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Thermodynamics of DNA:Sensitizer recognition. Characterizing binding motifs with all-atom simulations

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Supplementary Information

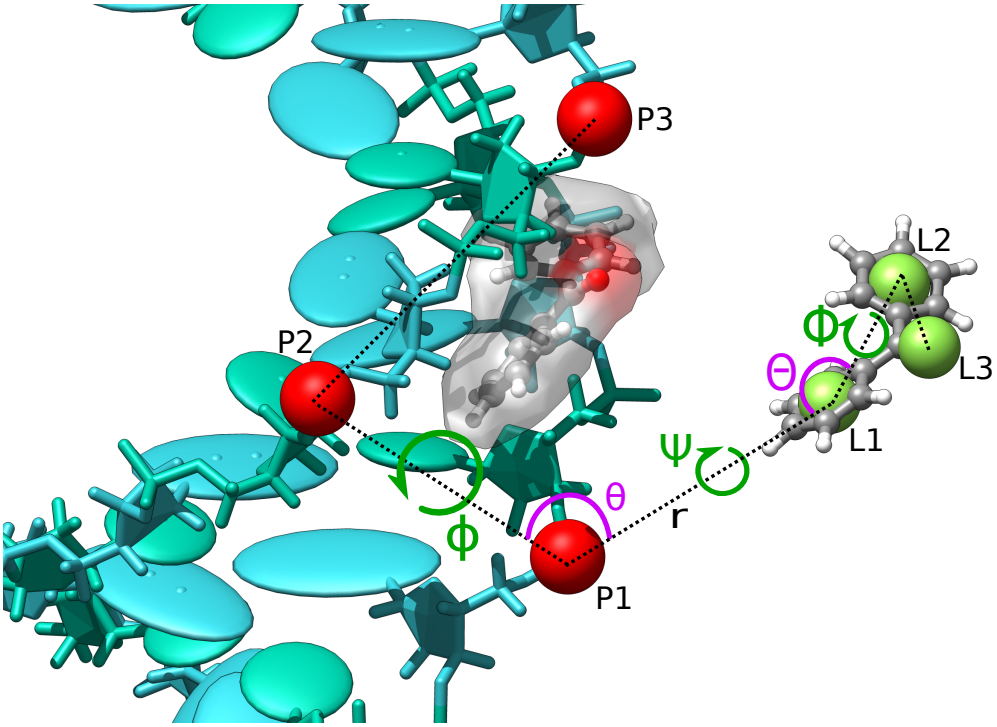

Figure 1: Representation of the set of parameters defining the position of BNZ bound to the minor groove. For both DNA and BNZ, a triplet of points, P1,P2,P3 (red spheres) and L1,L2,L3 (green spheres) respectively, is defined arbitrarily. The position of BNZ is defined by three spherical coordinates (r (P1-L1), θ (L1-P1-P2), ϕ (L1-P1-P2-P3)) whereas its relative orientation is described by three Euler angles (Θ (P1-L1-L2), Φ (P1-L1-L2-L3), Ψ (P2-P1-L1-L2)). For clarity, inserted BNZ (gray surface) has been splitted out of the complex.

Table 1: Harmonic restraints applied on DNA/BNZ in the DBI binding mode. Parameter equilibrium values and force constants are given.

r	L1-P1 = 7.7 Å ; k_r = 1.0 Å^{-2}
Θ	P1-L1-L2 = 160° ; k_Θ = 0.1 kcal.mol.Å^{-2}
Φ	P1-L1-L2-L3 = -45° ; k_Φ = 0.1 kcal.mol.Å^{-2}
Ψ	P2-P1-L1-L2 = -10°; k_Ψ = 0.1 kcal.mol.Å^{-2}
θ	L1-P1-P2 = 27° ; k_θ = 0.1 kcal.mol.Å^{-2}
ϕ	L1-P1-P2-P3 = 32° ; k_ϕ = 0.1 kcal.mol.Å^{-2}
RMSD	k_{RMSD} = 15. kcal.mol.Å^{-2}

Table 2: Harmonic restraints applied on DNA/BNZ in the minor groove binding mode. Parameter equilibrium values and force constants are given.

r	L1-P1 = 5.7 Å ; k_r = 1.0 Å^{-2}
Θ	P1-L1-L2 = 77° ; k_Θ = 0.1 kcal.mol.Å^{-2}
Φ	P1-L1-L2-L3 = -100° ; k_Φ = 0.1 kcal.mol.Å^{-2}
Ψ	P2-P1-L1-L2 = -174°; k_Ψ = 0.1 kcal.mol.Å^{-2}
θ	L1-P1-P2 = 74° ; k_θ = 0.1 kcal.mol.Å^{-2}
ϕ	L1-P1-P2-P3 = 9.0° ; k_ϕ = 0.1 kcal.mol.Å^{-2}
RMSD	k_{RMSD} = 7. kcal.mol.Å^{-2}

Analytical expressions for estimating the contribution of positional and orientational restraints to ΔG^{bulk}_{rest}. The constant C° insures conversion to the standard state concentration ($= 1/1661\text{Å}^3$). Equilibrium values and force constants of the harmonic potentials are given in Table 1 and Table 2.

$$\begin{aligned}
\Delta G^{bulk}_{r,\theta,\phi} &= -k_b T \ln(F_t C^\circ) \\
F_t &= \int_0^\infty dr r^2 \int_0^\pi d\theta \sin\theta \int_{-\pi}^{\pi} d\phi \exp^{-\beta u(r,\theta,\phi)} \\
u(r,\theta,\phi) &= \frac{1}{2}\Big(k_r(r-r_0)^2 + k_\theta(\theta-\theta_0)^2 + k_\phi(\phi-\phi_0)^2\Big)
\end{aligned} \tag{1}$$

$$\begin{aligned}
\Delta G^{bulk}_{\Theta,\Phi,\Psi} &= -k_b T \ln(F_r) \\
F_r &= \frac{1}{8\pi^2} \int_0^\pi d\Theta \sin(\Theta) \int_{-\pi}^{\pi} d\Phi \int_{-\pi}^{\pi} d\Psi \exp^{-\beta u(\Theta,\Phi,\Psi)} \\
u(\Theta,\Phi,\Psi) &= \frac{1}{2}\Big(k_\Theta(\Theta-\Theta_0)^2 + k_\Phi(\Phi-\Phi_0)^2 + k_\Psi(\Psi-\Psi_0)^2\Big)
\end{aligned} \tag{2}$$

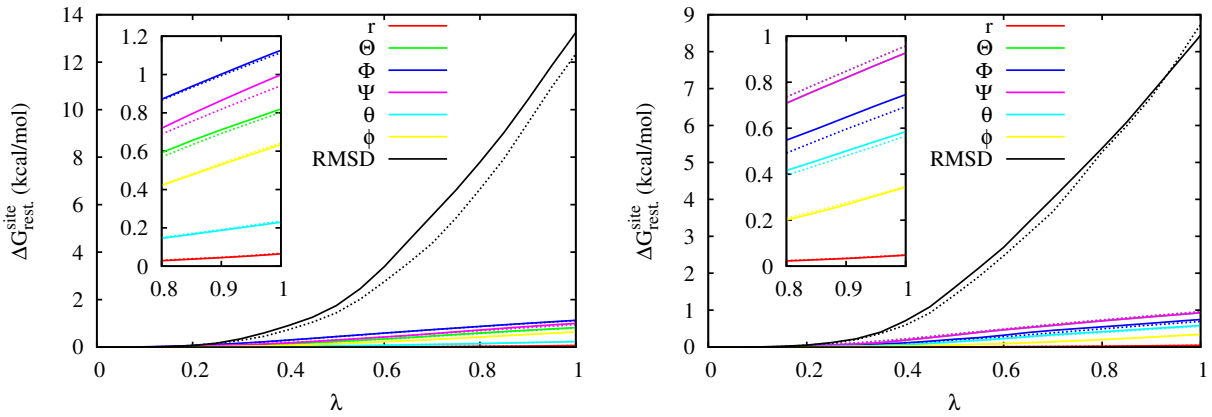

Figure 2: Free energy contributions of each geometrical restraints for the DI (left) and MinGB (right) binding modes.

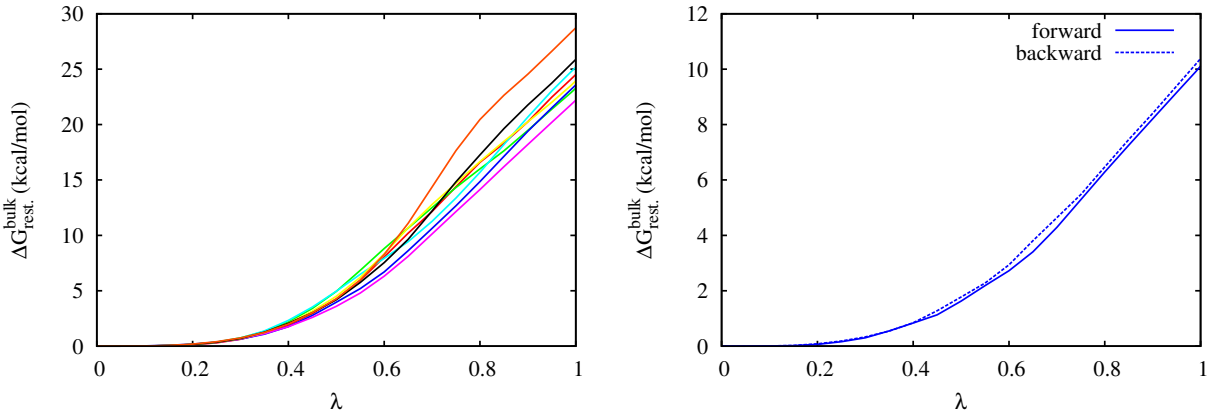

Figure 3: Free energy contributions of the RMSD restraint in the unbound form of (left) DI mode (14 forward runs) and (right) MinGB mode (forward and backward runs).

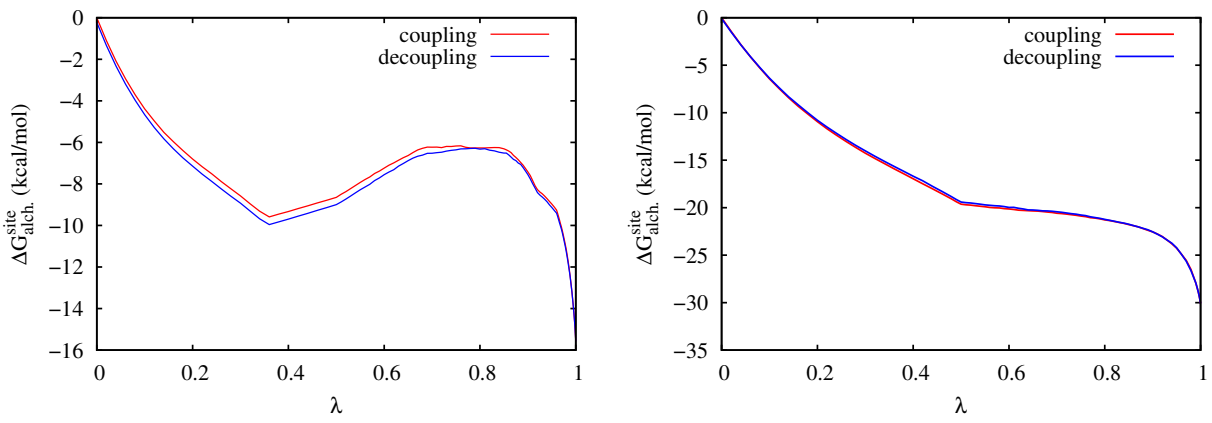

Figure 4: Free energy perturbation changes for the coupling and decoupling of BNZ in the bound form of DNA for (left) DI mode and (right) MinGB binding mode.

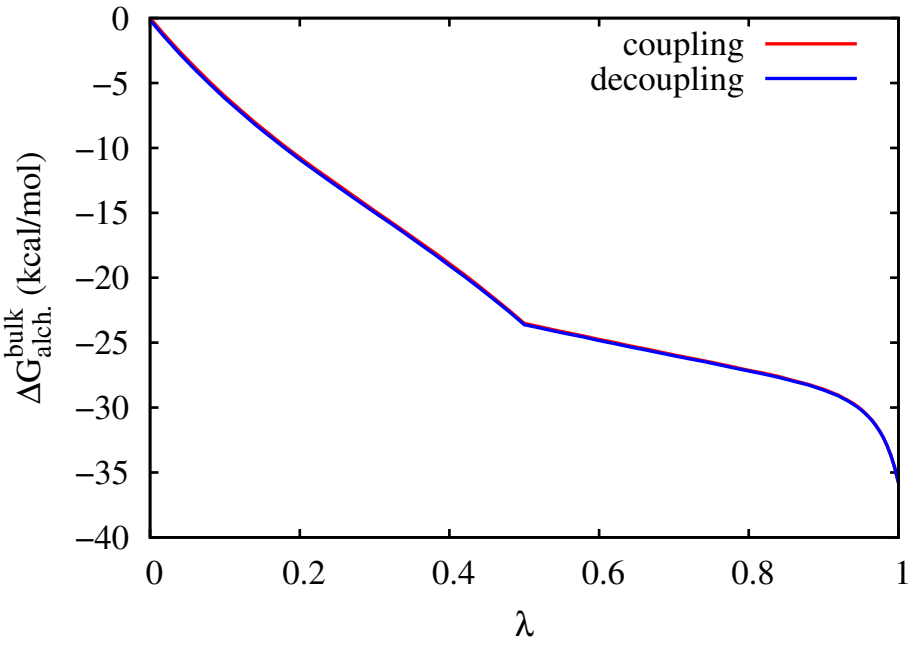

Figure 5: Free energy perturbation changes for the coupling and decoupling of BNZ from the bulk.

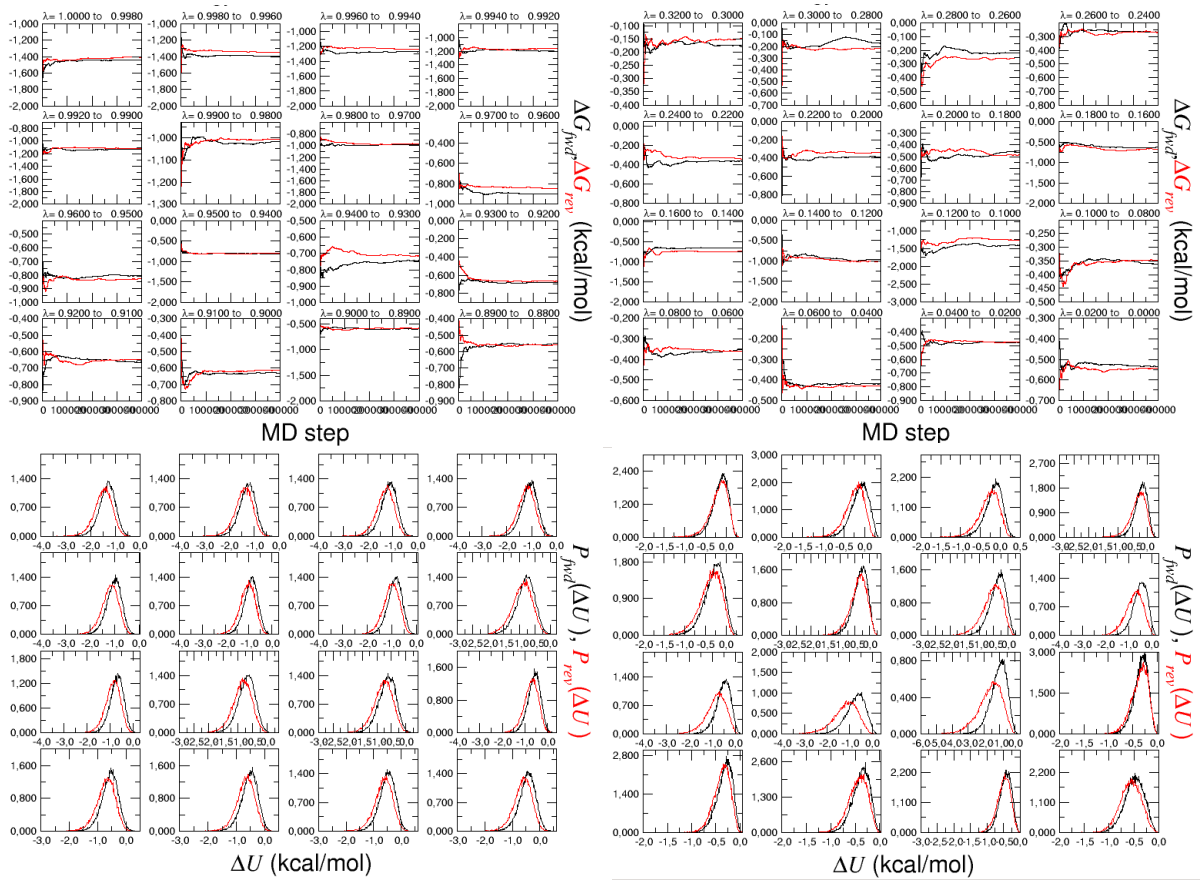

Figure 6: Forward and backward free energy changes (top) and probability distributions (bottom) as given by ParseFEP for the first 16 windows and last 16 windows for decoupling BNZ from DNA in the MinGB binding mode.