



Figure S1: Correlations between structural complexity and the rates of folding and unfolding at the transition midpoint.

Correlations are shown for the folding/unfolding rate at the transition midpoint ($\log k_f = \log k_u$) for A) ACO and B) LRO. Rates at the transition midpoint are used because the thermodynamic stability is zero allowing for the correction of effects owing to differing stabilities.

Table S1. Correlations and linear fits of unfolding and folding rate constants, measures of native structure and thermodynamic stability extended

Parameter x	Parameter y	Dataset (Size)	Linear Fit: $y = b + m \cdot x$		Pearson Correlation	
			m	b	R	P ^a
ACO	$\log k_f = \log k_u$	Full (108)	-0.32	3.8	-0.76	8.2×10^{-22}
		Two-State (73)	-0.40	4.7	-0.80	2.0×10^{-17}
		Multi-State (35)	-0.19	1.7	-0.70	2.3×10^{-6}
		Alpha (33)	-0.43	4.9	-0.71	3.4×10^{-6}
		Beta (34)	-0.52	5.9	-0.86	4.7×10^{-11}
		Mixed (41)	-0.14	1.0	-0.61	2.2×10^{-5}
		Maxwell (28)	-0.21	2.2	-0.69	4.6×10^{-5}
LRO	$\log k_f = \log k_u$	Full (108)	-1.4	5.1	-0.83	1.9×10^{-28}
		Two-State (73)	-1.4	5.5	-0.85	1.8×10^{-21}
		Multi-State (35)	-0.98	3.2	-0.71	1.9×10^{-6}
		Alpha (33)	-1.8	6.0	-0.77	1.7×10^{-7}
		Beta (34)	-1.7	6.6	-0.85	1.3×10^{-10}
		Mixed (41)	-0.85	2.8	-0.61	2.3×10^{-5}
		Maxwell (28)	-1.2	4.6	-0.81	1.4×10^{-7}
RCO	$\log k_f$	Full (108)	-3.9	2.5	-0.08	3.9×10^{-1} NS
		Two-State (73)	-16	4.9	-0.34	2.8×10^{-3}
		Multi-State (35)	-0.036	1.1	0.00	1.0×10^0 NS
		Alpha (33)	27	0.7	0.51	2.4×10^{-3}
		Beta (34)	7.7	0.28	0.15	4.0×10^{-1} NS
		Mixed (41)	12	-0.55	0.27	8.8×10^{-2} NS
		Maxwell (28)	-19	5.3	-0.56	1.7×10^{-3}
RCO	$\log k_u$	Full (108)	0.65	-1.6	0.01	9.3×10^{-1} NS
		Two-State (73)	-9.2	0.36	-0.12	3.1×10^{-1} NS
		Multi-State (35)	-1.9	-2.3	-0.02	9.0×10^{-1} NS
		Alpha (33)	51	-4.7	0.52	2.0×10^{-3}
		Beta (34)	39	-8.1	0.46	6.4×10^{-3}
		Mixed (41)	7.9	-4.1	0.14	3.8×10^{-1} NS
		Maxwell (28)	-14	0.3	-0.26	1.7×10^{-1} NS
RCO	$\log k_f = \log k_u$	Full (108)	-2.2	0.024	-0.04	7.0×10^{-1} NS
		Two-State (73)	-12	1.8	-0.17	1.4×10^{-1} NS
		Multi-State (35)	-2.1	-0.87	-0.04	8.1×10^{-1} NS
		Alpha (33)	42	-2.8	0.48	4.6×10^{-3}
		Beta (34)	29	-5.5	0.38	2.7×10^{-2}
		Mixed (41)	4.8	-2.0	0.14	4.0×10^{-1} NS
		Maxwell (28)	-14	1.7	-0.39	3.9×10^{-2}
TCD	$\log k_f$	Full (108)	-2.8	4.8	-0.37	7.5×10^{-5}
		Two-State (73)	-5.0	7.6	-0.65	5.6×10^{-10}
		Multi-State (35)	-1.4	2.4	-0.21	2.3×10^{-1} NS
		Alpha (33)	2.0	2.0	0.19	2.9×10^{-1} NS
		Beta (34)	-3.9	5.8	-0.42	1.2×10^{-2}
		Mixed (41)	0.99	0.085	0.14	3.9×10^{-1} NS
		Maxwell (28)	-3.6	6.4	-0.60	6.5×10^{-4}

TCD	log k_u	Full (108)	-4.1	2.6	-0.35	2.4×10^{-4}
		Two-State (73)	-6.7	6.0	-0.55	6.1×10^{-7}
		Multi-State (35)	-2.3	-0.47	-0.20	2.4×10^{-1} NS
		Alpha (33)	1.4	-0.39	0.07	6.9×10^{-1} NS
		Beta (34)	-2.3	0.82	-0.15	3.8×10^{-1} NS
		Mixed (41)	-0.23	-2.8	-0.03	8.7×10^{-1} NS
		Maxwell (28)	-3.8	2.5	-0.42	2.5×10^{-2}
TCD	log $k_f = \log k_u$	Full (108)	-3.9	3.6	-0.40	1.6×10^{-5}
		Two-State (73)	-6.4	6.8	-0.59	4.2×10^{-8}
		Multi-State (35)	-1.7	0.43	-0.24	1.6×10^{-1} NS
		Alpha (33)	0.037	1.5	0.00	1.0×10^0 NS
		Beta (34)	-3.8	3.4	-0.28	1.0×10^{-1} NS
		Mixed (41)	-0.17	-1.1	-0.03	8.5×10^{-1} NS
		Maxwell (28)	-3.5	3.4	-0.55	2.7×10^{-3}
SRO	log k_f	Full (108)	0.55	-1.7	0.35	2.1×10^{-4}
		Two-State (73)	0.66	-1.9	0.44	8.3×10^{-5}
		Multi-State (35)	0.62	-3.2	0.40	1.7×10^{-2}
		Alpha (33)	-0.85	10.	-0.37	3.4×10^{-2}
		Beta (34)	-0.38	3.6	-0.08	6.6×10^{-1} NS
		Mixed (41)	-0.33	3.3	-0.11	5.0×10^{-1} NS
		Maxwell (28)	0.59	-1.6	0.50	7.4×10^{-3}
SRO	log k_u	Full (108)	0.68	-6.0	0.27	4.0×10^{-3}
		Two-State (73)	0.68	-5.5	0.28	1.5×10^{-2}
		Multi-State (35)	1.1	-10.	0.43	9.1×10^{-3}
		Alpha (33)	-2.5	21	-0.57	5.7×10^{-3}
		Beta (34)	-2.1	9.8	-0.26	1.4×10^{-1} NS
		Mixed (41)	0.83	-8.4	0.22	1.7×10^{-1} NS
		Maxwell (28)	0.71	-6.5	0.40	3.6×10^{-2}
SRO	log $k_f = \log k_u$	Full (108)	0.63	-4.5	0.31	1.0×10^{-3}
		Two-State (73)	0.73	-4.7	0.35	2.6×10^{-3}
		Multi-State (35)	0.67	-5.8	0.43	1.0×10^{-2}
		Alpha (33)	-2.0	18	-0.53	1.5×10^{-3}
		Beta (34)	-1.9	9.5	-0.26	1.4×10^{-1} NS
		Mixed (41)	0.56	-4.9	0.23	1.4×10^{-1} NS
		Maxwell (28)	0.63	-4.7	0.49	8.0×10^{-3}
NonLocalCO	log k_f	Full (108)	-0.17	5.2	-0.59	1.1×10^{-11}
		Two-State (73)	-0.13	4.8	-0.46	4.3×10^{-5}
		Multi-State (35)	-0.19	5.3	-0.74	3.6×10^{-7}
		Alpha (33)	-0.11	5.4	-0.58	4.5×10^{-4}
		Beta (34)	-0.27	6.2	-0.77	7.7×10^{-8}
		Mixed (41)	-0.14	4.4	-0.53	3.3×10^{-4}
		Maxwell (28)	-0.03	2.9	-0.14	4.7×10^{-1} NS
NonLocalCO	log k_u	Full (108)	-0.31	4.5	-0.71	7.1×10^{-18}
		Two-State (73)	-0.32	4.7	-0.69	2.0×10^{-11}
		Multi-State (35)	-0.28	3.9	-0.70	3.5×10^{-6}
		Alpha (33)	-0.27	5.3	-0.74	6.6×10^{-7}
		Beta (34)	-0.45	6.0	-0.79	3.6×10^{-8}
		Mixed (41)	-0.22	2.0	-0.65	3.4×10^{-6}
		Maxwell (28)	-0.14	0.98	-0.45	1.6×10^{-2}

NonLocalCO	$\log k_f = \log k_u$	Full (108)	-0.23	4.3	-0.65	1.5×10^{-14}
		Two-State (73)	-0.25	4.7	-0.62	4.5×10^{-9}
		Multi-State (35)	-0.18	3.0	-0.70	2.3×10^{-6}
		Alpha (33)	-0.22	5.4	-0.70	5.0×10^{-6}
		Beta (34)	-0.42	6.4	-0.81	5.3×10^{-9}
		Mixed (41)	-0.12	1.5	-0.59	5.1×10^{-5}
		Maxwell (28)	-0.085	1.2	-0.38	4.6×10^{-2}
LocalCO	$\log k_f$	Full (108)	0.28	0.96	0.56	4.5×10^{-10}
		Two-State (73)	0.24	1.5	0.57	1.7×10^{-7}
		Multi-State (35)	0.58	-0.70	0.60	1.4×10^{-4}
		Alpha (33)	0.12	2.6	0.44	1.1×10^{-2}
		Beta (34)	0.74	-0.077	0.66	2.5×10^{-5}
		Mixed (41)	0.58	-0.12	0.28	8.1×10^{-2} NS
		Maxwell (28)	0.50	0.91	0.62	4.5×10^{-4}
LocalCO	$\log k_u$	Full (108)	0.47	-3.3	0.60	4.9×10^{-12}
		Two-State (73)	0.43	-2.7	0.64	1.6×10^{-9}
		Multi-State (35)	0.84	-5.1	0.54	8.8×10^{-4}
		Alpha (33)	0.27	-1.3	0.54	1.3×10^{-3}
		Beta (34)	1.2	-4.5	0.66	2.1×10^{-5}
		Mixed (41)	0.99	-5.2	0.38	1.5×10^{-2}
		Maxwell (28)	0.78	-3.9	0.63	2.9×10^{-3}
LocalCO	$\log k_f = \log k_u$	Full (108)	0.42	-1.8	0.65	4.3×10^{-14}
		Two-State (73)	0.39	-1.5	0.65	6.0×10^{-10}
		Multi-State (35)	0.63	-3.0	0.64	3.9×10^{-5}
		Alpha (33)	0.26	-0.32	0.57	4.7×10^{-4}
		Beta (34)	1.1	-3.3	0.68	8.3×10^{-6}
		Mixed (41)	0.72	-2.9	0.43	4.5×10^{-3}
		Maxwell (28)	0.62	-2.2	0.71	2.4×10^{-5}
N α	$\log k_f$	Full (108)	-0.048	4.3	-0.64	7.3×10^{-14}
		Two-State (73)	-0.042	4.1	-0.47	2.4×10^{-5}
		Multi-State (35)	-0.050	4.3	-0.80	9.0×10^{-9}
		Alpha (33)	-0.037	5.0	-0.72	2.2×10^{-6}
		Beta (34)	-0.076	4.6	-0.72	1.8×10^{-6}
		Mixed (41)	-0.041	3.6	-0.66	3.3×10^{-6}
		Maxwell (28)	-0.0089	2.7	-0.17	3.9×10^{-1} NS
N α	$\log k_u$	Full (108)	-0.078	2.2	-0.68	8.4×10^{-16}
		Two-State (73)	-0.094	2.7	-0.65	3.3×10^{-10}
		Multi-State (35)	-0.070	2.0	-0.69	5.6×10^{-6}
		Alpha (33)	-0.070	3.5	-0.72	1.8×10^{-6}
		Beta (34)	-0.15	4.1	-0.84	4.1×10^{-10}
		Mixed (41)	-0.047	-0.26	-0.60	3.5×10^{-5}
		Maxwell (28)	-0.031	-0.46	-0.39	4.0×10^{-2}
N α	$\log k_f = \log k_u$	Full (108)	-0.060	2.6	-0.63	1.8×10^{-13}
		Two-State (73)	-0.077	3.1	-0.61	1.1×10^{-8}
		Multi-State (35)	-0.046	1.8	-0.71	1.9×10^{-6}
		Alpha (33)	-0.060	4.0	-0.71	3.3×10^{-6}
		Beta (34)	-0.13	4.5	-0.84	4.2×10^{-10}
		Mixed (41)	-0.029	0.39	-0.58	6.1×10^{-5}
		Maxwell (28)	-0.020	0.33	-0.35	6.7×10^{-2} NS

CC	log k_f	Full (108)	32	-16	0.69	1.7×10^{-16}
		Two-State (73)	27	-13	0.61	9.5×10^{-9}
		Multi-State (35)	59	-32	0.83	9.9×10^{-10}
		Alpha (33)	25	-11	0.73	1.2×10^{-6}
		Beta (34)	28	-15	0.73	1.2×10^{-6}
		Mixed (41)	31	-16	0.51	5.9×10^{-4}
		Maxwell (28)	2.8	0.69	0.05	7.9×10^{-1} NS
CC	log k_u	Full (108)	57	-34	0.78	3.3×10^{-23}
		Two-State (73)	56	-34	0.80	2.4×10^{-17}
		Multi-State (35)	83	-48	0.71	1.6×10^{-6}
		Alpha (33)	49	-28	0.75	5.2×10^{-7}
		Beta (34)	53	-32	0.83	1.1×10^{-9}
		Mixed (41)	44	-28	0.58	6.9×10^{-5}
		Maxwell (28)	38	-23	0.48	9.9×10^{-3}
CC	log $k_f = \log k_u$	Full (108)	47	-27	0.78	2.4×10^{-23}
		Two-State (73)	48	-28	0.77	2.5×10^{-15}
		Multi-State (35)	57	-33	0.79	2.0×10^{-8}
		Alpha (33)	45	-25	0.78	7.1×10^{-8}
		Beta (34)	47	-28	0.83	1.0×10^{-9}
		Mixed (41)	26	-16	0.54	2.9×10^{-4}
		Maxwell (28)	18	-11	0.32	9.4×10^{-2} NS
L	log k_f	Full (108)	-0.024	4.3	-0.64	1.2×10^{-13}
		Two-State (73)	-0.021	4.1	-0.46	3.5×10^{-5}
		Multi-State (35)	-0.025	4.4	-0.80	7.6×10^{-9}
		Alpha (33)	-0.018	5.0	-0.72	2.8×10^{-6}
		Beta (34)	-0.037	4.6	-0.70	3.4×10^{-6}
		Mixed (41)	-0.020	3.6	-0.64	6.4×10^{-6}
		Maxwell (28)	-0.0040	2.6	-0.16	4.3×10^{-1} NS
L	log k_u	Full (108)	-0.093	2.3	-0.68	6.7×10^{-16}
		Two-State (73)	-0.046	2.7	-0.65	4.2×10^{-10}
		Multi-State (35)	-0.036	2.2	-0.69	3.6×10^{-6}
		Alpha (33)	-0.035	3.6	-0.72	2.4×10^{-6}
		Beta (34)	-0.073	4.3	-0.84	6.2×10^{-10}
		Mixed (41)	-0.023	-0.21	-0.60	3.5×10^{-5}
		Maxwell (28)	-0.015	-0.44	-0.39	3.8×10^{-2}
L	log $k_f = \log k_u$	Full (108)	-0.030	2.6	-0.64	1.5×10^{-13}
		Two-State (73)	-0.038	3.2	-0.61	1.2×10^{-8}
		Multi-State (35)	-0.023	1.9	-0.71	1.5×10^{-6}
		Alpha (33)	-0.030	4.0	-0.71	3.8×10^{-6}
		Beta (34)	-0.065	4.6	-0.83	9.7×10^{-10}
		Mixed (41)	-0.014	0.43	-0.58	6.4×10^{-5}
		Maxwell (28)	-0.0098	0.34	-0.35	6.5×10^{-2} NS
L	ΔG_{F-U}	Full (108)	-0.021	-2.7	-0.42	4.6×10^{-6}
		Two-State (73)	-0.035	-1.9	-0.57	1.2×10^{-7}
		Multi-State (35)	-0.014	-3.0	-0.29	9.5×10^{-2} NS
		Alpha (33)	-0.023	-2.0	-0.54	1.2×10^{-3}
		Beta (34)	-0.049	-0.42	-0.68	1.1×10^{-5}
		Mixed (41)	-0.0047	-5.1	-0.10	5.5×10^{-1} NS
		Maxwell (28)	-0.015	-4.2	-0.31	1.1×10^{-1} NS

L ^(2/3)	log k _f	Full (108)	-0.18	5.7	-0.67	4.1x10 ⁻¹⁵
		Two-State (73)	-0.16	5.3	-0.51	3.5x10 ⁻⁶
		Multi-State (35)	-0.20	6.2	-0.81	3.0x10 ⁻⁹
		Alpha (33)	-0.14	6.0	-0.75	6.4x10 ⁻⁷
		Beta (34)	-0.24	6.1	-0.72	1.4x10 ⁻⁶
		Mixed (41)	-0.15	4.8	-0.64	6.8x10 ⁻⁶
		Maxwell (28)	-0.028	2.8	-0.14	4.9x10 ⁻¹ NS
L ^(2/3)	log k _u	Full (108)	-0.30	4.7	-0.72	1.3x10 ⁻¹⁸
		Two-State (73)	-0.36	5.5	-0.72	8.3x10 ⁻¹³
		Multi-State (35)	-0.28	4.7	-0.71	2.1x10 ⁻⁶
		Alpha (33)	-0.27	5.7	-0.77	2.0x10 ⁻⁷
		Beta (34)	-0.48	7.1	-0.86	1.0x10 ⁻¹⁰
		Mixed (41)	-0.18	1.3	-0.60	3.4x10 ⁻⁵
		Maxwell (28)	-0.13	0.74	-0.42	2.6x10 ⁻²
L ^(2/3)	log k _f = log k _u	Full (108)	-0.24	4.6	-0.69	2.6x10 ⁻¹⁶
		Two-State (73)	-0.30	5.5	-0.68	5.5x10 ⁻¹¹
		Multi-State (35)	-0.19	3.6	-0.74	4.8x10 ⁻⁷
		Alpha (33)	-0.24	5.9	-0.76	2.3x10 ⁻⁷
		Beta (34)	-0.42	7.1	-0.85	1.7x10 ⁻¹⁰
		Mixed (41)	-0.11	1.4	-0.59	5.5x10 ⁻⁵
		Maxwell (28)	-0.081	1.0	-0.37	5.5x10 ⁻² NS
L ^(2/3)	ΔG _{F-U}	Full (108)	-0.17	-1.3	-0.46	4.2x10 ⁻⁷
		Two-State (73)	-0.27	0.23	-0.63	2.4x10 ⁻⁹
		Multi-State (35)	-0.11	-2.0	-0.29	8.8x10 ⁻² NS
		Alpha (33)	-0.18	-0.53	-0.59	3.2x10 ⁻⁴
		Beta (34)	-0.32	1.4	-0.69	6.2x10 ⁻⁶
		Mixed (41)	-0.037	-4.8	-0.10	5.4x10 ⁻¹ NS
		Maxwell (28)	-0.14	-2.8	-0.35	6.5x10 ⁻² NS
L ^(1/2)	log k _f	Full (108)	-0.52	7.0	-0.68	1.1x10 ⁻¹⁵
		Two-State (73)	-0.46	6.5	-0.53	1.2x10 ⁻⁶
		Multi-State (35)	-0.61	7.9	-0.82	2.1x10 ⁻⁹
		Alpha (33)	-0.40	7.0	-0.75	3.9x10 ⁻⁷
		Beta (34)	-0.66	7.5	-0.73	9.9x10 ⁻⁷
		Mixed (41)	-0.46	6.1	-0.64	7.5x10 ⁻⁶
		Maxwell (28)	-0.077	3.0	-0.12	5.3x10 ⁻¹ NS
L ^(1/2)	log k _u	Full (108)	-0.89	7.0	-0.74	6.0x10 ⁻²⁰
		Two-State (73)	-1.0	8.1	-0.75	4.1x10 ⁻¹⁴
		Multi-State (35)	-0.86	7.2	-0.71	1.7x10 ⁻⁶
		Alpha (33)	-0.80	7.7	-0.79	6.3x10 ⁻⁸
		Beta (34)	-1.3	9.8	-0.86	4.7x10 ⁻¹¹
		Mixed (41)	-0.54	2.8	-0.60	3.5x10 ⁻⁵
		Maxwell (28)	-0.40	1.9	-0.43	2.1x10 ⁻²
L ^(1/2)	log k _f = log k _u	Full (108)	-0.70	6.4	-0.71	9.2x10 ⁻¹⁸
		Two-State (73)	-0.87	7.7	-0.70	3.9x10 ⁻¹²
		Multi-State (35)	-0.57	5.3	-0.75	2.8x10 ⁻⁷
		Alpha (33)	-0.70	7.7	-0.79	5.7x10 ⁻⁸
		Beta (34)	-1.2	9.5	-0.86	7.8x10 ⁻¹¹
		Mixed (41)	-0.34	2.3	-0.59	5.3x10 ⁻⁵
		Maxwell (28)	-0.25	1.8	-0.37	5.1x10 ⁻¹ NS

L ^(1/2)	ΔG_{F-U}	Full (108)	-0.50	0.054	-0.48	1.2x10 ⁻⁷
		Two-State (73)	-0.79	2.2	-0.65	4.1x10 ⁻¹⁰
		Multi-State (35)	-0.34	-1.0	-0.30	8.5x10 ⁻² NS
		Alpha (33)	-0.54	0.87	-0.61	1.7x10 ⁻⁴
		Beta (34)	-0.87	3.2	-0.69	5.2x10 ⁻⁶
		Mixed (41)	-0.11	-4.5	-0.10	5.4x10 ⁻¹ NS
		Maxwell (28)	-0.44	-1.4	-0.37	5.0x10 ⁻² NS
log L	log k _f	Full (108)	-5.7	13	-0.69	2.0x10 ⁻¹⁶
		Two-State (73)	-4.9	12	-0.57	1.4x10 ⁻⁷
		Multi-State (35)	-8.0	18	-0.82	1.4x10 ⁻⁹
		Alpha (33)	-4.3	11	-0.75	4.3x10 ⁻⁷
		Beta (34)	-6.2	13	-0.74	5.5x10 ⁻⁷
		Mixed (41)	-5.7	13	-0.63	1.2x10 ⁻⁵
		Maxwell (28)	-0.69	3.6	-0.09	6.6x10 ⁻¹ NS
log L	log k _u	Full (108)	-10	18	-0.78	6.5x10 ⁻²³
		Two-State (73)	-11	20	-0.79	6.2x10 ⁻¹⁷
		Multi-State (35)	-11	21	-0.72	1.1x10 ⁻⁶
		Alpha (33)	-8.7	17	-0.81	9.4x10 ⁻⁹
		Beta (34)	-12	21	-0.87	2.1x10 ⁻¹¹
		Mixed (41)	-6.8	11	-0.60	4.0x10 ⁻⁵
		Maxwell (28)	-5.4	8.6	-0.46	1.4x10 ⁻²
log L	log k _f = log k _u	Full (108)	-8.1	15	-0.76	1.4x10 ⁻²¹
		Two-State (73)	-9.3	17	-0.76	9.5x10 ⁻¹⁵
		Multi-State (35)	-7.6	15	-0.77	5.9x10 ⁻⁸
		Alpha (33)	-7.8	16	-0.83	3.1x10 ⁻⁹
		Beta (34)	-11	19	-0.87	3.2x10 ⁻¹¹
		Mixed (41)	-4.3	7.4	-0.59	4.9x10 ⁻⁵
		Maxwell (28)	-3.2	5.6	-0.38	4.8x10 ⁻²
log L	ΔG_{F-U}	Full (108)	-5.9	6.7	-0.53	4.8x10 ⁻⁹
		Two-State (73)	-8.3	11	-0.69	1.4x10 ⁻¹¹
		Multi-State (35)	-4.6	4.6	-0.30	7.6x10 ⁻² NS
		Alpha (33)	-6.1	7.5	-0.65	3.7x10 ⁻⁵
		Beta (34)	-8.0	11	-0.70	5.0x10 ⁻⁶
		Mixed (41)	-1.5	-2.6	-0.11	5.1x10 ⁻¹ NS
		Maxwell (28)	-6.4	6.8	-0.43	2.4x10 ⁻²

Individual correlations and linear fits are shown for subsets of the data as in Fig. 1. Additionally, values for the commonly used dataset of Maxwell et al. are shown for comparison.

^a two-tailed probability value.

^{NS} Correlation is not significant at the 0.05 level (5.0×10^{-2}).

$\Delta G_{F-U} = G_F - G_U = -RT \ln (k_f / k_u)$, where R is the gas constant and T is the absolute temperature in Kelvin, gives the Gibbs free energy of the folded state relative to the unfolded state.

$\log k_f = \log k_u$ where the thermodynamic stability of the protein is zero, is used to correct for the possible effects of differing stabilities.

Relative Contact Order (RCO) is calculated as by Plaxco et al. [1].

Absolute Contact Order (ACO) is calculated as by Ivankov et al. [2].

Long Range Order (LRO) is calculated as by Gromiha et al. [3].

Short Range Order (SRO), local contact order (LocalCO), and non-local contact order (NonLocalCO) are calculated as by Zou and Ozkan [4].

Total Contact Distance (TCD) is calculated as by Zhou and Zhou [5].

Clustering Coefficient (CC) is calculated as by Micheletti [6].

N_{α} was calculated as by Ouyang and Liang [7].

In the case of all of the above parameters the original equations and cutoffs were used, except for definitions of contact, which were all made consistent with ACO by counting a contact between residues when any heavy atoms had a distance $< 6.0 \text{ \AA}$.

Various dependencies on length were suggested by various works [8-13].

Table SII. Dataset

Protein Name	PDB (residues)	Kinetic State	Class	PDB Length	$\log k_f = \log k_u^a$	$\log k_f$ (s^{-1}) ^a	$\log k_u$ (s^{-1}) ^a	ΔG_{F-U} (kcal/mol)	Source
Colicin E7 immunity protein	1AYI	Two	α	85	1.22	3.13	1.00	-2.90	[14]
Telomeric protein DNA-binding domain, human	1BA5	Two	α	49	0.69	2.56	0.52	-2.78	[15]
Immunoglobulin binding B-domain	1BDD (2-59)	Two	α	58	2.52	5.08	1.82	-4.44	[15]
16th domain of brain α -spectrin	1CUN (7-112)	Two	α	106	-0.87	2.08	-2.61	-6.40	[15]
17th domain of brain α -spectrin	1CUN (113-219)	Two	α	107	-1.48	1.48	-3.39	-6.64	[15]
FADD death-domain, human	1E41 (93-192)	Two	α	100	-0.26	2.95	-1.30	-5.81	[15]
Rap1 myb-domain, human	1FEX	Two	α	59	1.69	3.56	1.26	-3.14	[15]
Myb transforming protein	1IDY	Two	α	54	1.35	3.78	0.74	-4.15	[15]
Colicin E9 immunity protein	1IMQ	Two	α	85	-0.61	3.17	-0.83	-5.45	[14]
Trp-Cage Miniprotein	1L2Y	Two	α	20	5.65	5.43	4.99	-0.59	[15]
Lyme disease variable surface antigen	1L8W (29-335)	Two	α	307	-2.04	0.88	-3.68	-6.22	[14]
Lambda repressor	1LMB	Two	α	80	2.26	4.52	1.39	-4.27	[14]
Acyl-coenzyme A binding protein, cow	1NTI	Two	α	86	-0.13	3.04	-1.69	-6.46	[14]
Protein yjbJ	1RYK	Two	α	69	2.78	3.95	1.95	-2.73	[14]
BBA5 mini-protein	1T8J	Two	α	23	5.43	5.12	5.73	0.83	[15]
15th domain of brain alpha-spectrin	1U5P	Two	α	110	1.74	4.78	0.13	-6.34	[15]
Villin Headpiece	1VII	Two	α	36	4.60	4.08	2.30	-2.43	[16]
Dihydrolipolysine acetyltransferase, <i>G. stearothermophilus</i>	1W4G	Two	α	45	2.52	4.44	1.30	-4.28	[17]
Dihydrolipolysine succinyltransferase, <i>E. coli</i>	1W4H	Two	α	45	4.00	5.11	3.78	-1.82	[17]
Pyruvate dehydrogenase E2, <i>P. aerophilum</i>	1W4J	Two	α	51	3.26	5.32	2.74	-3.52	[17]
<i>de novo</i> designed 3-helix bundle	2A3D	Two	α	73	5.39	5.30	3.30	-2.73	[16]
Peripheral subunit-binding domain, Dihydrolipoamide acetyltransferase	2PDD	Two	α	42	4.26	4.26	2.35	-2.61	[18]

E3-binding domain of BBL	2WXC	Two	α	47	3.47	4.86	2.87	-2.73	[15]
Cold shock protein, <i>B. caldolyticus</i>	1C9O	Two	β	66	0.09	3.13	-0.17	-4.50	[15]
Cold shock protein, <i>B. subtilis</i>	1CSP	Two	β	67	1.17	2.82	1.00	-2.49	[15]
Formin Binding Protein 28	1E0L	Two	β	37	4.00	4.60	3.73	-1.18	[15]
WW prototype	1E0M	Two	β	37	3.34	3.87	3.08	-1.07	[15]
9th fibronectin domain	1FNF	Two	β	90	-0.96	-0.39	-1.26	-1.18	[15]
Cold shock protein, <i>T. maritima</i>	1G6P	Two	β	66	-1.13	2.74	-1.74	-6.10	[15]
Hisactophilin	1HCD	Two	β	117	-2.82	1.35	-4.69	-8.23	[19]
sso7d	1JIC	Two	β	62	0.26	3.04	-1.39	-6.04	[15]
Abp1 SH3 domain	1JO8	Two	β	58	-0.91	1.09	-1.17	-3.08	[14]
Fibronectin type III WL-12 chitinase A1	1K85 (559-644)	Two	β	86	-1.65	0.61	-3.04	-4.98	[15]
E2 component alpha-ketoacid dehydrogenase	1K8M	Two	β	87	-2.04	-0.39	-3.39	-4.09	[15]
Yes kinase-associated protein	1K9Q (5-44)	Two	β	40	3.04	3.65	2.91	-1.01	[15]
Internalin B SH3 domain	1M9S (391-466)	Two	β	76	0.04	1.74	-0.74	-3.38	[14]
Cold shock protein, <i>E. coli</i>	1MJC	Two	β	69	0.69	2.30	0.61	-2.31	[15]
Beta-hairpin	1PGB (41-56)	Two	β	16	5.21	5.21	5.21	0.00	[15]
PinWW	1PIN (6-39)	Two	β	34	3.95	4.04	1.82	-3.02	[15]
PI3 SH3 domain	1PNJ	Two	β	84	-2.08	-0.43	-3.17	-3.73	[15]
Oncoprotein p13mtcp1	1QTU (1-109)	Two	β	109	-3.69	0.00	-4.78	-6.52	[15]
Fyn SH3 domain	1SHF	Two	β	59	-0.87	2.13	-1.87	-5.45	[14]
Spectrin SH3 domain	1SHG	Two	β	57	-1.61	0.48	-2.08	-3.50	[14]
Src SH3 domain	1SRL	Two	β	56	0.17	1.91	-0.56	-3.38	[14]
Fibronectin type III tenascin	1TEN	Two	β	89	-1.91	0.48	-3.34	-5.21	[15]
18th module of muscle protein twitchin	1WIT	Two	β	93	-2.56	0.17	-3.56	-5.09	[15]
Sho1 SH3 domain	2VKN	Two	β	66	-0.35	0.92	-1.08	-2.73	[14]
Symfoil1	3O49	Two	β	123	-3.08	0.74	-3.91	-6.34	[20]
Symfoil4P	3O4D	Two	β	123	-4.69	2.13	-5.99	-11.08	[20]

ThreeFoil	3PG0	Two	β	140	-7.43	-3.87	-8.95	-6.93	[21]
Muscle acylphosphatase	1APS	Two	$\alpha\beta$	98	-3.17	-0.69	-3.91	-4.38	[14]
C-terminal domain of protein L9	1DIV (58-149)	Two	$\alpha\beta$	92	-1.91	1.43	-3.43	-6.64	[14]
N-terminal domain of protein L9	1DIV (1-56)	Two	$\alpha\beta$	56	0.83	2.87	0.00	-3.90	[14]
LysM Domain	1E0G	Two	$\alpha\beta$	48	1.61	3.04	1.02	-2.75	[15]
FK506 binding protein	1FKB	Two	$\alpha\beta$	107	-2.26	0.69	-3.52	-5.75	[14]
Apoflavodoxin, <i>Anabaena</i>	1FTG	Two	$\alpha\beta$	168	-0.09	1.22	-1.17	-3.26	[15]
Tm1083	1J5U	Two	$\alpha\beta$	123	-0.39	2.97	-2.28	-7.17	[14]
Chemotaxis protein CheW	1K0S	Two	$\alpha\beta$	143	-2.17	3.21	-5.25	-11.55	[14]
Cyclophilin A	1LOP	Two	$\alpha\beta$	164	-1.30	2.87	-4.52	-10.07	[15]
Ribosomal protein L23	1N88	Two	$\alpha\beta$	96	-1.04	0.87	-1.69	-3.50	[14]
ADAh2	1O6X	Two	$\alpha\beta$	81	0.65	2.95	-0.17	-4.27	[14]
B1 domain of protein G	1PGB	Two	$\alpha\beta$	56	-0.17	2.74	-0.74	-4.74	[14]
Histidine containing phosphocarrier protein	1POH	Two	$\alpha\beta$	85	-1.30	1.17	-2.69	-5.27	[15]
C-terminal domain of spore coat protein S	1PRS (91-173)	Two	$\alpha\beta$	83	-3.52	-0.87	-4.04	-4.32	[15]
N-terminal domain spore coat protein S	1PRS (1-90)	Two	$\alpha\beta$	90	-2.00	1.30	-4.08	-7.35	[15]
Ras binding domain	1RFA	Two	$\alpha\beta$	78	-0.09	3.65	-1.22	-6.64	[14]
Ribosomal protein S6	1RIS	Two	$\alpha\beta$	97	-1.69	2.65	-3.60	-8.53	[14]
Src SH2 domain	1SPR	Two	$\alpha\beta$	103	-0.61	3.78	-1.52	-7.23	[14]
Ubiquitin	1UBQ	Two	$\alpha\beta$	76	-0.65	3.17	-2.95	-8.35	[14]
Spliceosomal protein U1A	1URN	Two	$\alpha\beta$	96	-0.17	2.01	-5.09	-9.68	[14]
Common-type acylphosphatase	2ACY	Two	$\alpha\beta$	98	-1.91	0.35	-2.82	-4.32	[15]
Chymotrypsin inhibitor 2	2CI2	Two	$\alpha\beta$	64	-1.52	2.52	-4.47	-9.54	[14]
B1 domain of Protein L	2PTL (18-77)	Two	$\alpha\beta$	60	-0.61	1.78	-1.43	-4.38	[14]
Pit1 homeodomain	1AU7 (103-160)	Multi	α	58	3.21	4.21	2.08	-2.90	[15]
FKBP-Rapamycin binding domain	1AUE	Multi	α	92	-1.04	2.61	-2.35	-6.75	[15]
p19ink4d CDK inhibitor	1BD8	Multi	α	156	-0.83	1.26	-1.00	-3.08	[15]

Engrailed homeodomain	1ENH	Multi	α	54	3.52	4.56	3.30	-1.72	[15]
Acyl-coenzyme A binding protein, yeast	1ST7	Multi	α	86	-0.17	3.69	2.78	-1.24	[15]
FF domain, human hypa	1UZC	Multi	α	69	1.00	3.30	0.61	-3.67	[15]
Tumour suppressor protein p16	2A5E (9-156)	Multi	α	148	0.17	1.52	0.09	-1.95	[15]
Phage 434 cro protein	2CRO	Multi	α	64	0.13	1.61	-0.22	-2.49	[15]
T4 lysozyme	2LZM	Multi	α	164	-2.48	1.78	-6.08	-10.72	[15]
Myotrophin	2MYO	Multi	α	118	-0.13	2.04	-1.39	-4.68	[15]
Ileal lipid binding protein	1EAL	Multi	β	127	-1.22	0.56	-2.13	-3.67	[15]
Intestinal fatty acid binding protein	1IFC	Multi	β	131	-1.22	1.48	-2.00	-4.74	[15]
FGF-1	1JQZ	Multi	β	136	-2.87	0.56	-3.08	-4.98	[20]
Cellular retinol binding protein II	1OPA	Multi	β	133	-2.17	0.61	-4.00	-6.28	[15]
Barnase	1RNB	Multi	β	109	-1.87	1.13	-3.95	-6.93	[15]
Titin IG repeat 27	1TIU	Multi	β	89	-3.00	1.56	-3.30	-6.64	[15]
10th type III fibronectin domain	1TTF	Multi	β	94	-0.22	2.39	-3.65	-8.23	[15]
Apical domain of GroEL	1AON (191-345)	Multi	$\alpha\beta$	155	-1.48	-0.65	-2.48	-2.49	[15]
Third PDZ domain from PSD-95	1BFE	Multi	$\alpha\beta$	110	-0.09	1.30	-1.48	-3.79	[15]
Barstar	1BTA	Multi	$\alpha\beta$	89	-0.61	1.48	-1.17	-3.61	[15]
Cellular retinoic acid binding protein I	1CBI	Multi	$\alpha\beta$	136	-2.91	-1.39	-4.26	-3.91	[15]
PDZ2 domain from PTP-BL	1GM1	Multi	$\alpha\beta$	94	-0.52	0.35	-1.00	-1.84	[15]
Hydrogenase maturation protein	1GXT	Multi	$\alpha\beta$	88	-0.35	1.91	-2.95	-6.64	[15]
Indole-3-glycerolphosphate synthase	1IGS (27-248)	Multi	$\alpha\beta$	222	-3.87	-2.00	-5.91	-5.33	[15]
Staphylococcal nuclease	1JOO	Multi	$\alpha\beta$	149	-2.30	1.00	-3.65	-6.34	[15]
C-terminal domain of phosphoglycerate kinase	1PHP (176-394)	Multi	$\alpha\beta$	219	-2.21	-1.69	-4.69	-4.09	[15]
N-terminal domain of phosphoglycerate kinase	1PHP (1-175)	Multi	$\alpha\beta$	175	-0.56	1.00	-1.82	-3.85	[15]
Trp-Synthase α -subunit	1QOP (Chain A)	Multi	$\alpha\beta$	265	-2.48	-1.09	-3.87	-3.79	[15]
Dihydrofolate reductase	1RA9	Multi	$\alpha\beta$	159	-2.26	-1.39	-2.65	-1.72	[15]

Cell-cycle regulatory protein p13suc1	1SCE	Multi	$\alpha\beta$	97	-0.43	1.82	-2.65	-6.10	[15]
Carbonic anhydrase	1V9E	Multi	$\alpha\beta$	259	-4.60	-1.82	-10.42	-11.73	[15]
Ribonuclease H1, <i>E. coli</i>	2RN2	Multi	$\alpha\beta$	155	-2.00	0.04	-5.21	-7.17	[15]
Villin 14T	2VIK	Multi	$\alpha\beta$	126	-0.69	2.17	-1.78	-5.39	[15]
Chemotactic protein	3CHY	Multi	$\alpha\beta$	128	-0.56	0.43	-1.91	-3.20	[15]
Ribonuclease H1, <i>C. tepidum</i>	3H08	Multi	$\alpha\beta$	139	-1.74	0.83	-6.08	-9.42	[15]
Average (# proteins)									
Full (108)					-0.28	2.00	-1.50	-4.77	
Two-State (74)					0.02	2.42	-1.03	-4.71	
Multi-State (34)					-1.06	1.08	-2.50	-4.89	
Alpha (33)					1.54	3.50	0.68	-3.84	
Beta (34)					-0.83	1.54	-1.78	-4.53	
Mixed (41) ^b					-1.30	1.17	-3.01	-5.71	
Maxwell (28) ^c					-0.54	2.27	-1.81	-5.56	
Min (# proteins)									
Full (108)					-7.43	-3.87	-10.42	-11.73	
Two-State (74)					-7.43	-3.87	-8.95	-11.55	
Multi-State (34)					-4.60	-2.00	-10.42	-11.73	
Alpha (33)					-2.48	0.88	-6.08	-10.72	
Beta (34)					-7.43	-3.87	-8.95	-11.08	
Mixed (41) ^b					-4.06	-2.00	-10.42	-11.73	
Maxwell (28) ^c					-3.17	-0.69	-5.23	-11.55	
Max (# proteins)									
Full (108)					5.65	5.43	5.73	0.83	
Two-State (74)					5.65	5.43	5.73	0.83	
Multi-State (34)					3.52	4.56	3.30	-1.24	
Alpha (33)					5.65	5.43	5.73	0.83	
Beta (34)					5.21	5.21	5.21	0.00	
Mixed (41) ^b					1.61	3.78	1.02	-1.72	
Maxwell (28) ^c					2.78	4.52	1.95	-2.73	
Standard Deviation (# proteins)									
Full (108)					2.40	1.88	2.92	2.53	
Two-State (74)					2.60	1.83	2.92	2.52	
Multi-State (34)					1.66	1.66	2.69	2.58	
Alpha (33)					2.27	1.36	2.59	2.25	
Beta (34)					2.59	1.75	2.90	2.42	
Mixed (41) ^b					1.29	1.63	2.05	2.57	
Maxwell (28) ^c					1.32	1.23	1.85	2.37	

^a all values refer to 25 °C

^b Mixed refers to the $\alpha\beta$ structure class.

^c the set "Maxwell" is listed as source "[14]".

$\log k_f = \log k_u$ is the experimentally determined mid-transition (denaturation midpoint) folding (equal to unfolding) rate, where the thermodynamic stability of the protein is zero.

$\Delta G_{F-U} = G_F - G_U = -RT \ln (k_f / k_u)$, where R is the gas constant and T is the absolute temperature in Kelvin (298.15), gives the Gibbs free energy of the folded state relative to the unfolded state.

Table SIII. Single Mutation Effects on Folding and Unfolding Rates

Protein	Number of Mutations	Average Change in k_f (x-fold) ^a	Average Change in k_u (y-fold) ^a	Relative change (y-fold / x-fold)
Muscle AcP	22	3.16	8.12	2.57
FKBP12	34	2.25	29.64	13.18
L23	17	2.03	104.11	51.35
CTL9	24	3.98	131.22	33.00
α -spectrin SH3 (D48G)	14	5.12	13.45	2.63
CI2	65	3.32	65.21	19.64
Src-SH3	54	2.79	9.22	3.30
Protein L	68	1.75	44.83	25.60
Fyn-SH3	34	7.01	26.90	3.84
bACBP	30	3.54	134.25	37.89
Ubiquitin	27	4.41	232.79	52.75
Protein G	31	2.87	14.97	5.22
ADA2h	18	1.78	4.70	2.64
NTL9	24	1.94	18.48	9.54
sso7d	20	2.15	7.19	3.35
CspB	21	3.01	7.89	2.62
Im9	25	12.32	83.70	6.80
cyt b562	39	2.82	173.39	61.59
yACBP	18	5.28	161.14	30.54
FBP28 WW	45	1.40	2.83	2.02
E3DB (F166W)	22	3.30	16.80	5.08
BdpA (Y15W)	45	2.84	12.97	4.57
BdpA (N29H,Q33W)	20	1.70	9.32	5.49
BpdA (E48W)	20	2.35	6.39	2.72
POB (L146A, Y166W)	22	3.37	6.99	2.07
Per Protein Average ^b	25	3.46	53.06	15.34
Per Mutation Average ^c	759	3.30	52.58	15.95

^a change is calculated as $e^{|\ln k_{wt} - \ln k_{mut}|}$. Thus, a two-fold slower rate or two-fold faster rate for the mutant would both be a 2.0 fold change in rate. Reported values are the average across all mutations for that protein.

^b average across the dataset weighting each protein equally.

^c average across the dataset weighting each mutation equally.

It should be noted that the vast majority of mutations in the dataset [22] are simple truncation mutations and hence, the relationships shown may not be representative of a more general set of mutations.

References: Supplementary Information

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