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Biomolecular Conformational Changes and Ligand Binding: From Kinetics to Thermodynamics

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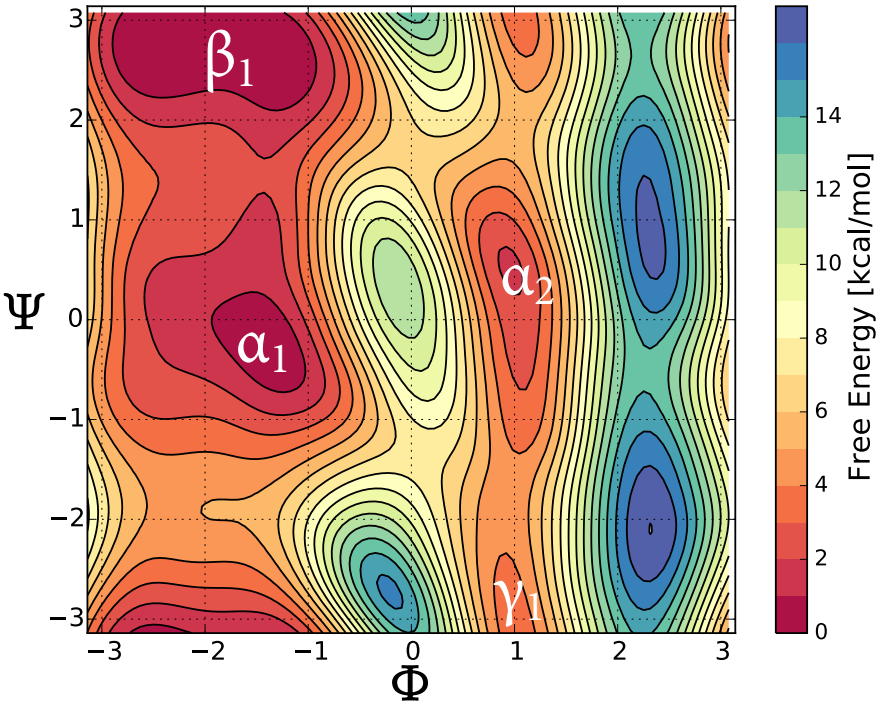

Fig. S1 Potential of mean force of the Ala2 model system. The PMF was obtained from metadynamics simulations using Φ and Ψ as CVs. Four metastable states (α_1, β_1, γ_1 and α_2) are labelled.

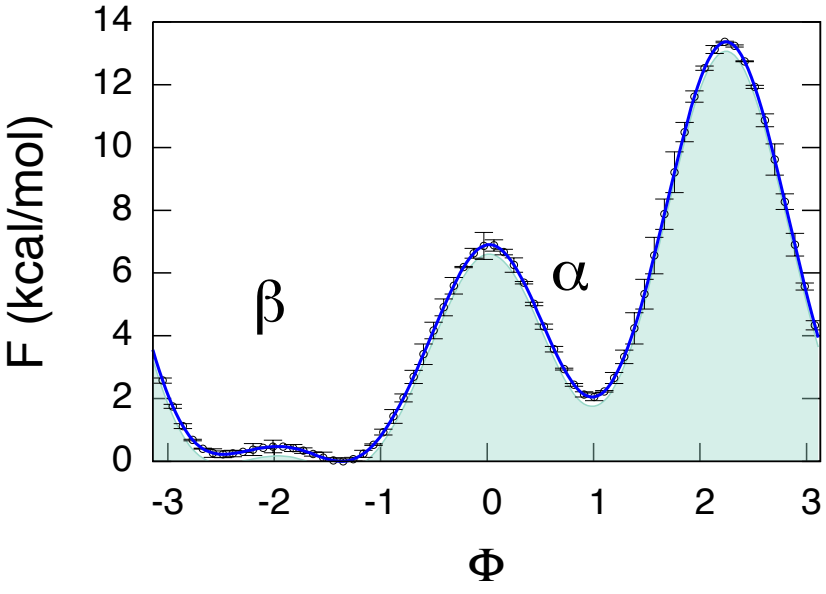

Fig. S2 Potential of mean force as a function Φ of Ala2 in implicit solvent at 300K. For simplicity, the system is coarse grained into two stable states, α and β, as labelled. The free energy difference $\Delta G_{\alpha-\beta}$ is 2.6±0.1 kcal/mol as obtained by the summation of the populations on the two sides of the barrier.

Table S1 Comparison between τ and the mean time $\mu = \frac{\sum_{i=1}^{n} t_i}{n}$

	τ	μ
$A \rightarrow B$	27.5±5.1 ns	26.7±3.5 ns
$B \rightarrow A$	1.4±0.5 ns	1.7±0.4 ns
$A \rightarrow C$	722.4±136.6 ns	643.3±89.5 ns
$C \rightarrow A$	6.9±0.9 ns	6.1±0.8 ns
$A \rightarrow D$	10.7±2.0 μs	4.1±0.5 μs [a]
$D \rightarrow A$	7.7±1.0 ns	6.0±0.6 ns
$B \rightarrow C$	23.3±4.7 ns	21.3±3.3 ns
$C \rightarrow B$	3.0±0.6 ns	2.9±0.4 ns
$B \rightarrow D$	709.7±130.0 ns	661.6±74.2 ns
$D \rightarrow B$	6.1±1.6 ns	4.6±0.5 ns
$C \rightarrow D$	8.1±1.4 ns	7.9±1.0 ns
$D \rightarrow C$	0.5±0.1 ns	0.6±0.1 ns

[a] The mean time for the $A \rightarrow D$ transitions are underestimated when simply calculating the average because not all simulations resulted in successful transitions. As described in the main text, we instead used the maximum-likelihood estimator that takes this into account.

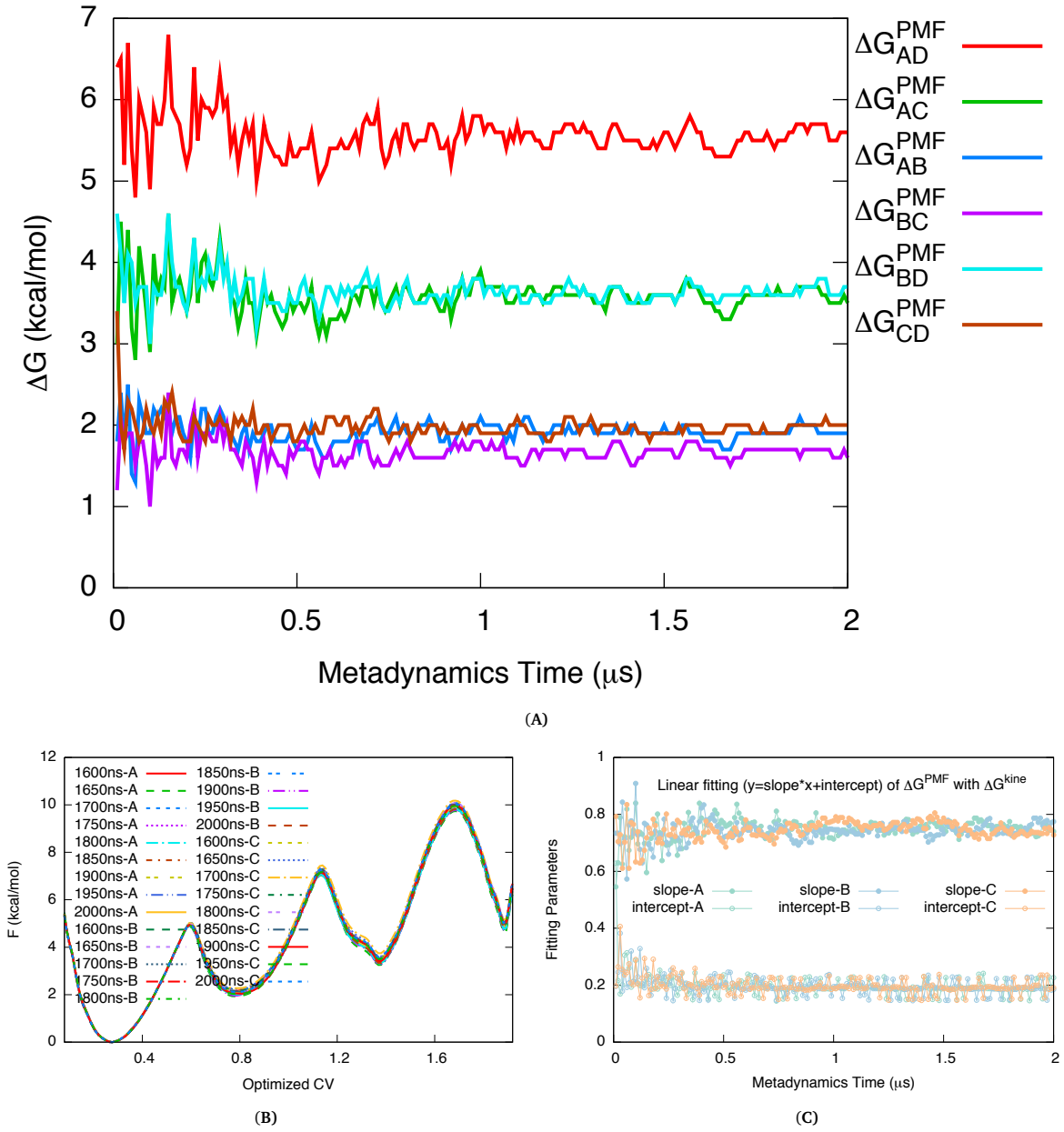

Fig. S3 Convergence of the estimated ΔG^{PMF} of the five-residue peptide during the well-tempered metadynamics simulation. (A) The time evolution of ΔG_{RP}^{PMF} in metadynamics simulation in the first of three independent metadynamics simulations (named A, B and C). (B) The PMF curves of the last 400 ns of the three metadynamics simulations. (C) The slopes and intercepts of the linear fit of ΔG^{kine} and ΔG^{PMF} as a function of simulation time.

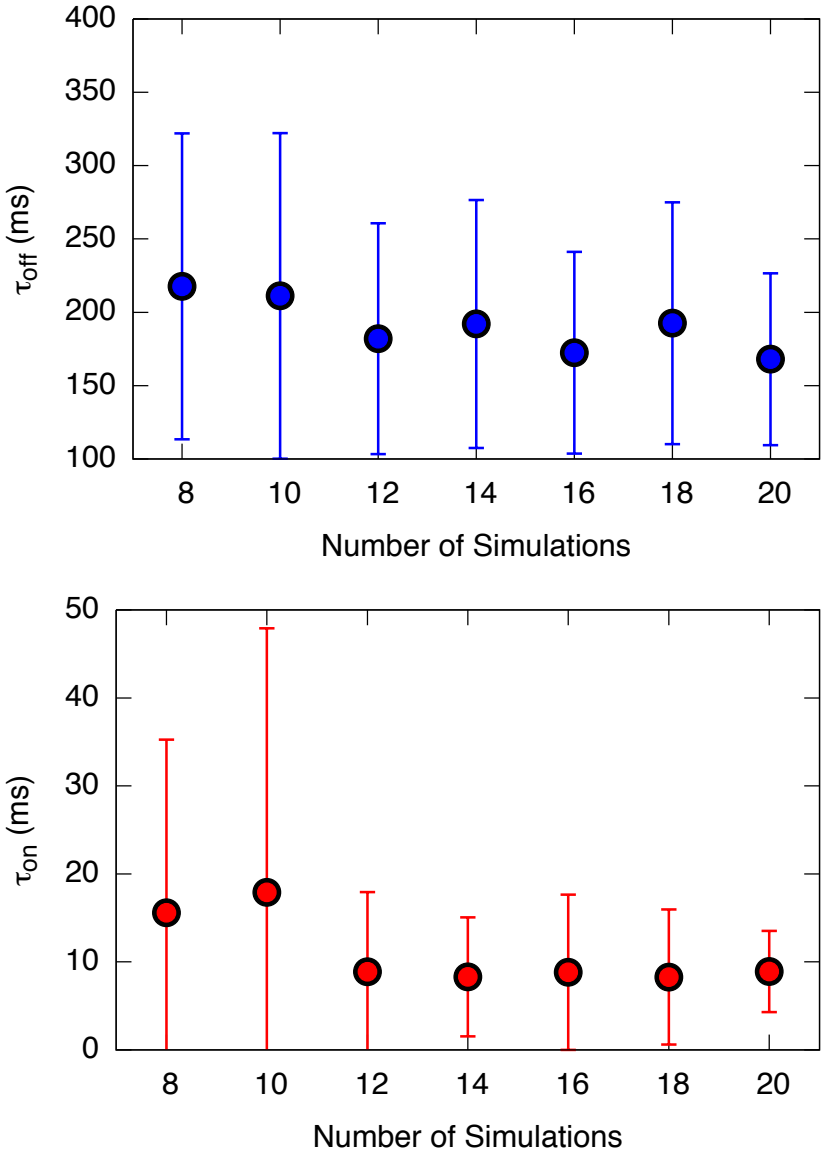

Fig. S4 Association and dissociation times for benzene and L99A T4L as a function of number of independent simulations. Error bars represent the standard deviation of τ obtained from a bootstrap analysis with 50 subsamples.

PLUMED settings of MetaD Simulation of Ace-Ala3-Nme

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FLUSH STRIDE=500

ALPHABETA ...
ATOMS1=@phi-2 REFERENCE=1.25
LABEL=c1
... ALPHABETA

ALPHABETA ...
ATOMS1=@psi-2 REFERENCE=1.25
LABEL=c2
... ALPHABETA

ALPHABETA ...
ATOMS1=@phi-3 REFERENCE=1.25
LABEL=c3
... ALPHABETA

ALPHABETA ...
ATOMS1=@psi-3 REFERENCE=1.25
LABEL=c4
... ALPHABETA

ALPHABETA ...
ATOMS1=@phi-4 REFERENCE=1.25
LABEL=c5
... ALPHABETA

ALPHABETA ...
ATOMS1=@psi-4 REFERENCE=1.25
LABEL=c6
... ALPHABETA

COMBINE LABEL=sum_abs ARG=c1,c2,c3,c4,c5,c6 POWERS=1,1,1,1,1,1
COEFFICIENTS=0.6228,0.1201,0.5643,0.1102,0.5153,0.0403 PERIODIC=NO

METAD ...
 ARG=sum_abs
 HEIGHT=2.0
 BIASFACTOR=25
 TEMP=300.0
 SIGMA=0.03
 PACE=500
 LABEL=WTMetaD
... METAD

PRINT STRIDE=500 ARG=* FILE=COLVAR
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PLUMED settings of InMetaD Simulation of Ace-Ala3-Nme

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MOLINFO MOLTYPE=protein STRUCTURE=Ref.pdb

FLUSH STRIDE=500

ALPHABETA ATOMS1=@phi-2 REFERENCE=1.25 LABEL=c1
ALPHABETA ATOMS1=@phi-3 REFERENCE=1.25 LABEL=c3
ALPHABETA ATOMS1=@phi-4 REFERENCE=1.25 LABEL=c5
ALPHABETA ATOMS1=@psi-2 REFERENCE=1.25 LABEL=c2
ALPHABETA ATOMS1=@psi-3 REFERENCE=1.25 LABEL=c4
ALPHABETA ATOMS1=@psi-4 REFERENCE=1.25 LABEL=c6

COMBINE LABEL=sum_abs ARG=c1,c2,c3,c4,c5,c6 POWERS=1,1,1,1,1,1
COEFFICIENTS=0.6228,0.1201,0.5643,0.1102,0.5153,0.0403 PERIODIC=NO

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 ARG=sum_abs
 HEIGHT=0.4
 BIASFACTOR=25
 TEMP=300.0
 SIGMA=0.04
 PACE=10000
 GRID_MIN=-0.02 GRID_MAX=2.0 GRID_BIN=200
 LABEL=WTMetaD

 ACCELERATION
... METAD

COMMITTOR ...
  ARG=sum_abs
  STRIDE=5000
  BASIN_LL1=1.85
  BASIN_UL1=2.0
... COMMITTOR

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PLUMED settings of InMetaD simulations of L99A T4L-BNZ

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WHOLEMOLECULES ENTITY0=1-2881

cavity: COM ATOMS=1668,1728,1804,1867,1925,1980,2052
lig: COM ATOMS=2870,2872,2874

D1: DISTANCE ATOMS=1347,lig
D2: DISTANCE ATOMS=1457,lig
D3: DISTANCE ATOMS=1515,lig
D4: DISTANCE ATOMS=1533,lig
D5: DISTANCE ATOMS=1582,lig
D6: DISTANCE ATOMS=1720,lig
D7: DISTANCE ATOMS=1776,lig
D8: DISTANCE ATOMS=1786,lig
D9: DISTANCE ATOMS=1907,lig
D10: DISTANCE ATOMS=2010,lig
D11: DISTANCE ATOMS=2076,lig
D12: DISTANCE ATOMS=2290,lig
D13: DISTANCE ATOMS=2668,lig
D14: DISTANCE ATOMS=1954,lig
D15: DISTANCE ATOMS=2349,lig
D16: DISTANCE ATOMS=1999,lig
D17: DISTANCE ATOMS=cavity,lig

rmsd: RMSD REFERENCE=LigRMSDRef.pdb TYPE=OPTIMAL

CONTACTMAP ...
ATOMS1=1347,lig  REFERENCE1=1.0  WEIGHT1=1.0
ATOMS2=1457,lig  REFERENCE2=1.0  WEIGHT2=1.0
ATOMS3=1515,lig  REFERENCE3=1.0  WEIGHT3=1.0
ATOMS4=1533,lig  REFERENCE4=1.0  WEIGHT4=1.0
ATOMS5=1582,lig  REFERENCE5=1.0  WEIGHT5=1.0
ATOMS6=1720,lig  REFERENCE6=1.0  WEIGHT6=1.0
ATOMS7=1776,lig  REFERENCE7=1.0  WEIGHT7=1.0
ATOMS8=1786,lig  REFERENCE8=1.0  WEIGHT8=1.0
ATOMS9=1907,lig  REFERENCE9=1.0  WEIGHT9=1.0
ATOMS10=2010,lig REFERENCE10=1.0 WEIGHT10=1.0
ATOMS11=2076,lig REFERENCE11=1.0 WEIGHT11=1.0
ATOMS12=2290,lig REFERENCE12=1.0 WEIGHT12=1.0
ATOMS13=2668,lig REFERENCE13=1.0 WEIGHT13=1.0

#F114_CZ -- COM of BNZ
ATOMS14=1954,lig REFERENCE14=0.0 WEIGHT14=1.0
ATOMS15=2349,lig REFERENCE15=0.0 WEIGHT15=1.0
ATOMS16=1999,lig REFERENCE16=0.0 WEIGHT16=1.0

# NTD-BNZ
ATOMS17=cavity,lig  REFERENCE17=1.0 WEIGHT17=2.8

SWITCH1={RATIONAL R_0=0.60 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
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SWITCH2={RATIONAL R_0=0.62 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH3={RATIONAL R_0=0.54 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH4={RATIONAL R_0=0.62 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH5={RATIONAL R_0=0.59 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH6={RATIONAL R_0=0.40 D_0=0.1 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH7={RATIONAL R_0=0.64 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH8={RATIONAL R_0=0.72 D_0=0.3 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH9={RATIONAL R_0=0.60 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH10={RATIONAL R_0=0.61 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH11={RATIONAL R_0=0.70 D_0=0.3 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH12={RATIONAL R_0=0.94 D_0=0.3 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH13={RATIONAL R_0=0.50 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH14={RATIONAL R_0=0.60 D_0=0.2 NN=6 MM=10 D_MAX=1.5 STRETCH}
SWITCH15={RATIONAL R_0=0.60 D_0=0.2 NN=6 MM=10 D_MAX=1.5 STRETCH}
SWITCH16={RATIONAL R_0=0.60 D_0=0.2 NN=6 MM=10 D_MAX=1.5 STRETCH}
SWITCH17={RATIONAL R_0=1.20 D_0=0.4 NN=6 MM=10 D_MAX=3.5 STRETCH}
#SWITCH17={RATIONAL R_0=0.40 D_0=0.2 NN=6 MM=20 D_MAX=1.5 STRETCH}
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CMDIST
... CONTACTMAP

CONTACTMAP ...
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ATOMS3=1515,lig  REFERENCE3=0.0  WEIGHT3=1.0
ATOMS4=1533,lig  REFERENCE4=0.0  WEIGHT4=1.0
ATOMS5=1582,lig  REFERENCE5=0.0  WEIGHT5=1.0
ATOMS6=1720,lig  REFERENCE6=0.0  WEIGHT6=1.0
ATOMS7=1776,lig  REFERENCE7=0.5  WEIGHT7=1.0
ATOMS8=1786,lig  REFERENCE8=0.0  WEIGHT8=1.0
ATOMS9=1907,lig  REFERENCE9=0.0  WEIGHT9=1.0
ATOMS10=2010,lig REFERENCE10=0.0 WEIGHT10=1.0
ATOMS11=2076,lig REFERENCE11=0.0 WEIGHT11=1.0
ATOMS12=2290,lig REFERENCE12=0.5 WEIGHT12=1.0
ATOMS13=2668,lig REFERENCE13=0.0 WEIGHT13=1.0

#F114_CZ -- COM of BNZ
ATOMS14=1954,lig REFERENCE14=1.0 WEIGHT14=3.0
ATOMS15=2349,lig REFERENCE15=1.0 WEIGHT15=2.0
ATOMS16=1999,lig REFERENCE16=1.0 WEIGHT16=1.0

# NTD-BNZ
ATOMS17=cavity,lig  REFERENCE17=1.0 WEIGHT17=1.0

SWITCH1={RATIONAL R_0=0.60 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
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SWITCH7={RATIONAL R_0=0.64 D_0=0.2 NN=6 MM=20 D_MAX=2.0 STRETCH}
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SWITCH11={RATIONAL R_0=0.70 D_0=0.3 NN=6 MM=20 D_MAX=2.0 STRETCH}
SWITCH12={RATIONAL R_0=0.94 D_0=0.3 NN=6 MM=20 D_MAX=2.0 STRETCH}
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SWITCH15={RATIONAL R_0=0.60 D_0=0.2 NN=6 MM=10 D_MAX=1.5 STRETCH}
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ATOMS4=1533,lig  REFERENCE4=0.0  WEIGHT4=1.0
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ATOMS8=1786,lig  REFERENCE8=0.0  WEIGHT8=1.0
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ATOMS11=2076,lig REFERENCE11=0.0 WEIGHT11=1.0
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#F114_CZ -- COM of BNZ
ATOMS14=1954,lig REFERENCE14=0.0 WEIGHT14=1.0
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SWITCH16={RATIONAL R_0=0.60 D_0=0.2 NN=6 MM=10 D_MAX=1.5 STRETCH}
SWITCH17={RATIONAL R_0=1.20 D_0=0.4 NN=6 MM=10 D_MAX=3.5 STRETCH}

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CMDIST
... CONTACTMAP

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p2: PATHMSD REFERENCE=path.pdb LAMBDA=56.0

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TEMP=298
HEIGHT=0.2
FILE=HILLS
FMT=%12.4f
LABEL=meta

PACE=25000
ACCELERATION

... METAD

COMMITTOR ...
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STRIDE=50000
BASIN_LL1=2.6
BASIN_UL1=10.0
... COMMITTOR

PRINT ARG=* STRIDE=250 FILE=COLVAR FMT=%10.3f
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