Supporting Information

GGM repeats

The 1PCQ crystal structure was augmented with unstructured Gly-Gly-Met C-terminal repeats from the wild type sequence of GroEL using MacPymol. The Gly-Gly-Met repeats were built into a set of seven helices bundled cylindrically to fit inside GroEL. The repeats alone were simulated with a stochastic Langevin integrator at 1500 K for 60 ps, and the resulting randomized configuration was grafted onto the 1PCQ crystal structure. The tails tended to tangle at the bottom of the chamber, although on the time scale simulated it is unlikely that they could be considered to have equilibrated conformationally. The 5 nm-tall waist of the cavity in which waters were counted, however, was chosen to be just above where the tails tended to extend, in order to minimize the impact of this slow time scale on measurements.

Definition of the Water Layer

The water layer considered was 5 nm in height, measured from 1 nm below the center of mass of the chaperonin (just above the tangle of GGM repeats) to 4 nm above the center of mass. This region was chosen to encompass both mutated loci on the chaperonin surface. In four angstrom vertical slices, r.m.s. radius d of alpha carbons was calculated, and waters were counted whose oxygens lay between d and d – 1 nm of the z-axis. The cutoff of 1 nm was originally chosen as an approximate range within which solvent-mediated forces started to come into play in previously published simulations, but when we varied the cutoff from 0.5 nm to 1.5 nm we found the high correlation to be robust to this variation (Figure S1)

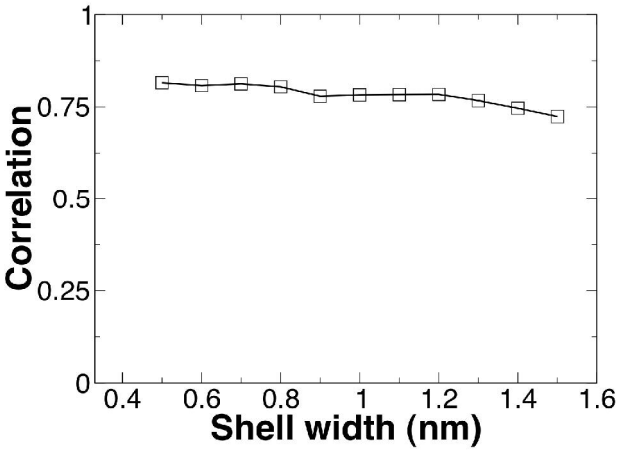


Figure S1
R-squared for waters in surface layer versus experimental folding rate of DM-MBP as a function of surface layer width.

The definition we chose for the water layer tends to count the waters in the deepest grooves in the surface of the cavity. This tendency arises because radially thicker parts of the chaperonin will tend to exclude more volume from a broader range of radii less than the mean-square radius within which the water layer is measured. The result of this criterion is a water layer that is thinner in the narrower part of the chaperonin cavity, where the cavity walls are thicker. Since maltose binding protein is broad enough (~ 7 nm measured in 1OMP.pdb from www.rcsb.org) that it would be expected to fit quite snugly inside the chaperonin (a cavity that ranges from roughly 5.5 to 8.5 nm in diameter) it is sensible to employ a measure that leads naturally to a thinner water lay where the cavity is narrower. As is apparent in Figure S2, our measure fits this description, and it should be noted that an alternative possible explanation to the one suggested in the text for the observed difference between the impact on folding of mutations at loci 253 and 359 is that locus 253 resides higher up in the cavity, where the water layer is thinner.

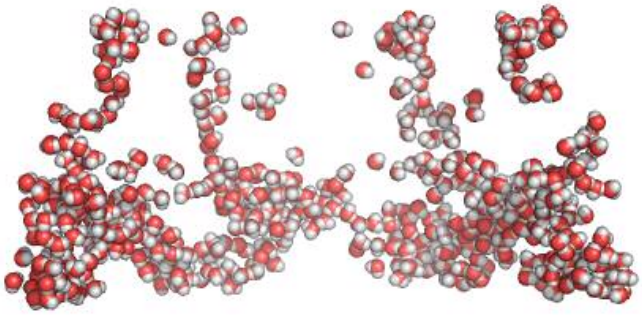
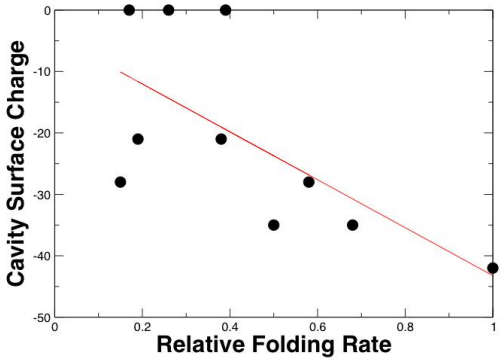
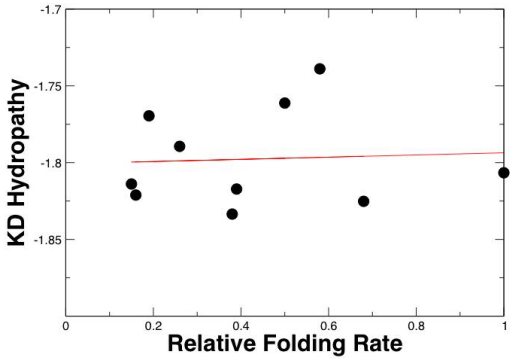


Figure S2
Waters counted in a layer between radius d and d – 1 nm for one frame of the wild type trajectory.

Alternative predictors

We plotted both cavity surface charge and area-weighted Kyte-Doolittle hydropathy of each mutant against experimentally measured folding rate to test their ability to predict chaperonin activity. The correlation coefficient for surface charge was –.66, while for KD hydropathy it was .06:


Cavity Surface Charge
0
-10
-20
-30
-40
-50
0
0.2
0.4
0.6
0.8
1
Relative Folding Rate


KD Hydropathy
-1.7
-1.75
-1.8
-1.85
0
0.2
0.4
0.6
0.8
1
Relative Folding Rate