Supplemental information:

Standard REMD simulations were carried out with Amber version 8 [31]. For trpzip2 all covalent bonds were constrained using SHAKE [32]. A 2fs time step was used and temperatures were maintained using weak coupling [33] to a bath with a time constant of 0.5 ps^{-1}. All non-bonded interactions were calculated at each time step (i.e. no cutoff was used). In order to permit comparison to our previously published data, the simulations used the Amber ff99 force field with modified backbone parameters [34]. Steepest descent energy minimization was performed for 500 steps prior to REMD simulations. Simulations used the Generalized Born solvation model [35] with GB^{HCT} [36] implementation in Amber. Scaling factors were taken from the TINKER modeling package [37].

Standard REMD simulations were performed using 14 replicas for trpzip2, covering a temperature range of ~260 – 570K with an expected exchange probability of 15%. Additional replicas were manually placed between 300 K and 370 K to increase statistics around the experimentally observed melting transition. Exchanges between neighboring replicas were attempted at 1ps intervals. R-REMD simulations employed the same temperature distribution with the exception that replicas at temperatures above 400K were replaced by the reservoir, as described previously. [28]

Cluster analysis was performed using MOIL-View [38] , using backbone RMSD as a similarity criterion with average linkage. Clusters were formed with a bottom-up approach using a similarity cutoff of 2.0 Å.