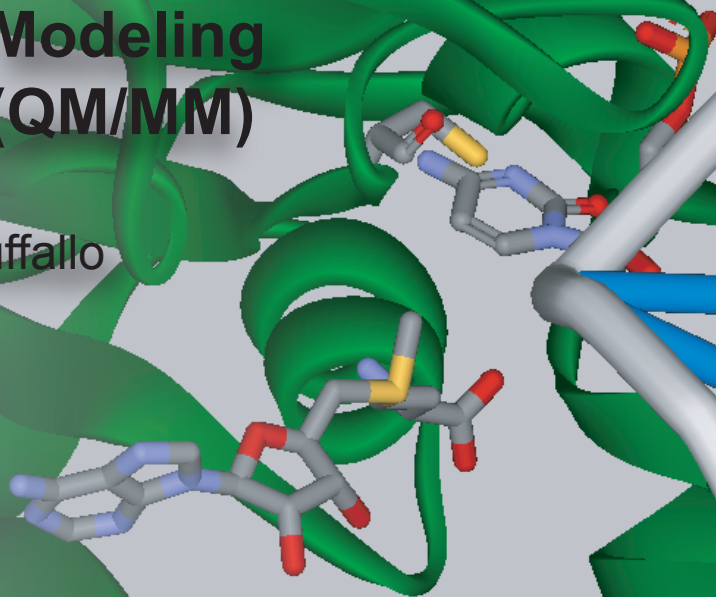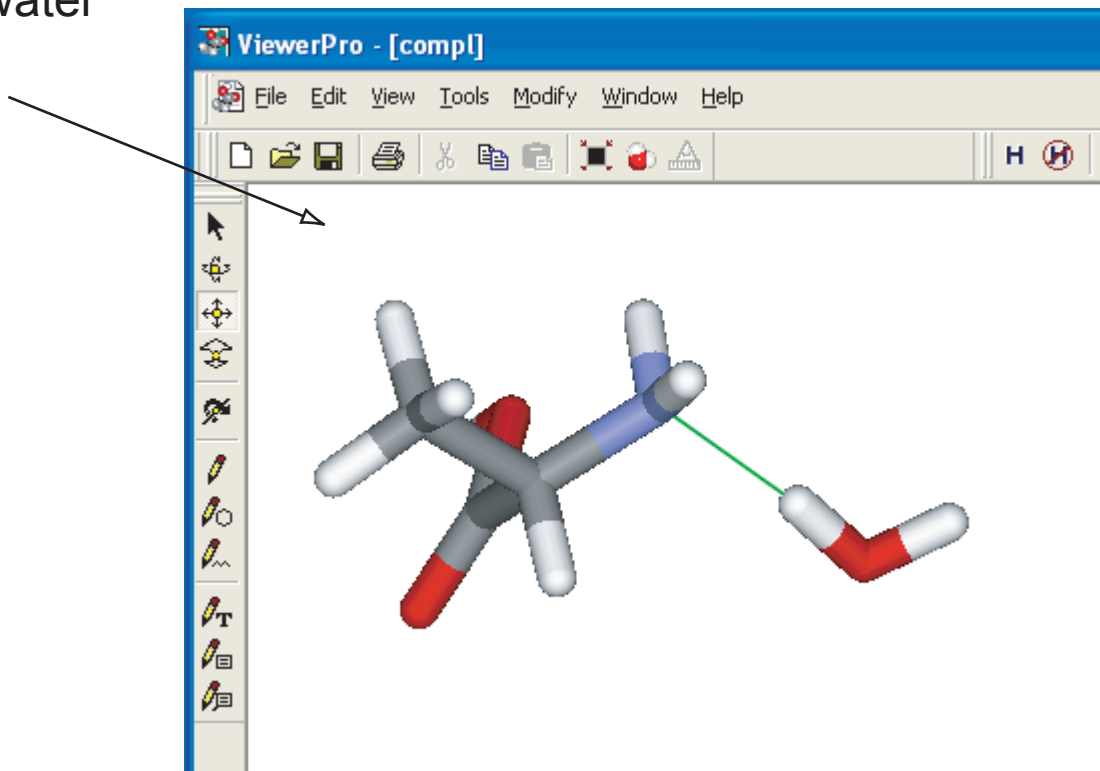Marek

Freindorf

Molecular Modeling
Examples (QM/MM)

University at Buffallo

April 2007

QM/MM calculations of alanine water dimer

Geometry optimization
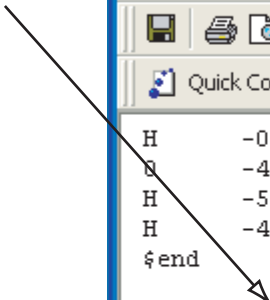of the alanine water
dimer

QM/MM calculations of alanine water dimer
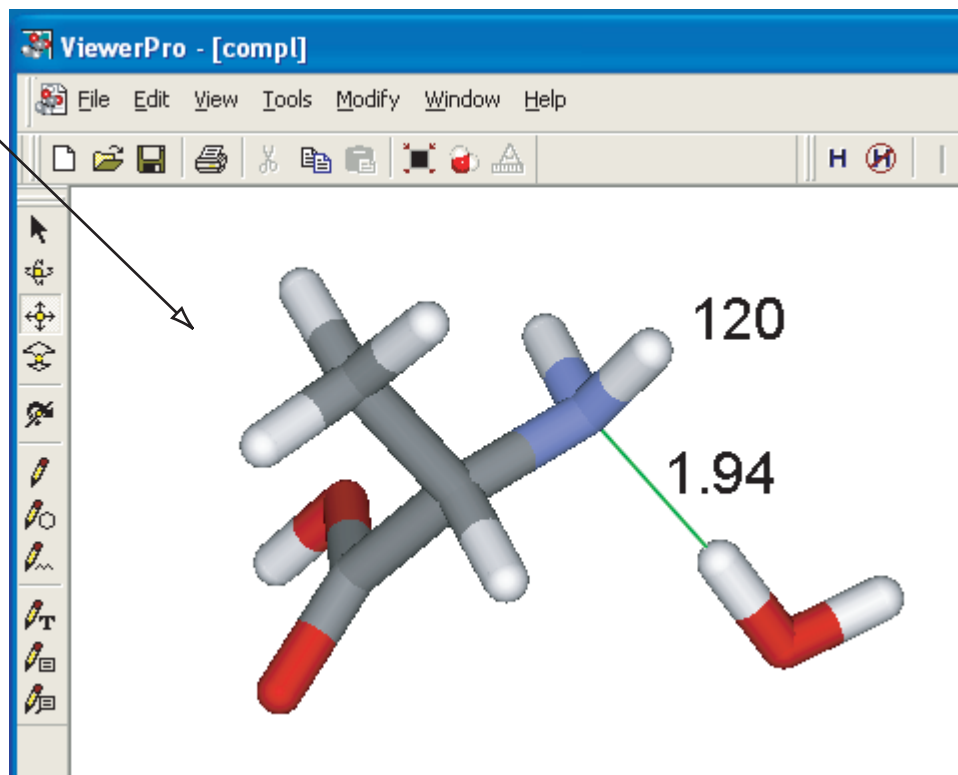
Technical details of
the QM calculations

```
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
```
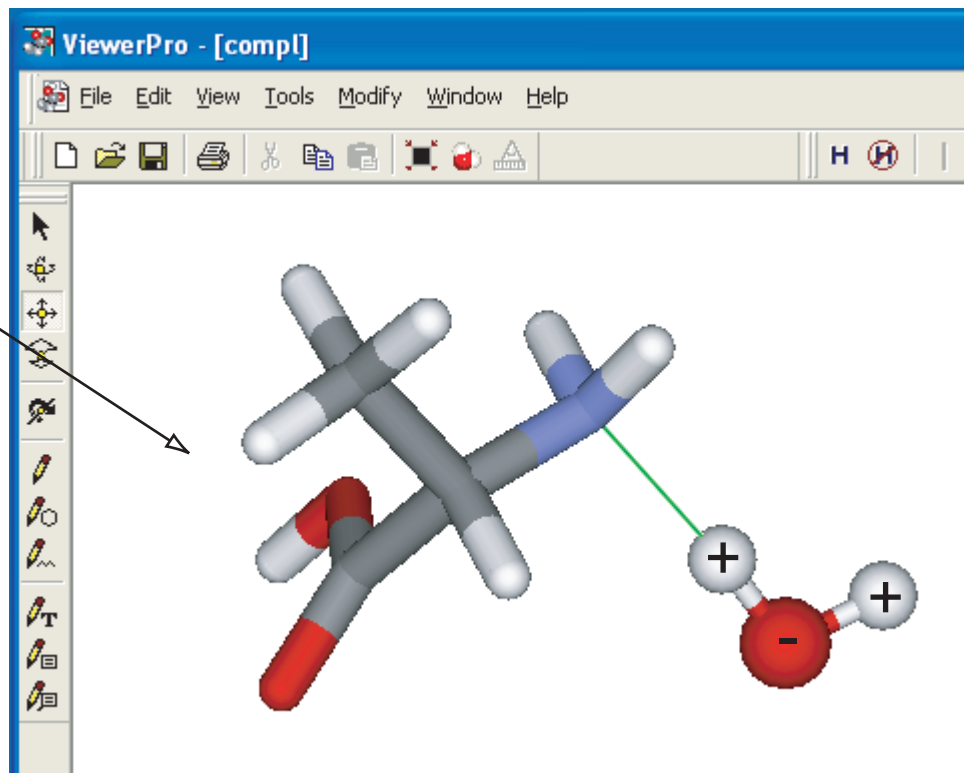
QM/MM calculations of alanine water dimer

Final structure after QM geometry optimization
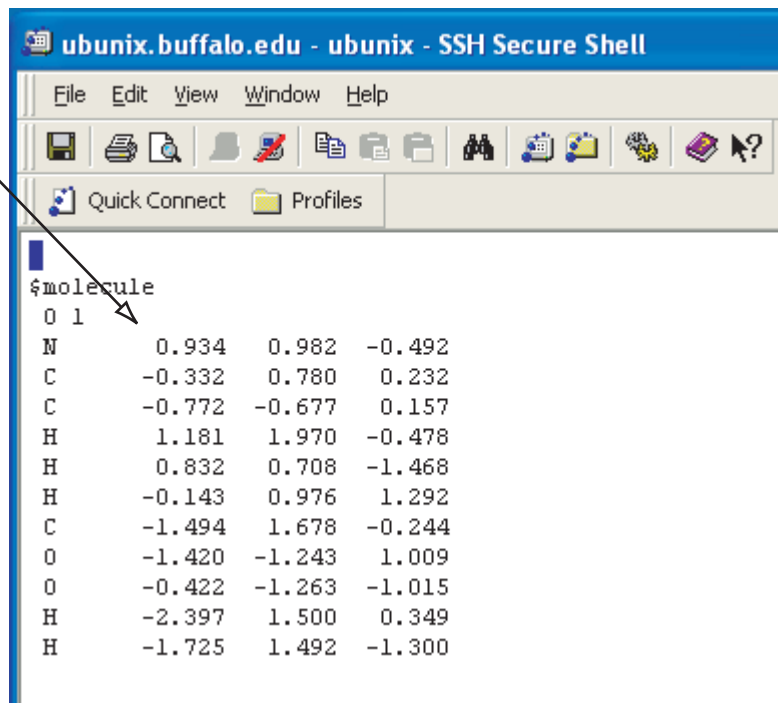
QM/MM calculations of alanine water dimer

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

QM/MM calculations of alanine water dimer
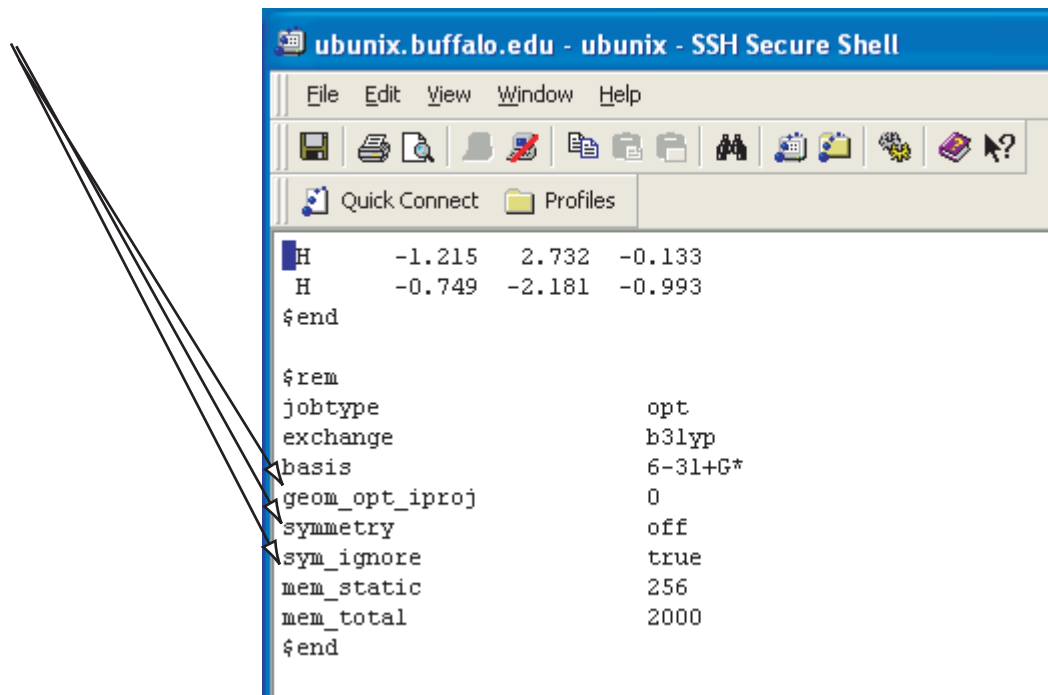
Cartesian coordinates
of the alanine only

```
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File  Edit  View  Window  Help

Quick Connect    Profiles

$molecule
 0 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

```
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File   Edit   View   Window   Help

  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
```
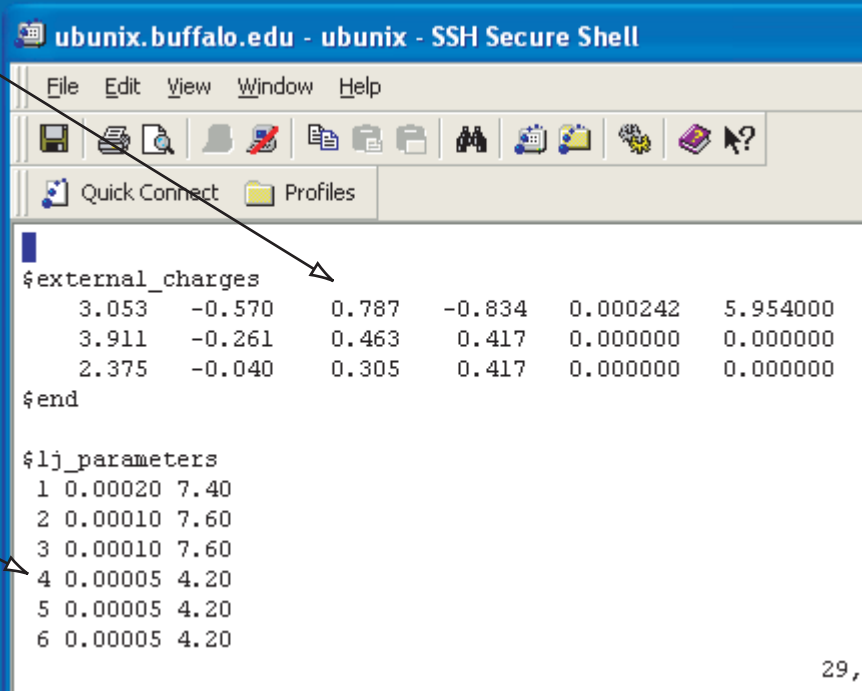
QM/MM calculations of alanine water dimer

MM atoms are represented by point charges and vdW spheres

vdW spheres of the QM atoms

```
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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,
```
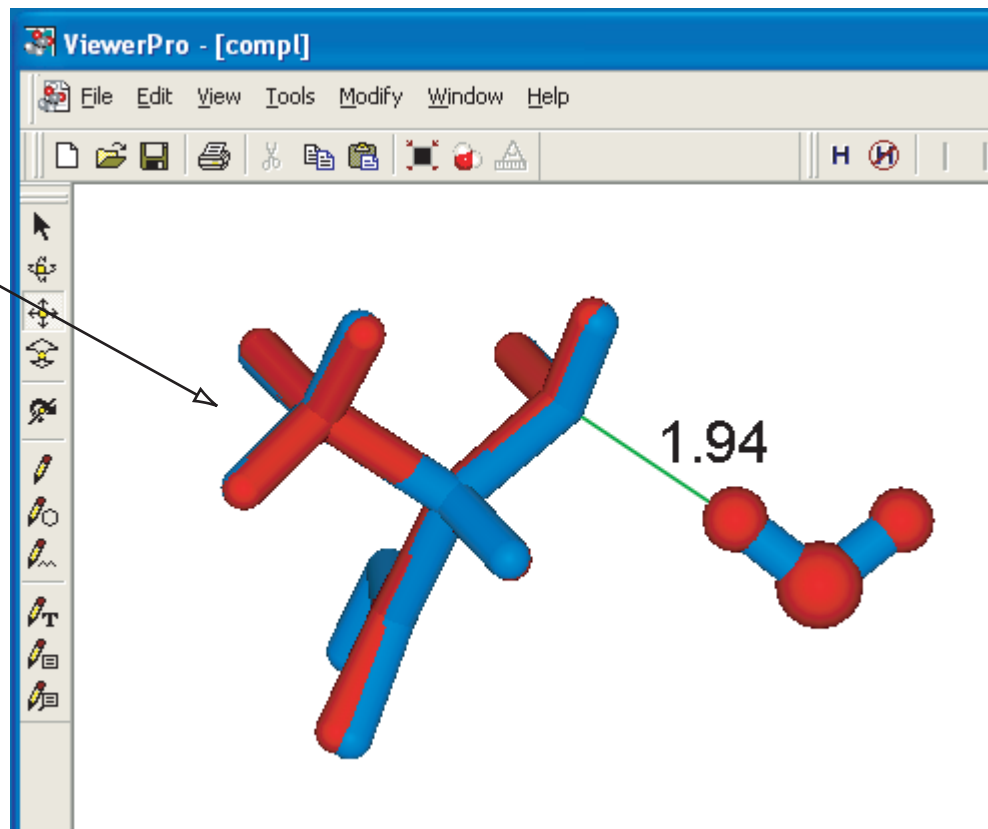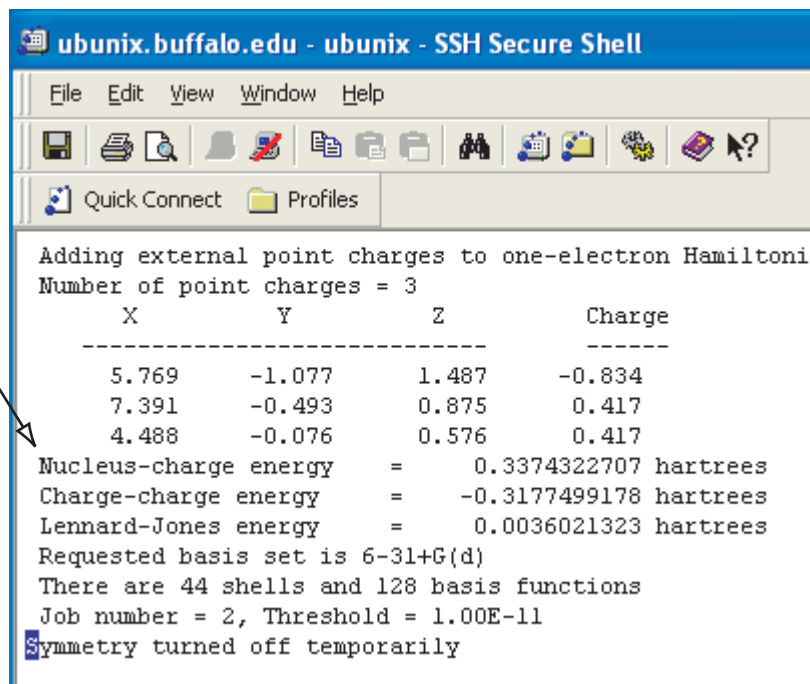
QM/MM calculations of alanine water dimer

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

QM/MM calculations of alanine water dimer

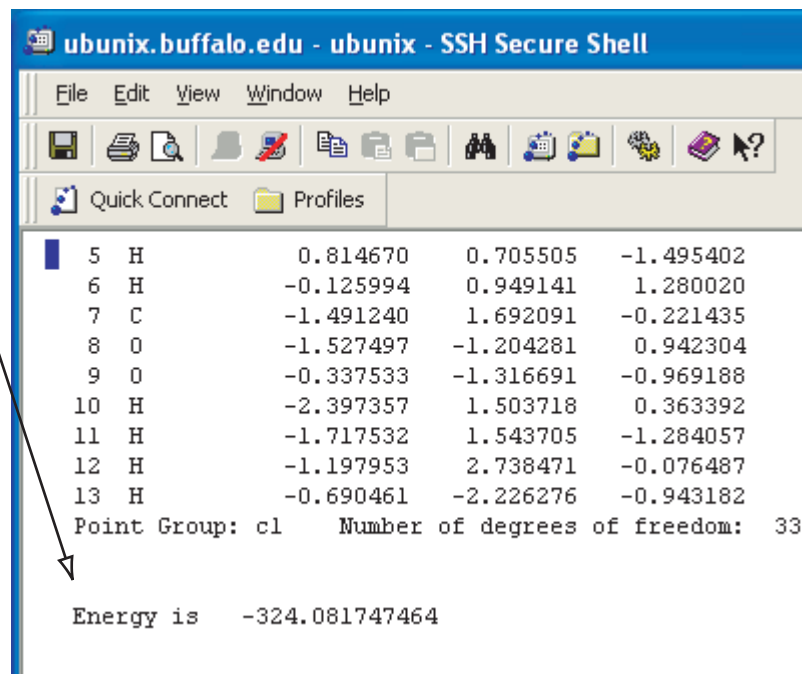Energy components in the QM/MM calculations

```
ubunix.buffalo.edu - ubunix - SSH Secure Shell

File  Edit  View  Window  Help

Quick Connect    Profiles

Adding external point charges to one-electron Hamiltoni
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

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
```
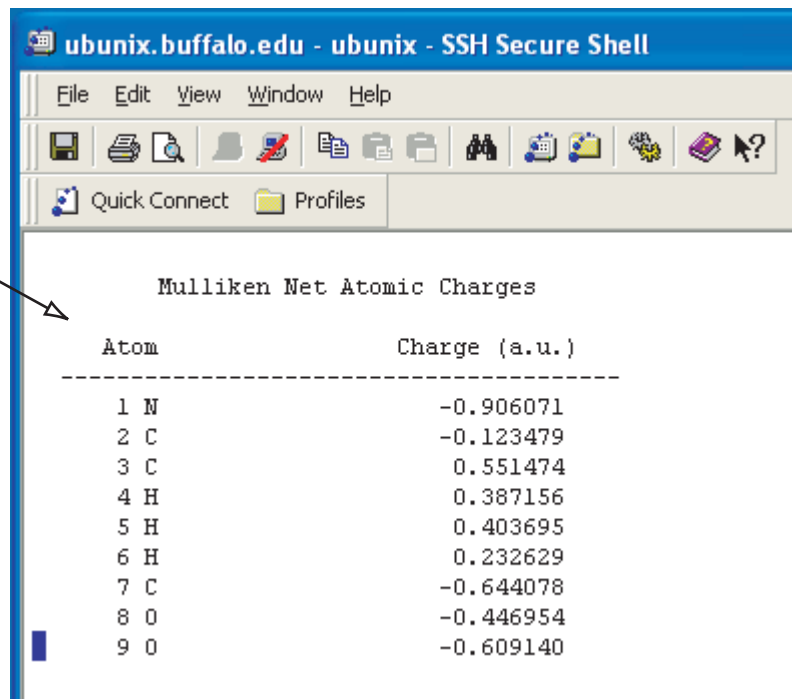
QM/MM calculations of alanine water dimer

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

```
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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


```
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File   Edit   View   Window   Help

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
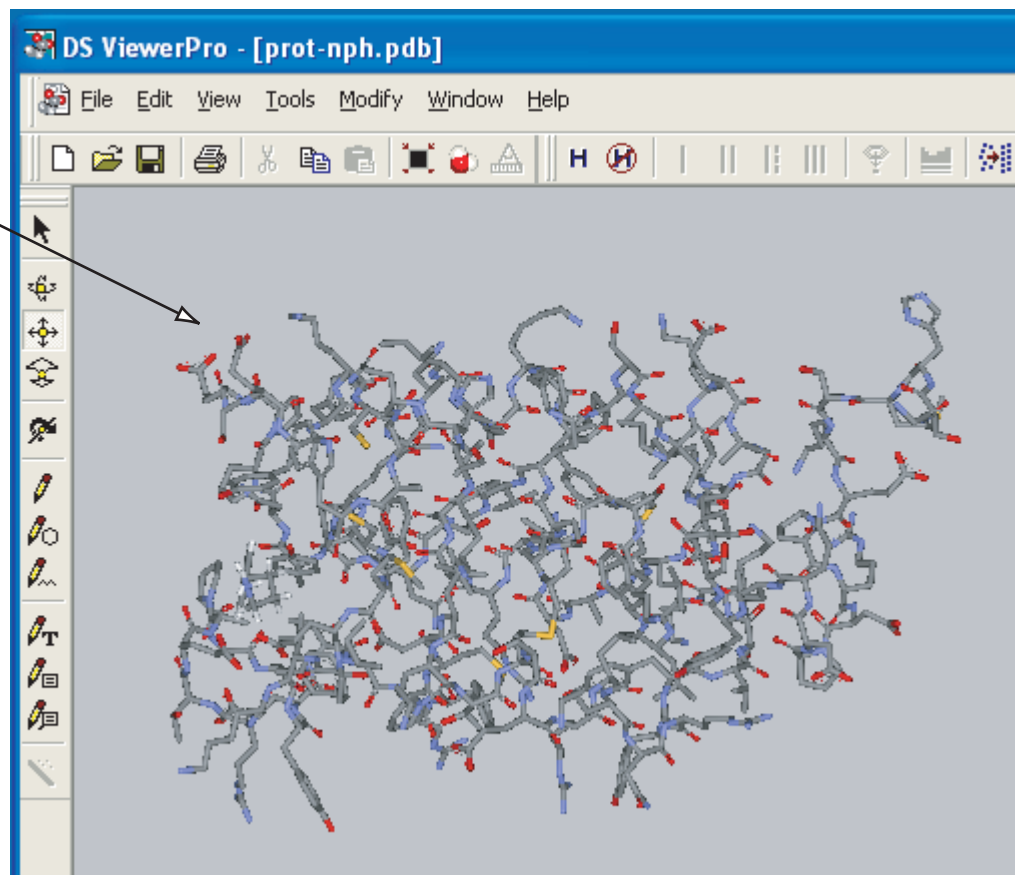
QM/MM calculations of active site of PCAF
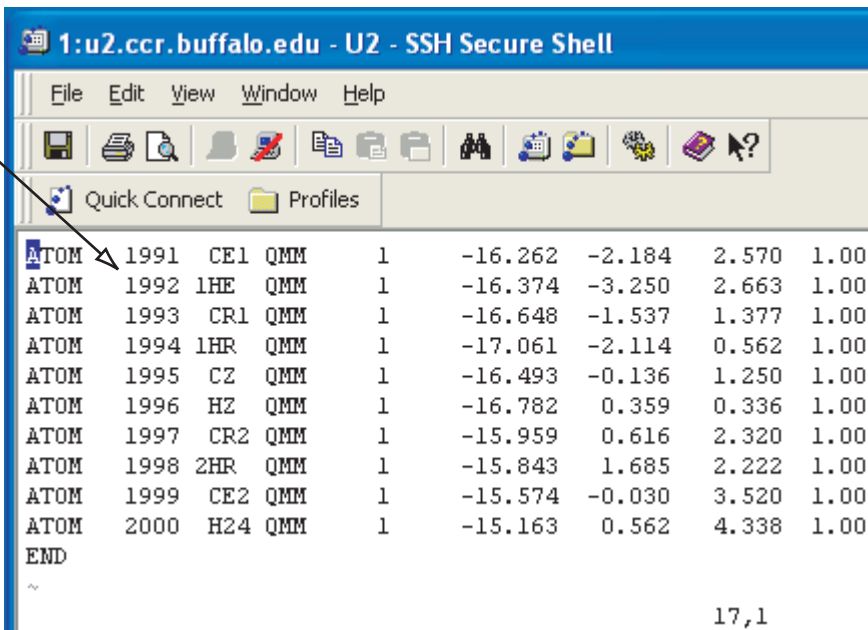
The ligand of
the PCAF
protein
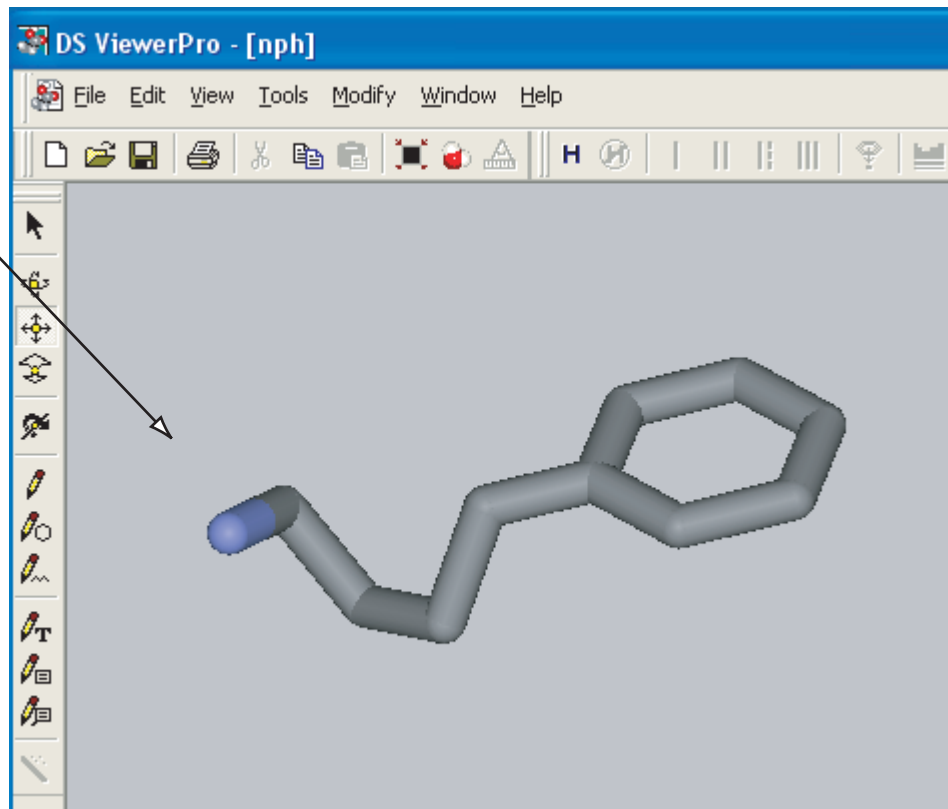
QM/MM calculations of active site of PCAF

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


```
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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
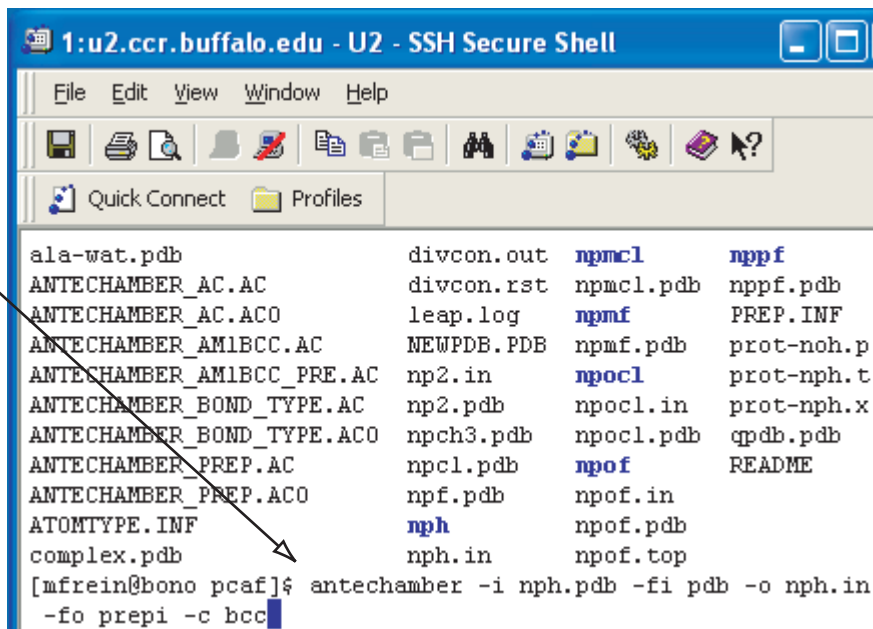
The ligand with
hydrogen atoms
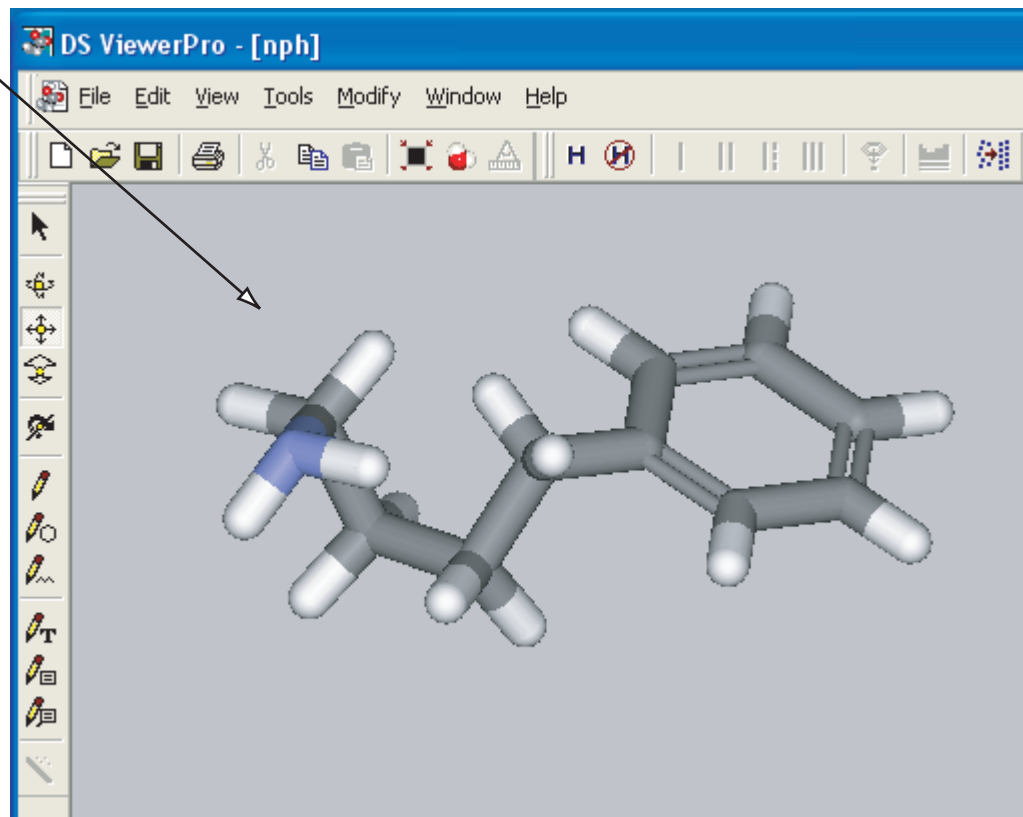
QM/MM calculations of active site of PCAF

Antechamber program creating the preparations file of the ligand
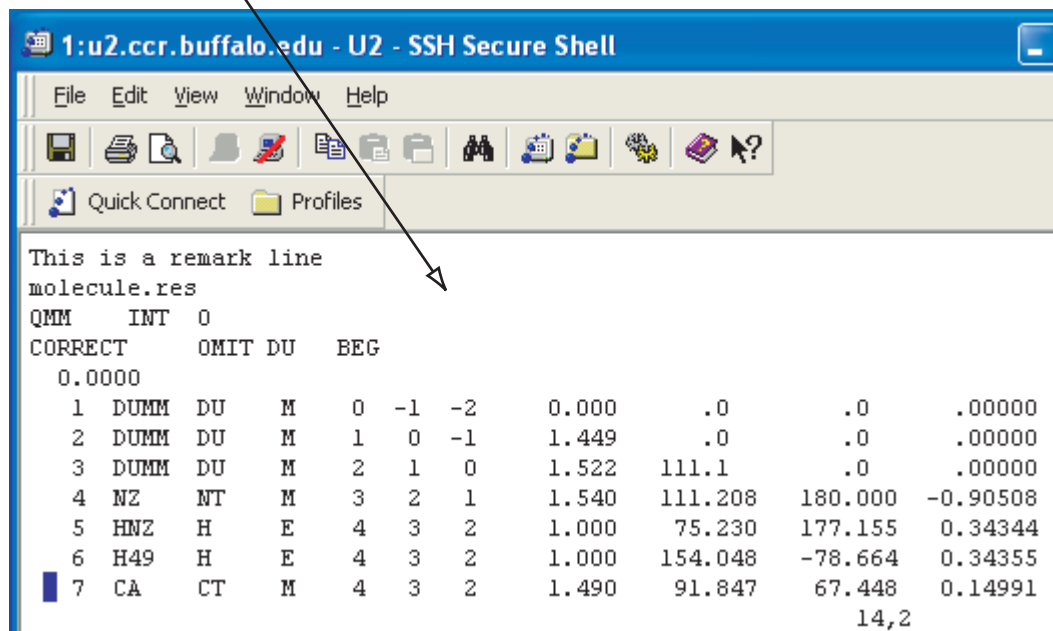
QM/MM calculations of active site of PCAF

The preparation file, generated by
the "antechamber" program

QM/MM calculations of active site of PCAF

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

The "tleap" program reading the preparation file
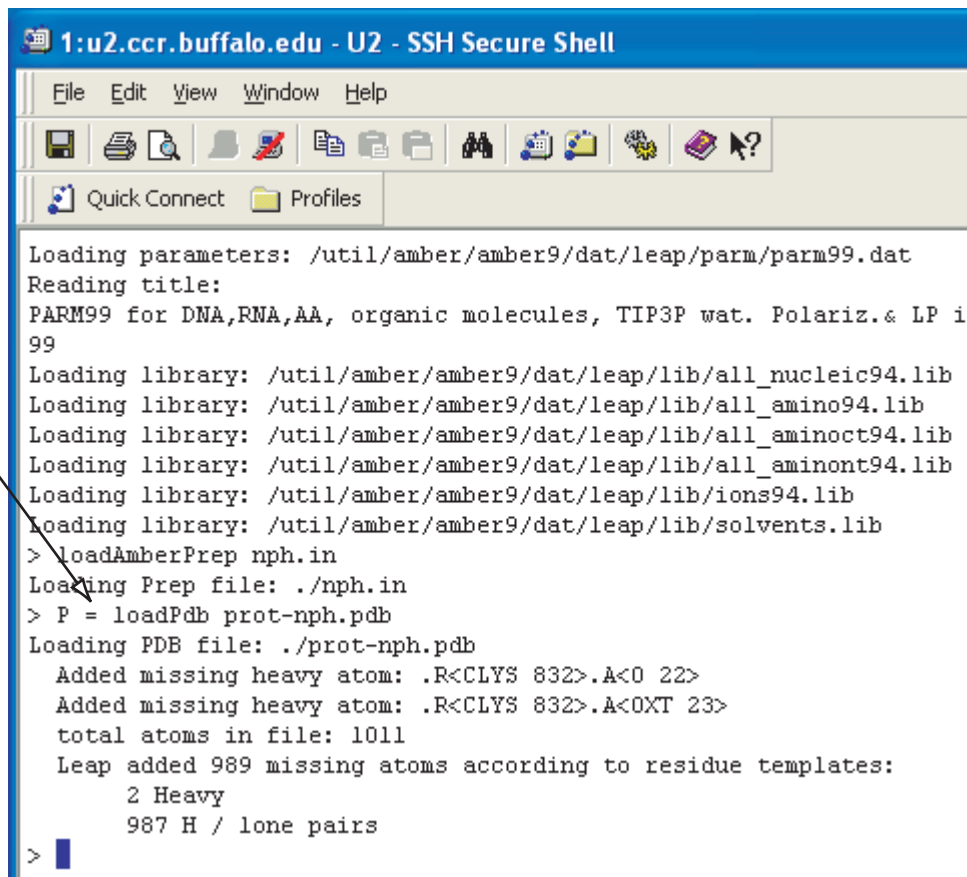
```
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Quick Connect    Profiles

nph.pdb    prt.in         prt.pbs   prt.xyz   qchem2pdb.inp   qmmm_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_aminoct94.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
```

QM/MM calculations of active site of PCAF

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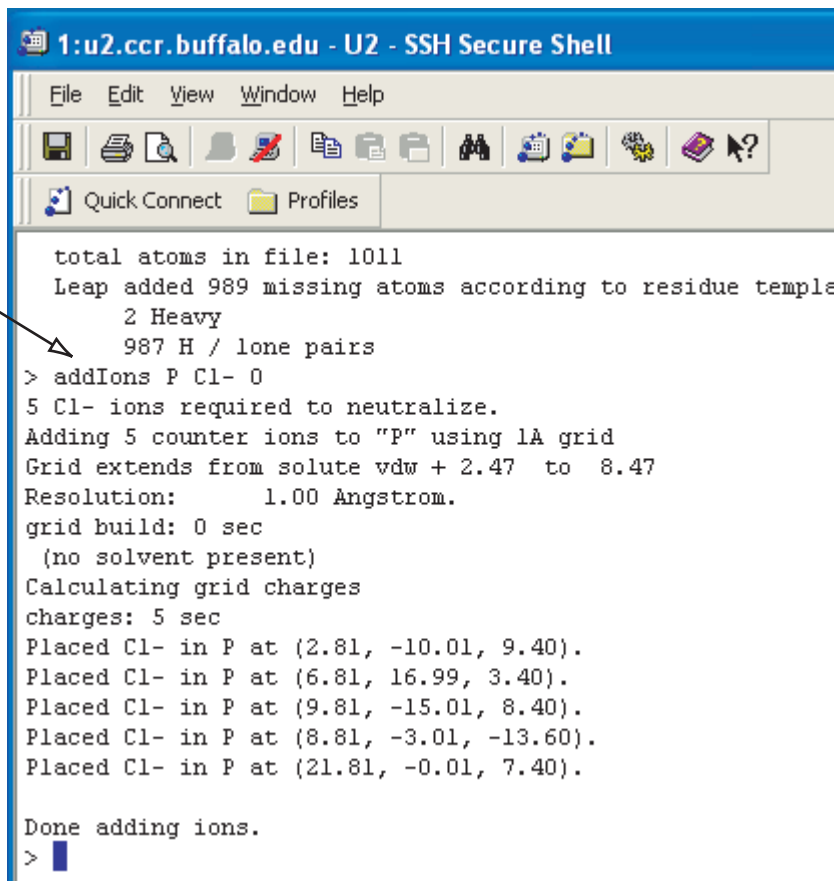

```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File   Edit   View   Window   Help

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_aminoct94.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

QM/MM calculations of active site of PCAF

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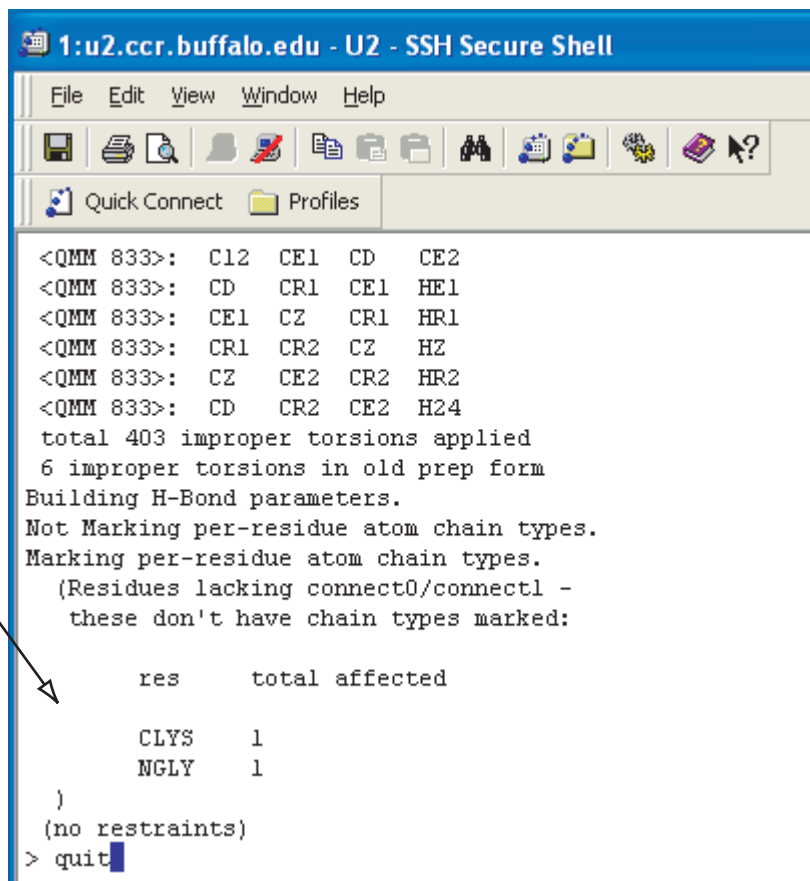

```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File   Edit   View   Window   Help

Quick Connect    Profiles

> 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

Quiting the "tleap" program

QM/MM calculations of active site of PCAF

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

```
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
         Quit
[mfrein@bono nph]$ ls
leap.log  prot-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
```
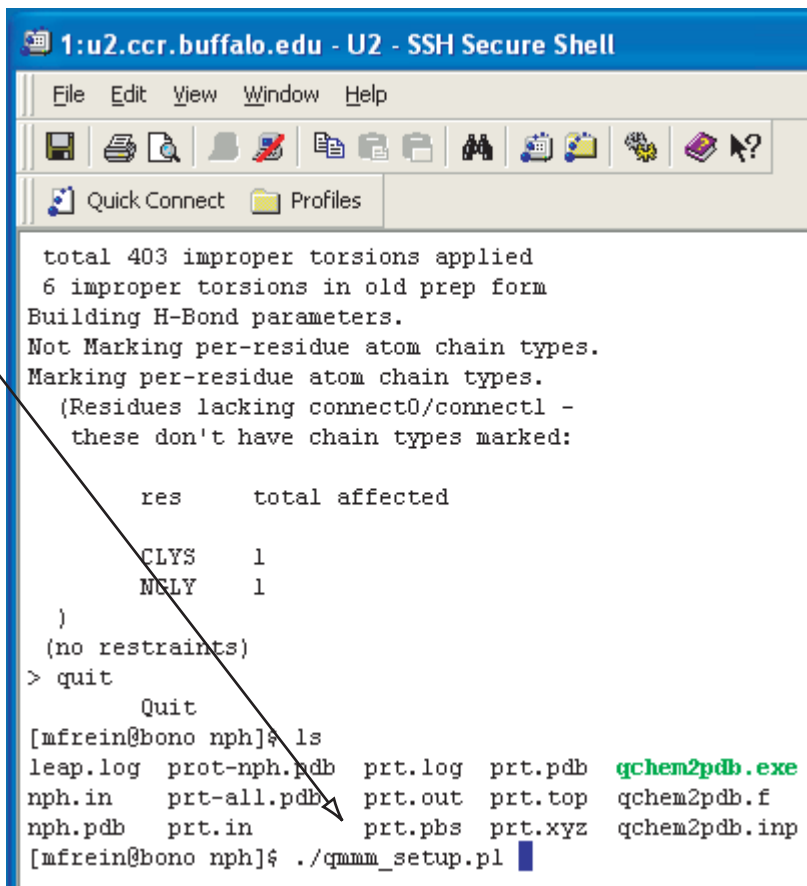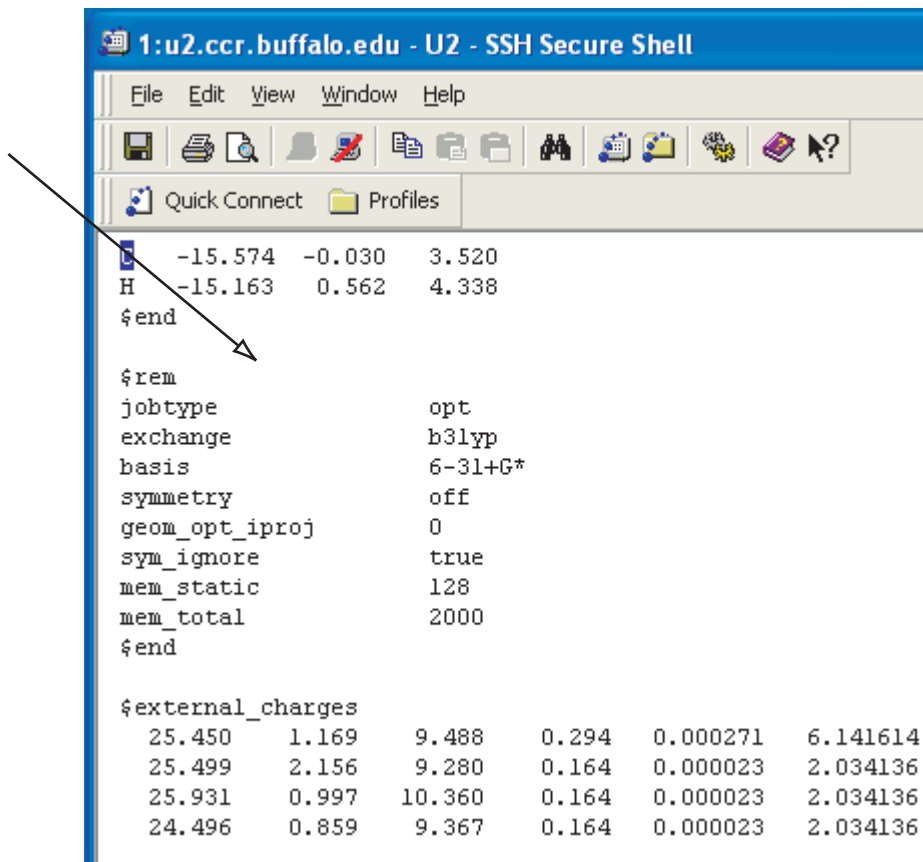
QM/MM calculations of active site of PCAF

The input file for the QM/MM calculations
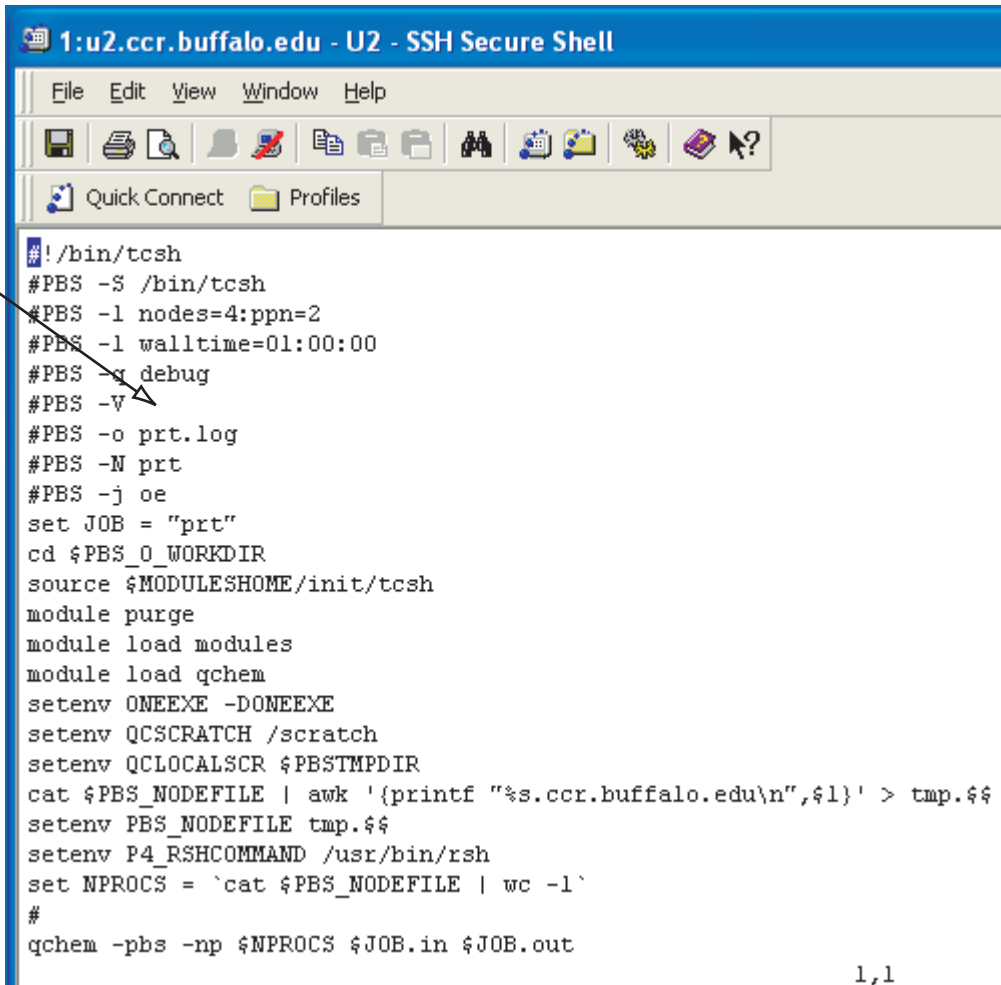
QM/MM calculations of active site of PCAF

The PBS script for the QM/MM calculations

File   Edit   View   Window   Help

Quick Connect   Profiles

```
#!/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

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)
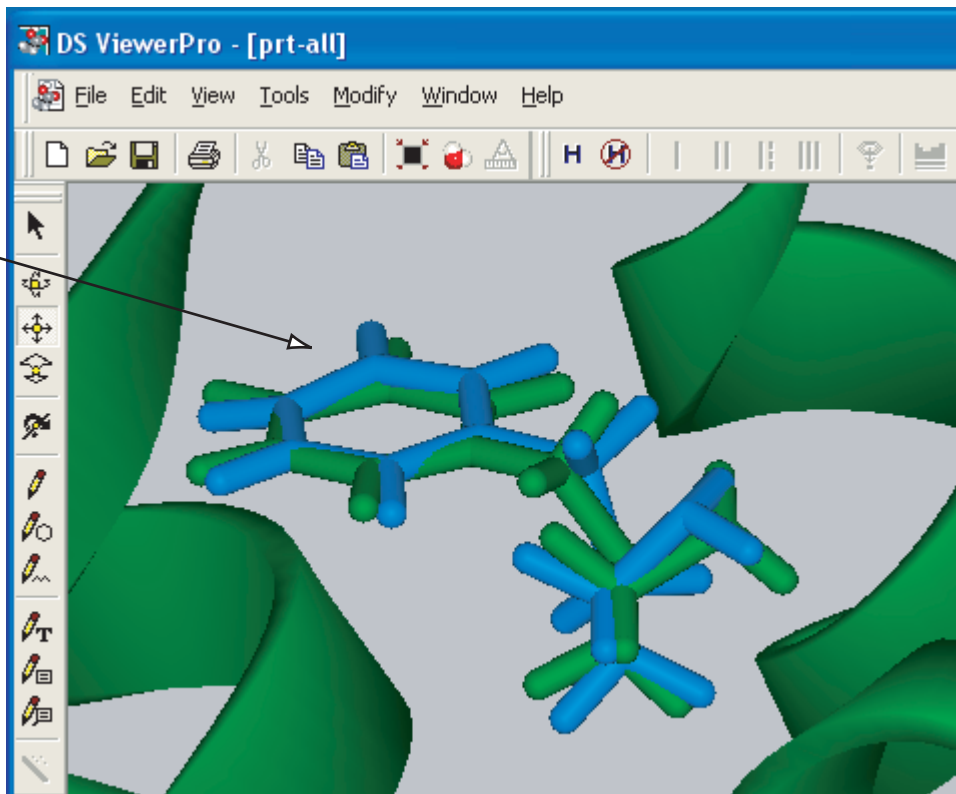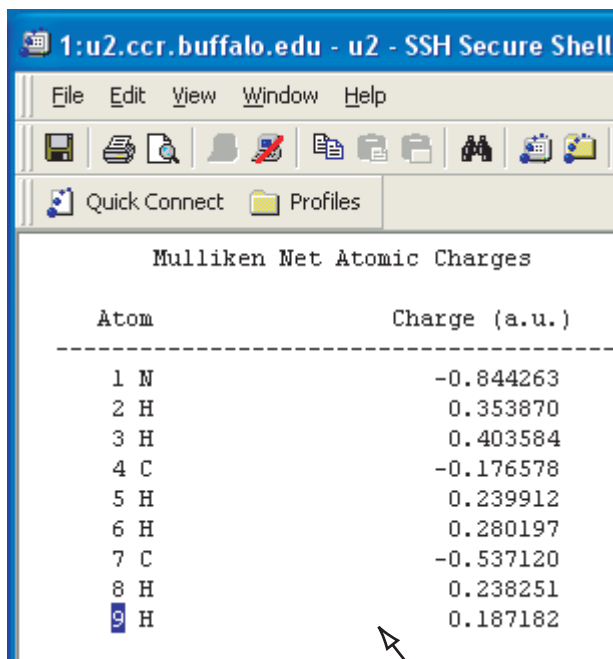
QM/MM calculations of active site of PCAF


```
 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: cl    Number of degrees

Energy is   -502.786817363
```

```
 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: cl    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
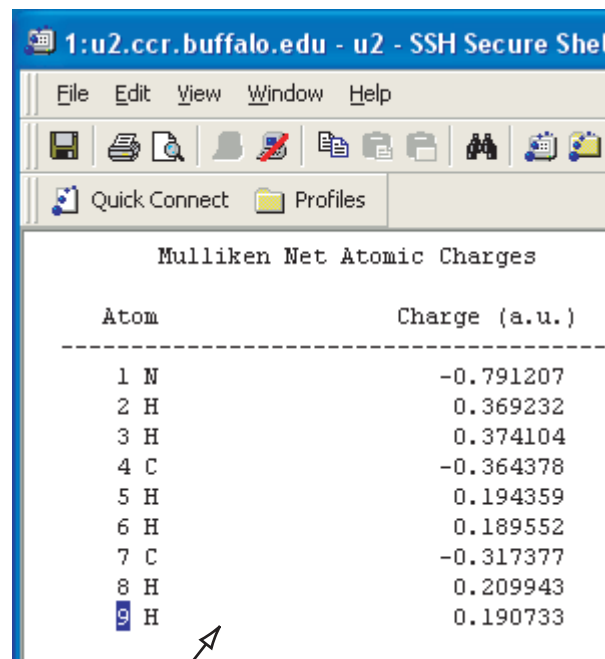
```
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File   Edit   View   Window   Help

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
```

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

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 10^10)
              0.0000
  Dipole Moment (Debye)
      X        2.2011      Y        -2.6519
     Tot       3.4491
```
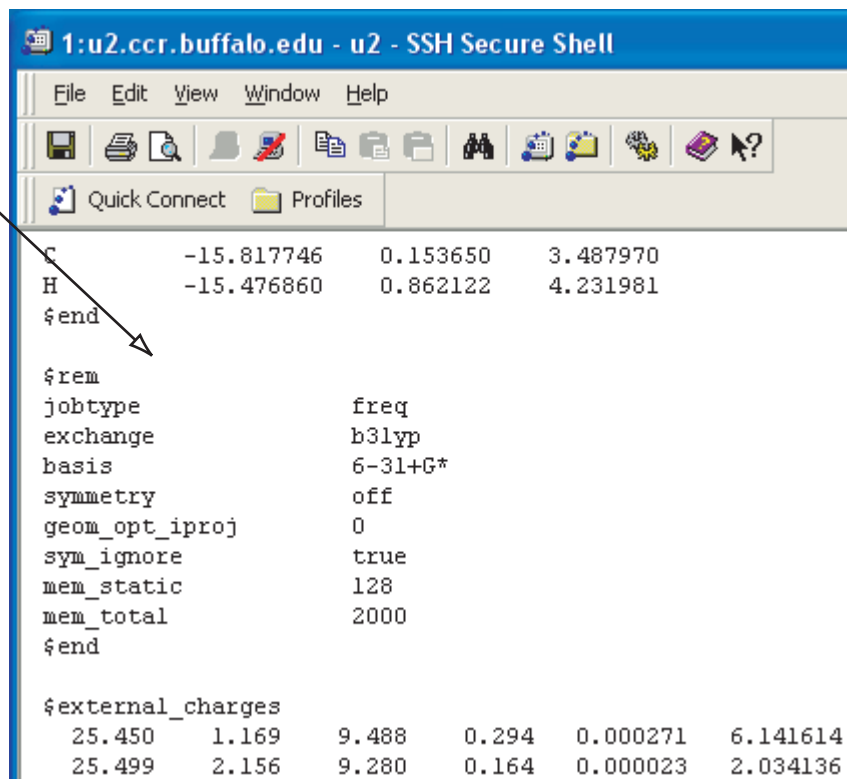
```
1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell
File  Edit  View  Window  Help

Quick Connect    Profiles

  25 C                       -0.083434
  26 H                        0.173589
--------------------------------------------
Sum of atomic charges =       0.000000

--------------------------------------------
                    Cartesian Multipole Moments
--------------------------------------------
  Charge (ESU x 10^10)
              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
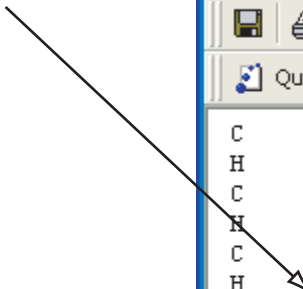
QM/MM calculations of active site of PCAF

Final results of the oscillation hessian calculations


```
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

Left terminal window (1:u2.ccr.buffalo.edu - u2 - SSH Sec):

```
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
```

Right terminal window (2:u2.ccr.buffalo.edu - u2 - SSH Se):

```
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
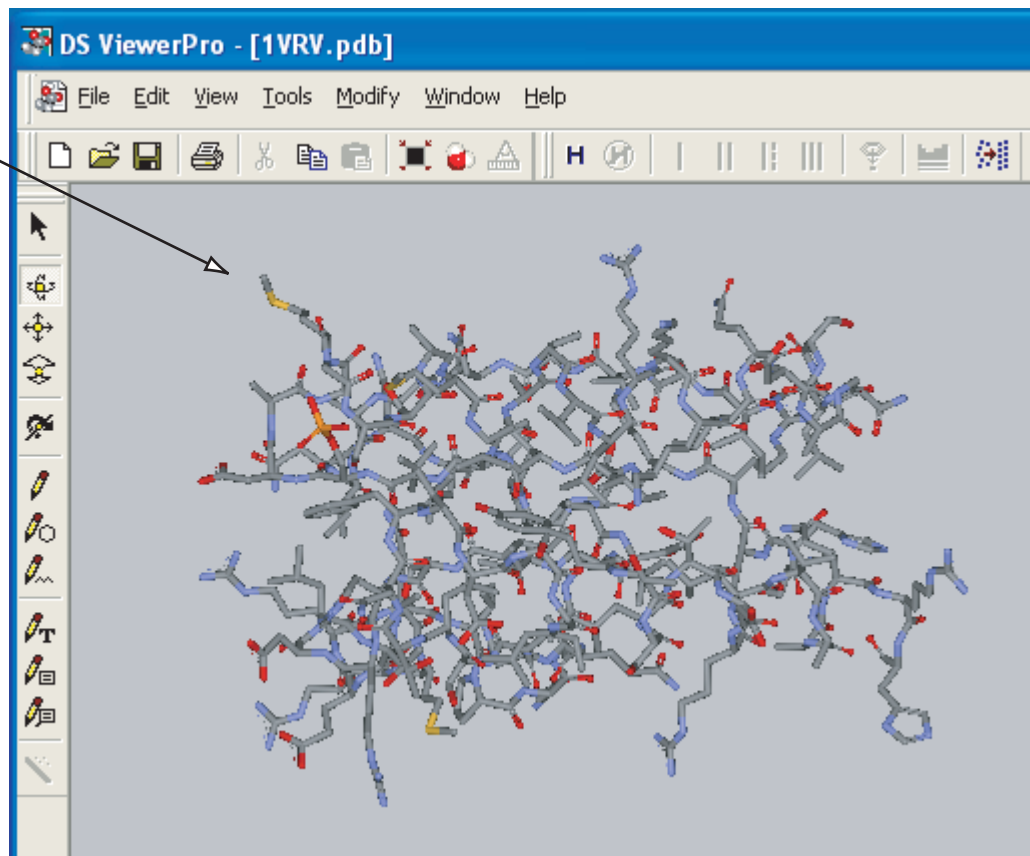
QM/MM calculations of active site of mannitol enzyme

The active site of the enzyme, which is connected by two chemical bonds with the protein backbone
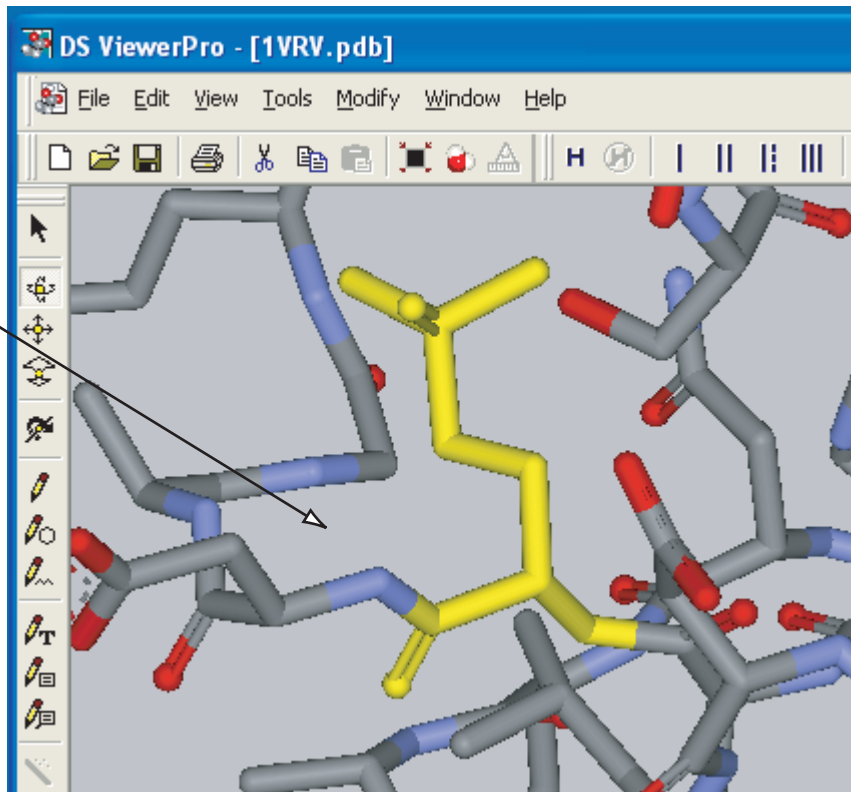
QM/MM calculations of active site of mannitol enzyme

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
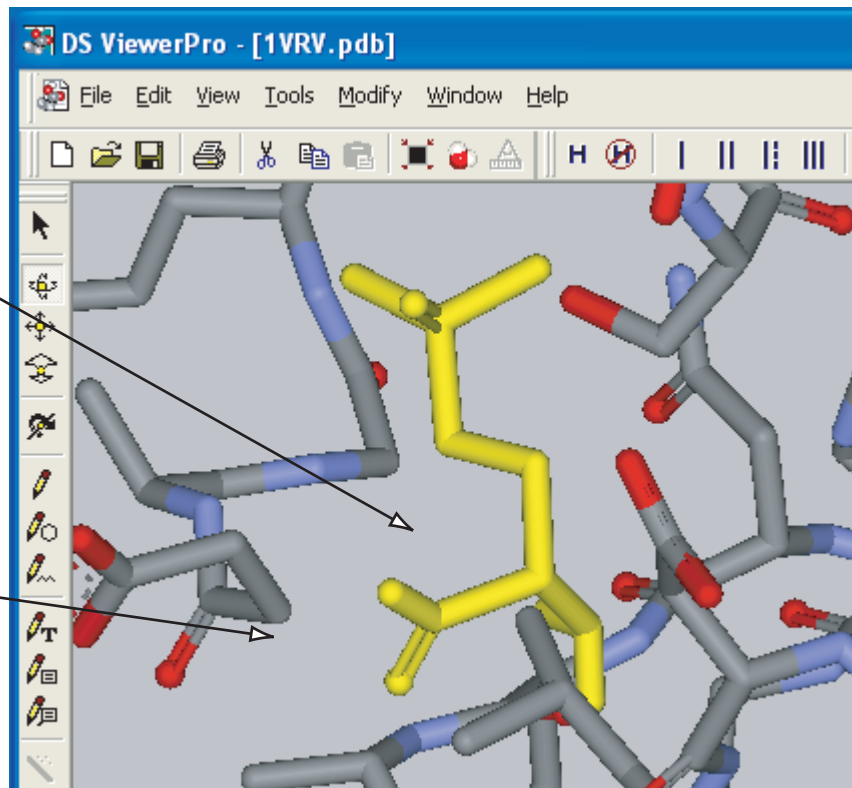
QM/MM calculations of active site of mannitol enzyme
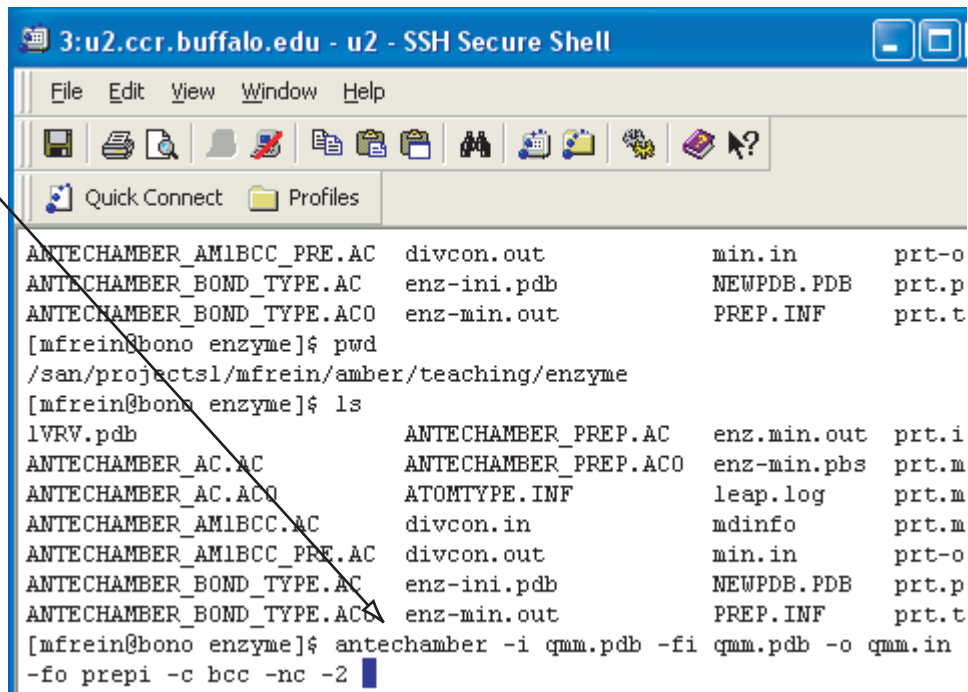
The active site of the enzyme has been temporary separated from the protein structure
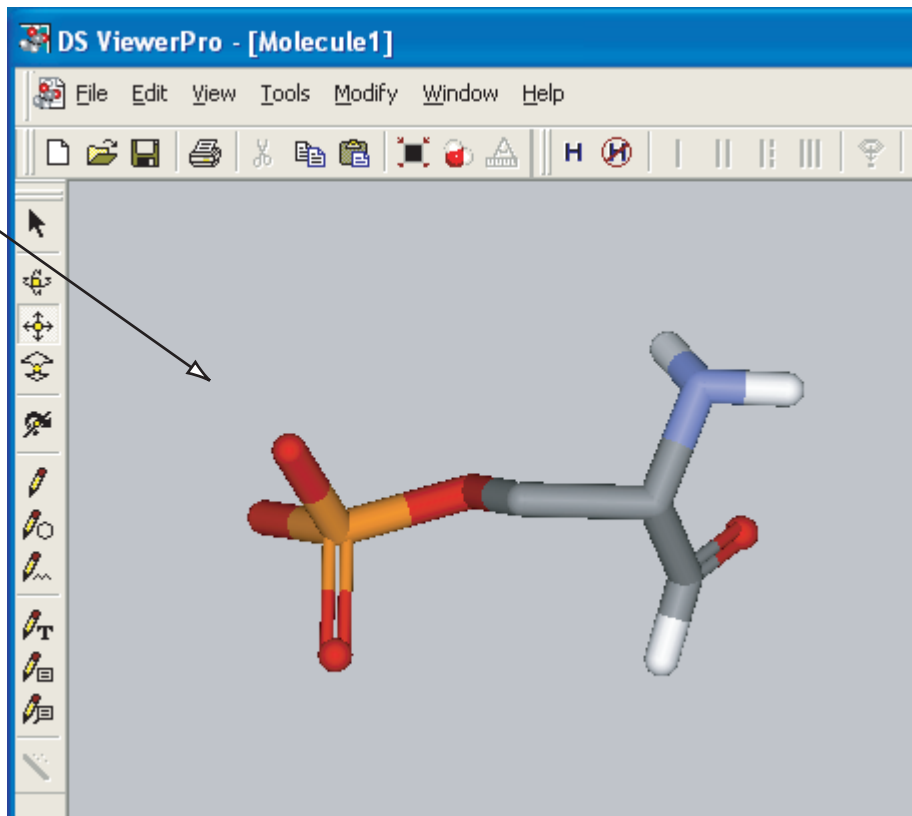
QM/MM calculations of active site of mannitol enzyme

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

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

File  Edit  View  Window  Help

Quick Connect    Profiles

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.INF         prt.t
[mfrein@bono enzyme]$ pwd
/san/projects1/mfrein/amber/teaching/enzyme
[mfrein@bono enzyme]$ ls
1VRV.pdb                     ANTECHAMBER_PREP.AC     enz.min.out      prt.i
ANTECHAMBER_AC.AC            ANTECHAMBER_PREP.ACO    enz-min.pbs      prt.m
ANTECHAMBER_AC.ACO           ATOMTYPE.INF            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.INF         prt.t
[mfrein@bono enzyme]$ antechamber -i qmm.pdb -fi qmm.pdb -o qmm.in
-fo prepi -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
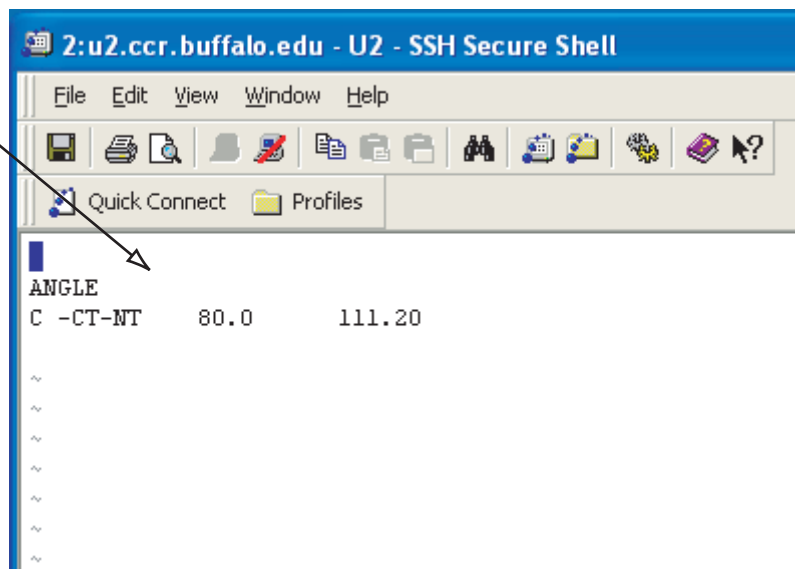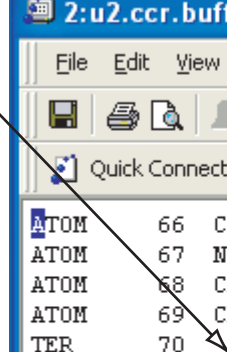
QM/MM calculations of active site of mannitol enzyme

The new pdb structure of the active site has been merged with the protein structure
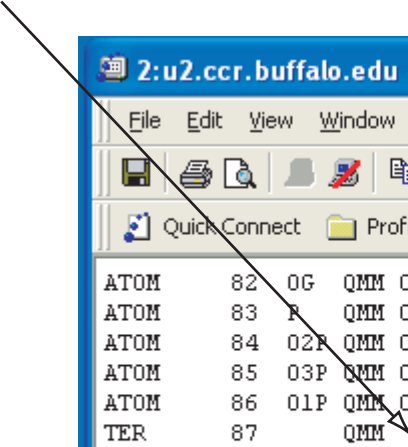
```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File   Edit   View   Window   Help

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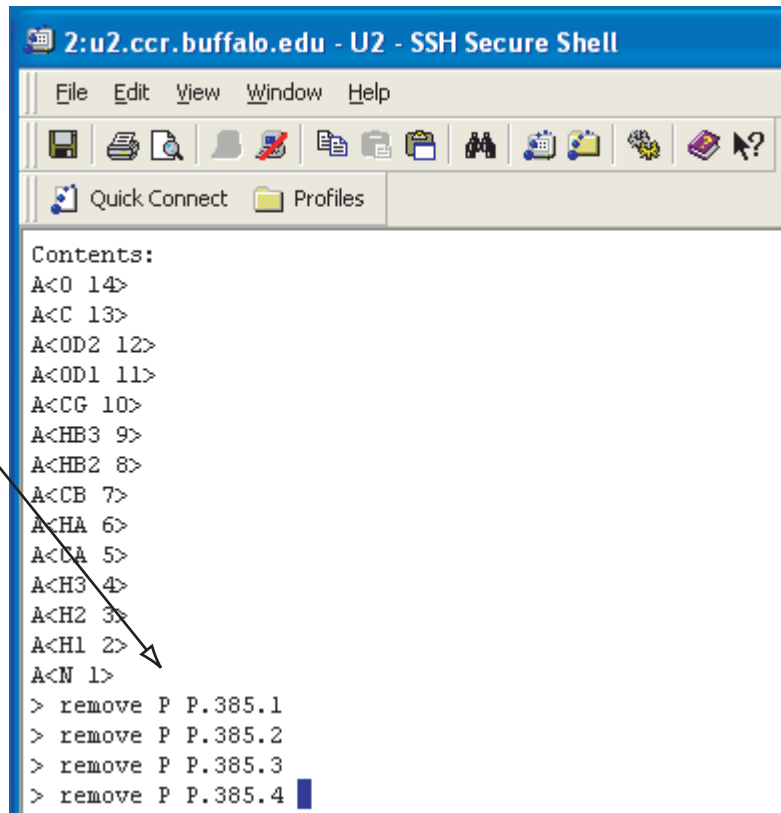
The main backbone of
the protein has been
divided into three chains

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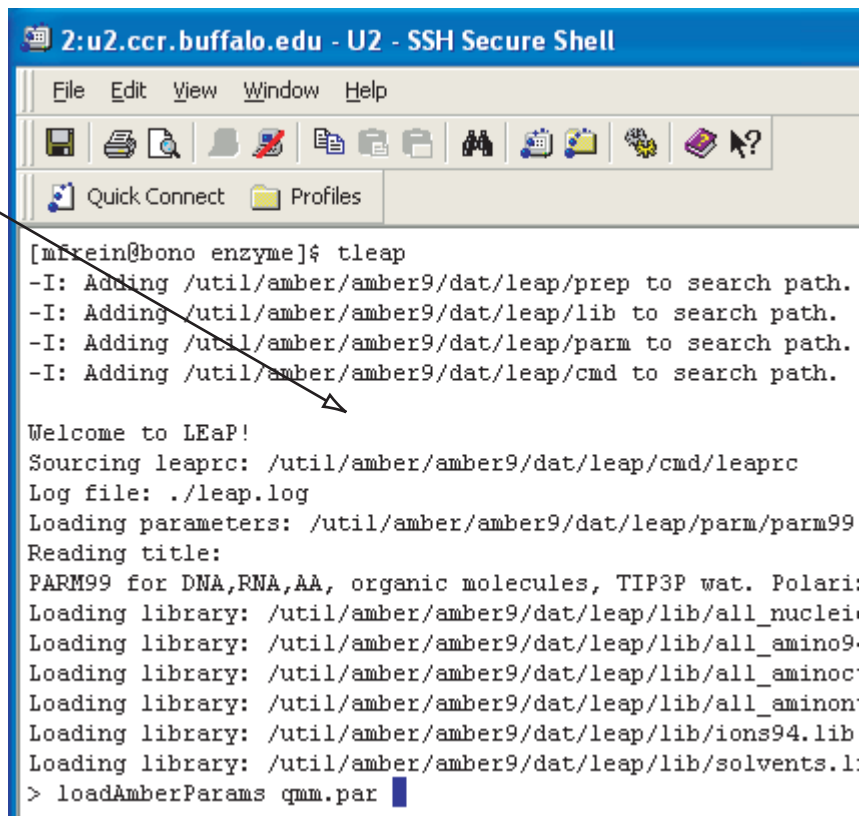
File   Edit   View   Window   Help

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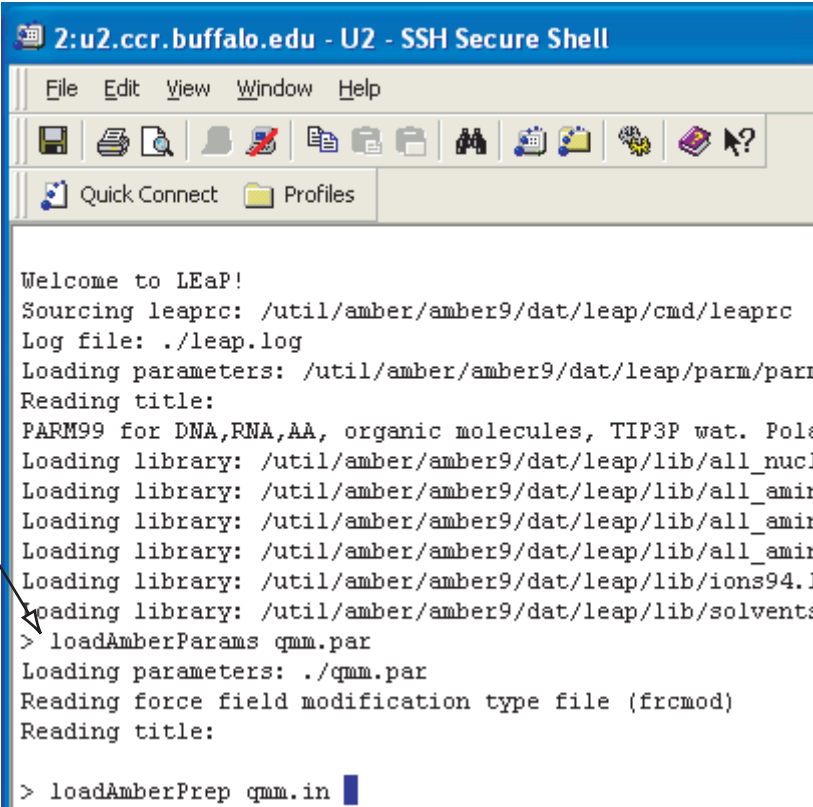
```
[mfrein@bono enzyme]$ tleap
-I: Adding /util/amber/amber9/dat/leap/prep to search path.
-I: Adding /util/amber/amber9/dat/leap/lib to search path.
-I: Adding /util/amber/amber9/dat/leap/parm to search path.
-I: Adding /util/amber/amber9/dat/leap/cmd to search path.

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
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_amino9·
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.l·
> 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

QM/MM calculations of active site of mannitol enzyme

After loading the PDB file of the system, the program generated additional atoms
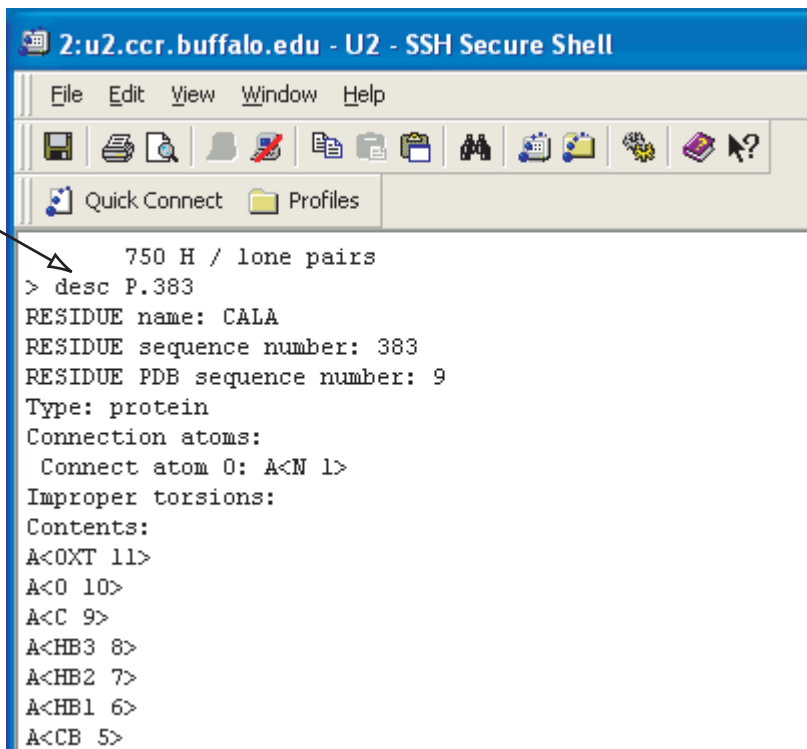
```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File  Edit  View  Window  Help

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<0 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

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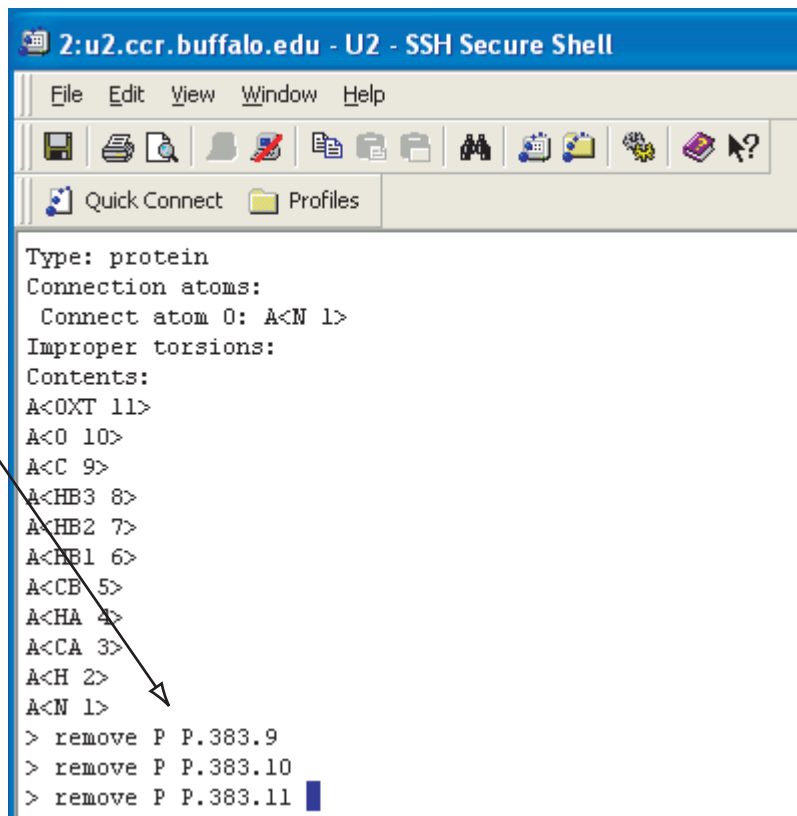
```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File  Edit  View  Window  Help

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
```

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
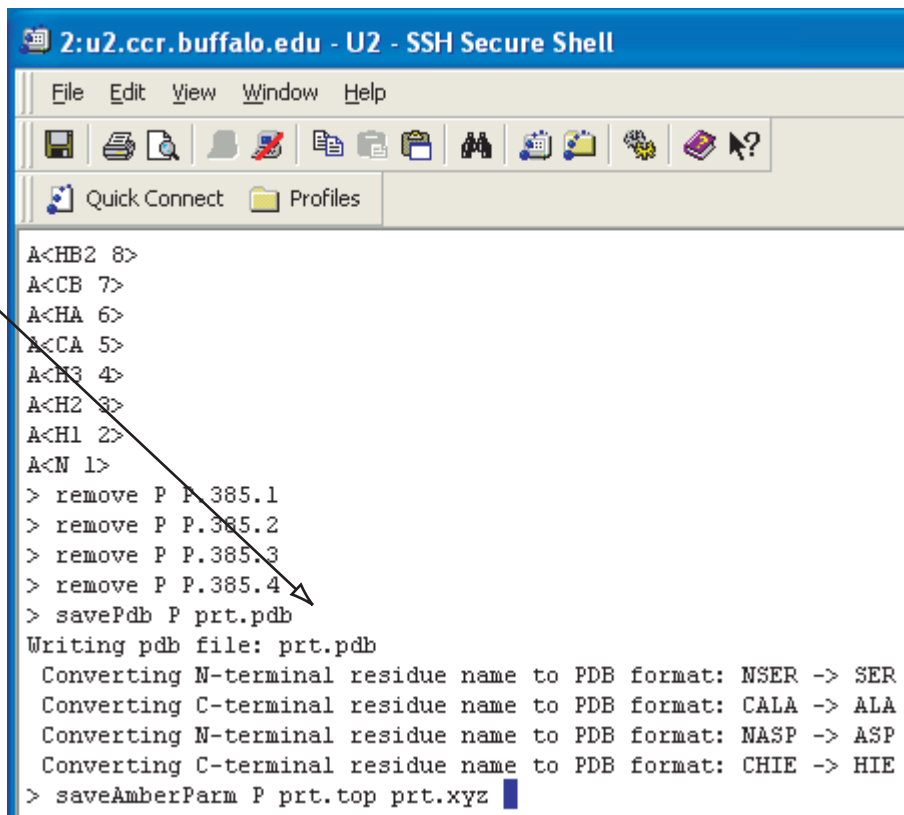

```
2:u2.ccr.buffalo.edu - U2 - SSH Secure Shell

File  Edit  View  Window  Help

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<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
```

QM/MM calculations of active site of mannitol enzyme

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

QM/MM calculations of active site of mannitol enzyme

The input file for minimization of all hydrogens

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

File   Edit   View   Window   Help

Quick Connect    Profiles

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=)',
/
```

QM/MM calculations of active site of mannitol enzyme
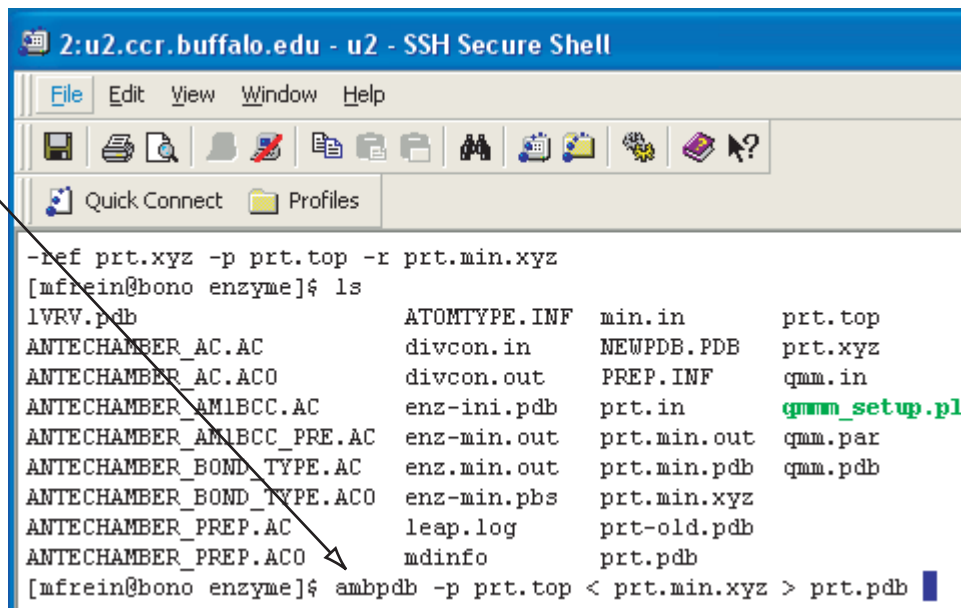
The pbs script for minimization

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

Quick Connect    Profiles

#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


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

File  Edit  View  Window  Help

Quick Connect    Profiles

-ref prt.xyz -p prt.top -r prt.min.xyz
[mfrein@bono enzyme]$ ls
1VRV.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_AM1BCC.AC       enz-ini.pdb    prt.in        qmmm_setup.pl
ANTECHAMBER_AM1BCC_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

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
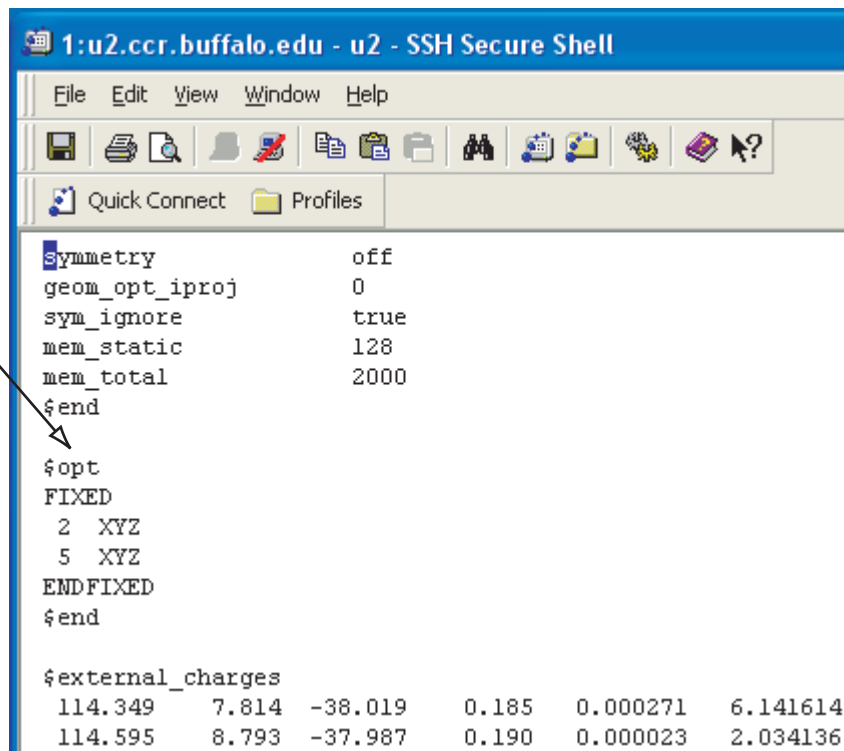

```
1:u2.ccr.buffalo.edu - u2 - SSH Secure Shell

File   Edit   View   Window   Help

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

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

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
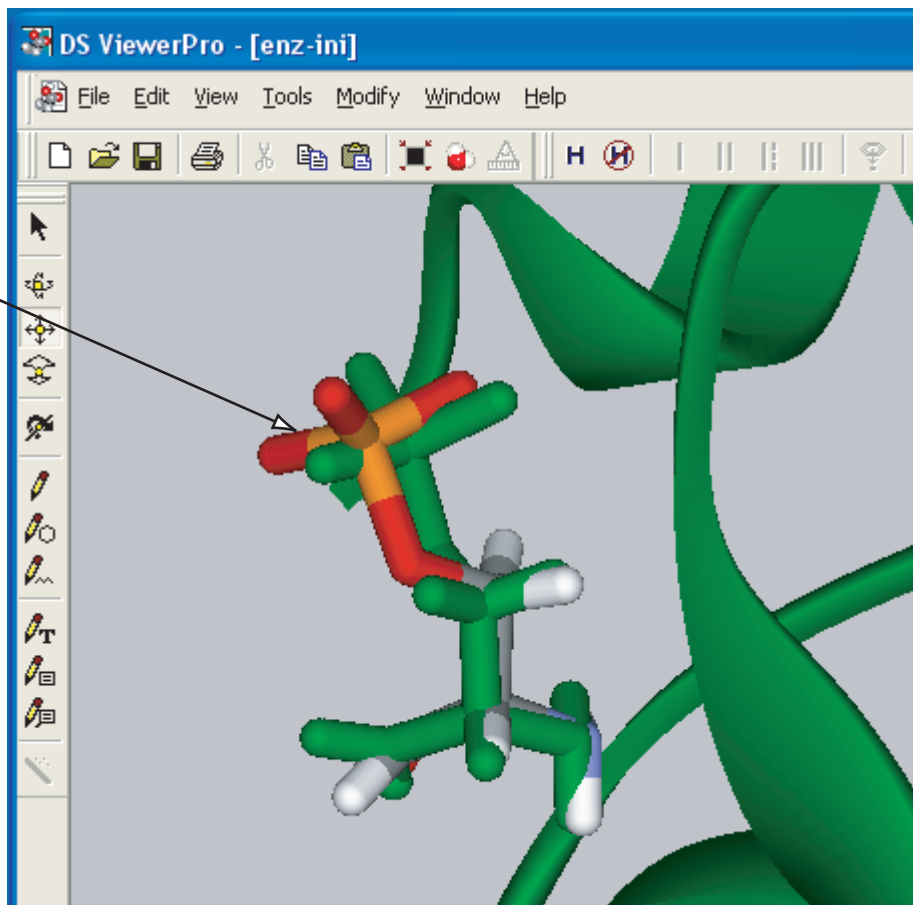
QM/MM calculations of active site of mannitol enzyme

The fixed atoms used in the caclulations
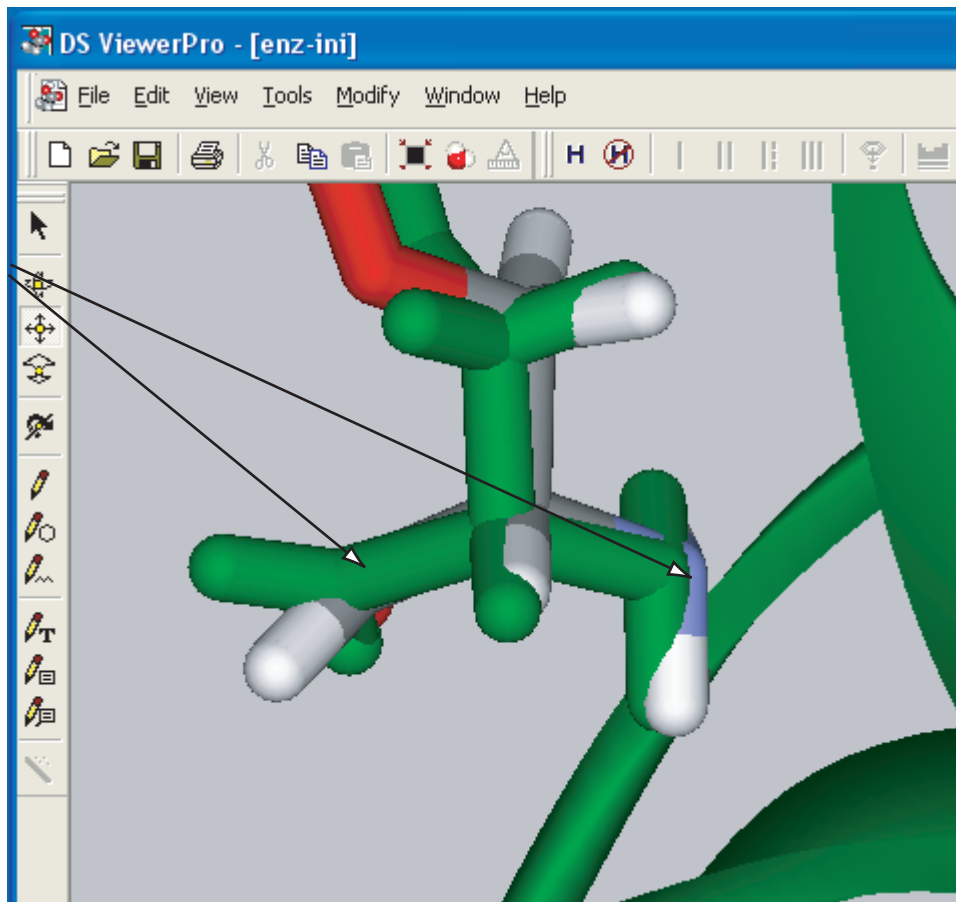
QM/MM calculations of chemical reaction in renin protein

Experimental
structure of
the renin
protein
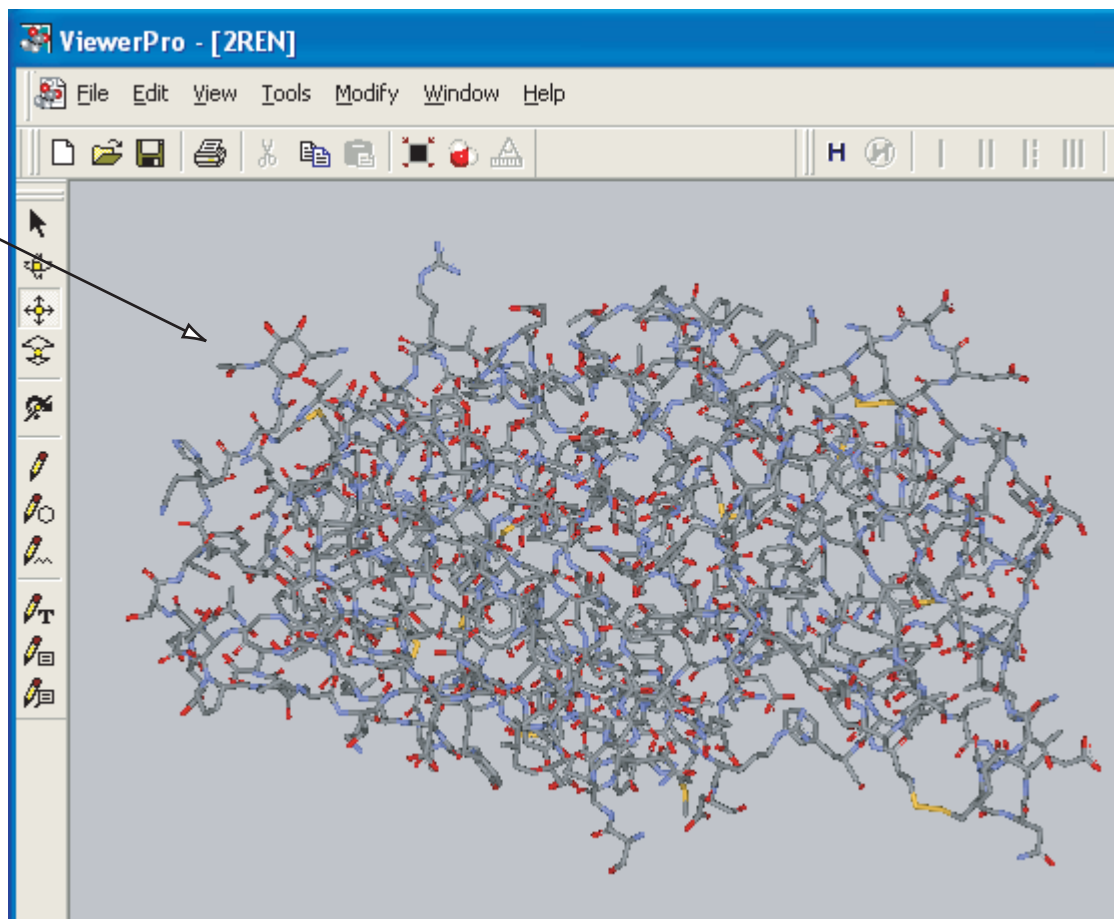
QM/MM calculations of chemical reaction in renin protein

The active site of the renin protein
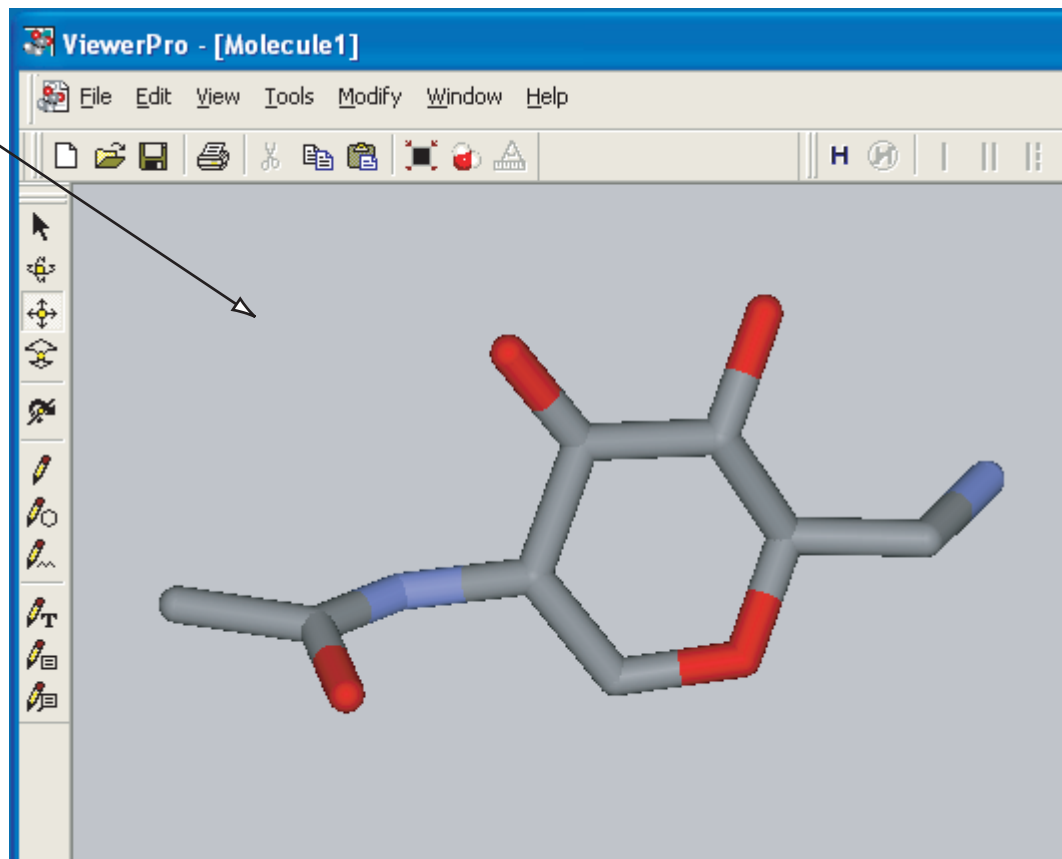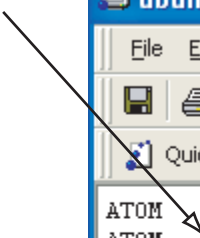
QM/MM calculations of chemical reaction in renin protein

The protonation reaction of the renin ligand

The pdb file of
the renin ligand
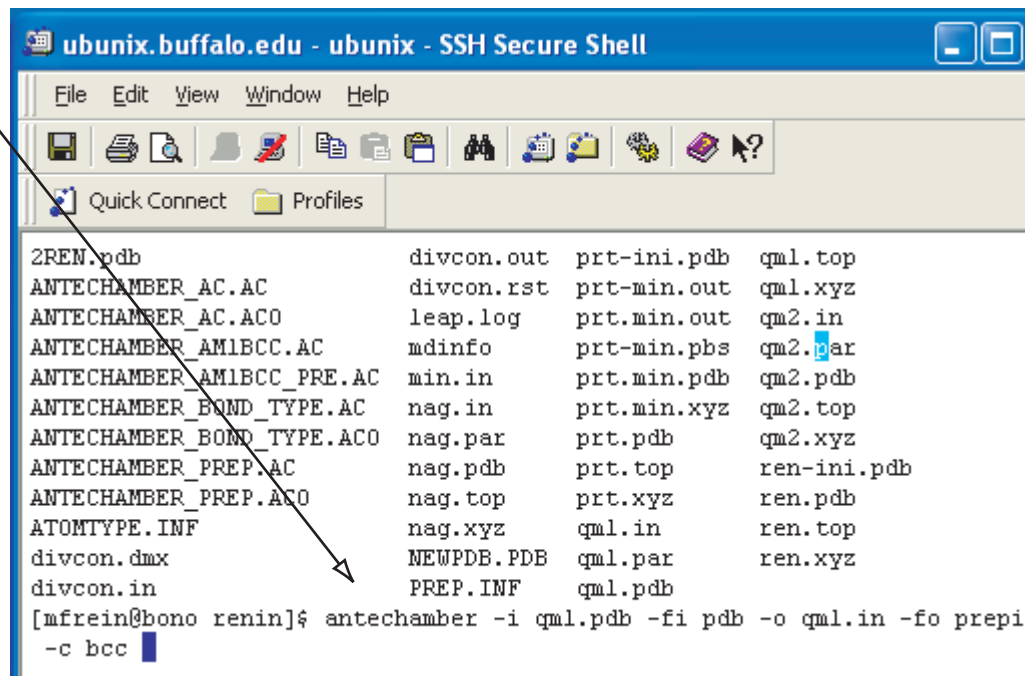
File   Edit   View   Window   Help

Quick Connect   Profiles

```
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


```
ubunix.buffalo.edu - ubunix - SSH Secure Shell

File  Edit  View  Window  Help

Quick Connect    Profiles

2REN.pdb                    divcon.out    prt-ini.pdb   qml.top
ANTECHAMBER_AC.AC           divcon.rst    prt-min.out   qml.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       qml.in        ren.top
divcon.dmx                  NEWPDB.PDB    qml.par       ren.xyz
divcon.in                   PREP.INF      qml.pdb
[mfrein@bono renin]$ antechamber -i qml.pdb -fi pdb -o qml.in -fo prepi
 -c bcc
```
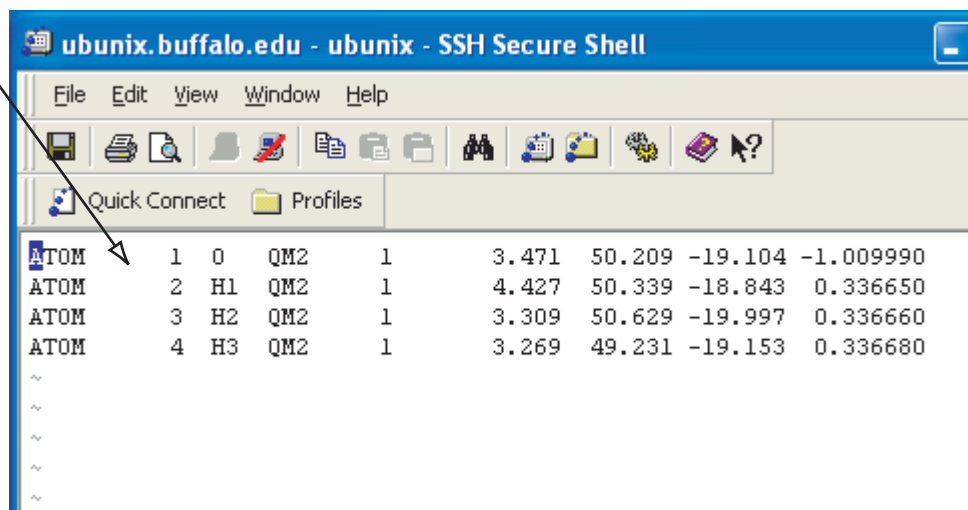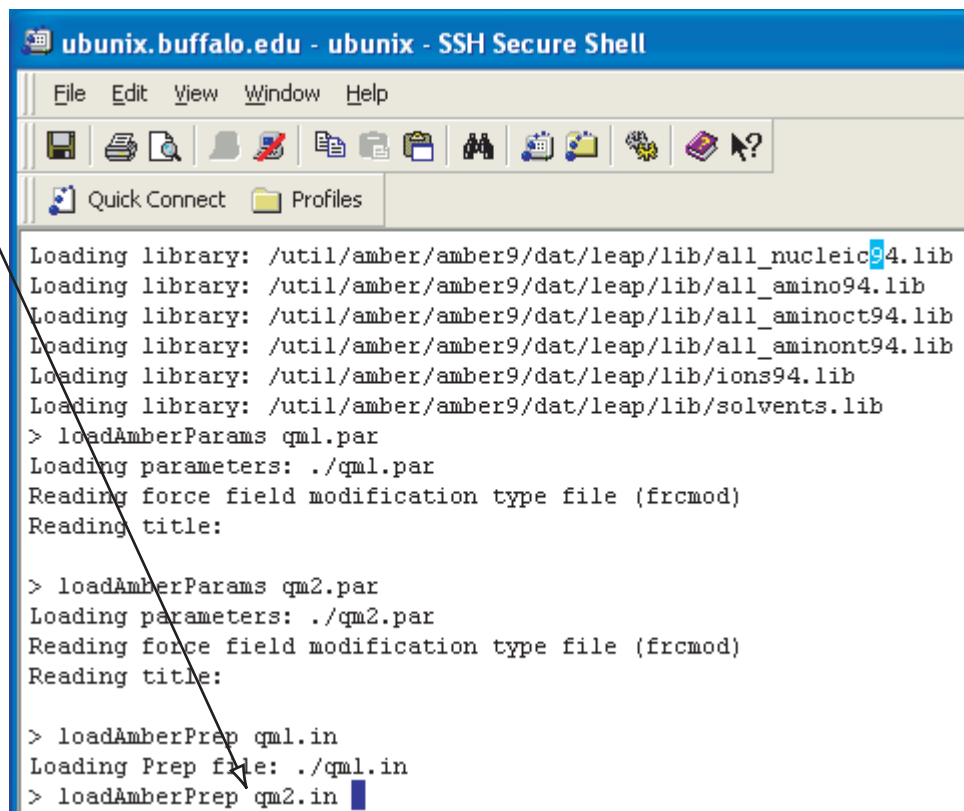
The parameter file of
the ligand

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

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
~
~
~
~
~
```

Generating the preparation file for the substrat

QM/MM calculations of chemical reaction in renin protein

The parameter file
of the substrat
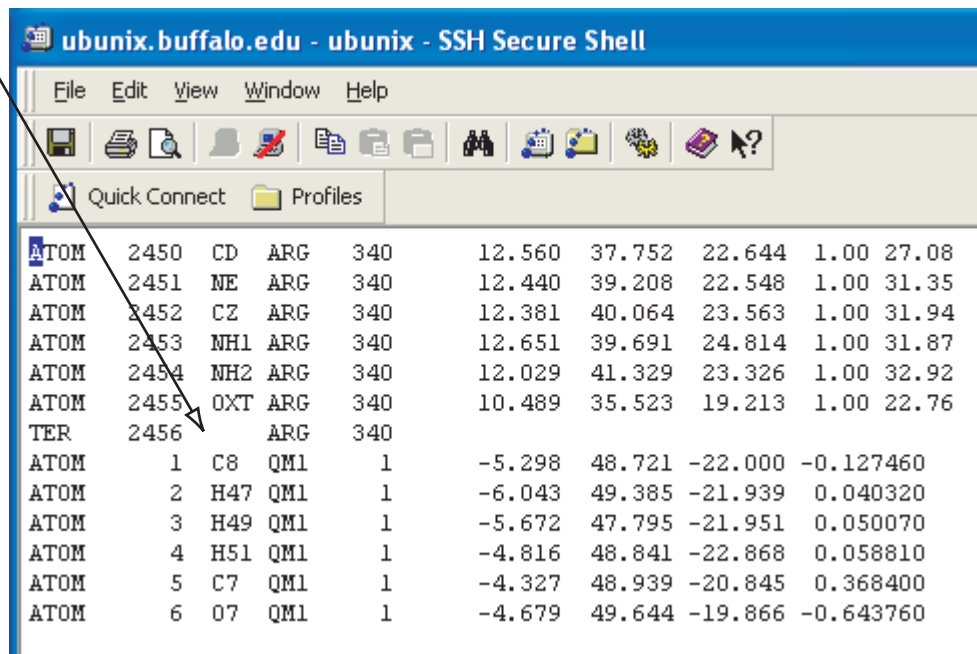
QM/MM calculations of chemical reaction in renin protein
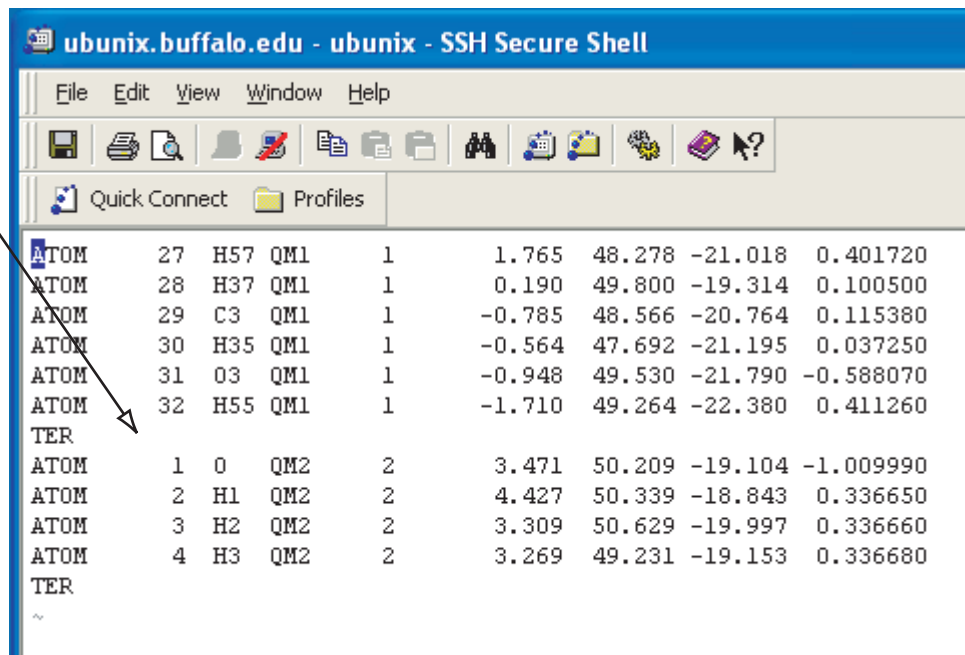
Merging the ligand pdb file with the protein structure


```
ubunix.buffalo.edu - ubunix - SSH Secure Shell

File  Edit  View  Window  Help

Quick Connect    Profiles

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


```
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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
~
```
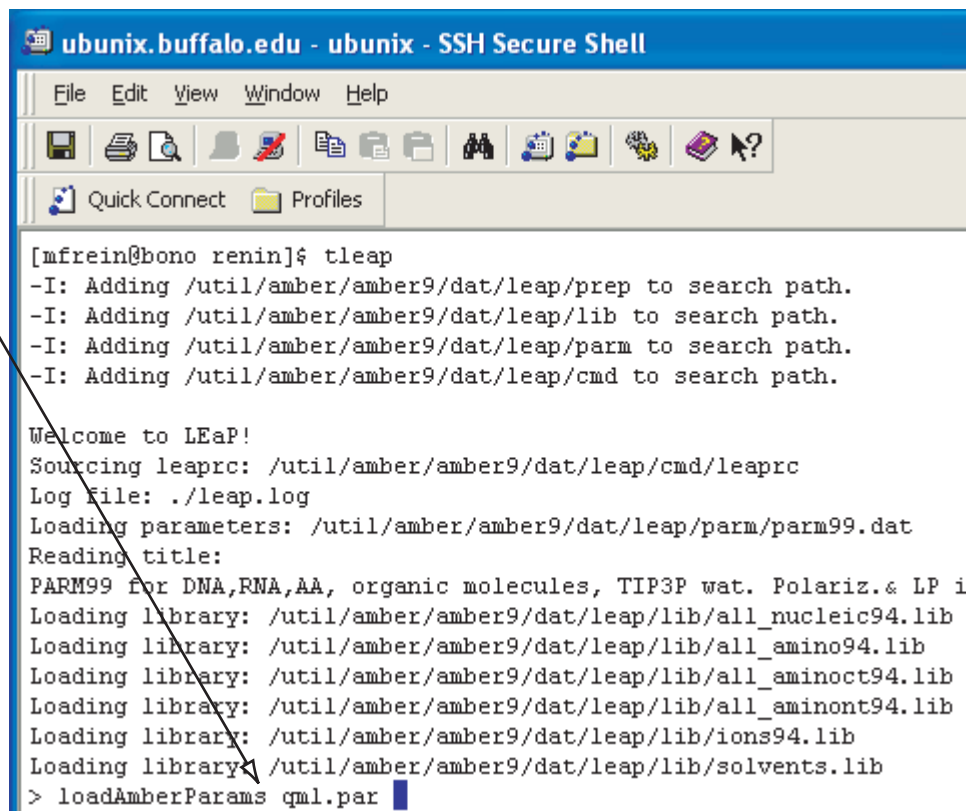
QM/MM calculations of chemical reaction in renin protein

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

QM/MM calculations of chemical reaction in renin protein

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

QM/MM calculations of chemical reaction in renin protein

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


```
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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_aminoct94.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

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

Quick Connect    Profiles

Loading library: /util/amber/amber9/dat/leap/lib/all_aminoct94.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
```
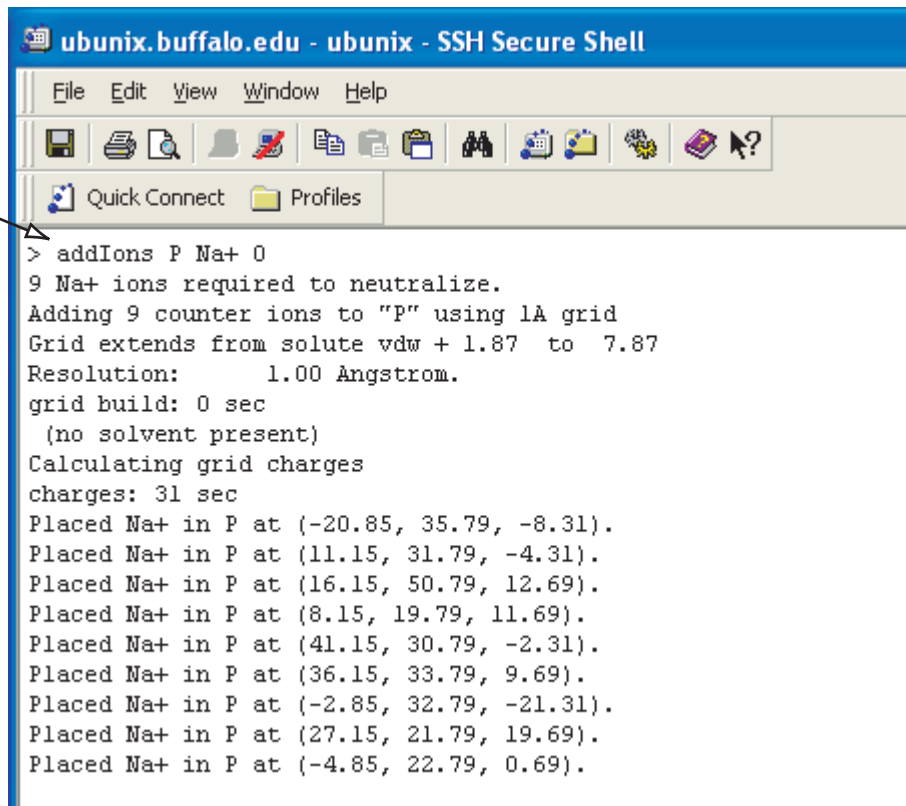
Removing atoms of
the protein which
are too close to the
ligand

```
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<HA 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 (Na+) to neutralize the protein system
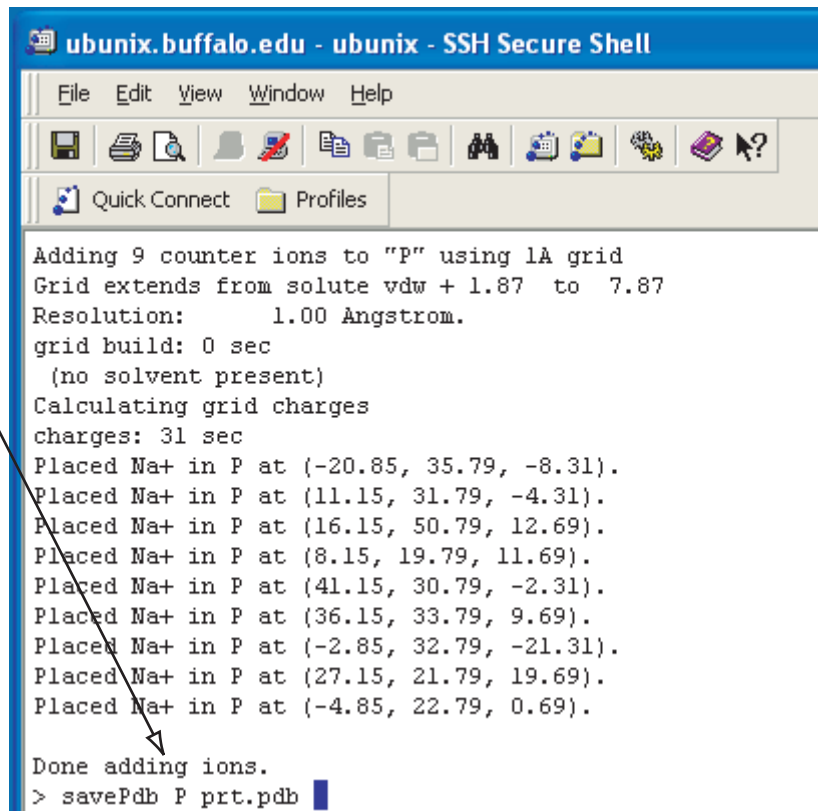
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File   Edit   View   Window   Help

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

QM/MM calculations of chemical reaction in renin protein

Saving the topology and the coordinates files
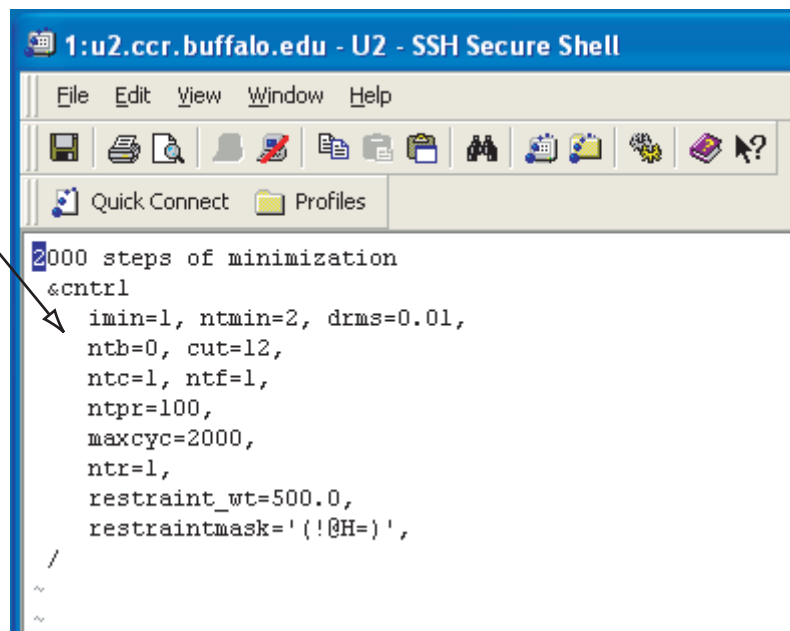

```
1:u2.ccr.buffalo.edu - U2 - SSH Secure Shell

File   Edit   View   Window   Help

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

```
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=)',
 /
~
~
```

QM/MM calculations of chemical reaction in renin protein

The pbs script for the minimization
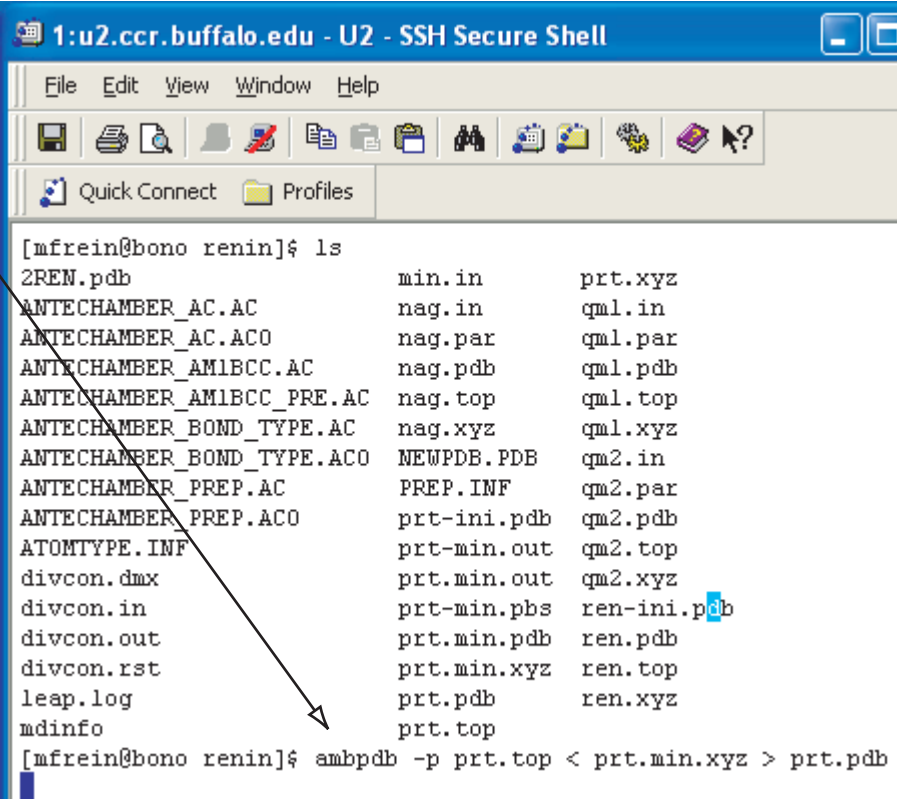
```
#PBS -l nodes=2:GM:ppn=2
#PBS -q debug
#PBS -m e
#PBS -j oe
#PBS -o prt-min.out
#
source $MODULESHOME/init/tcsh
module load amber/8
#
# Set number of processors to number requested from PBS
# (requires nodes=1:ppn=N syntax)
#
set NP = `cat $PBS_NODEFILE | wc -l`
#
cd $PBS_O_WORKDIR
#
$DO_PARALLEL $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
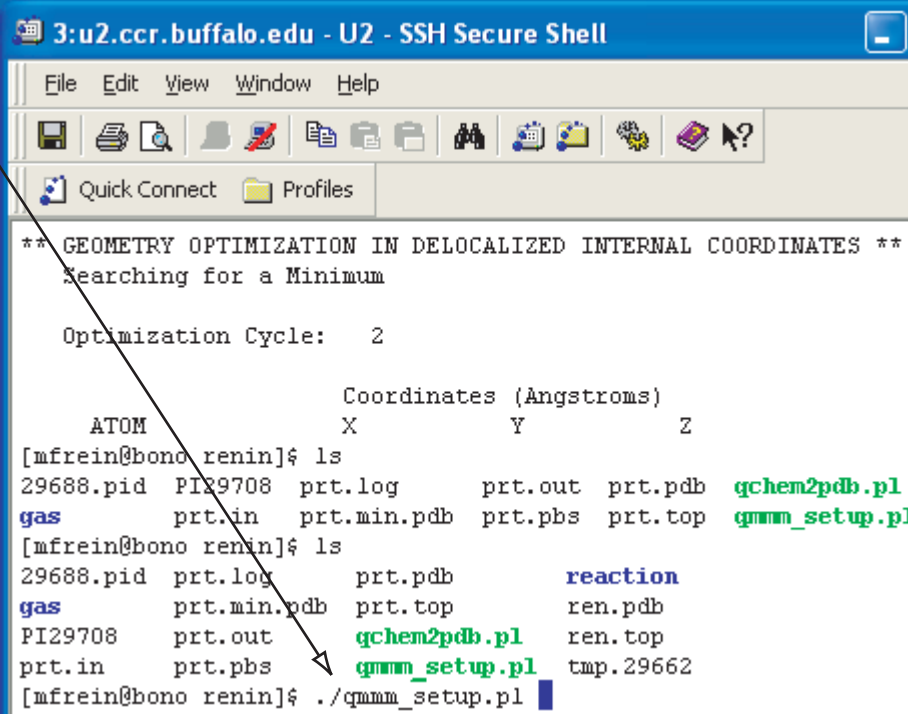

```
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File   Edit   View   Window   Help

Quick Connect    Profiles

[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
```

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

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
 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:
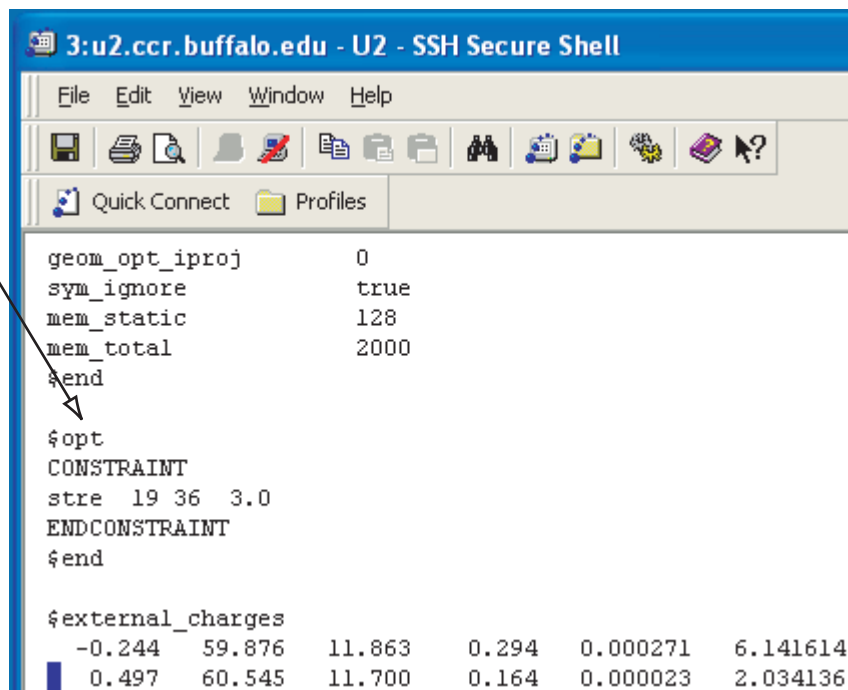
N-H distance
O-H distance
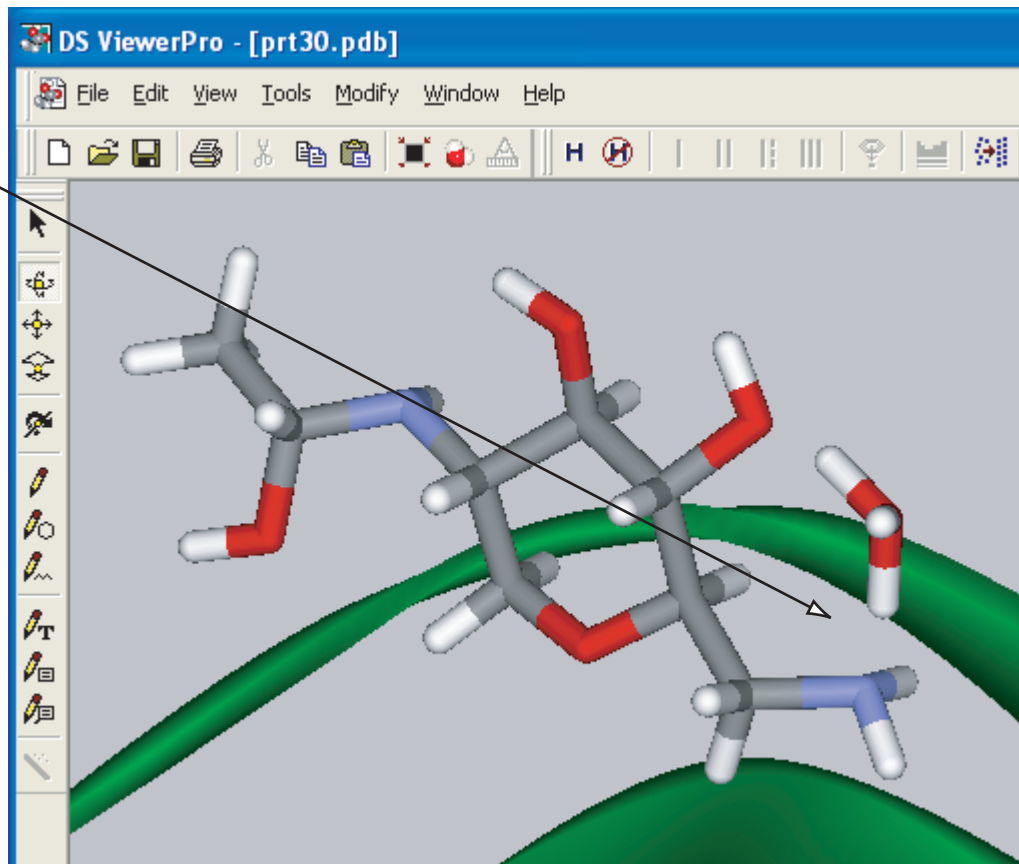
QM/MM calculations of chemical reaction in renin protein

The calculations for
the reactants valley

N-H distance
constrained
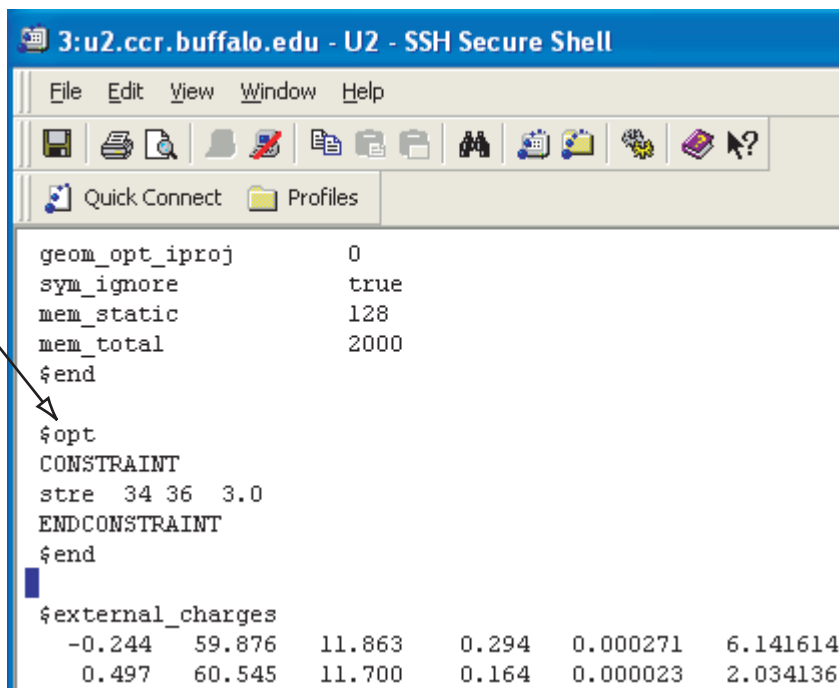
```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell

File   Edit   View   Window   Help

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
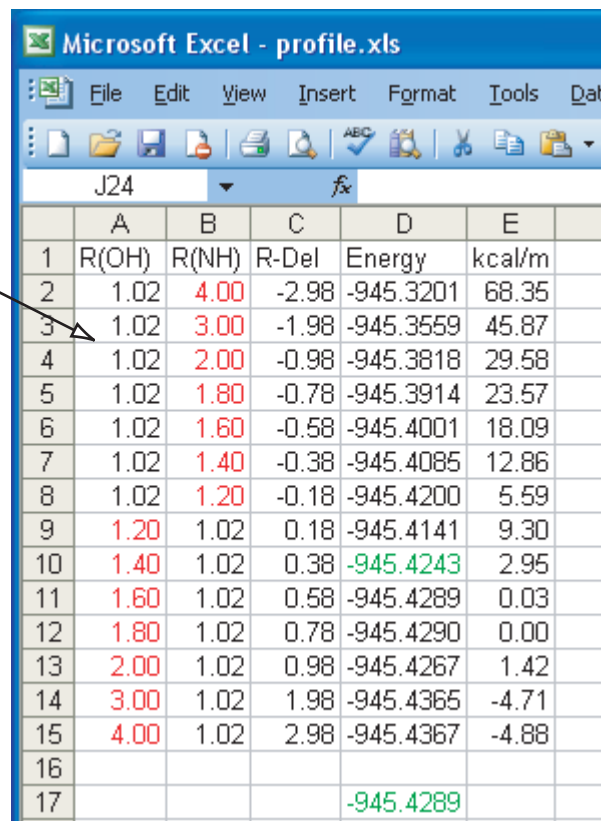
O-H distance
constrained

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

File   Edit   View   Window   Help

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
```

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

Microsoft Excel - profile.xls

| File | Edit | View | Insert | Format | Tools | Dat |

J24   fx
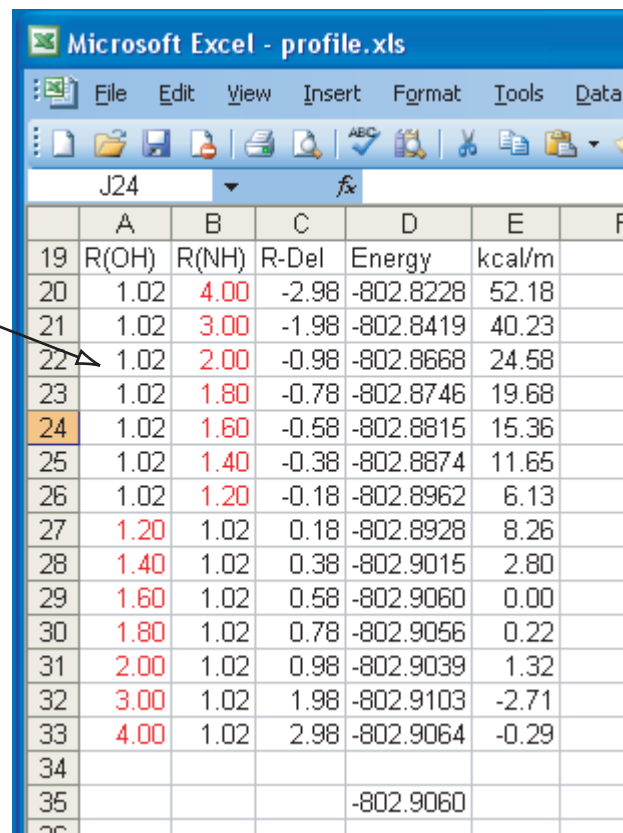
	A	B	C	D	E
1	R(OH)	R(NH)	R-Del	Energy	kcal/m
2	1.02	4.00	-2.98	-945.3201	68.35
3	1.02	3.00	-1.98	-945.3559	45.87
4	1.02	2.00	-0.98	-945.3818	29.58
5	1.02	1.80	-0.78	-945.3914	23.57
6	1.02	1.60	-0.58	-945.4001	18.09
7	1.02	1.40	-0.38	-945.4085	12.86
8	1.02	1.20	-0.18	-945.4200	5.59
9	1.20	1.02	0.18	-945.4141	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

Microsoft Excel - profile.xls

File   Edit   View   Insert   Format   Tools   Data

J24

	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
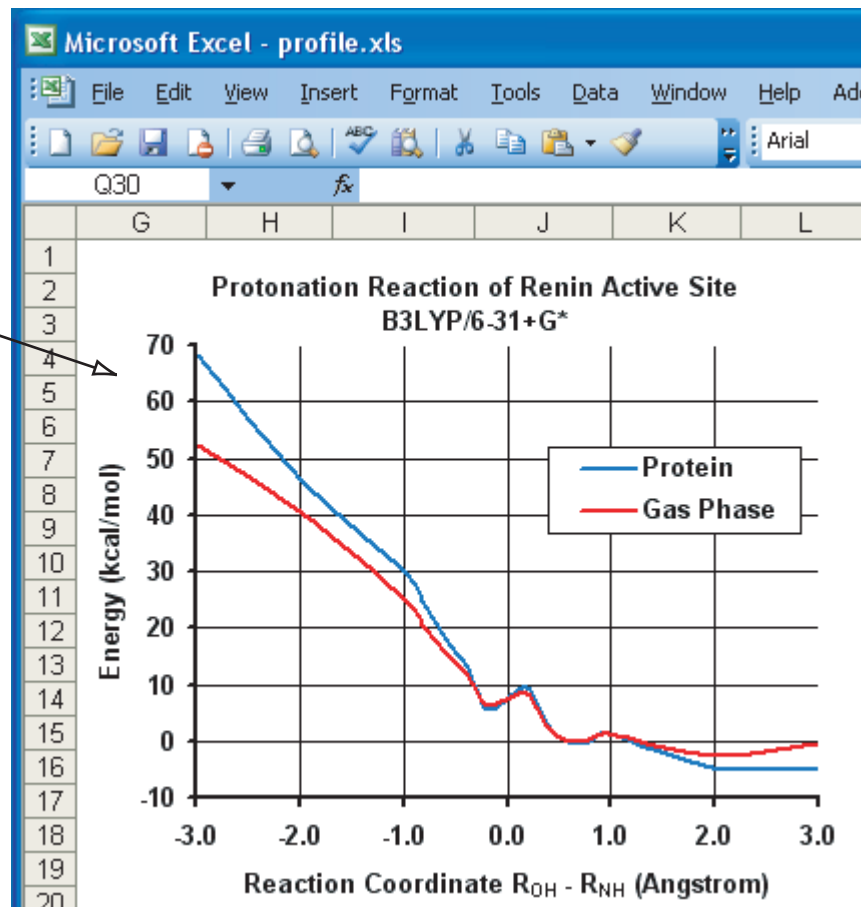
QM/MM electronic excitations in yellow protein

Experimental structure of the yellow protein
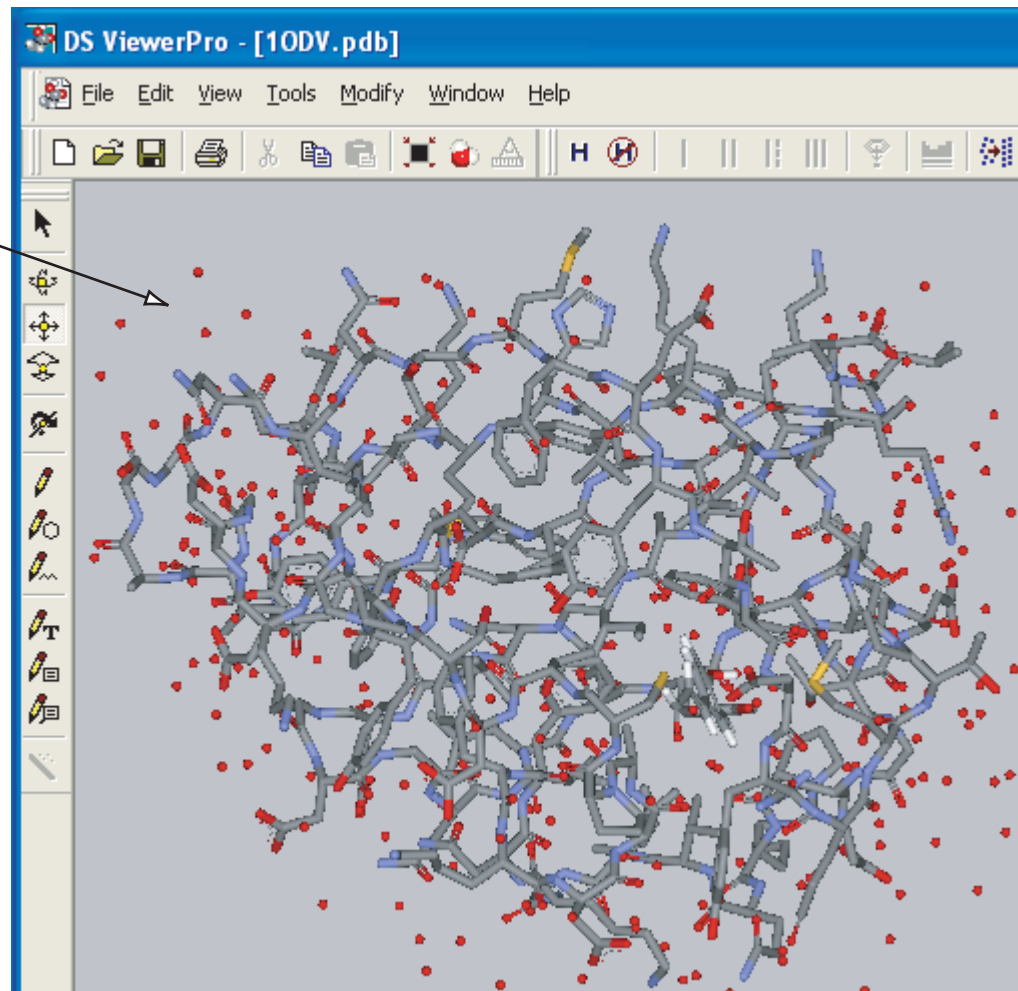
QM/MM electronic excitations in yellow protein
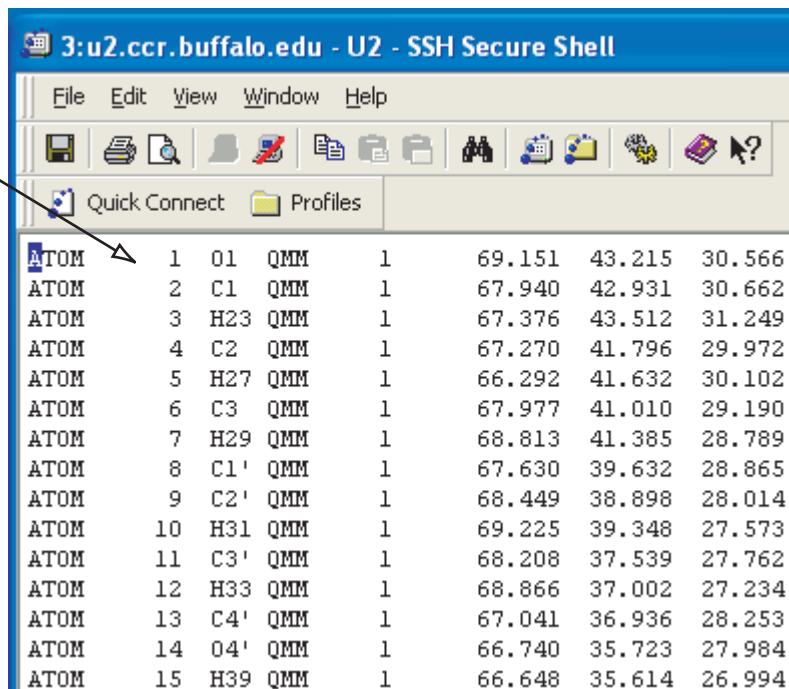
The active site of the yellow protein
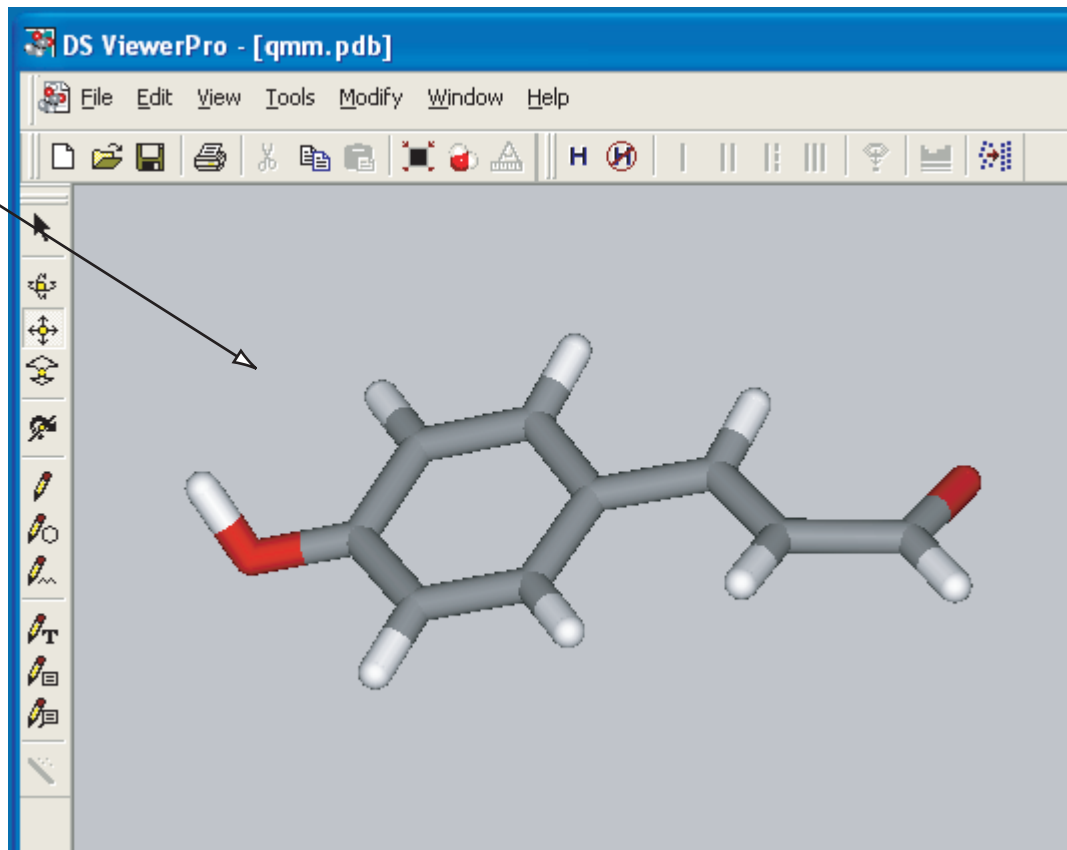
QM/MM electronic excitations in yellow protein

The pdf file of the ligand
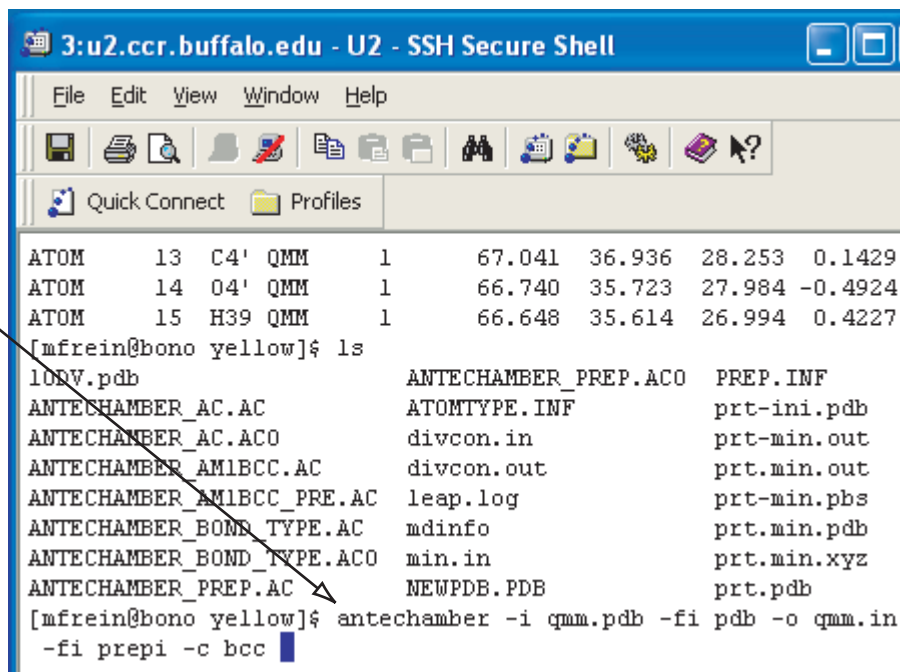
```
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File   Edit   View   Window   Help

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
```

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

QM/MM electronic excitations in yellow protein

Creating the parameter
file of the ligand

QM/MM electronic excitations in yellow protein

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

QM/MM electronic excitations in yellow protein

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

QM/MM electronic excitations in yellow protein

Loading the preparation file of the ligand

QM/MM electronic excitations in yellow protein

Loading the pdb file of the protein and the ligand

Removing protein
atoms which are too
close to the ligand


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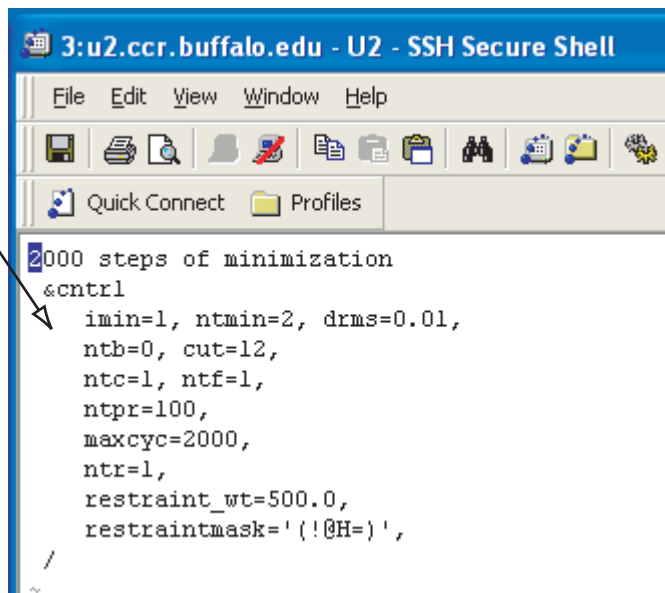
```
3:u2.ccr.buffalo.edu - U2 - SSH Secure Shell
File   Edit   View   Window   Help

  Quick Connect      Profiles

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
```

QM/MM electronic excitations in yellow protein

Creating the input file
for the minimization

```
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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=)',
 /
 ~
```

Creating the pbs
script for the
minimization
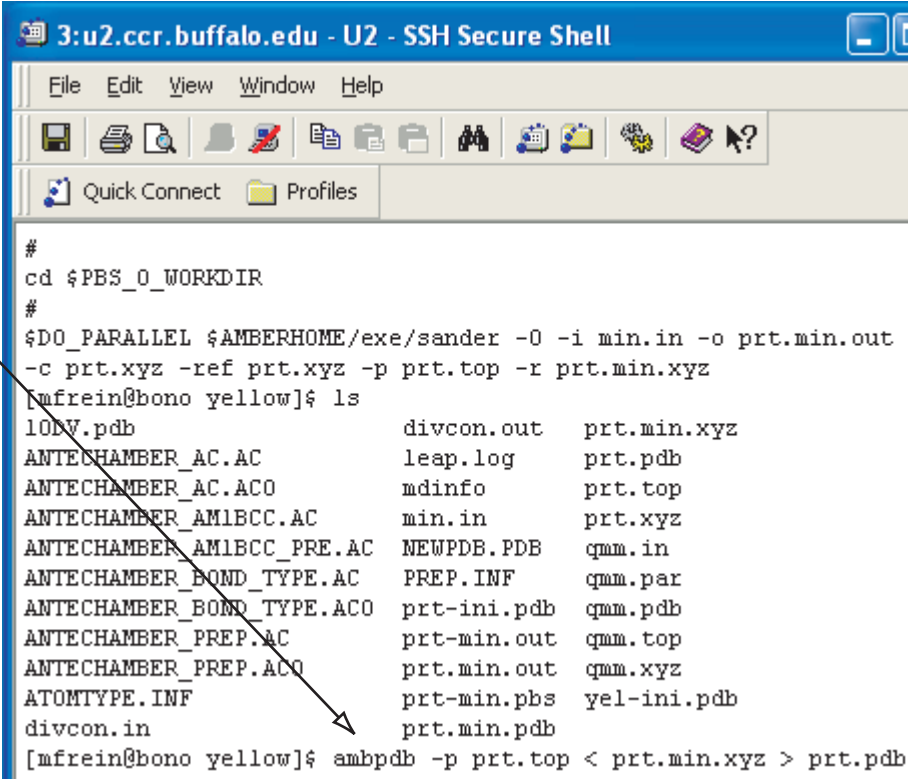
QM/MM electronic excitations in yellow protein

Converting the minimized coordinates into the pdb format

QM/MM electronic excitations in yellow protein

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

QM/MM electronic excitations in yellow protein

Geometry optimization
of the ligand inside the
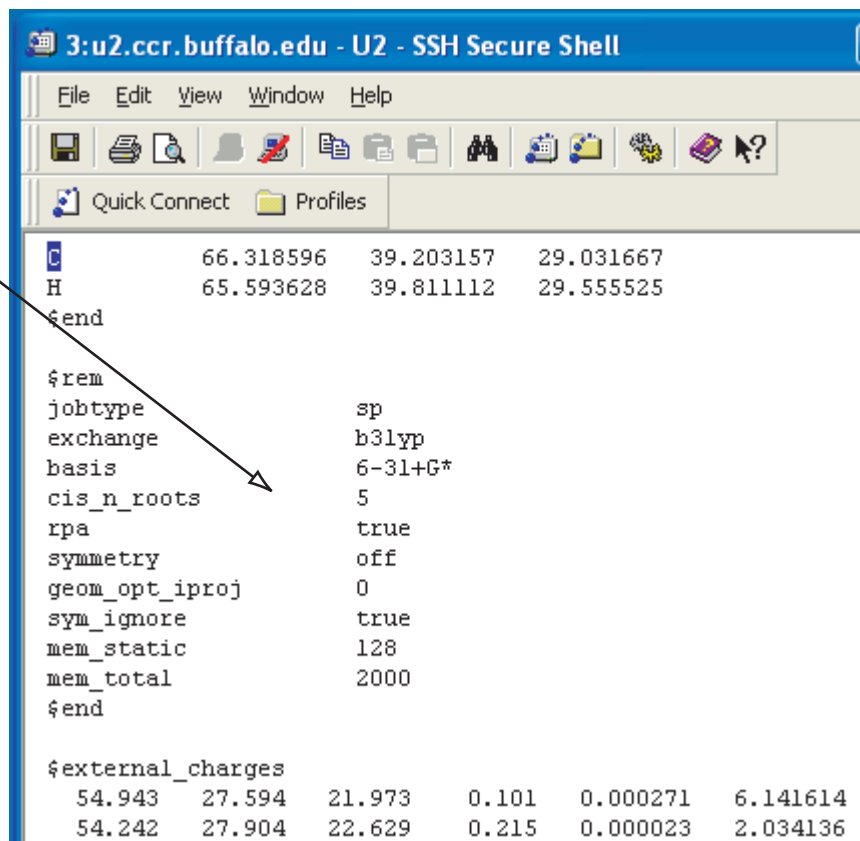protein

QM/MM electronic excitations in yellow protein

The calculated optimal geometry of the ligand inside the protein
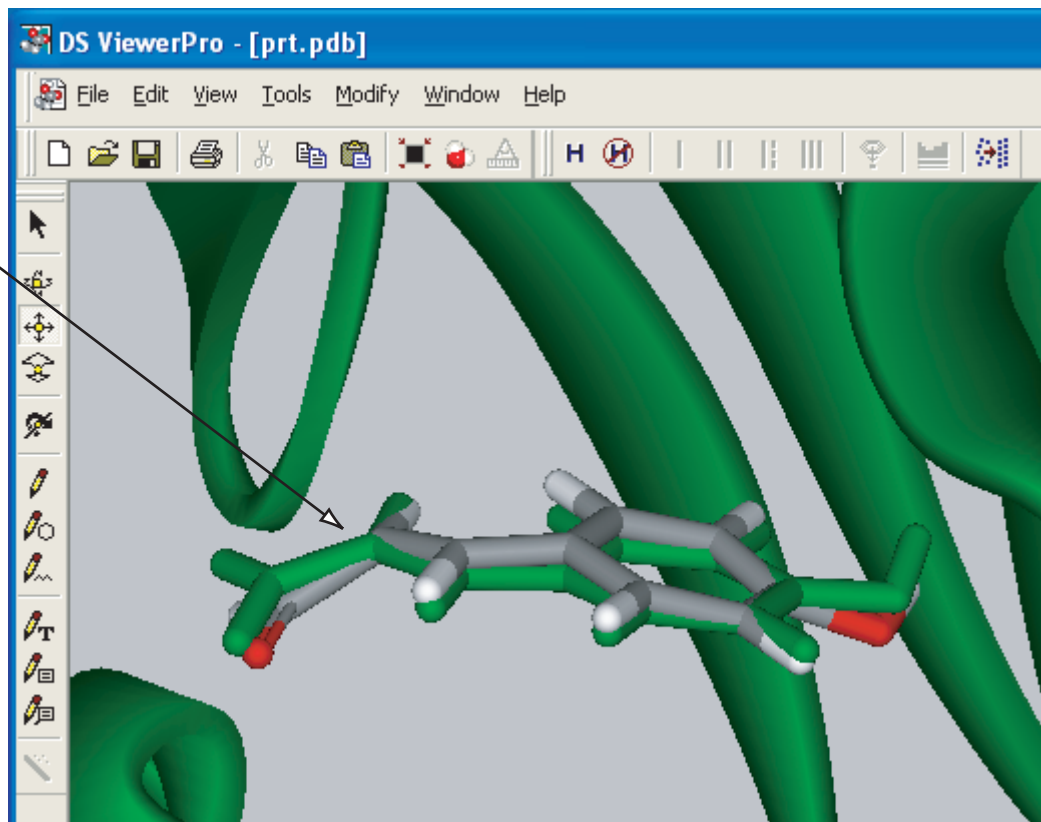
QM/MM electronic excitations in yellow protein

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

QM/MM electronic excitations in yellow protein

The excitation energy of the first excited singlet electronic state

```
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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
```
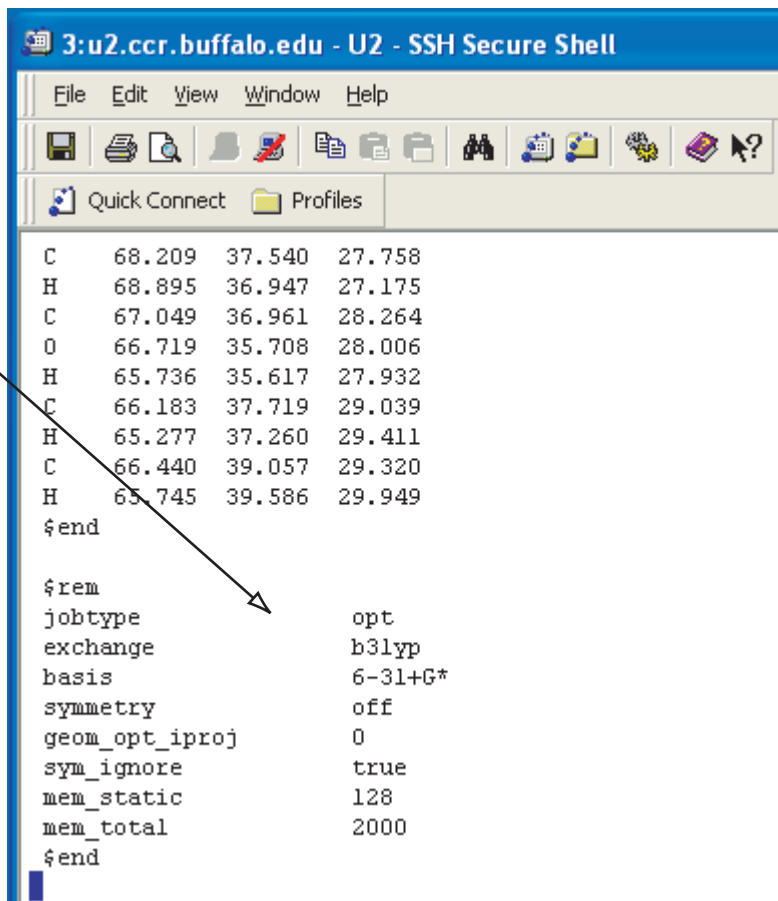
QM/MM electronic excitations in yellow protein

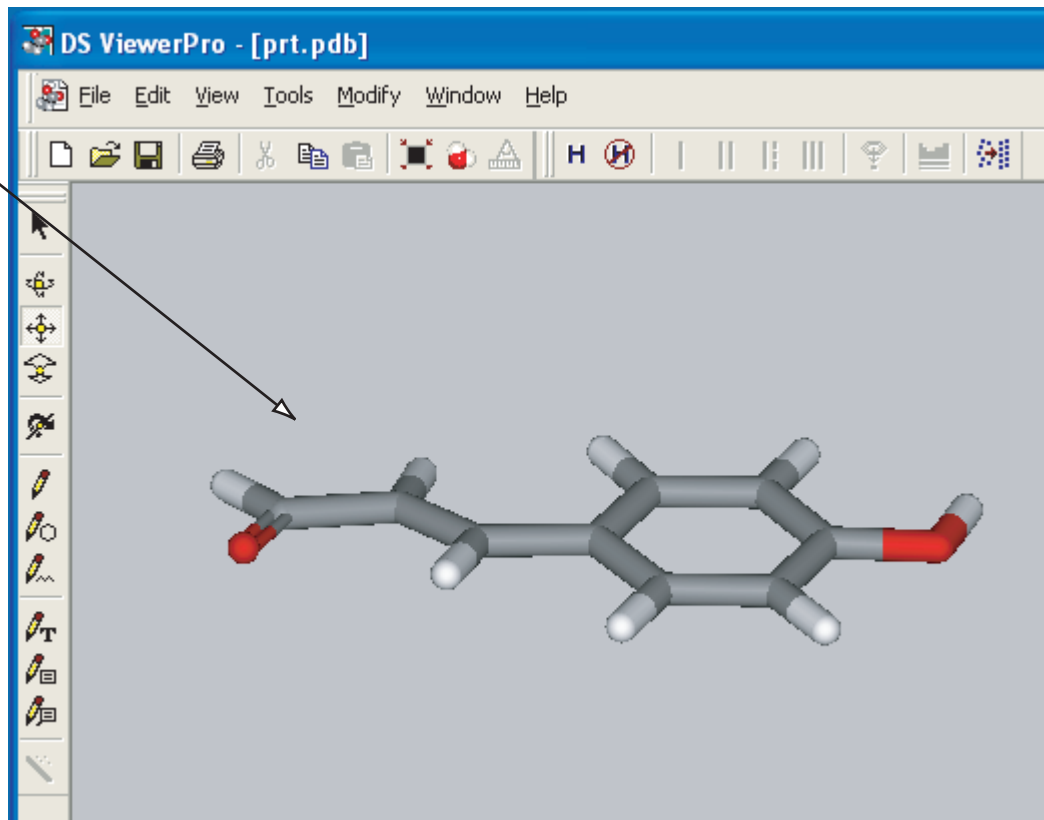Geometry optimization of the ligand in the gas phase

```
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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
```
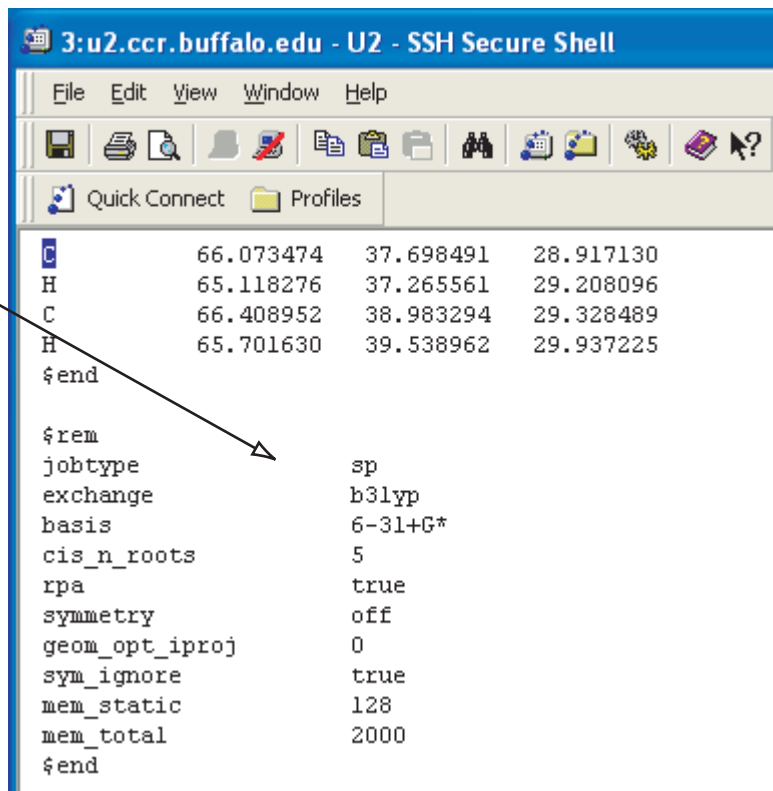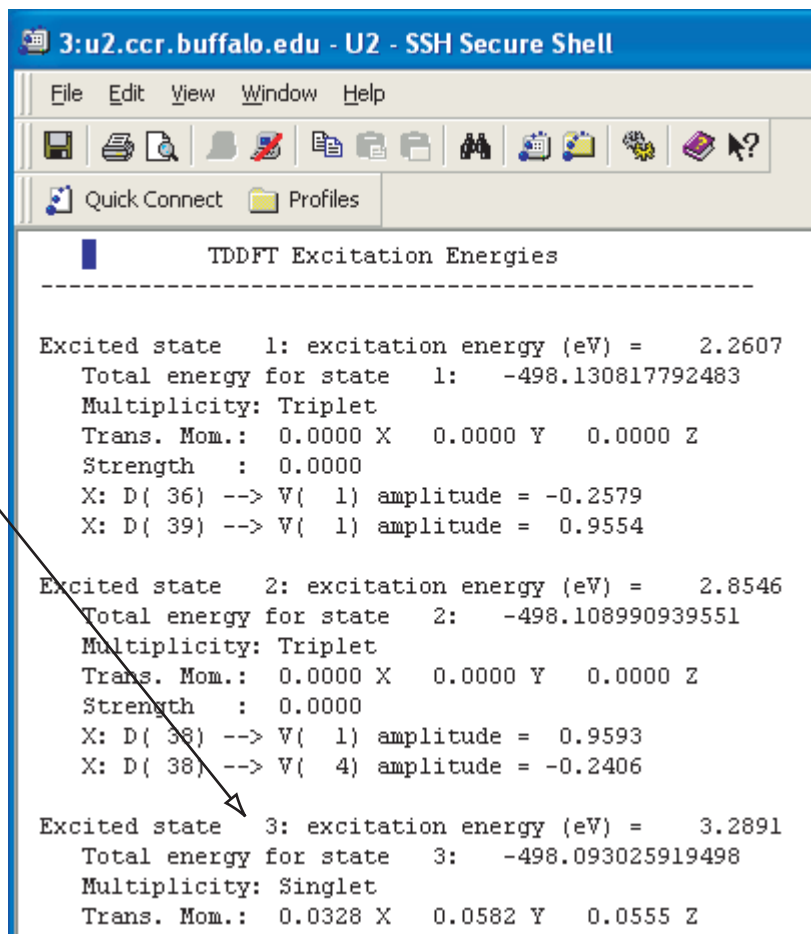
The calculated optimal geometry of the ligand in the gas phase

QM/MM electronic excitations in yellow protein

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

QM/MM electronic excitations in yellow protein

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

QM/MM electronic excitations in yellow proteins

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

ΔE(cal.) = -23 nm

ΔE(exp.) = -14 nm

E(cal.) = 377 nm

E(cal.) = 354 nm