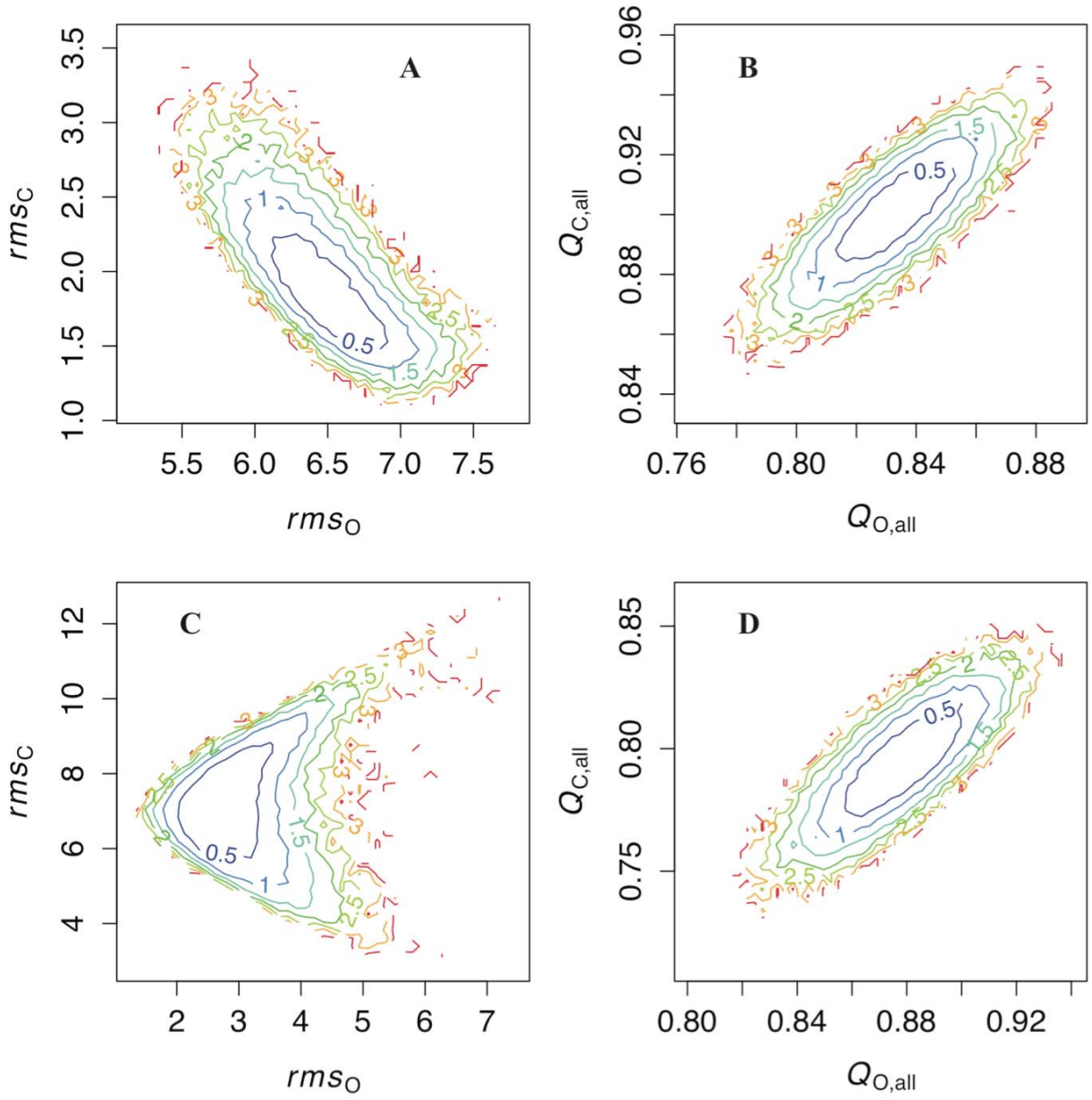

Figure S1: single-well simulations
Simulations were carried out for 150 ns with the single-well O and C Go potentials, with contact energies scaled by a factor of 2.5 and the generic bond angle potential on. A,B: Simulation starting from the C crystal structure using the C potential. C,D: Simulation starting from the O crystal structure using the O potential.

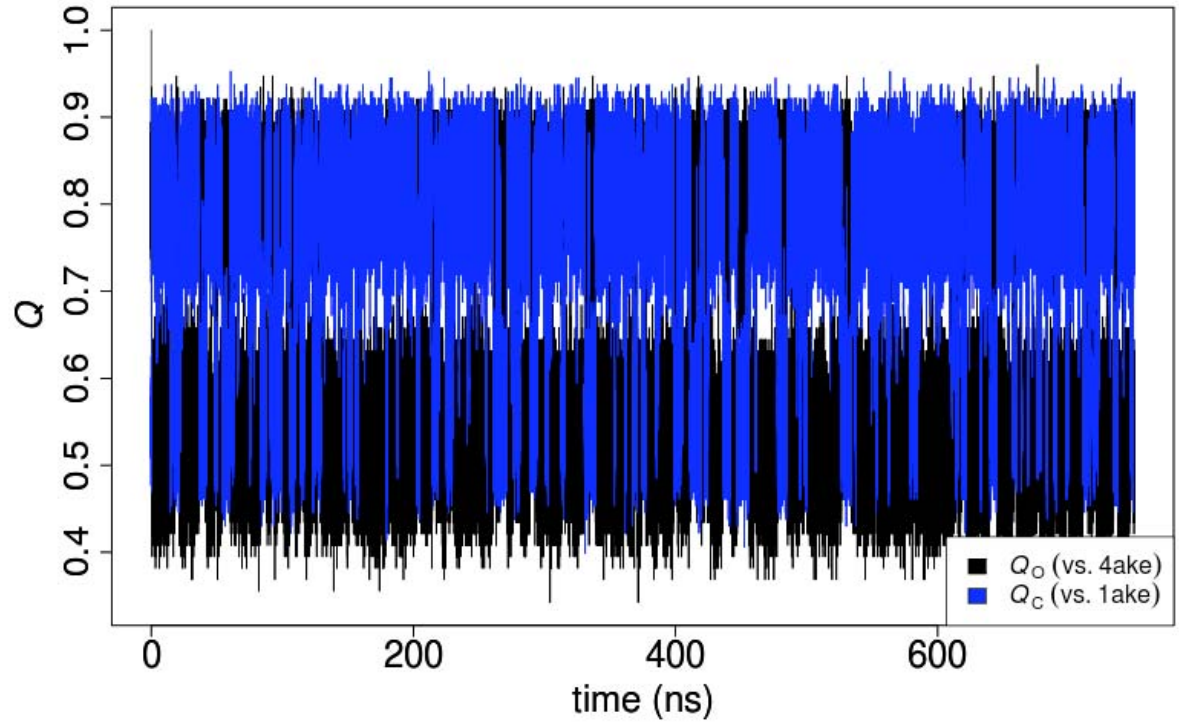

Figure S2: Trajectory of bound simulation along Q_O and Q_C reaction coordinates

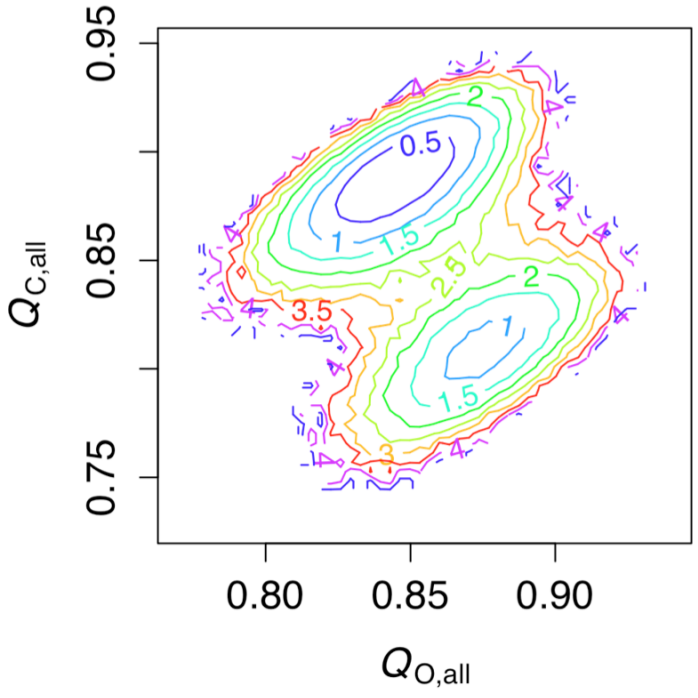

Figure S3: PMF of the bound simulation along $Q_{O,all}$ and $Q_{C,all}$ reaction coordinates

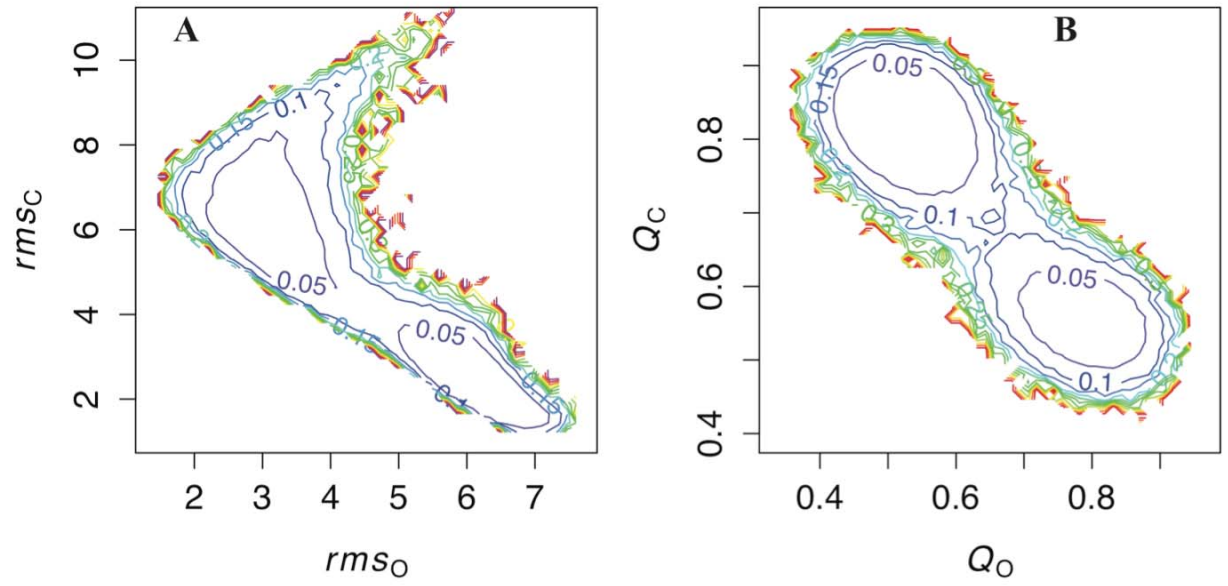

Figure S4: uncertainty in the global PMFs of the bound simulation
Uncertainties (kcal/mol) are calculated as described in the methods of the main text.

sim	Keq	rate
Oxtal	3.33	334
O1	2.60	329
O2	2.32	331
O3	4.09	255
Cxtal	2.46	341
C1	3.20	299
C2	4.19	277
C3	2.78	328
mean	3.12	312
Sd	0.72	31

Table S1: Variation of key quantities among bound simulations
Oxtal and Cxtal simulations were started from the O and C crystal structures, respectively. O1-3 and C1-3 were started from randomly selected O ensemble and C ensemble structures, respectively, taken from the Oxtal trajectory. Otherwise, all independent simulations use the same parameters as the Oxtal simulation. The rate is defined as the number of transitions (in either direction) per μs of simulation time. Sd indicates standard deviation.

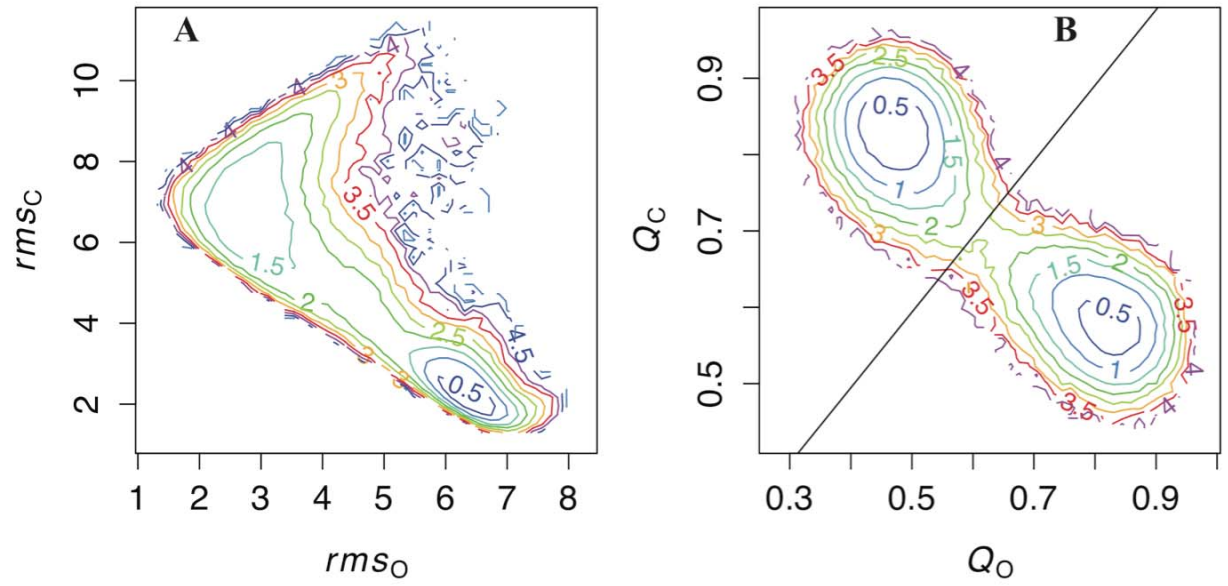

Figure S5: PMFs of the apo simulation in global Cartesian and contact reaction coordinates
For legend, see figure 1 of the main text.

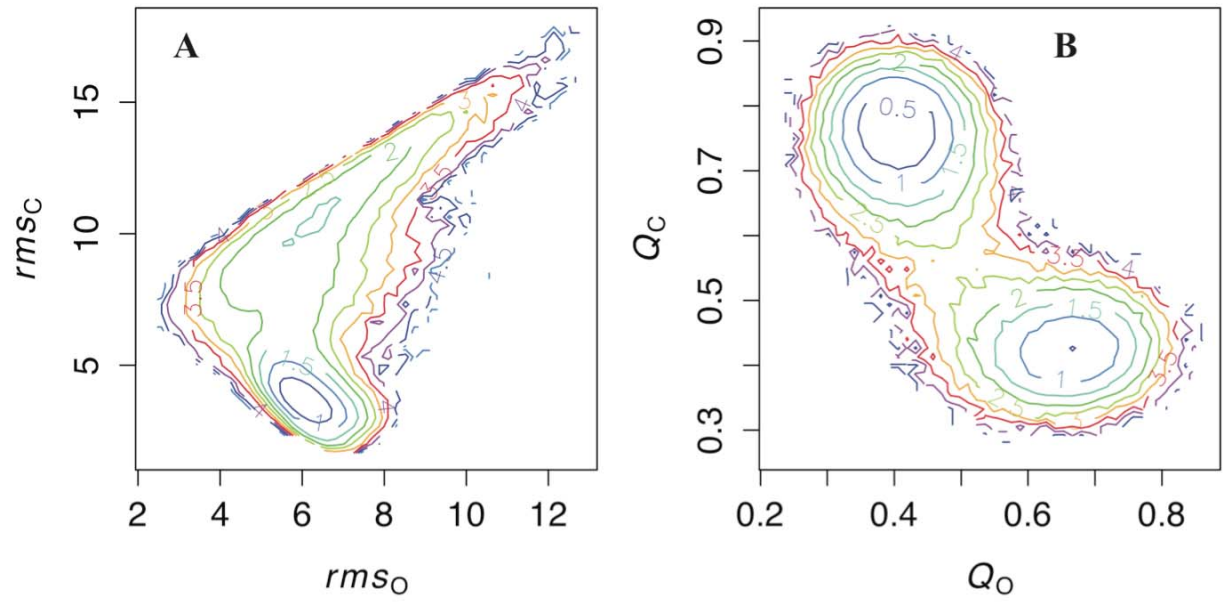

Figure S6: PMFs of the simulation with ligand-mediated interactions added and contact scaling factor of 1.7
For legend, see figure 1 of the main text.

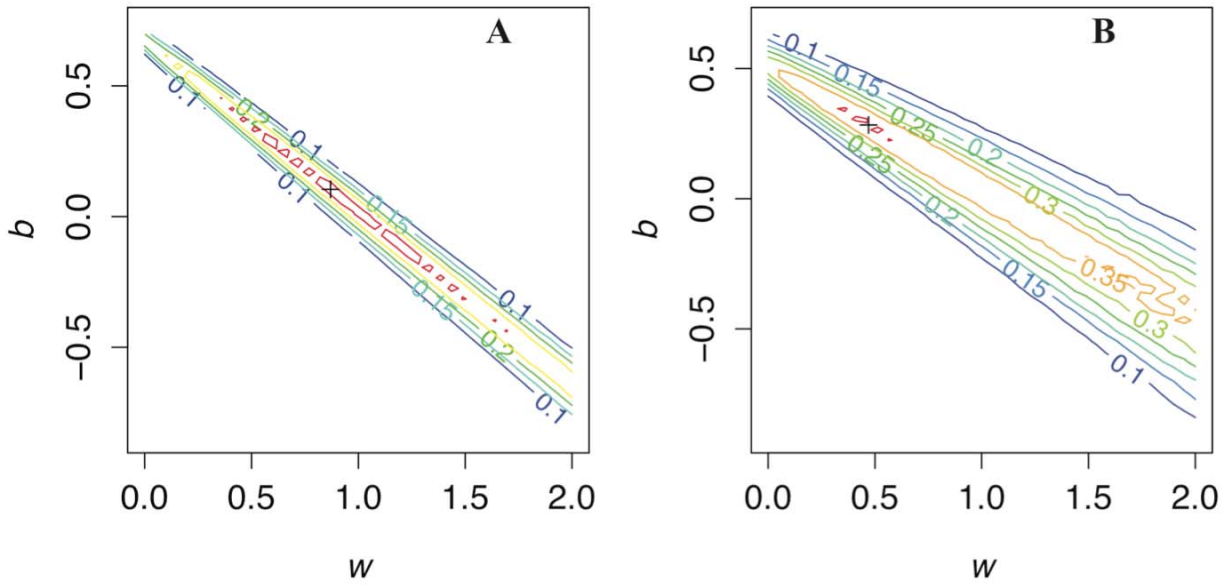

Figure S7: optimization of reaction coordinate for TSE
'+' marks the bin with the optimum $p(\mathrm{TP}|w,b)$.

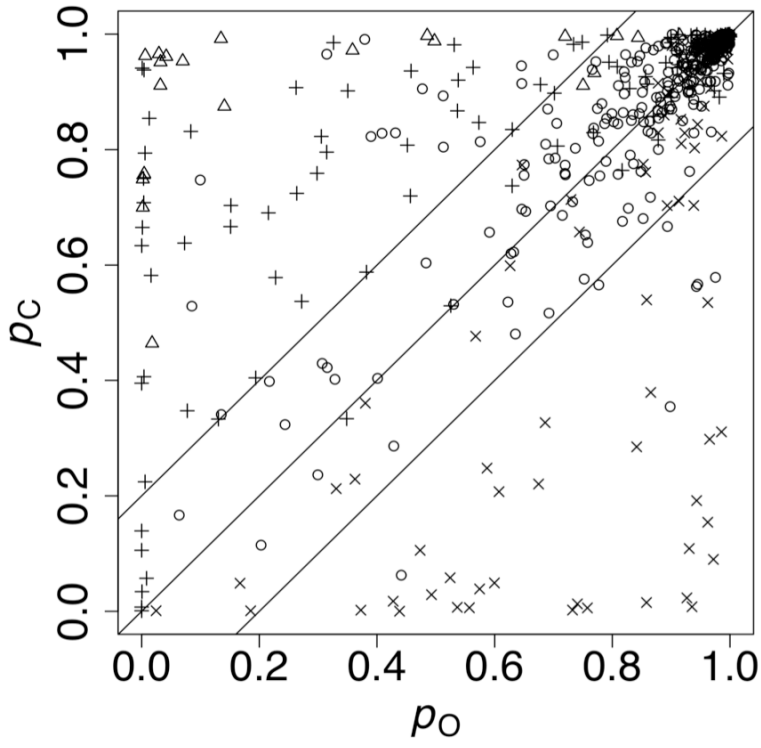

Figure S8: contact probabilities in the O and C simulation ensembles
x, +, and circle symbols indicate contacts present in open only, and closed only, and both *crystal structures*, respectively, and triangles indicate ligand-mediated contacts added to the closed state Gō potential. For each point, $p_{O(C)}$ is the probability that the corresponding contact exists in the O(C) ensemble, with a C_α distance cutoff of 1.1 times the native contact distance. Diagonal lines indicate y=x and y=x±0.2.

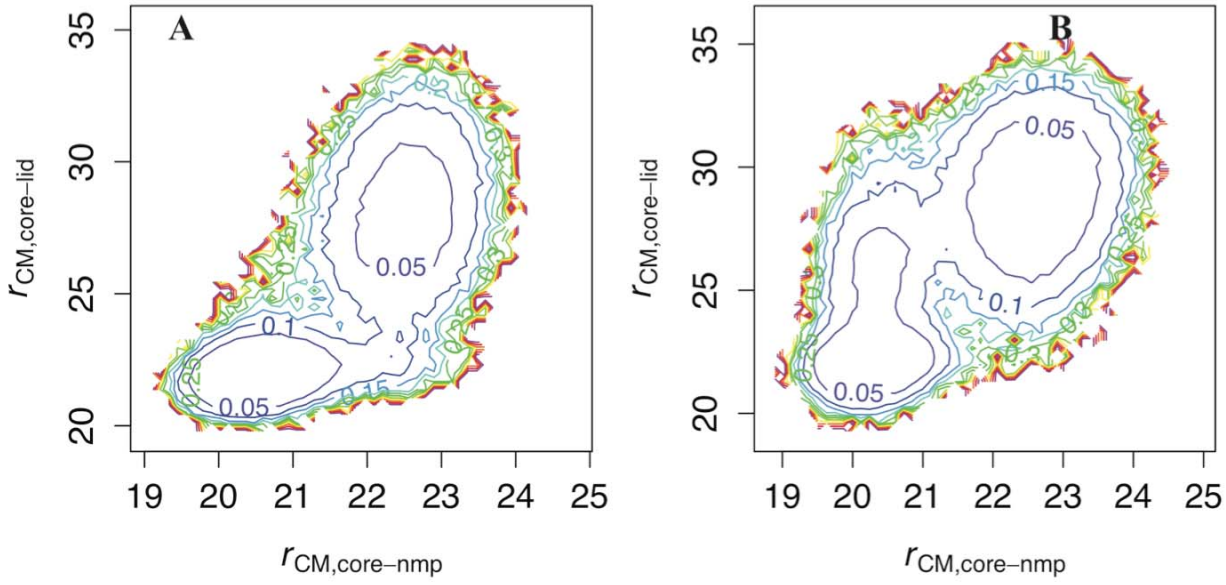

Figure S9: uncertainty for Figure 2 of the bound simulation
Uncertainties (kcal/mol) are calculated as described in the methods of the main text.

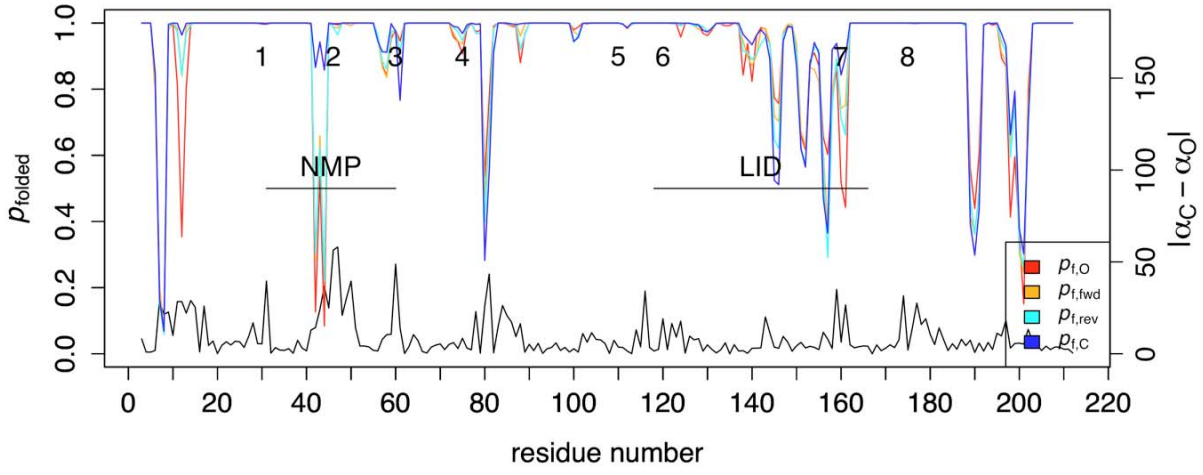

Figure S10: Closing (fwd) vs. opening (rev) transition state sub-ensemble dihedral properties.

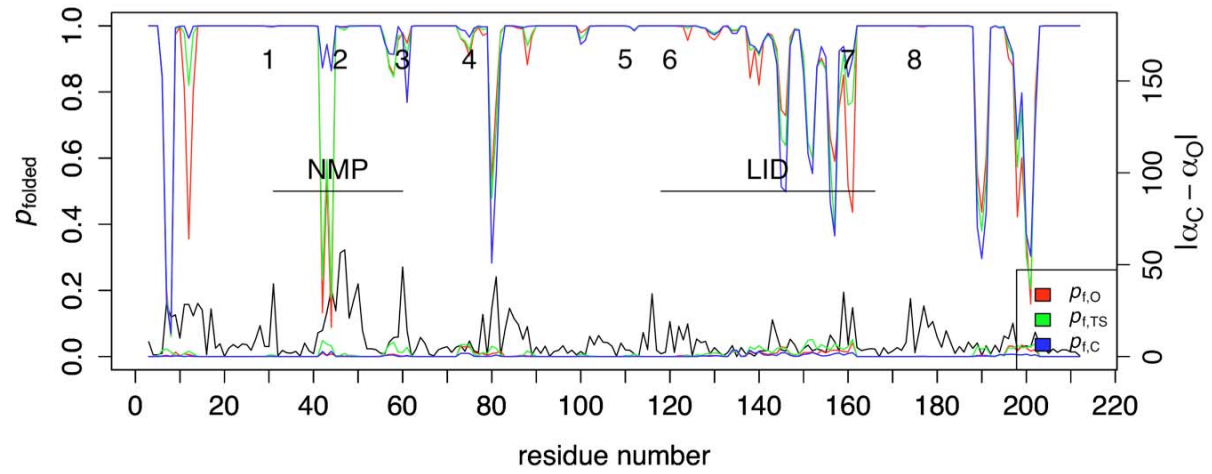

Figure S11: uncertainties for dihedral calculations of the bound simulation
The upper curves show the average of p_{folded} curves for each of the three ensembles among the eight independent 750 ns p_{folded} simulations, and the lower curves show the corresponding standard deviations.

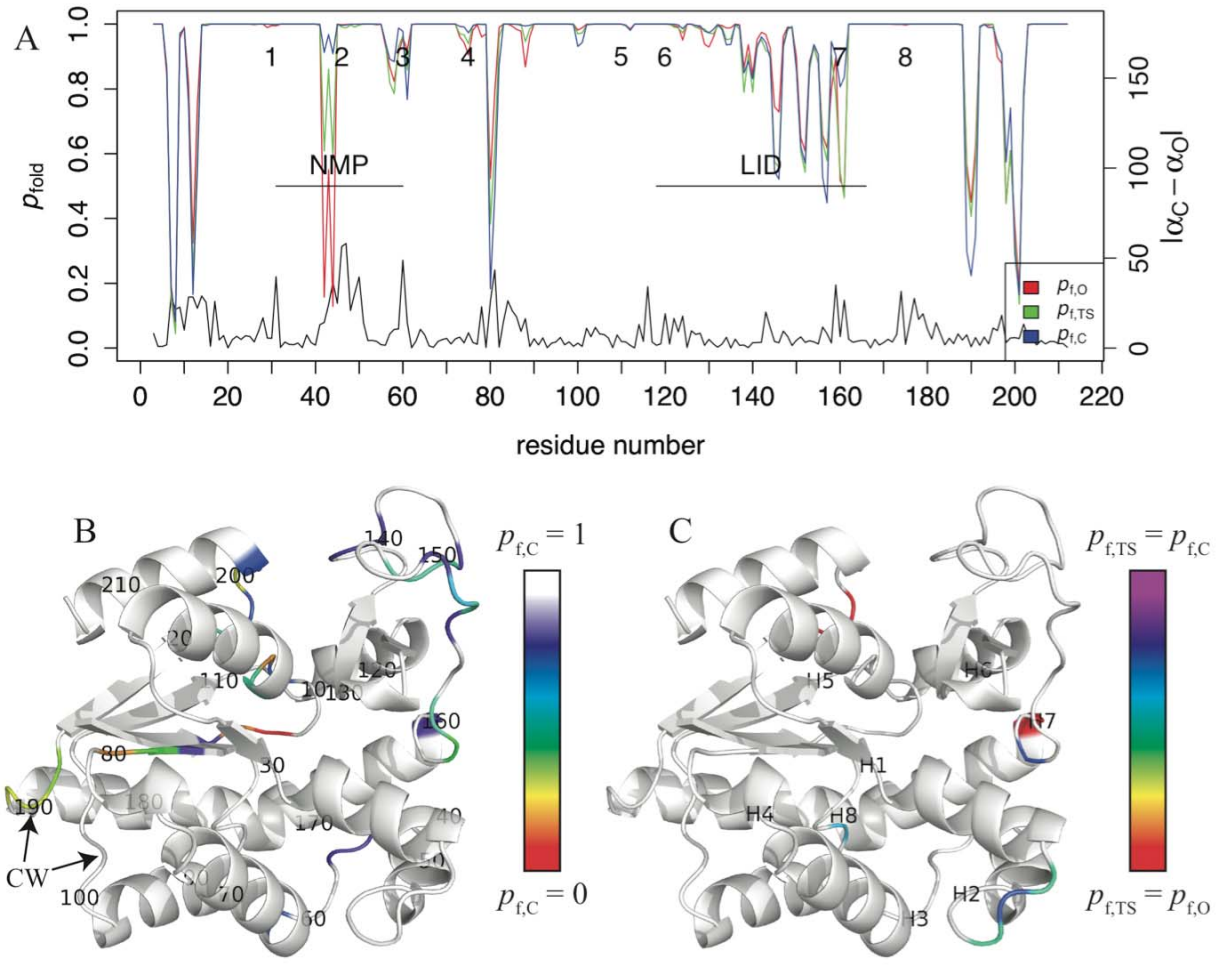

Figure S12: Unfolding dynamics in open, closed, and transition state ensembles of the apo simulation

For legend, see figure 3 of the main text.

group	core	nmp	lid	core-nmp	core-lid	nmp-lid
common	255	31	72	17	20	0
O-unique	43	8	13	6	6	0
C-unique	61	15	5	11	11	3
ligand-mediated	3	4	1	3	11	0

Table S2: Contacts at different domains and interfaces in the O and C states
'common' contacts occur in both O and C crystal structures, O-unique contacts occur only in the O crystal structure, C-unique contacts occur only in the C structure, and ligand-mediated interactions are added to the C potential of the bound simulation as described in the methods of the main text.

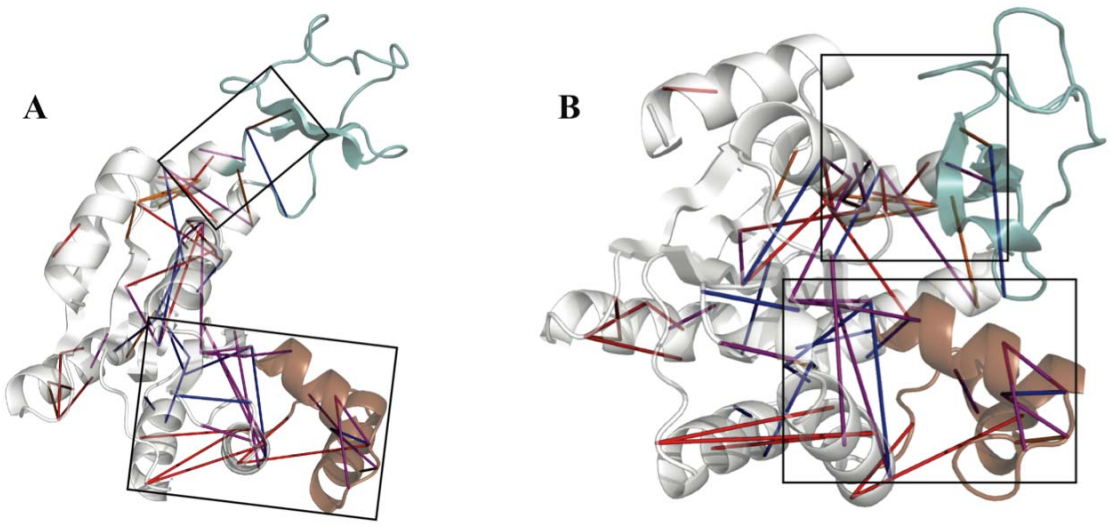

Figure S13: Important O-characteristic and C-characteristic contacts in the transition state ensemble of the apo simulation
For legend, see figure 4 of the main text (parts A and B).