Speed of conformational change: comparing explicit and implicit solvent molecular dynamics simulations
Supporting Material

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Methods

The use of effective Born radius as a metric of atom burial.

By definition, the effective Born radius B (see Eq. (4)) of a charge (atom) is inversely proportional to the desolvation penalty of taking it from water into the low dielectric interior of the protein, in the absence of all other charges. Thus, in general, one expects the degree of atom's burial δ beneath the molecular surface to correlate with its effective Born radius. In fact (1), for a perfect sphere of radius A inside a high dielectric solvent, the effective radius $B = A(1 - (\delta - A)^2/A^2)$, which increases monotonically with δ. Near the surface, R is directly proportional to the degree of burial. For non-spherical shapes and deeply buried groups the relationship is less linear and more of an approximation.

Simulation protocol

The following protocol was used for MD simulations, unless otherwise stated in the text. The simulations consisted of five stages – minimization, heating, two equilibration stages and the production stage. The Amber12 script for each of these stages is shown below. "xxx" in the following refers to the number of solute groups.

```
Minimization - PME
 &cntrl
  imin=1,           ! mimimize
  maxcyc=2000,      ! number of minimization steps
  ntb=1,            ! with periodic box
  igb=0,            ! pme
  cut=8,            ! cutoff for electrostatics
  ntr=1,            ! use restraints
  ntx=1,            ! input: formatted coord only
  irest=0,          ! input: not a restart file
  ntpr=10,          ! output: print every 10 steps
  ntwx=0,           ! output: no trajectory
  ntwr=500000,      ! output: restart file written at the end
  iwrap=0,          ! output: do not wrap coord in restart/traj (for pme)
 /
RESTRAIN ALL
5.0
RES 1 xxx
END

Minimization - GB
```


0006-3495/08/09/2624/12 $2.00

```
 &cntrl
  imin=1,           ! mimimize
  maxcyc=2000,      ! run for n steps of minimization
  ntb=0,            ! no box
  igb=5,            ! OBC gb
  cut=9999.0,       ! no cutoff for electrostatics
  rgbmax=15.0,      ! gb: cutoff for Born radii
  saltcon=0.145,    ! gb: salt concentration
  gbsa=0,           ! gb: do not include surface area term
  ntr=1,            ! use restraints
  ntx=1,            ! input: formatted coord only
  irest=0,          ! input: not a restart
  ntpr=10,          ! output: print every 10 steps
  ntwe=0,           ! output: do not write energy and temperature file
  ntwx=0,           ! output: no trajectory
  ntwprt=0,         ! output: all atoms written to traj
  ntwr=500000,      ! output: restart file written at the end
 /
RESTRAIN ALL
5.0
RES 1 9999
END

Heating - PME
 &cntrl
  imin=0,           ! MD, not mimimization
  ig=-1,            ! random seed based on date/time
  nstlim=300000,    ! number of steps
  dt=0.002,         ! time step (ps)
  ntc=2,            ! shake: constrain H bonds
  ntf=2,            ! shake: ignore H bond interactions
  ntt=3,            ! 3 = langevin dynamics
  gamma_ln=0.01,    ! collision frequency for langevin dynamics
  tempi=0.0,        ! initial temperature
  temp0=300.0,      ! reference temperature
  ntp=0,            ! no pressure scaling (const volume)
  ntb=1,            ! periodic boundary for const volume md
  igb=0,            ! pme
  cut=8.0,          ! cutoff for electrostatics
  ntr=1,            ! use restraints
  ntx=1,            ! input: formatted coord only
  irest=0,          ! input: not a restart
  ntpr=500,         ! output: print every 500 steps
  ntwx=0,           ! output: no trajectory
  ntwprt=0,         ! output: all atoms written to traj
  ntwr=500000,      ! output: restart file written at the end
  iwrap=0,          ! output: do not wrap coord in restart/traj (for pme)
 /
RESTRAIN ALL
1.0
RES 1 xxx
END

Heating - GB
 &cntrl
```

```
  imin=0,           ! MD, not mimimization
  ig=-1,            ! random seed based on date/time
  nstlim=300000,    ! number of  steps
  dt=0.002,         ! time step (ps)
  ntc=2,            ! shake: constrain H bonds
  ntf=2,            ! shake: ignore H bond interactions
  ntt=3,            ! 3 = langevin dynamics
  gamma_ln=0.01,    ! collision frequency for langevin dynamics
  tempi=0.0,        ! initial temperature
  temp0=300.0,      ! reference temperature
  ntp=0,            ! no pressure scaling (const volume)
  ntb=0,            ! no box
  igb=5,            ! OBC gb
  cut=9999.0,       ! no cutoff for electrostatics
  rgbmax=15.0,      ! gb: cutoff for Born radii
  saltcon=0.145,    ! gb: salt concentration
  gbsa=0,           ! gb: include surface area term
  ntr=1,            ! use restraints
  ntx=1,            ! input: formatted coord only
  irest=0,          ! input: not a restart
  ntpr=50,          ! output: print every n steps
  ntwe=0,           ! output: do not write energy and temperature file
  ntwx=0,           ! output: no trajectory
  ntwprt=0,         ! output: n atoms written to traj (0=all atoms)
  ntwr=500000,      ! output: restart file written at the end
 /
RESTRAIN ALL
1.0
RES 1 9999
END

Equilibration 1 PME - Only differences from Heating are shown here
  nstlim=1000000,   ! number of  steps
  tempi=300.0,      ! initial temperature
  ntp=1,            ! isotropic pressure scaling (const pressure)
  ntb=2,            ! periodic boundary condition for const pressure md
/
RESTRAIN ALL
0.1

Equilibration 1 GB - Only differences from Heating are shown here
  nstlim=1000000,   ! number of  steps
  tempi=300.0,      ! initial temperature
/
RESTRAIN ALL
0.1

Equilibration 2 - Only differences from Equilibration 1 are shown here
RESTRAIN ALL
0.01

Production - Only differences from Equilibration 2 are shown here
  nstlim=100000000, ! number of  steps
  ntr=0,            ! no restraints
```

Calculation of standard error

Standard error se of the mean is calculated as $se = \sigma/\sqrt{n}$, where σ is the standard deviation and n is the number of samples. For the product or ratio of two means, the standard error in the resulting product ($f = m_1 m_2$) or ratio ($f = m_1/m_2$) is calculated as:

$$se_f = f\sqrt{\left(\frac{se_1}{m_1}\right)^2 + \left(\frac{se_2}{m_2}\right)^2} \quad (1)$$

where se_f is the standard error of the resulting product or ratio of the mean values m_1 and m_2 with standard errors of se_1 and se_2 respectively.

Results and discussion

Analysis of dihedral angle flips

We analyzed the relationship between frequency of dihedral angle flips and (1) depth of burial within the protein as measured by effective Born radii, (2) extent of hydrogen bonding between side chains and water as measured by percent of samples with such hydrogen bonds, (3) difference in side-chain conformation as measured by residue RMSD, and (4) type of side-chain. However, the correlations in each of these cases were not statistically significant. Figure 1 shows that there is little correlation between residue burial depth and the difference between GB and PME χ_1/χ_2 dihedral angle flips – correlation coefficient $<$ 0.5. Figure 2 shows that there is little or no correlation between the difference in χ_1 and χ_2 dihedral flips and residue H-bonds

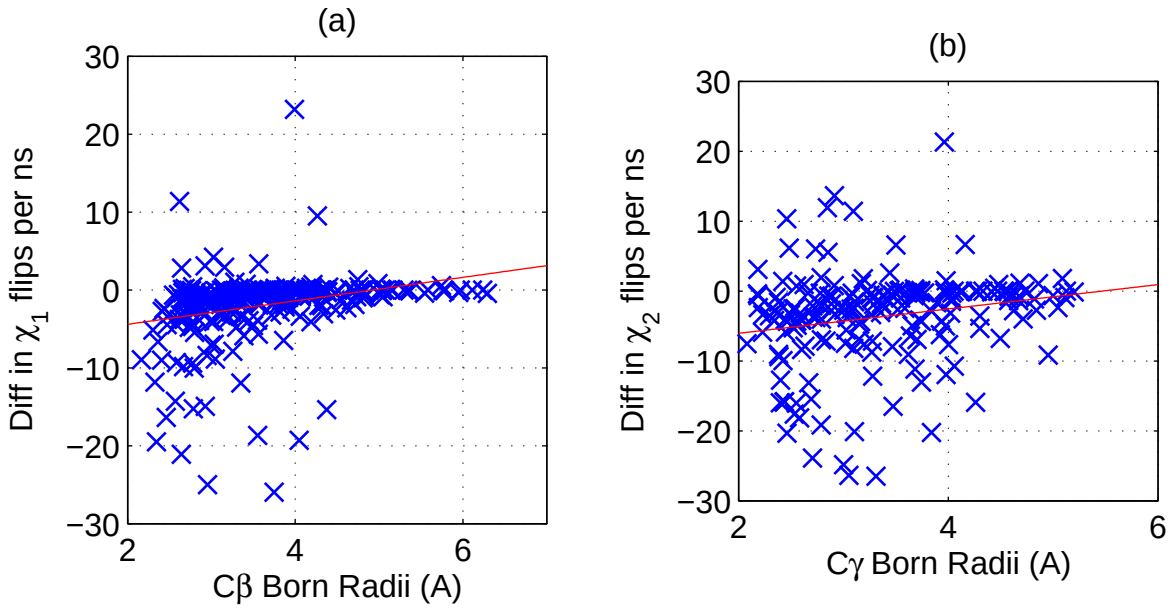

Figure 1: Difference in frequency of χ_1 and χ_2 dihedral angle flips as a function of residue burial depth. Depth of burial is measured as the Born radius of a residue's C_β atom for (a) χ_1 angles, and as the C_γ atom for (b) χ_2 angles.

(correlation coefficient $<$ 0.1). Figure 3 shows that there is little correlation between side chain flexibility as measured by per residue RMS difference, and χ_1 or χ_2 dihedral angle flips (correlation coefficient $<$ 0.5). Figure 4 shows that, excluding outliers, on average there is no significant difference in the frequency of χ_1/χ_2 dihedral angle flips.

For the 770 ns simulations considered here, the GB simulation explores different conformations than the explicit solvent (TIP3P) PME simulation. Figure 5 shows that the backbone RMSD relative to the starting structure is 1.6 Å for the explicit solvent (TIP3P) PME simulation compared to 4.5 Å for the GB simulation. Therefore to compare the χ_1 and χ_2 angles for the two simulations on an equal footing, we only considered groups where the distribution of the χ_1 and χ_2 angles were similar for the GB and explicit solvent (TIP3P) PME simulations, i.e. the frequency at which the dihedral angle ranges were sampled, differ by less than 10%. Figure 6 shows an example where the χ_1 and χ_2 angles sampled by the explicit solvent (TIP3P) PME and GB simulations are similar.

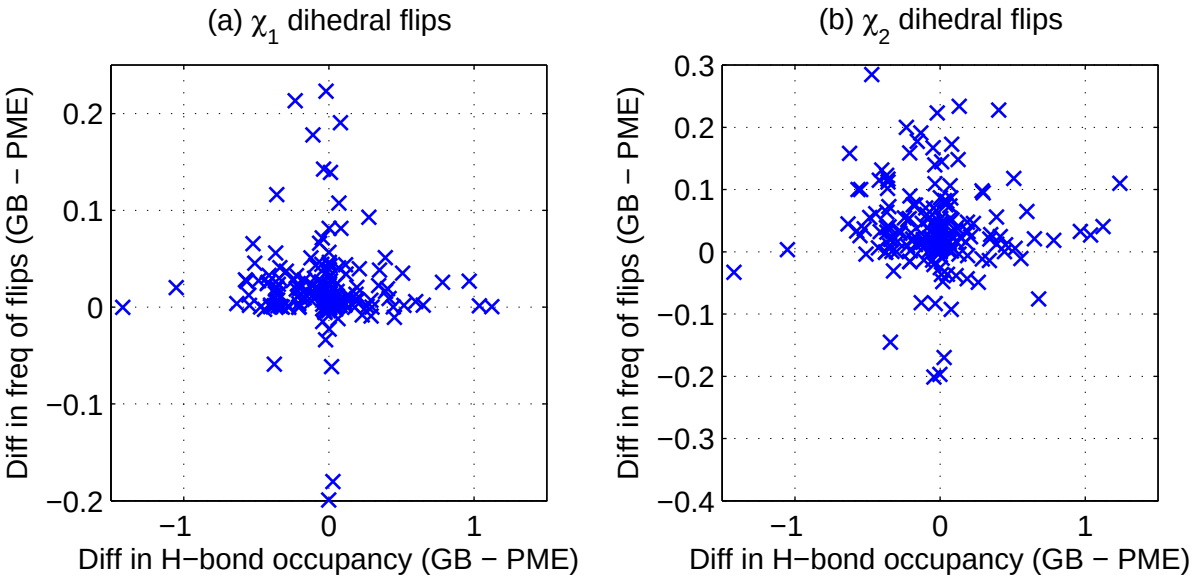

Figure 2: Difference (GB - PME) in χ_1 and χ_2 dihedral angle flips as a function of difference in H-bond occupancy.

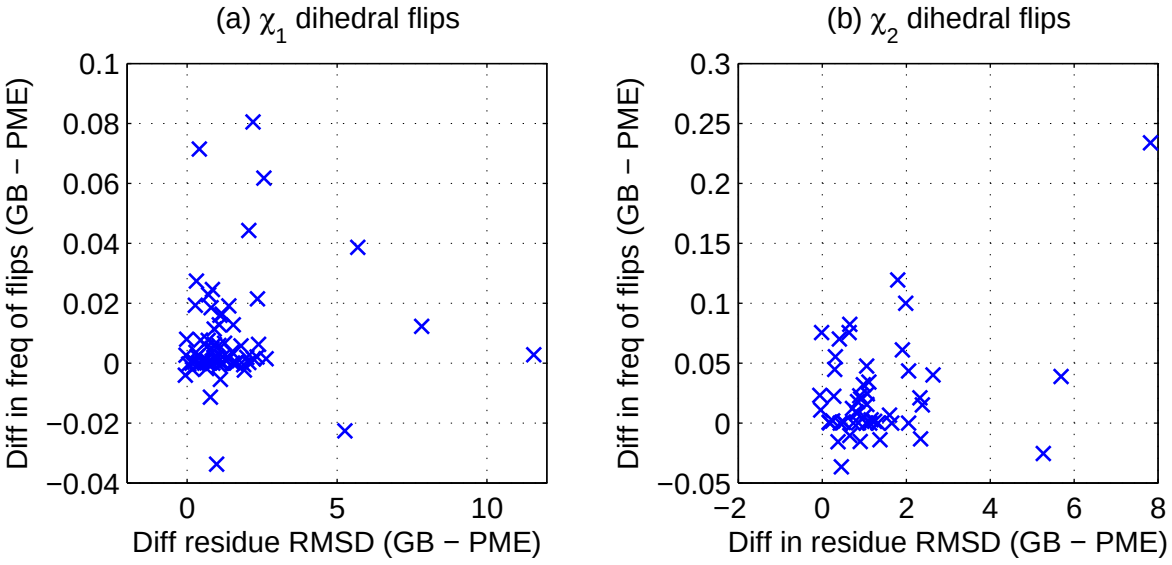

Figure 3: Difference in average frequency of χ_1 dihedral angle flips as a function of per residue RMS difference. RMS difference is measured relative to the backbone heavy atoms from the starting structure.

Free energy landscape temperature dependence

The CLN025 mini-protein folding simulations were run at the experimental melting temperature of 340 K. At this temperature the folded and unfolded states are expected to be sampled equally. However, due to limitations of the force fields and solvation models used, neither the explicit solvent TIP3P PME, nor the implicit solvent GB simulation equally sample the folded and unfolded states at the experimental melting temperature. For the GB model 260 K is more representative of the melting temperature, where the folded and unfolded states are sampled approximately equally ($\sim$ 11 and 15% respectively) (Fig. 7)

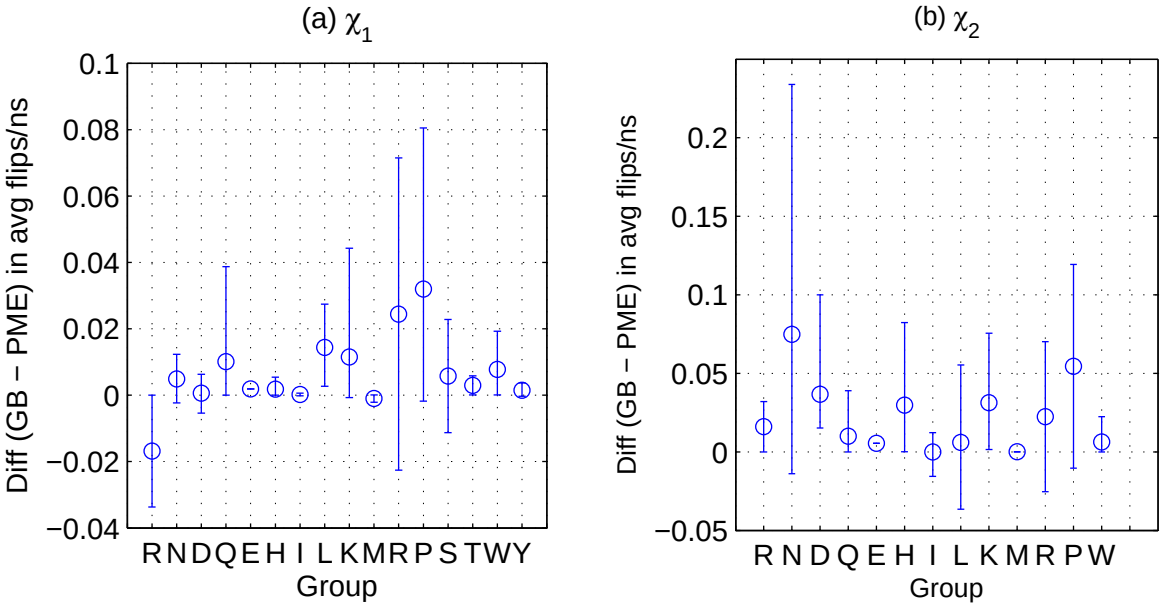

Figure 4: Difference (GB - PME) in average frequency of χ_1 and χ_2 dihedral angle flips as a function of residue type. Error bars indicate minimum and maximum values.

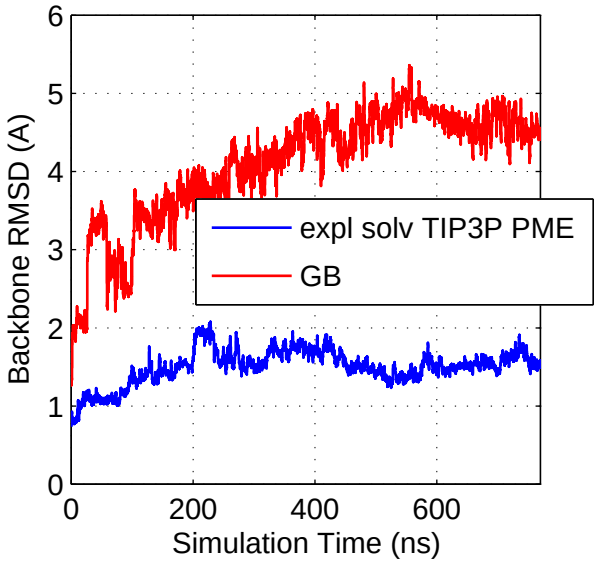

Figure 5: 770 ns simulations of 1GYM using the explicit solvent (TIP3P) PME and GB methods. Root mean square difference (RMSD) of backbone heavy atoms is relative to the starting structure. Figure shows moving average values averaged over 0.5 ns, with connecting lines shown to guide the eye.

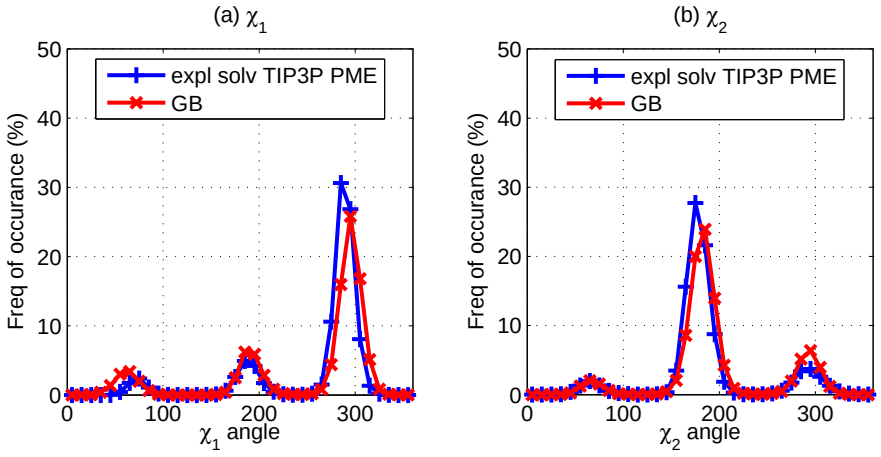

Figure 6: χ_1 and χ_2 angles sampled for residue GLN262 from the explicit solvent (TIP3P) PME and GB simulations of 1GYM. Both the explicit solvent (TIP3P) PME and GB simulations sample all three ranges of χ_1 and χ_2 angles, 0:120, 120:240, and 240:360. For calculating sampling frequency, the angles are grouped into 36 bins of 10 degrees each. Connecting lines are shown to guide the eye.

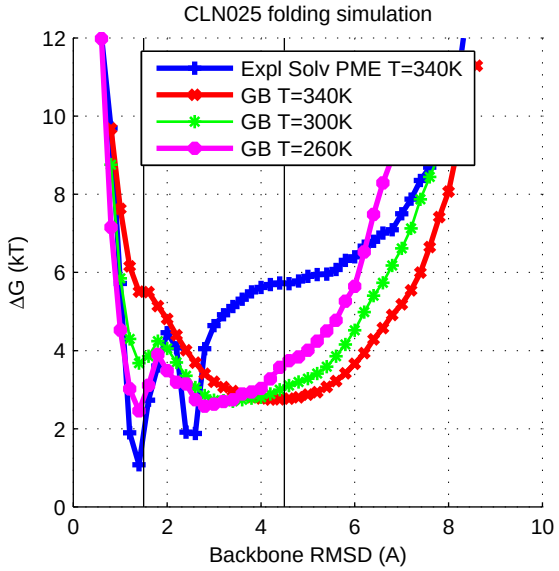

Figure 7: CLN025 mini-protein folding: Dependence of free energy landscape on temperature. GB simulations at T=340, 300 and 260K are shown with the explicit solvent TIP3P PME simulation at T=340K included for comparison. The horizontal lines represent RMSD = 1.5 and 4.5 Å. Folded states are states with RMSD $<$ 1.5 Å and unfolded states are states with RMSD $>$ 4.5 Å. The trajectory is sampled every 100 ps for calculating the RMSD values shown here.

References

1. Grycuk, T., 2003. Deficiency of the Coulomb-field approximation in the generalized Born model: An improved formula for Born radii evaluation. J. Chem. Phys. 119:4817–4826.