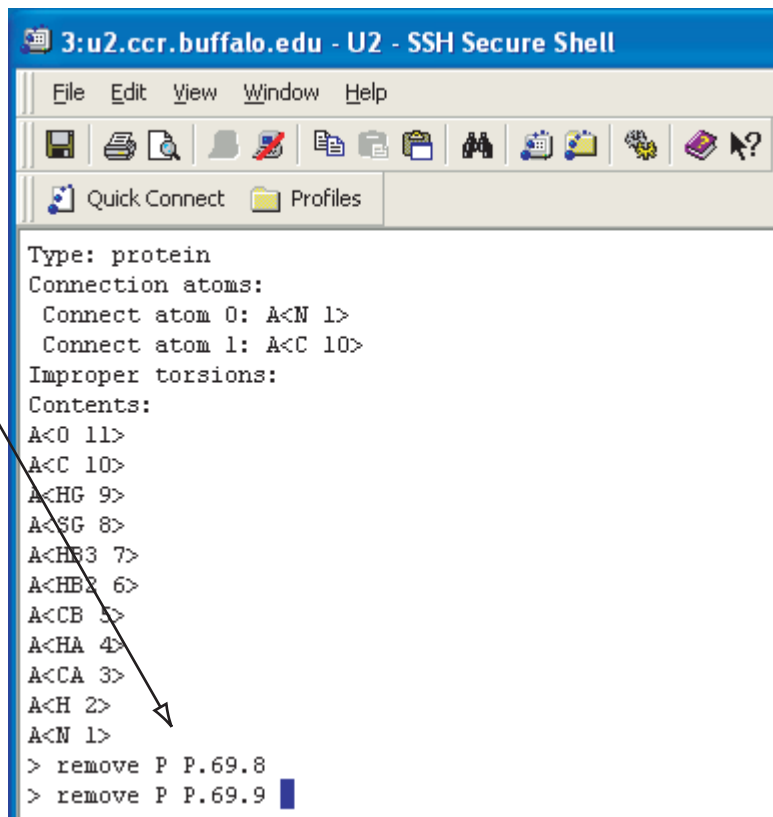
Sourcing leaprc: /util/amber/amber9/dat/leap/cmd/leaprc
Log file: ./leap.log
Loading parameters: /util/amber/amber9/dat/leap/parm/parm9
Reading title:
PARM99 for DNA,RNA,AA, organic molecules, TIP3P wat. Polar
Loading library: /util/amber/amber9/dat/leap/lib/all_nucle
Loading library: /util/amber/amber9/dat/leap/lib/all_aminc
Loading library: /util/amber/amber9/dat/leap/lib/all_aminc
Loading library: /util/amber/amber9/dat/leap/lib/all_aminc
Loading library: /util/amber/amber9/dat/leap/lib/ions94.li
Loading library: /util/amber/amber9/dat/leap/lib/solvents.
> loadAmberParams qmm.par
Loading parameters: ./qmm.par
Reading force field modification type file (frcmod)
Reading title:

> loadAmberPrep qmm.in
Loading Prep file: ./qmm.in
> P = loadPdb prt-ini.pdb
```

# QM/MM electronic excitations in yellow protein

---

Removing protein  
atoms which are too  
close to the ligand



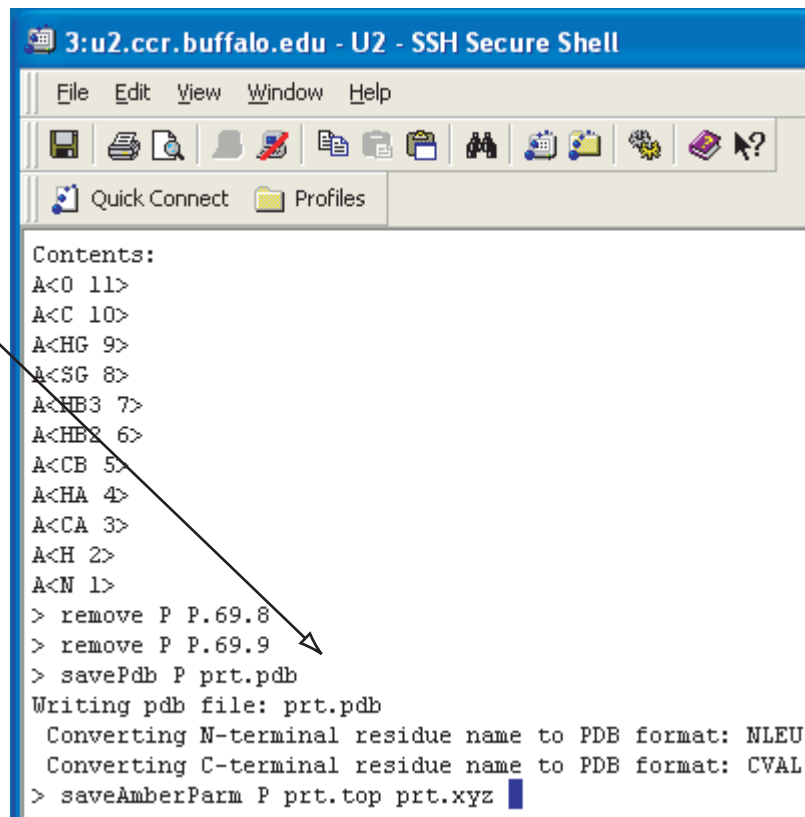
```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

Type: protein
Connection atoms:
  Connect atom 0: A<N 1>
  Connect atom 1: A<C 10>
Improper torsions:
Contents:
A<O 11>
A<C 10>
A<HG 9>
A<SG 8>
A<HB3 7>
A<HB2 6>
A<CB 5>
A<HA 4>
A<CA 3>
A<H 2>
A<N 1>
> remove P P.69.8
> remove P P.69.9
```

# QM/MM electronic excitations in yellow protein

---

Saving the pdb, the topology and the coordinates files of the protein system



The screenshot shows a terminal window titled "3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons. The main area of the terminal displays the following text:

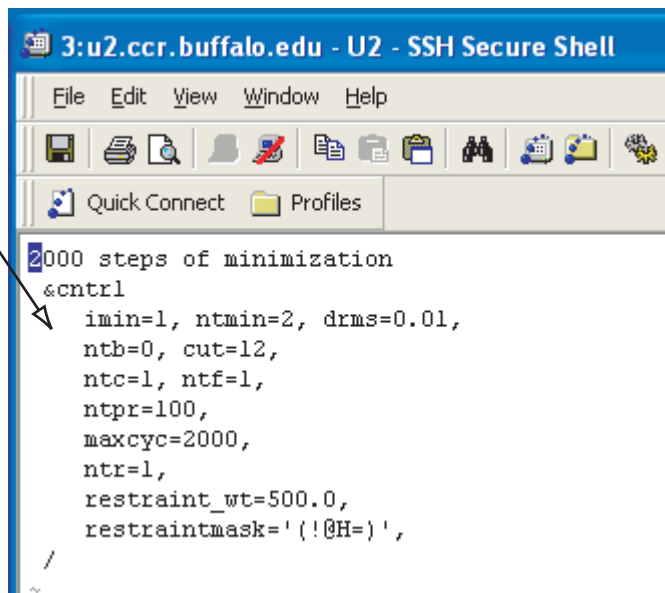
```
Contents:
A<O 11>
A<C 10>
A<HG 9>
A<SG 8>
A<HB3 7>
A<HB2 6>
A<CB 5>
A<HA 4>
A<CA 3>
A<H 2>
A<N 1>
> remove P P.69.8
> remove P P.69.9
> savePdb P prt.pdb
Writing pdb file: prt.pdb
  Converting N-terminal residue name to PDB format: NLEU
  Converting C-terminal residue name to PDB format: CVAL
> saveAmberParm P prt.top prt.xyz
```

An arrow points from the text "Saving the pdb, the topology and the coordinates files of the protein system" to the command "> savePdb P prt.pdb" in the terminal output.

# QM/MM electronic excitations in yellow protein

---

Creating the input file  
for the minimization

A screenshot of an SSH Secure Shell window titled "3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell". The window has a menu bar with "File", "Edit", "View", "Window", and "Help". Below the menu bar is a toolbar with various icons. A "Quick Connect" button and a "Profiles" folder icon are also visible. The main text area shows a minimization input file with the following content:

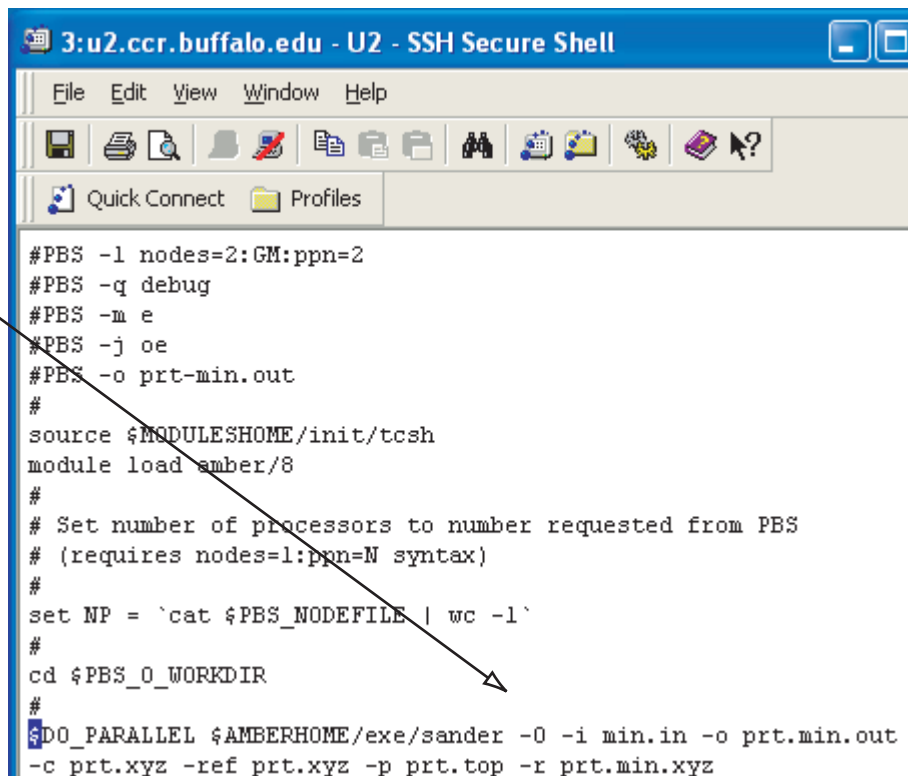
```
2000 steps of minimization
&cntrl
  imin=1, ntmin=2, drms=0.01,
  ntb=0, cut=12,
  ntc=1, ntf=1,
  ntp=100,
  maxcyc=2000,
  ntr=1,
  restraint_wt=500.0,
  restraintmask='(!@H=)',
/
```

An arrow points from the text "Creating the input file for the minimization" to the first line of the input file, "2000 steps of minimization".

# QM/MM electronic excitations in yellow protein

---

Creating the pbs  
script for the  
minimization



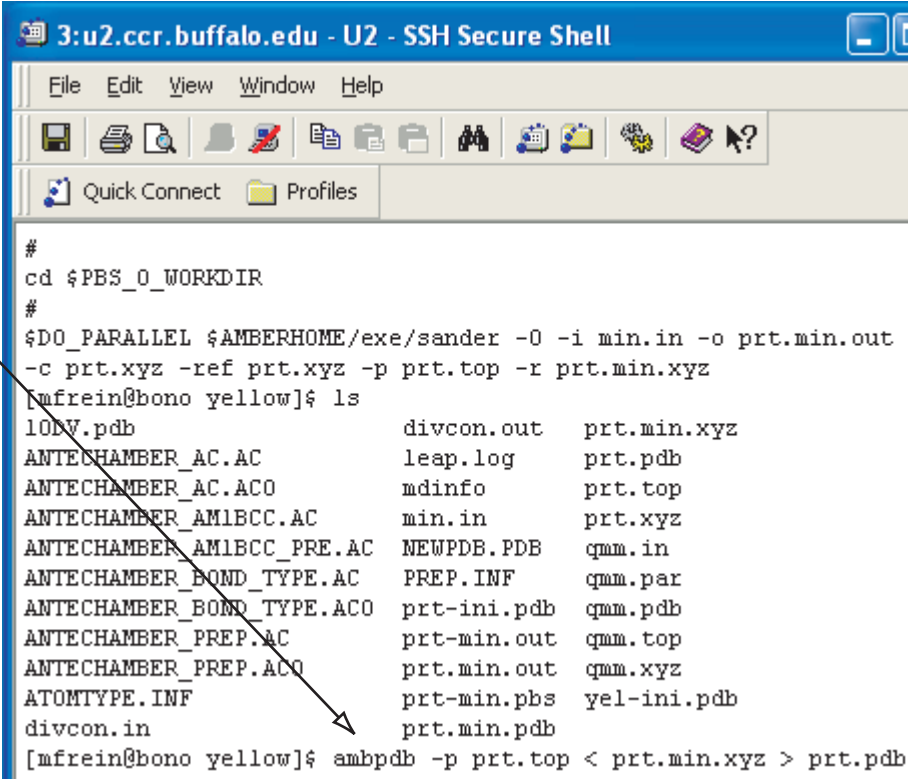
```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

#PBS -l nodes=2:GM:ppn=2
#PBS -q debug
#PBS -m e
#PBS -j oe
#PBS -o prt-min.out
#
source $MODULESHOME/init/tcsh
module load amber/8
#
# Set number of processors to number requested from PBS
# (requires nodes=1:ppn=N syntax)
#
set NP = `cat $PBS_NODEFILE | wc -l`
#
cd $PBS_O_WORKDIR
#
$DO_PARALLEL $AMBERHOME/exe/sander -O -i min.in -o prt.min.out
-c prt.xyz -ref prt.xyz -p prt.top -r prt.min.xyz
```

# QM/MM electronic excitations in yellow protein

---

Converting the  
minimized  
coordinates into  
the pdb format



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons: Disk, Printer, Magnifying Glass, User, Eraser, Document, Folder, Mail, Calendar, Clock, Gear, Bookmarks, Mouse]
Quick Connect Profiles

#
cd $PBS_O_WORKDIR
#
$DO_PARALLEL $AMBERHOME/exe/sander -O -i min.in -o prt.min.out
-c prt.xyz -ref prt.xyz -p prt.top -r prt.min.xyz
[mfrein@bono yellow]$ ls
10DV.pdb                divcon.out             prt.min.xyz
ANTECHAMBER_AC.AC       leap.log               prt.pdb
ANTECHAMBER_AC.ACO      mdinfo                 prt.top
ANTECHAMBER_AM1BCC.AC   min.in                 prt.xyz
ANTECHAMBER_AM1BCC_PRE.AC NEWPDB.PDB             qmm.in
ANTECHAMBER_BOND_TYPE.AC PREP.INF               qmm.par
ANTECHAMBER_BOND_TYPE.ACO prt-ini.pdb            qmm.pdb
ANTECHAMBER_PREP.AC     prt-min.out            qmm.top
ANTECHAMBER_PREP.ACO    prt.min.out            qmm.xyz
ATOMTYPE.INF            prt-min.pbs            yel-ini.pdb
divcon.in               prt.min.pdb
[mfrein@bono yellow]$ ambpdb -p prt.top < prt.min.xyz > prt.pdb
```



# QM/MM electronic excitations in yellow protein

## Generating the q-chem input file for the QM/MM calculations

3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell

File Edit View Window Help

Quick Connect Profiles

```

10DV.pdb                divcon.out             prt.min.xyz
ANTECHAMBER_AC.AC       leap.log               prt.pdb
ANTECHAMBER_AC.ACO      mdinfo                 prt.top
ANTECHAMBER_AM1BCC.AC   min.in                 prt.xyz
ANTECHAMBER_AM1BCC_PRE.AC NEWPDB.PDB             qmm.in
ANTECHAMBER_BOND_TYPE.AC PREP.INF                qmm.par
ANTECHAMBER_BOND_TYPE.ACO prt-ini.pdb            qmm.pdb
ANTECHAMBER_PREP.AC     prt-min.out            qmm.top
ANTECHAMBER_PREP.ACO    prt-min.out            qmm.xyz
ATOMTYPE.INF            prt-min.pbs            yel-ini.pdb
divcon.in               prt-min.pdb

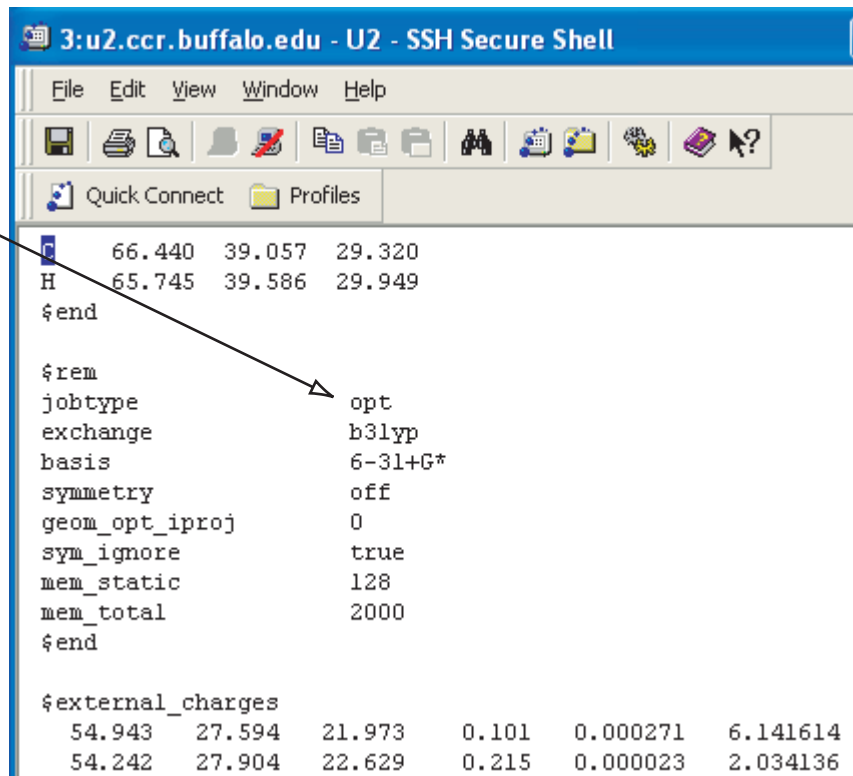
[mfrein@bono yellow]$ pwd
/san/projects1/mfrein/amber/teaching/yellow
[mfrein@bono yellow]$ cd /san/projects1/mfrein/q-chem/teaching/yellow
[mfrein@bono yellow]$ ls
gas      prt.log  prt.pbs  prt.top  qmmm_setup.pl
prt.in   prt.out  prt.pdb  gchem2pdb.pl  tddft
[mfrein@bono yellow]$ ./qmmm_setup.pl

```

# QM/MM electronic excitations in yellow protein

---

Geometry optimization  
of the ligand inside the  
protein



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

C 66.440 39.057 29.320
H 65.745 39.586 29.949
$end

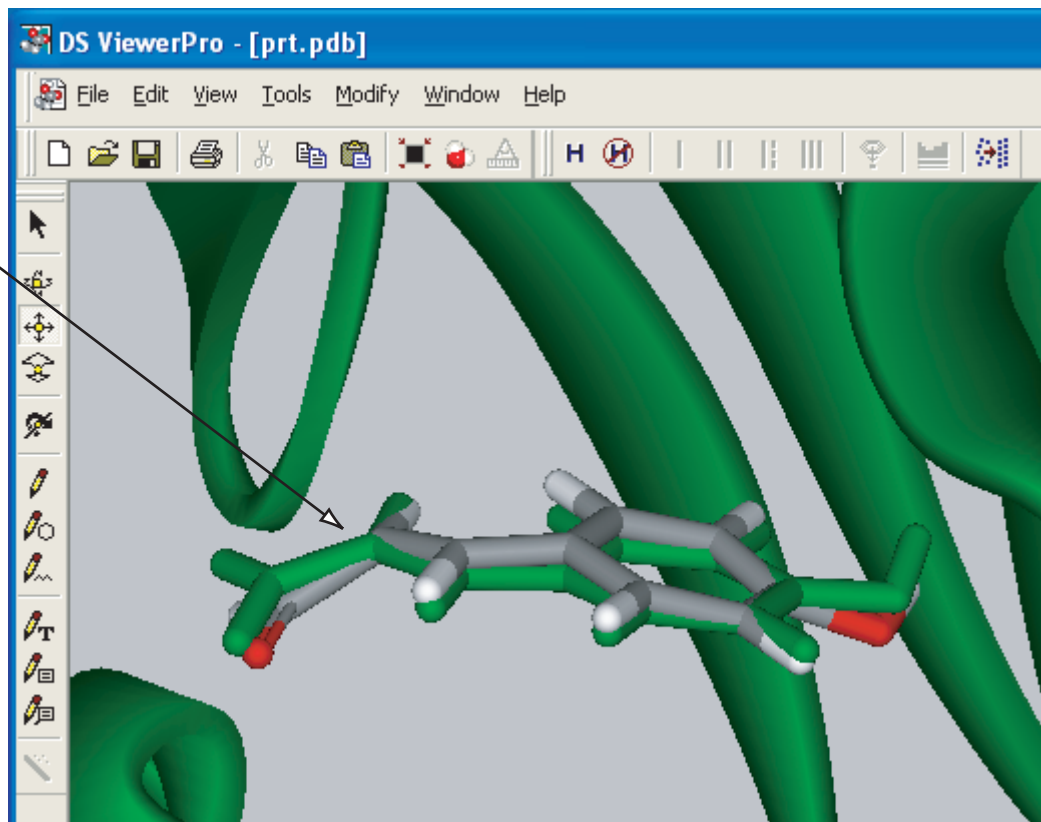
$rem
jobtype opt
exchange b3lyp
basis 6-31+G*
symmetry off
geom_opt_iproj 0
sym_ignore true
mem_static 128
mem_total 2000
$end

$external_charges
54.943 27.594 21.973 0.101 0.000271 6.141614
54.242 27.904 22.629 0.215 0.000023 2.034136
```

# QM/MM electronic excitations in yellow protein

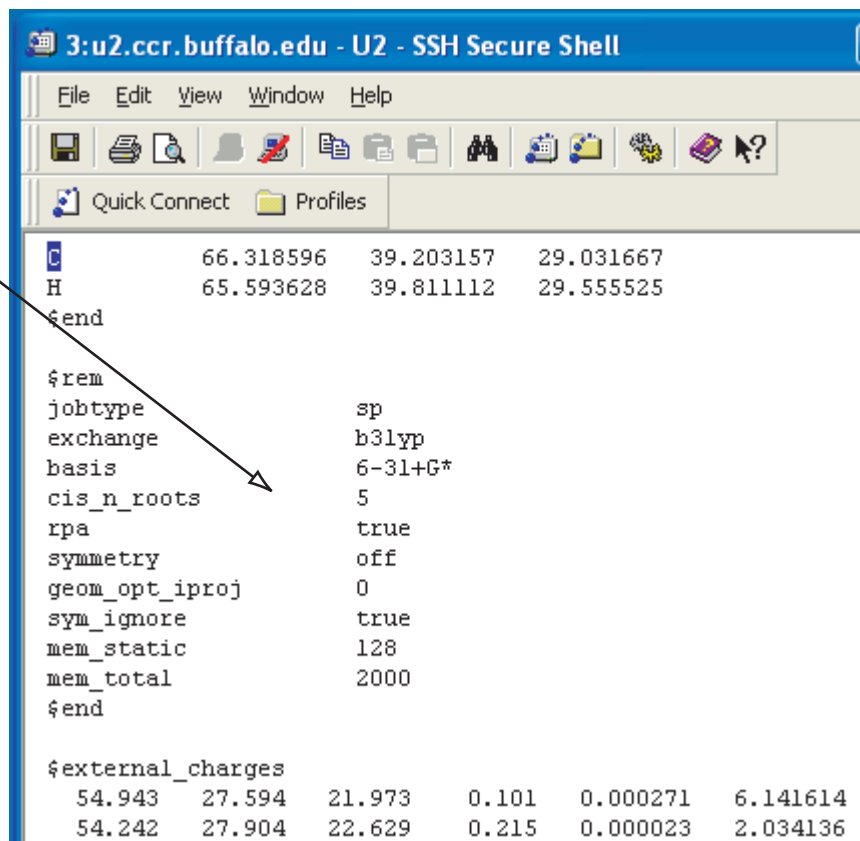
---

The calculated  
optimal geometry  
of the ligand  
inside the protein



# QM/MM electronic excitations in yellow protein

TDDFT calculations in the protein, based on the optimal geometry of the ligand in the protein



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
Quick Connect Profiles

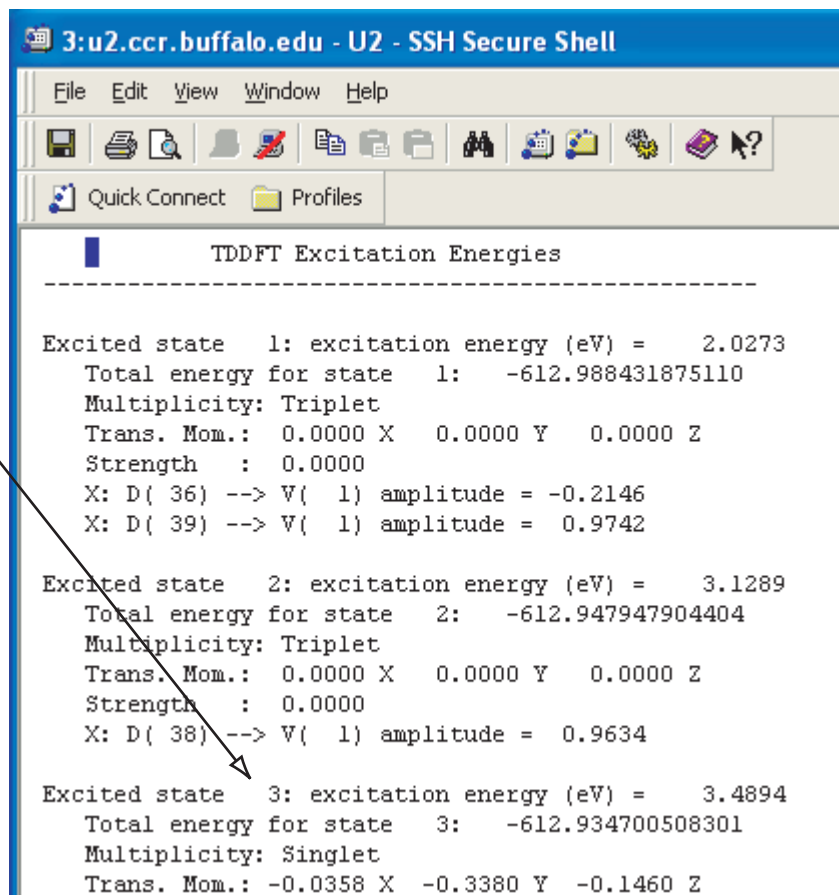
C 66.318596 39.203157 29.031667
H 65.593628 39.811112 29.555525
$end

$rem
jobtype sp
exchange b3lyp
basis 6-31+G*
cis_n_roots 5
rpa true
symmetry off
geom_opt_iproj 0
sym_ignore true
mem_static 128
mem_total 2000
$end

$external_charges
54.943 27.594 21.973 0.101 0.000271 6.141614
54.242 27.904 22.629 0.215 0.000023 2.034136
```

# QM/MM electronic excitations in yellow protein

The excitation energy of the first excited singlet electronic state



```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles

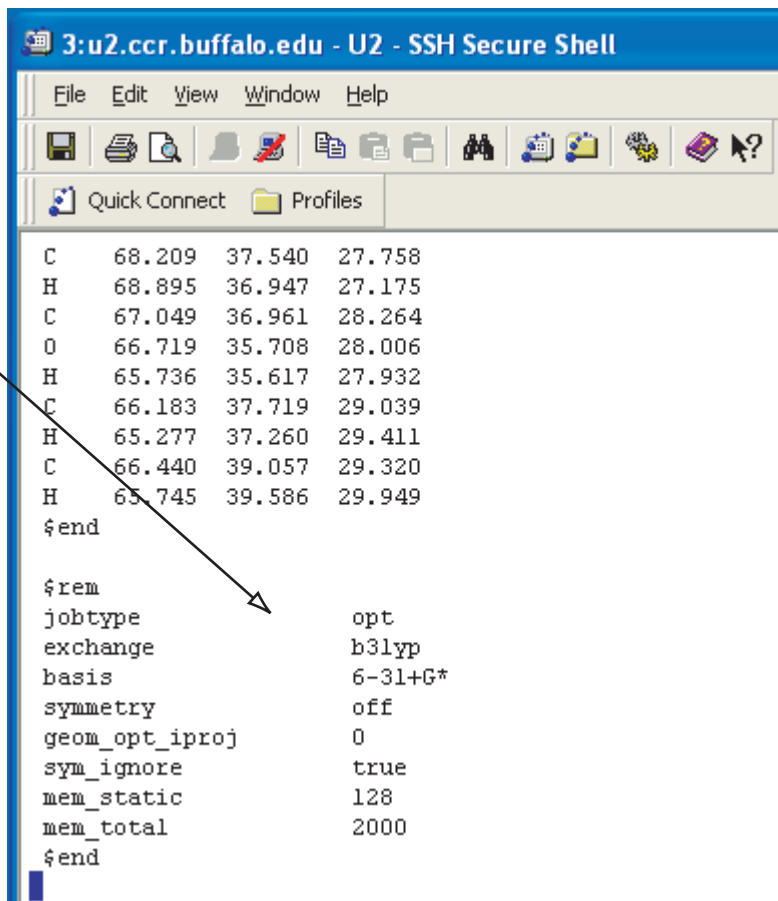
TDDFT Excitation Energies
-----
Excited state 1: excitation energy (eV) = 2.0273
Total energy for state 1: -612.988431875110
Multiplicity: Triplet
Trans. Mom.: 0.0000 X 0.0000 Y 0.0000 Z
Strength : 0.0000
X: D( 36) --> V( 1) amplitude = -0.2146
X: D( 39) --> V( 1) amplitude = 0.9742

Excited state 2: excitation energy (eV) = 3.1289
Total energy for state 2: -612.947947904404
Multiplicity: Triplet
Trans. Mom.: 0.0000 X 0.0000 Y 0.0000 Z
Strength : 0.0000
X: D( 38) --> V( 1) amplitude = 0.9634

Excited state 3: excitation energy (eV) = 3.4894
Total energy for state 3: -612.934700508301
Multiplicity: Singlet
Trans. Mom.: -0.0358 X -0.3380 Y -0.1460 Z
```

# QM/MM electronic excitations in yellow protein

Geometry optimization  
of the ligand in the gas  
phase



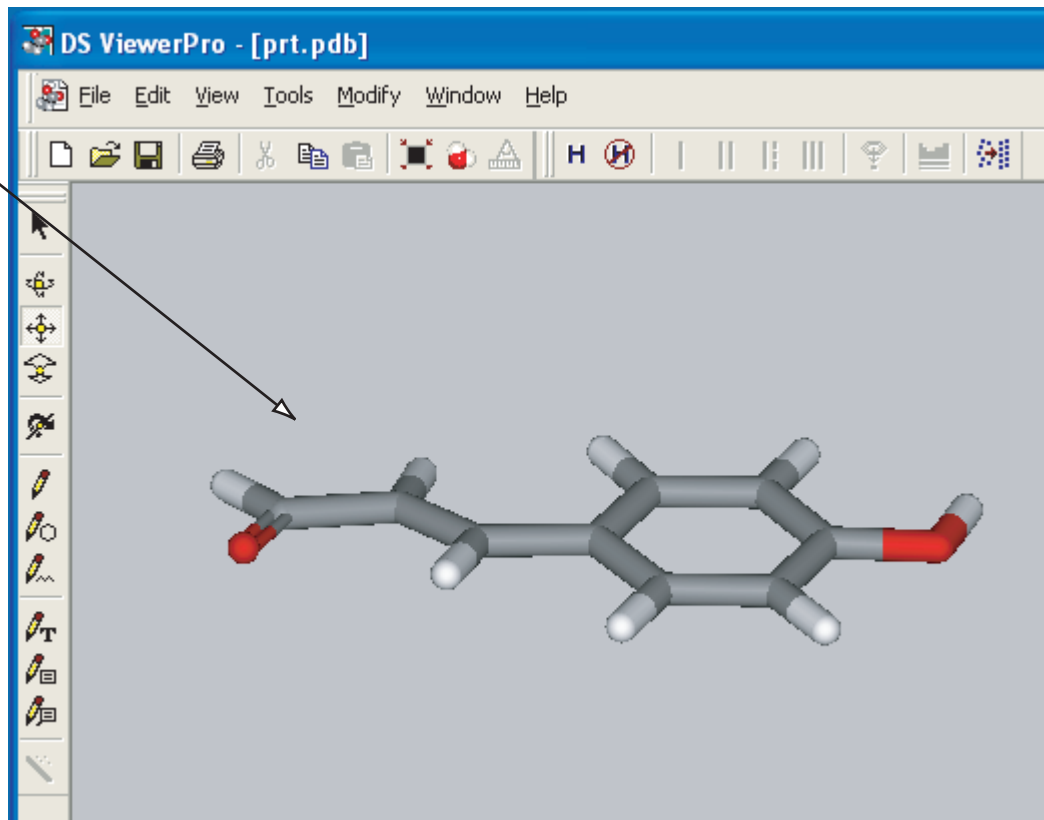
```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File Edit View Window Help
[Icons]
Quick Connect Profiles
C 68.209 37.540 27.758
H 68.895 36.947 27.175
C 67.049 36.961 28.264
O 66.719 35.708 28.006
H 65.736 35.617 27.932
C 66.183 37.719 29.039
H 65.277 37.260 29.411
C 66.440 39.057 29.320
H 65.745 39.586 29.949
$end

$rem
jobtype opt
exchange b3lyp
basis 6-31+G*
symmetry off
geom_opt_iproj 0
sym_ignore true
mem_static 128
mem_total 2000
$end
```

# QM/MM electronic excitations in yellow protein

---

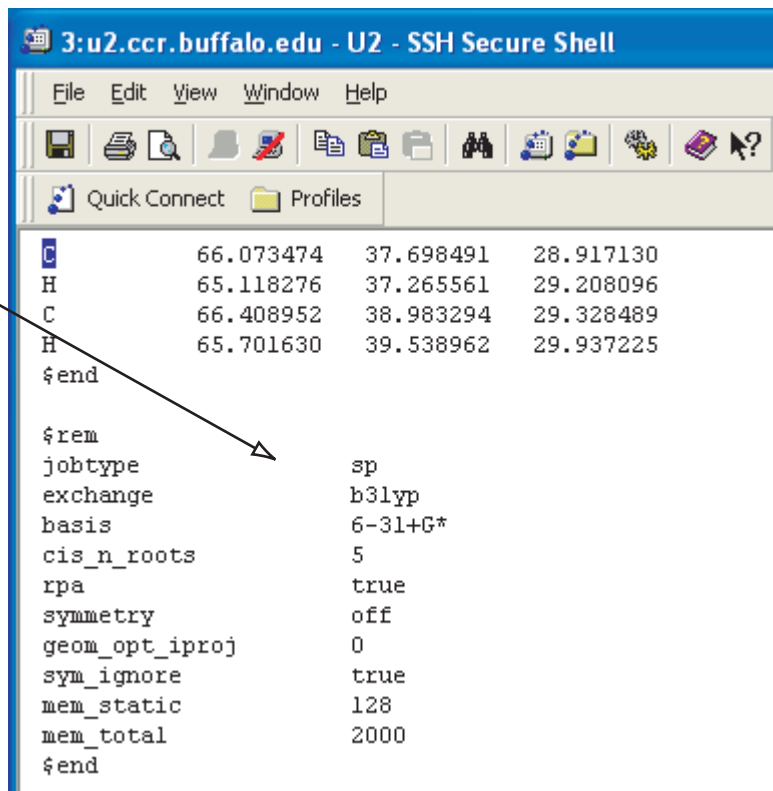
The calculated  
optimal geometry  
of the ligand in  
the gas phase



# QM/MM electronic excitations in yellow protein

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TDDFT calculations of the ligand in the gas phase, for the optimal geometry of the ligand in the gas phase



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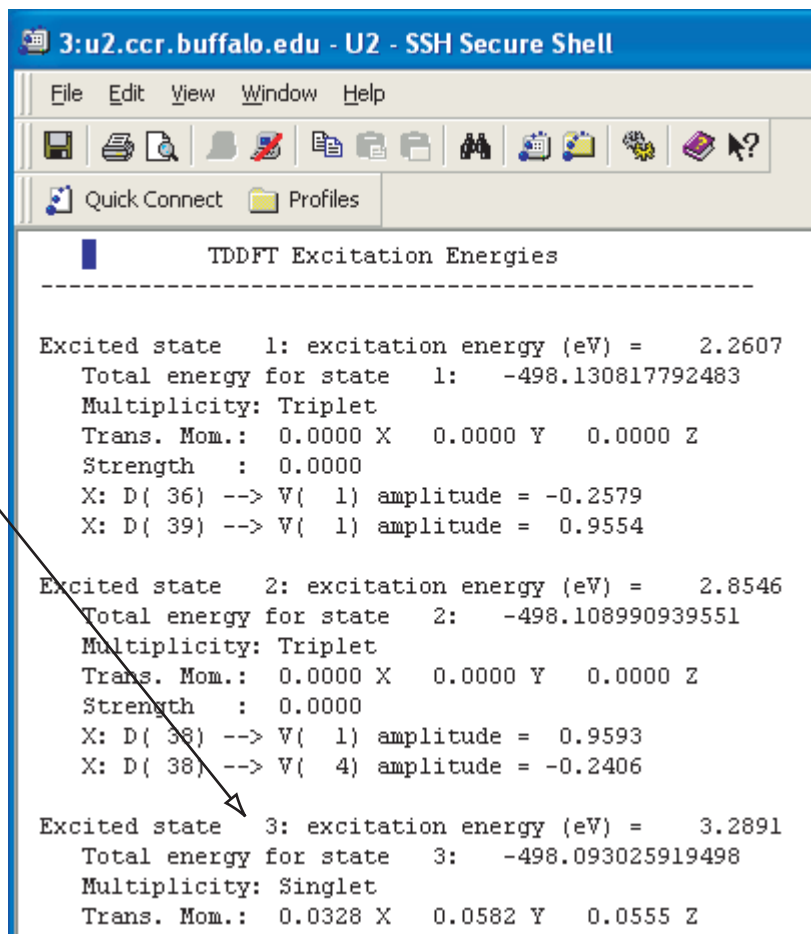
C      66.073474   37.698491   28.917130
H      65.118276   37.265561   29.208096
C      66.408952   38.983294   29.328489
H      65.701630   39.538962   29.937225
$end

$rem
jobtype                sp
exchange                b3lyp
basis                  6-31+G*
cis_n_roots             5
rpa                     true
symmetry                off
geom_opt_iproj          0
sym_ignore              true
mem_static              128
mem_total               2000
$end
```



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The excitation energy of the first excited singlet electronic state of the ligand



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TDDFT Excitation Energies
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Excited state 1: excitation energy (eV) = 2.2607
Total energy for state 1: -498.130817792483
Multiplicity: Triplet
Trans. Mom.: 0.0000 X 0.0000 Y 0.0000 Z
Strength : 0.0000
X: D( 36) --> V( 1) amplitude = -0.2579
X: D( 39) --> V( 1) amplitude = 0.9554

Excited state 2: excitation energy (eV) = 2.8546
Total energy for state 2: -498.108990939551
Multiplicity: Triplet
Trans. Mom.: 0.0000 X 0.0000 Y 0.0000 Z
Strength : 0.0000
X: D( 38) --> V( 1) amplitude = 0.9593
X: D( 38) --> V( 4) amplitude = -0.2406

Excited state 3: excitation energy (eV) = 3.2891
Total energy for state 3: -498.093025919498
Multiplicity: Singlet
Trans. Mom.: 0.0328 X 0.0582 Y 0.0555 Z
```

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The comparison the calculated excitation energies of the ligand with the experimental UV spectrum

$$\Delta E(\text{cal.}) = -23 \text{ nm}$$

$$\Delta E(\text{exp.}) = -14 \text{ nm}$$

