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Supporting Material

Molecular dynamics free energy calculations to assess the possibility of water existence in protein nonpolar cavities

Masataka Oikawa and Yoshiteru Yonetani

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Cavity hydration free energy $\Delta G_{\text{hyd}}^{0 \rightarrow n}$ has the four terms:

$$\Delta G_{\text{hyd}}^{0 \rightarrow n} = \Delta G_{\text{cavity}}^{0 \rightarrow n} - n\Delta G_{\text{bulk}}^{0 \rightarrow 1} - nk_{\text{B}}T \ln \left[\rho_{\text{bulk}} (2\pi k_{\text{B}}T / k_{\text{harm}})^{3/2} \right] + k_{\text{B}}T \ln n!$$

The first term $\Delta G_{\text{cavity}}^{0 \rightarrow n}$ is the sum of three components. These were calculated from the three different processes in which the restraining, electrostatic and vdW potentials were changed, respectively,

$$\begin{aligned} (U_1^{\text{ele}}, U_1^{\text{vdW}}, 0) &\rightarrow (U_1^{\text{ele}}, U_1^{\text{vdW}}, u^{\text{res}}) && : (\text{res}) \\ &\rightarrow (U_0^{\text{ele}}, U_1^{\text{vdW}}, u^{\text{res}}) && : (\text{ele}) \\ &\rightarrow (U_0^{\text{ele}}, U_0^{\text{vdW}}, u^{\text{res}}) && : (\text{vdW}) \end{aligned}$$

All the components are shown in the following Tables S1 (rigid) and S2 (flexible).

Table S1: Free energies calculated with the rigid model and their components [kcal/mol].

	Number of water molecules n				Number of water molecules n			
	1	2	3	4	1	2	3	4
	IL-1β				AvrPphB			
$\Delta G_{\text{cavity}}^{0 \rightarrow n}$	-1.5	-5.6	-8.4	-10.2	-1.5	-4.7	-7.6	-8.6
(res)	-0.3	-0.6	-1.5	-1.9	-0.2	-0.9	-2.2	-3.1
(ele)	-0.3	1.8	5.2	10.5	-0.8	0.9	5.4	10.7
(vdW)	-0.9	-6.8	-12.1	-18.8	-0.4	-4.6	-10.8	-16.2
$-n\Delta G_{\text{bulk}}^{0 \rightarrow 1}$	6.3	12.5	18.8	25.0	6.3	12.5	18.8	25.0
$\Delta G_{\text{harm}}^{0 \rightarrow n} *$	0.2	0.3	0.5	0.6	-0.3	-0.6	-0.9	-1.2
$k_{\text{B}}T \ln n!$	0.0	0.4	1.1	1.9	0.0	0.4	1.1	1.9
$\Delta G_{\text{hyd}}^{0 \rightarrow n}$	4.9	7.6	11.9	17.3	4.5	7.7	11.4	17.2
	trp repressor				hemoglobin			
$\Delta G_{\text{cavity}}^{0 \rightarrow n}$	-	-	-	-	-1.5	-2.6	-	-
(res)	-	-	-	-	-0.3	-0.6	-	-
(ele)	-	-	-	-	0.2	0.6	-	-
(vdW)	-	-	-	-	-1.4	-2.7	-	-
$-n\Delta G_{\text{bulk}}^{0 \rightarrow 1}$	-	-	-	-	6.4	12.8	-	-
$\Delta G_{\text{harm}}^{0 \rightarrow n} *$	-	-	-	-	-1.1	-2.2	-	-
$k_{\text{B}}T \ln n!$	-	-	-	-	0.0	0.4	-	-
$\Delta G_{\text{hyd}}^{0 \rightarrow n}$	-	-	-	-	3.8	8.4	-	-

$$* \Delta G_{\text{harm}}^{0 \rightarrow n} = -nk_{\text{B}}T \ln \left[\rho_{\text{bulk}} (2\pi k_{\text{B}}T / k_{\text{harm}})^{3/2} \right]$$

Table S2: Free energies calculated with the flexible model and their components [kcal/mol].

	Number of water molecules n				Number of water molecules n			
	1	2	3	4	1	2	3	4
	IL-1β				AvrPphB			
$\Delta G_{\text{cavity}}^{0 \rightarrow n}$	-2.5	-	-	-17.0	-2.2	-10.2	-11.6	-20.4
(res)	-0.6	-	-	-2.5	-0.8	-5.6	-3.2	-8.8
(ele)	-0.6	-	-	3.3	-0.7	0.6	1.7	4.6
(vdW)	-1.3	-	-	-17.8	-0.8	-5.2	-10.1	-16.3
$-n\Delta G_{\text{bulk}}^{0 \rightarrow 1}$	6.3	-	-	25.0	6.3	12.5	18.8	25.0
$\Delta G_{\text{harm}}^{0 \rightarrow n} *$	0.2	-	-	0.6	-0.3	-0.6	-0.9	-1.2
$k_{\text{B}}T \ln n!$	0.0	-	-	1.9	0.0	0.4	1.1	1.9
$\Delta G_{\text{hyd}}^{0 \rightarrow n}$	3.9	-	-	10.5	3.7	2.1	7.4	5.3
	trp repressor				hemoglobin			
$\Delta G_{\text{cavity}}^{0 \rightarrow n}$	-2.5	-5.9	-10.4	-16.9	-3.7	-7.8	-9.8	-
(res)	-1.2	-1.7	-3.1	-5.7	-2.2	-2.7	-3.0	-
(ele)	-1.0	0.7	2.4	4.3	0.2	0.7	1.5	-
(vdW)	-0.3	-4.9	-9.6	-15.5	-1.6	-5.8	-8.3	-
$-n\Delta G_{\text{bulk}}^{0 \rightarrow 1}$	6.3	12.5	18.8	25.0	6.4	12.8	19.2	-
$\Delta G_{\text{harm}}^{0 \rightarrow n} *$	-0.1	-0.1	-0.2	-0.3	-1.1	-2.2	-3.3	-
$k_{\text{B}}T \ln n!$	0.0	0.4	1.1	1.9	0.0	0.4	1.1	-
$\Delta G_{\text{hyd}}^{0 \rightarrow n}$	3.7	6.9	9.2	9.8	1.6	3.2	7.1	-

$$* \Delta G_{\text{harm}}^{0 \rightarrow n} = -nk_{\text{B}}T \ln \left[\rho_{\text{bulk}} (2\pi k_{\text{B}}T / k_{\text{harm}})^{3/2} \right]$$