

Supplementary Information for:

Reaction Mechanism of the Dengue Virus Serine Protease: A QM/MM study

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Samples of the input files used in the simulations

Preparation of input, using LEaP:

```
source leaprc.ff99SB
loadAmberParams frcmod.ionsjc_tip3p
INP = loadpdb file.pdb
addions INP Cl- 1
solvateOct INP TIP3PBOX 10.0
saveAmberParm INP file.prmtop file.mdcrd
quit
```

Molecular Dynamics Simulations

Energy minimization

```
&cntrl
  imin=1, ntx=1,
  maxcyc=1000, ncyc=100, ntp=100,
  ntmin=1,
  ntb=1, ntf=1, nmropt=1,
  igb=0, cut=10.0,
/
```

First heating stage: 0 K – 100 K, constant volume and temperature

```
&cntrl
  irest=0, ntx=1, iwrap=1,
  ntb=1, cut=10.0,
  ntp=1000, ntwx=1000, ntwr=1000,
  ntc=2, ntf=2,
  nstlim=50000, dt=0.002, nmropt=1,
  ntt=3, tempi=0.0, temp0=100.0, gamma_ln=2.0
/
&wt
  type='DUMPFREQ', istep1=1,
/
&wt type='END',
/
```

Second heating stage: 100 K – 300 K, constant volume and temperature

```
&cntrl
  irest=0, ntx=1, iwrap=1,
  ntb=1, cut=10.0,
  ntp=1000, ntwx=1000, ntwr=1000,
  ntc=2, ntf=2,
```

```
nstlim=50000, dt=0.002, nmropt=1,  
ntt=3, tempi=100.0, temp0=300.0, gamma_ln=2.0  
/  
&wt  
type='DUMPFREQ', istep1=1,  
/  
&wt type='END',  
/  

```

MD equilibration and production, constant pressure and temperature

```
&cntrl  
irest=1, ntx=5, iwrap=1,  
ntb=2, ntp=1, pres0=1.0, taup=1.0, cut=10.0,  
ntpr=100000, ntwx=100000, ntwr=100000,  
ntc=2, ntf=2,  
nstlim=100000000, dt=0.002,  
ntt=3, temp0=300.0, gamma_ln=2.0,  
ifqnt=0, igb=0, ioutfm=1  
/  

```

QM/MM-MD

Minimization

```
&cntrl  
imin=1, maxcyc=1000, ncyc=100, ntmin=1,  
cut=10, ntp=100, ntwr=50,  
iwrap=1, noshakemask='@501-521,898-913,1792-1806,2914-3003',  
ifqnt=1, nmropt=1,  
/  
&qmmm  
qmmask='@501-521,898-913,1792-1806,2914-3003',  
qmcharge=+1,  
qm_theory='PM3-PDDG',  
qmcut=10.0,  
printcharges=1,  
writepdb=1,  
/  
&wt type='DUMPFREQ', istep1=1,  
/  
&wt type='END',  
/  
DISANG=restraint.rst  
DUMPAVE=restraint.rst.out  
LISTIN=POUT  
LISTOUT=POUT
```

Heating

```
&cntrl  
imin=0, irest=0, ntx=1,  
ntb=1, ntt=3, gamma_ln=2.0,  
temp0=300.0, tempi=0.0, nmropt=1, cut=10,  
iwrap=1, ifqnt=1,  
ntc=2, ntf=2, ntp=0,  
nstlim=5000, dt=0.001,  
ntpr=100, ntwx=100, ntwr=100,  
noshakemask='@501-521,898-913,1792-1806,2914-3003'  
/  

```

```

&qmmm
  qmmask='@501-521,898-913,1792-1806,2914-3003'
  qmcharge=+1,
  printcharges=1,
  qmshake=0,
  qm_theory='PM3-PDDG',
  qmcut=10.0,
  writepdb=1,
/
&wt
type='DUMPFREQ', istep1=1,
/
&wt
type='TEMPO', istep1=0, istep2=2000,
value1=0.0, value2=300.0,
/
&wt
type='END',
/
DISANG=restraint.rst
DUMPAVE=restraint.rst.out
LISTIN=POUT
LISTOUT=POUT

```

Production

```

&cntrl
  irest=0, ntx=1, iwrap=1,
  ntb=2, ntp=1, pres0=1.0, taup=1.0, cut=10.0,
  ntp=100, ntwx=100, ntwr=100,
  ntc=2, ntf=2, noshakemask='@501-521,898-913,1792-1806,2914-3003',
  nstlim=50000, dt=0.001,
  ntt=3, temp0=300.0, gamma_ln=2.0,
  ifqnt=1, igb=0, nmropt=1
/
&qmmm
  qmmask='@501-521,898-913,1792-1806,2914-3003',
  qmcharge=+1,
  printcharges=1,
  qmshake=0,
  qm_theory='PM3-PDDG'
  qmcut=10.0
  printcharges=1,
  writepdb=1,
/
&wt type='DUMPFREQ', istep1=1,
/
&wt type='END',
/
DISANG=restraint.rst
DUMPAVE=restraint.rst.out
LISTIN=POUT
LISTOUT=POUT

```