Supporting Information

Probing the Effect of Conformational Constraint on Phosphorylated Ligand Binding to an SH2 Domain using Polarizable Force Field Simulations

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Temperatures in Replica Exchange Molecular Dynamics Simulations (in K)

260.00, 265.25, 270.59, 276.01, 281.76, 287.35, 293.03, 298.79, 304.63, 310.54, 316.57, 322.69, 328.90, 335.21, 341.63, 348.14, 354.75, 361.46, 368.27, 375.18, 382.20, 389.33, 396.57, 403.92, 411.38, 418.96, 426.66, 434.49, 442.43, 450.50, 458.68, 467.00, 475.45, 484.03, 492.74, 501.59, 510.58, 519.71, 528.98, 538.39, 547.93, 557.64, 567.50, 577.52, 587.69, 598.03, 608.03 and 619.03.

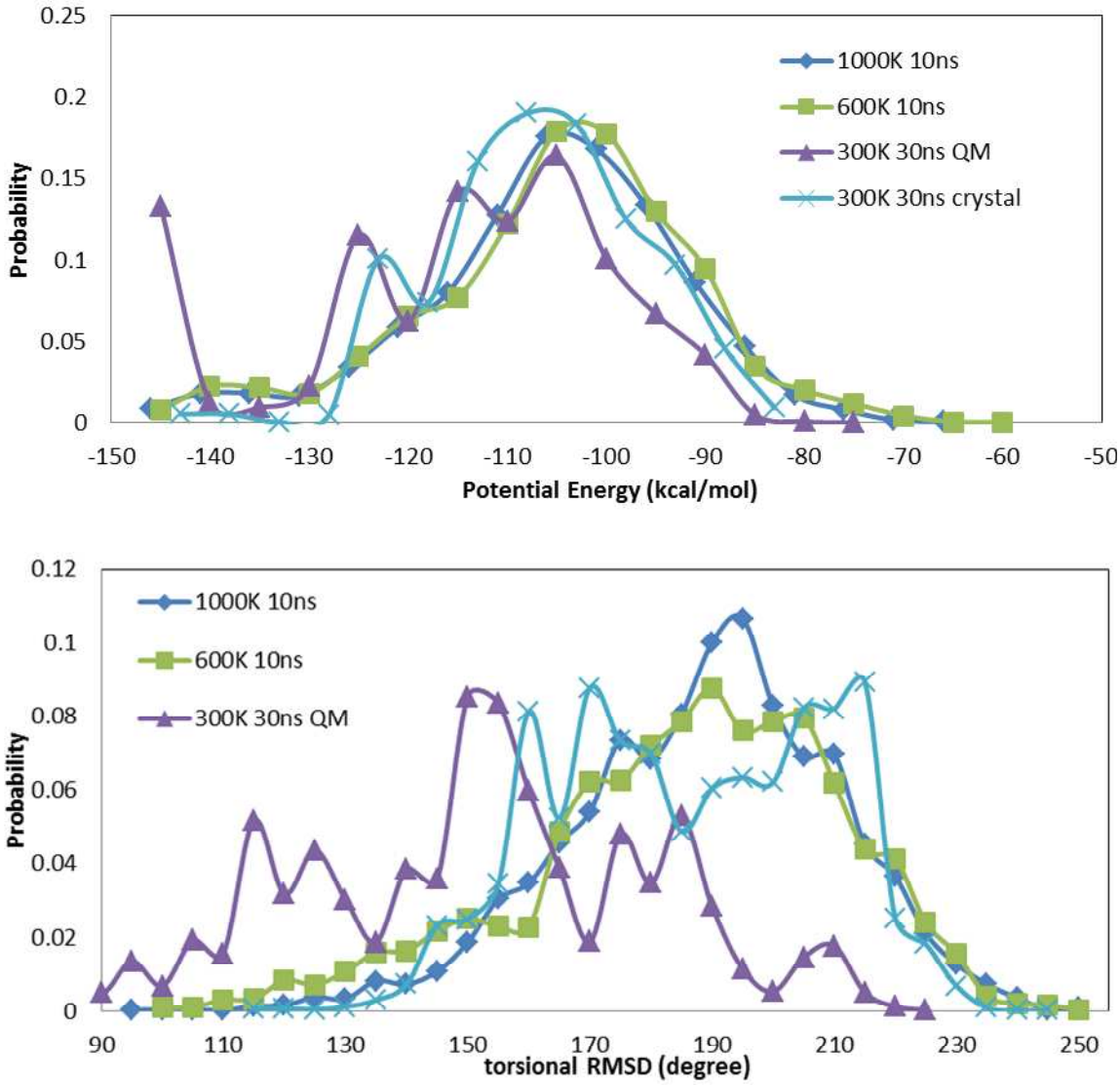

Figure S1. Potential energy distributions of configurations sampled at different temperatures (300 K, 600 K and 1000 K) and with different simulation length (10 ns and 30 ns). QM optimized structure and the structure taken from complex crystal structure are as the starting points for repeated simulations. The frames are sampled every 2 ps, and then minimized with a convergence of 0.1 kcal/mol/Å. Thus the conformational distributions we are examining are for 0K, even though the simulations have been done at high temperatures to accelerate the sampling process. The dihedral angles are measured

from 0~360 degree (instead of 0~180 degree) in order to capture all the different orientations. The QM optimized structure is selected as the reference to calculate torsional RMSDs for all snapshots.

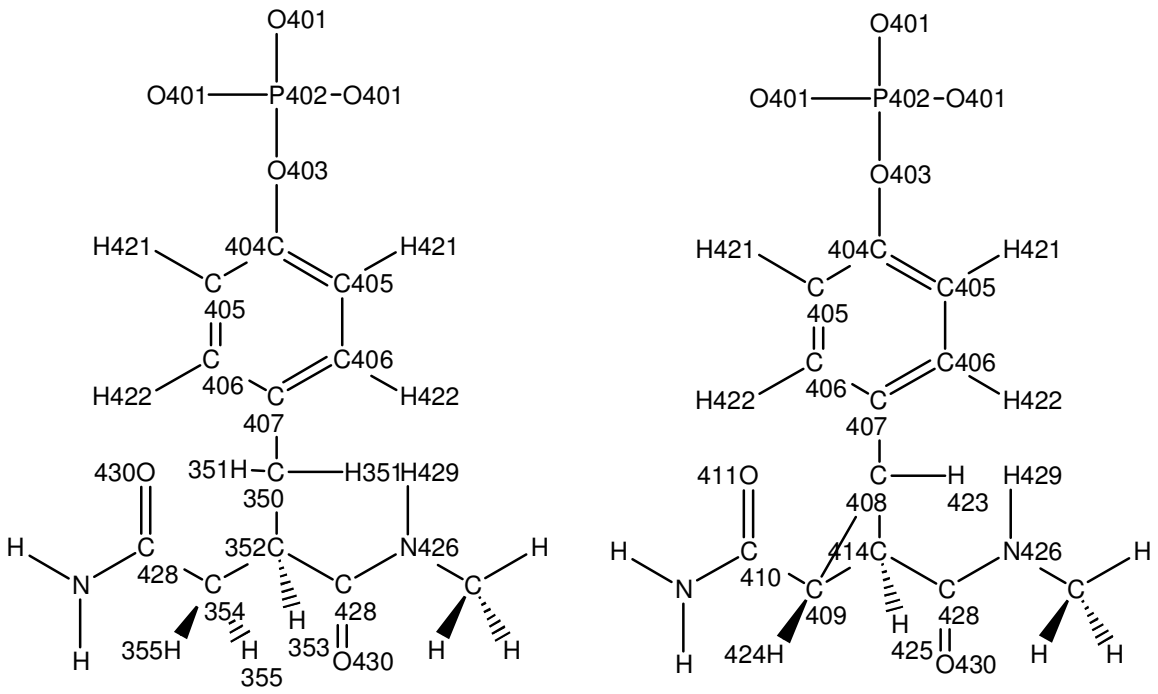

Figure S2. Atom types of model compounds used for parameterization. Parameters for C428, O430, N426 and H429 are transferred from AMOEBA PRO.

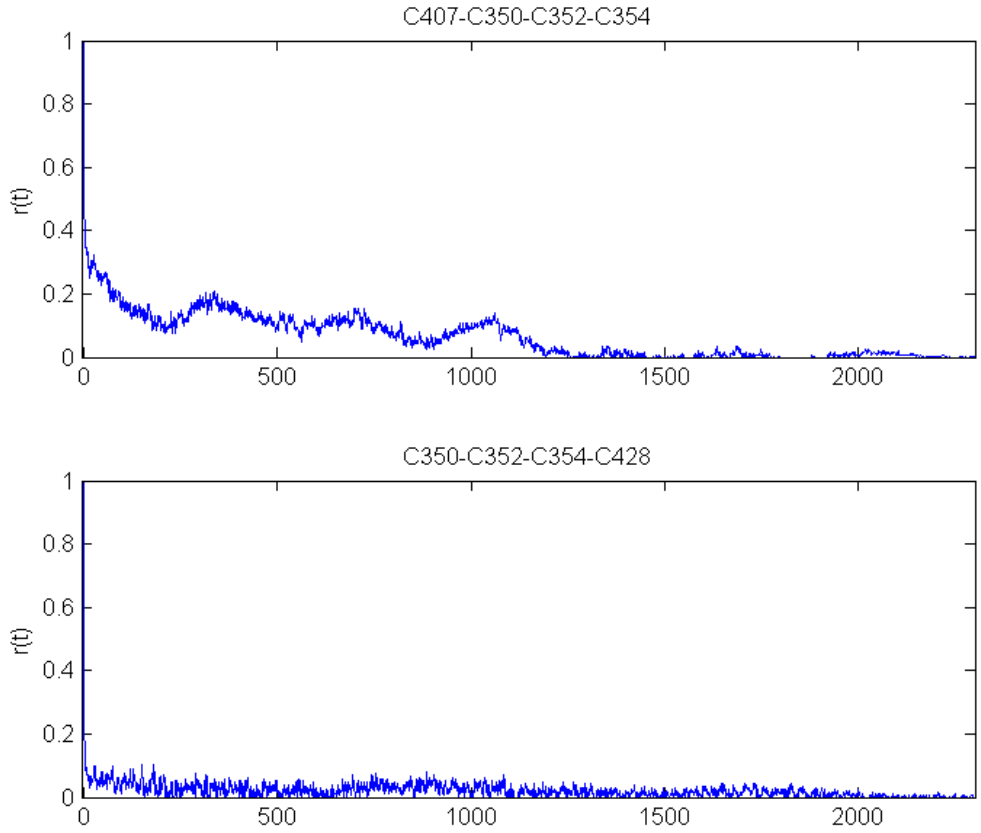

Figure S3. Autocorrelation of dihedral angle C407-C350-C352-C354 and C350-C352-C354-C428 of fpYVN in solvent from REMD simulation at 298 K.

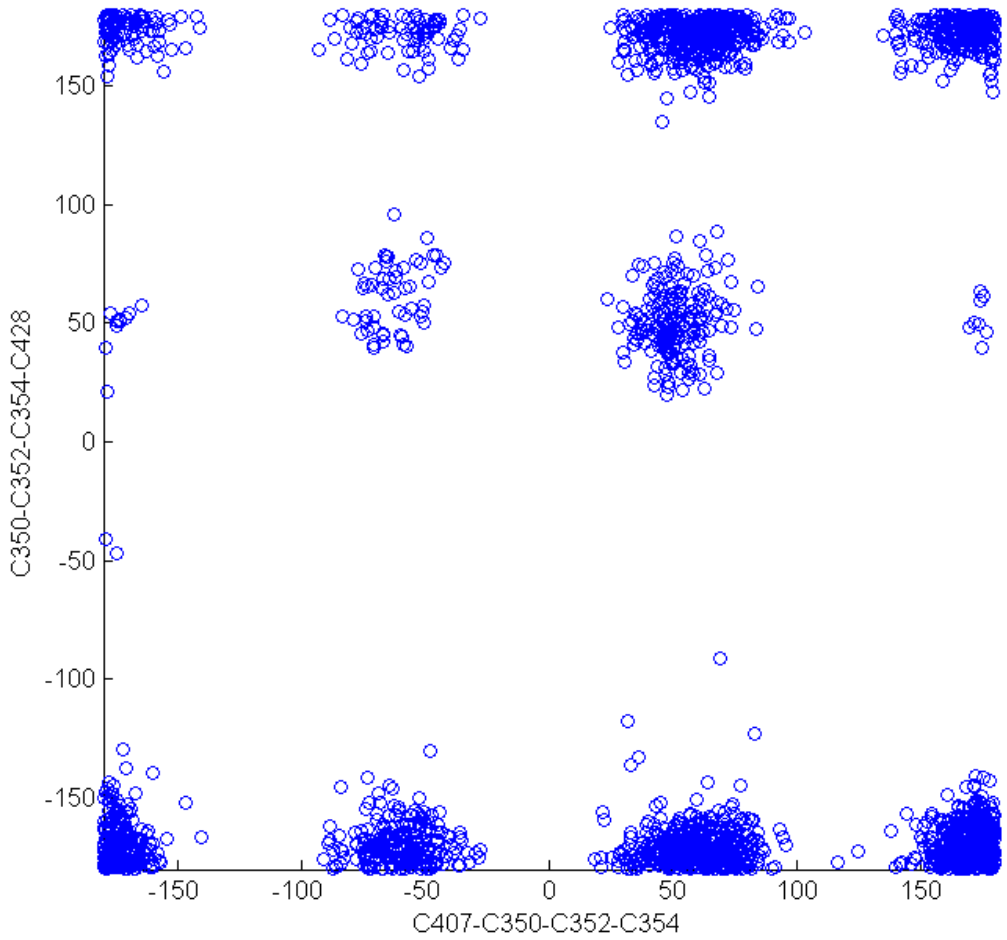

Figure S4. Conformational distribution of dihedral angle C407-C350-C352-C354 and C350-C352-C354-C428 of fpYVN in solvent from REMD simulation at 298 K.

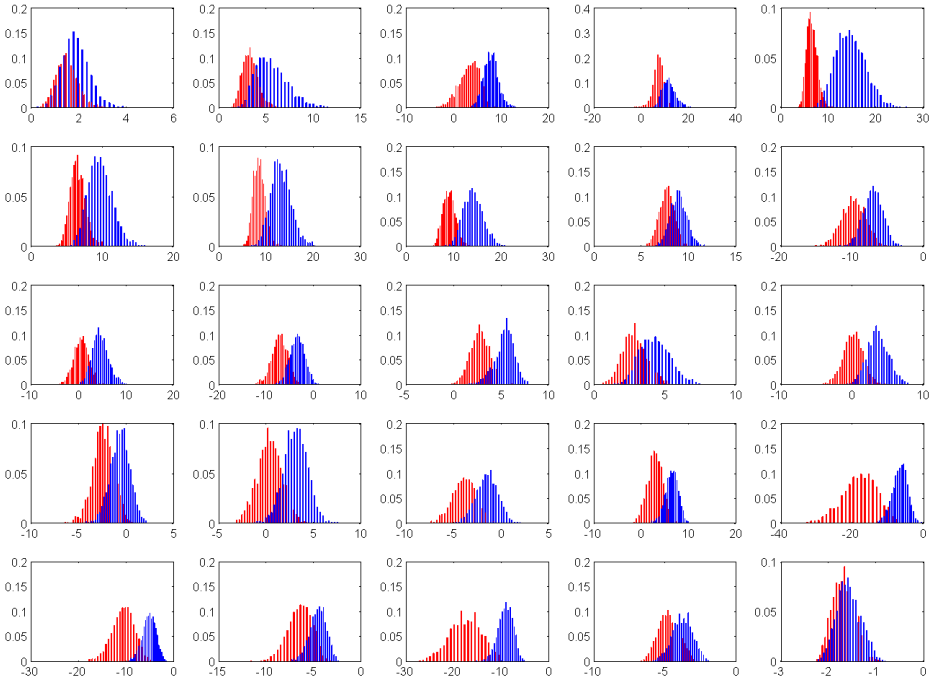

Figure S5. Overlap of potential energy differences calculated forward (blue) and backward (red) of perturbation from fpYVN to cpYVN in water. The X-axis represents the potential energy difference, and the Y-axis shows the probability.

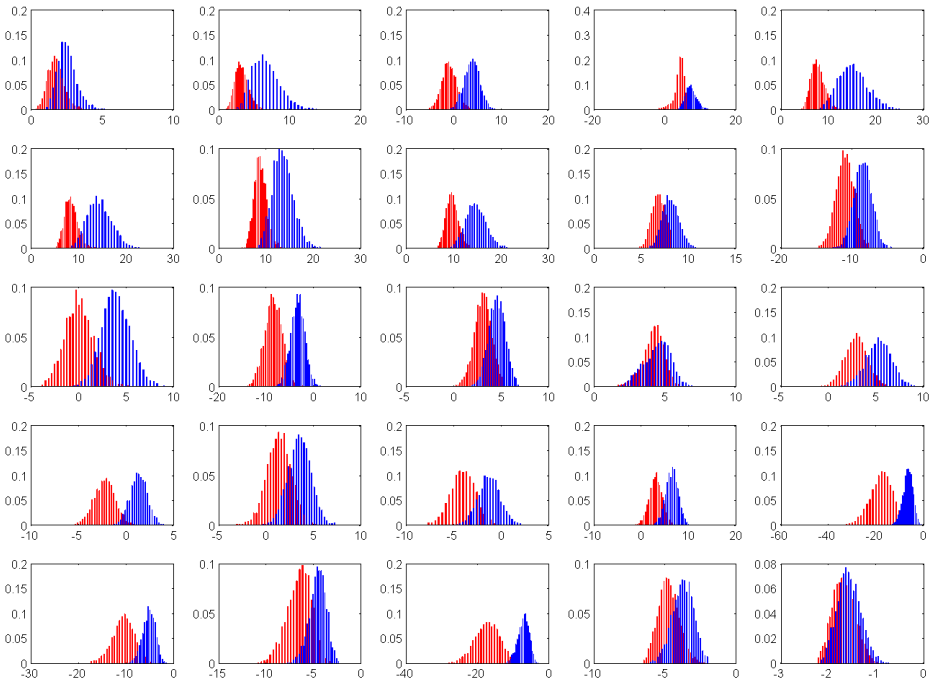

Figure S6. Overlap of potential energy differences calculated forward (blue) and backward (red) of perturbation from fpYVN to cpYVN in solvated complex. The X-axis represents the potential energy difference, and the Y-axis shows the probability.

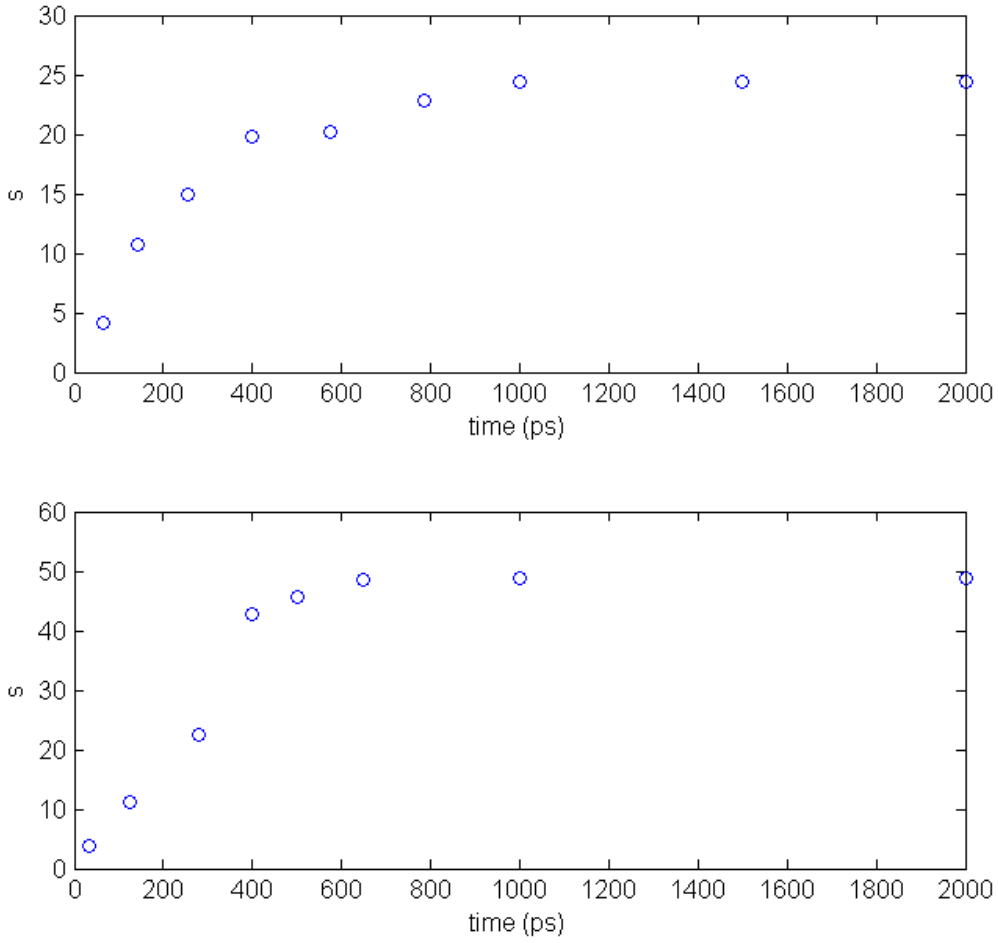

Figure S7. Statistical inefficiency of the free energy calculations for fpYVN->cpYVN in water (upper panel) and fpYVN in solvated complex (lower panel) at 298K.

#	complex		solvent		$\Delta\Delta G$
	$\Delta G_{complex}$	deviation	$\Delta G_{solvent}$	deviation	
26	24.392	0.000	26.670	0.000	-2.278
25	24.367	-0.025	26.645	-0.025	-2.278
24	24.467	0.075	26.595	-0.070	-2.128
23	24.524	0.132	26.508	-0.162	-1.984
22	24.385	-0.007	26.469	-0.201	-2.084
21	25.428	1.036	27.035	0.365	-1.607
20	24.685	0.293	26.897	0.227	-2.212
13	26.034	1.642	27.032	0.362	-0.998

Table S1. The dependence of relative binding free energy (fpYVN->cpYVN) at 298K on the number of intermediate steps in the alchemical calculation (energy in kcal/mol). Every 2nd (13 steps total), 4th (20 steps), 5th (21 steps), 6th (22 steps), 7th (23 steps), 10th (24 steps), 13th (23 steps with the middle step skipped) step is skipped respectively.

Force Field Parameters of the Model Compounds in Figure S2

#atom #atom type #atom class #atom name #description #atomic number #mass #connectivity

```
atom      401  401  O    " O401 "    8    15.999   1
atom      402  402  P    " P402 "   15    30.974   4
atom      403  403  O    " O403 "    8    15.999   2
atom      404  404  C    " C404 "    6    12.011   3
atom      405  404  C    " C405 "    6    12.011   3
atom      406  404  C    " C406 "    6    12.011   3
atom      407  404  C    " C407 "    6    12.011   3
atom      408  405  C    " C408 "    6    12.011   4
atom      409  406  C    " C409 "    6    12.011   4
atom      410  407  C    " C410 "    6    12.011   3
atom      411  408  O    " O411 "    8    15.999   1
atom      414  406  C    " C414 "    6    12.011   4
atom      423  414  H    " H423 "    1     1.008   1
atom      424  415  H    " H424 "    1     1.008   1
atom      425  415  H    " H425 "    1     1.008   1
atom      350  350  C    " C350  "   6    12.011   4
atom      354  354  C    " C354  "   6    12.011   4
atom      352  352  C    " C352  "   6    12.011   4
atom      351  351  H    " H351  "   1     1.008   1
atom      355  355  H    " H355  "   1     1.008   1
atom      353  353  H    " H353  "   1     1.008   1
```

#vdw #atom cluass #diameter #epsilon #scaling factor for H

```
vdw       401        3.360   0.1120
vdw       402        4.450   0.3900
vdw       403        3.405   0.1120
vdw       404        3.800   0.0910
vdw       405        3.820   0.1010
vdw       406        3.820   0.1010
vdw       407        3.820   0.1060
vdw       408        3.300   0.1120
vdw       414        2.960   0.0240   0.92
vdw       415        2.960   0.0240   0.92
vdw       350        3.820   0.1010
vdw       354        3.820   0.1010
vdw       352        3.820   0.1010
vdw       351        2.960   0.0240   0.92
vdw       355        2.960   0.0240   0.92
vdw       353        2.960   0.0240   0.92
```

#bond #atom class 1 #atom class 2 #force constant #bond length

```
bond      401  402      775.0   1.4924
bond      402  403      450.0   1.8897
bond      403  404      465.0   1.2769
bond      404  404      680.0   1.3975
```

```
bond      404  405      385.0    1.4997
bond      405  406      385.0    1.5059
bond      405  414      400.0    1.0795
bond      406  407      385.0    1.4955
bond      406  406      385.0    1.5116
bond      406  415      400.0    1.0740
bond      407  408      680.0    1.2059
bond      350  404      385.0    1.5128
bond      350  352      385.0    1.5486
bond      350  351      400.0    1.0864
bond      354  417      385.0    1.5253
bond      352  354      385.0    1.5639
bond      354  355      400.0    1.0826
bond      352  417      385.0    1.5287
bond      352  353      400.0    1.0844
#angle #atom class 1 #atom class 2 #atom class 3 #force constant #equilibrium angle
angle     401  402  401    89.88    117.42
angle     401  402  403    75.86     99.34
angle     402  403  404    95.30    122.17
angle     403  404  404    60.00    121.93
angle     404  404  404    60.00    119.99
angle     404  404  413    32.00    119.09
angle     404  404  405    60.00    121.69
angle     404  405  406    60.00    122.94
angle     404  405  414    38.00    116.06
angle     406  405  406    60.00     60.25
angle     406  405  414    38.00    111.42
angle     405  406  407    60.00    123.48
angle     405  406  406    60.00     59.87
angle     405  406  415    38.00    115.50
angle     406  406  407    60.00    119.61
angle     407  406  415    38.00    113.15
angle     406  406  415    38.00    115.00
angle     406  407  408    60.00    121.75
angle     350  404  404    60.00    120.79
angle     352  350  404    60.00    110.70
angle     351  350  404    38.00    111.43
angle     351  350  352    38.00    108.50
angle     351  350  351    34.50    106.14
angle     352  354  417    60.00    111.73
angle     355  354  417    38.00    108.50
angle     352  354  355    38.00    110.23
angle     355  354  355    34.50    107.53
angle     354  417  419    60.00    119.10
angle     354  417  416    60.00    117.10
angle     350  352  354    60.00    114.08
```

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angle      350  352  417     60.00     111.41
angle      350  352  353     38.00     107.12
angle      354  352  417     60.00     111.33
angle      353  352  354     38.00     106.83
angle      353  352  417     38.00     105.49
angle      352  417  419     60.00     123.74
angle      352  417  416     60.00     114.38
#stretch bend #atom class #force constant1 #force constant2 #force constant3
strbnd     402              7.20      4.30      0.00
strbnd     403             14.40      0.00      0.00
strbnd     404             38.00      0.00      0.00
strbnd     405             18.70     18.70      0.00
strbnd     406             18.70     18.70      0.00
strbnd     407             18.70     18.70      0.00
strbnd     350             18.70     11.50      0.00
strbnd     354             18.70     11.50      0.00
strbnd     352             18.70     11.50      0.00
#out of plane #atom class 1 #atom class 2 #force constant
opbend     404  403          1.60
opbend     404  404          0.80
opbend     404  405          1.60
opbend     407  406          0.65
opbend     407  408          0.65
opbend     404  350          0.20
opbend     417  354          0.20
opbend     417  419          0.20
opbend     417  416          0.20
opbend     417  352          0.20
#torsion #atom class 1 #atom class 2 #atom class 3 #atom class 4 #force constant #phase
angle #nth fold
torsion    413  404  404  413     0.000 0.0 1   4.070 180.0 2   0.000 0.0 3
torsion    404  404  404  405    -0.610 0.0 1   4.210 180.0 2   0.000 0.0 3
torsion    413  404  404  405     0.000 0.0 1   6.100 180.0 2   0.000 0.0 3
torsion    404  404  405  406    -3.034 0.0 1   1.393 111.0 2   1.590 0.0 3
torsion    404  404  405  414     0.000 0.0 1   0.000 180.0 2  -0.090 0.0 3
torsion    404  405  406  407     0.180 0.0 1   0.170 180.0 2   0.520 0.0 3
torsion    404  405  406  406     0.180 0.0 1   0.170 180.0 2   0.520 0.0 3
torsion    404  405  406  415     0.000 0.0 1   0.000 180.0 2   0.340 0.0 3
torsion    406  405  406  407     0.180 0.0 1   0.170 180.0 2   0.520 0.0 3
torsion    406  405  406  415     0.000 0.0 1   0.000 180.0 2   0.340 0.0 3
torsion    414  405  406  407     0.000 0.0 1   0.000 180.0 2   0.340 0.0 3
torsion    414  405  406  406     0.000 0.0 1   0.000 180.0 2   0.340 0.0 3
torsion    414  405  406  415     0.000 0.0 1   0.000 180.0 2   0.300 0.0 3
torsion    405  406  406  407     0.180 0.0 1   0.170 180.0 2   0.520 0.0 3
torsion    405  406  406  415     0.000 0.0 1   0.000 180.0 2   0.340 0.0 3
torsion    407  406  406  405     0.180 0.0 1   0.170 180.0 2   0.520 0.0 3
```

```
torsion    407  406  406  407     0.180 0.0 1   0.170 180.0 2   0.520 0.0 3
torsion    407  406  406  415     0.000 0.0 1   0.000 180.0 2   0.340 0.0 3
torsion    415  406  406  415     0.000 0.0 1   0.000 180.0 2   0.300 0.0 3
torsion    405  406  407  408    -3.300 0.0 1   2.510 180.0 2   1.180 0.0 3
torsion    405  406  407  409     0.000 0.0 1   0.000 180.0 2   0.800 0.0 3
torsion    406  406  407  408     0.000 0.0 1   0.000 180.0 2   0.000 0.0 3
torsion    406  406  407  409     0.000 0.0 1   0.000 180.0 2   0.000 0.0 3
torsion    415  406  407  408    -3.300 0.0 1   2.510 180.0 2   1.180 0.0 3
torsion    415  406  407  409     0.000 0.0 1   0.000 180.0 2   0.800 0.0 3
torsion    404  404  404  350    -0.610 0.0 1   4.210 180.0 2   0.000 0.0 3
torsion    413  404  404  350     0.000 0.0 1   6.100 180.0 2   0.000 0.0 3
torsion    352  350  404  404    -0.495 0.0 1   0.720 180.0 2  -0.484 0.0 3
torsion    351  350  404  404     0.000 0.0 1   0.000 180.0 2  -0.090 0.0 3
torsion    404  350  352  354    -2.284 0.0 1   1.340 180.0 3   0.000 0.0 3
torsion    404  350  352  417    -3.229 0.0 1   0.588 180.0 2   0.000 0.0 3
torsion    404  350  352  353     0.000 0.0 1   0.000 180.0 2   0.500 0.0 3
torsion    351  350  352  354     0.000 0.0 1   0.000 180.0 2   0.500 0.0 3
torsion    351  350  352  417     0.000 0.0 1   0.000 180.0 2   0.180 0.0 3
torsion    351  350  352  353     0.000 0.0 1   0.000 180.0 2   0.299 0.0 3
torsion    352  354  417  419     0.000 0.0 1   0.000 180.0 2   0.000 0.0 3
torsion    352  354  417  416     0.000 0.0 1   0.000 180.0 2   0.000 0.0 3
torsion    355  354  417  419     0.000 0.0 1   0.000 180.0 2   0.235 0.0 3
torsion    355  354  417  416     0.000 0.0 1   0.000 180.0 2  -0.010 0.0 3
torsion    350  352  354  417    -0.536 0.0 1   0.869 180.0 2  -0.995 0.0 3
torsion    417  352  354  417    -2.457 0.0 1   0.853 180.0 2  -0.025 0.0 3
torsion    353  352  354  417     0.000 0.0 1   0.000 180.0 2   0.500 0.0 3
torsion    350  352  354  355     0.000 0.0 1   0.000 180.0 2   0.500 0.0 3
torsion    417  352  354  355     0.000 0.0 1   0.000 180.0 2   0.500 0.0 3
torsion    353  352  354  355     0.000 0.0 1   0.000 180.0 2   0.500 0.0 3
torsion    424  416  417  354    -1.000 0.0 1   2.000 180.0 2   2.000 0.0 3
torsion    418  416  417  354     0.000 0.0 1   1.000 180.0 2   0.800 0.0 3
torsion    350  352  417  419    -3.000 0.0 1   0.000 180.0 2   0.000 0.0 3
torsion    350  352  417  416     3.000 0.0 1   0.000 180.0 2   0.000 0.0 3
torsion    354  352  417  419    -1.150 0.0 1   0.000 180.0 2   1.280 0.0 3
torsion    354  352  417  416     0.000 0.0 1   0.000 180.0 2   0.300 0.0 3
torsion    353  352  417  419     0.000 0.0 1   0.000 180.0 2   0.000 0.0 3
torsion    353  352  417  416     0.000 0.0 1   0.000 180.0 2   0.000 0.0 3
torsion    424  416  417  352    -1.000 0.0 1   2.000 180.0 2   2.000 0.0 3
torsion    418  416  417  352     0.000 0.0 1   1.000 180.0 2   0.800 0.0 3
torsion    352  417  416  421    -1.000 0.0 1   2.000 180.0 2   2.000 0.0 3
#polarizability #atom type #polarizability #polarize group
polarize   401   0.837   402
polarize   402   1.828   401   403
polarize   403   0.837   402
polarize   404   1.334   405
polarize   405   1.334   404   406   421
```

```
polarize   406   1.334   405   407   422
polarize   407   1.334   406
polarize   408   1.334   409   414   415   423
polarize   409   1.334   408   414   424
polarize   410   1.334   411   444
polarize   411   0.837   410
polarize   414   1.334   408   409   425
polarize   423   0.496   408
polarize   424   0.496   409
polarize   425   0.496   414
polarize   350   1.334   352   351
polarize   354   1.334   355
polarize   352   1.334   350   353
polarize   351   0.496   350
polarize   355   0.496   354
polarize   353   0.496   352
#multipole #atom type #local frames #monopole,dipole,quadrupole
multipole   401  402  401          -1.02024
                        -0.00509    0.00000    0.02124
                        -0.21597
                         0.00000   -0.20175
                         0.10909    0.00000    0.41772
multipole   402  403  404           1.75484
                         0.02795    0.00000    0.29813
                         0.12864
                         0.00000   -0.01112
                         0.16427    0.00000   -0.11752
multipole   403  402  404          -0.65419
                         0.15410    0.00000    0.04551
                         0.08581
                         0.00000    0.13303
                        -0.03766    0.00000   -0.21884
multipole   404  403  405           0.30569
                        -0.05638    0.00000   -0.10878
                        -0.02058
                         0.00000    0.15420
                        -0.02871    0.00000   -0.13362
multipole   405  404  406          -0.15435
                        -0.09942    0.00000   -0.37999
                        -0.05282
                         0.00000   -0.39415
                        -0.40538    0.00000    0.44697
multipole   406  405 -407           0.15385
                         0.15153    0.00000    0.52078
                        -0.72529
                         0.00000   -0.95398
```

```
                    -0.01560    0.00000    1.67927
multipole   407  406 -406          -0.14822
                     0.06758    0.00000   -0.44854
                     0.49878
                     0.00000   -0.50762
                    -0.84078    0.00000    0.00884
multipole   408  407  409          -0.01053
                     0.25957    0.00000   -0.42521
                     0.61143
                     0.00000   -0.42324
                    -0.39716    0.00000   -0.18819
multipole   409  410  408          -0.12452
                     0.26921    0.00000   -0.05962
                    -0.34013
                     0.00000   -0.52238
                    -0.54093    0.00000    0.86251
multipole   410  411  444           0.75664
                     0.16992    0.00000    0.40025
                     0.37203
                     0.00000    0.26442
                     0.01882    0.00000   -0.63645
multipole   411  410  444          -0.77899
                    -0.04005    0.00000   -0.15258
                    -0.24470
                     0.00000    0.13023
                    -0.07153    0.00000    0.11447
multipole   414  415  408          -0.27531
                     0.06593    0.00000    0.02909
                     0.11429
                     0.00000   -0.12510
                    -0.60512    0.00000    0.01081
multipole   423  408  407           0.05149
                    -0.01080    0.00000   -0.00337
                     0.02311
                     0.00000   -0.13107
                    -0.03020    0.00000    0.10796
multipole   424  409  408           0.08718
                    -0.05374    0.00000    0.08463
                    -0.02788
                     0.00000   -0.22397
                     0.11821    0.00000    0.25185
multipole   425  414  408           0.08030
                    -0.12310    0.00000   -0.17009
                    -0.13346
                     0.00000    0.23636
                    -0.05699    0.00000   -0.10290
```

```
multipole   428  430   354        0.85068
                      -0.01685    0.00000    0.27745
                       0.29463
                       0.00000   -0.41598
                      -0.00743    0.00000    0.12135
multipole   428  430   352        0.85068
                      -0.01685    0.00000    0.27745
                       0.29463
                       0.00000   -0.41598
                      -0.00743    0.00000    0.12135
multipole   430  428   352       -0.77770
                      -0.01897    0.00000   -0.21786
                      -0.61542
                       0.00000    0.33936
                       0.00866    0.00000    0.27606
multipole   430  428   354       -0.77770
                      -0.01897    0.00000   -0.21786
                      -0.61542
                       0.00000    0.33936
                       0.00866    0.00000    0.27606
multipole   350  407   352       -0.07300
                       0.54428    0.00000   -0.21148
                       0.55213
                       0.00000   -0.40597
                      -0.31298    0.00000   -0.14616
multipole   354  428   352       -0.12505
                       0.35636    0.00000    0.12083
                       0.85801
                       0.00000   -0.71012
                      -0.17159    0.00000   -0.14789
multipole   352  428   350       -0.42976
                       0.05048    0.00000    0.10288
                       0.24143
                       0.00000   -0.23770
                      -0.12466    0.00000   -0.00373
multipole   351  350   407        0.03751
                      -0.00850    0.00000   -0.09826
                      -0.15828
                       0.00000    0.18088
                      -0.03180    0.00000   -0.02260
multipole   355  354   428        0.08131
                       0.03321    0.00000   -0.08398
                       0.10608
                       0.00000    0.13680
                       0.09275    0.00000   -0.24288
multipole   353  352   350        0.07719
```

-0.02946	0.00000	0.06650
0.06868		
0.00000	0.22176	
-0.26490	0.00000	-0.29044

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