

FIGURE 45.1 Amyloid fibril formation arises from the concentration-dependent self-assembly of natively unfolded polypeptides (top) or partially denatured proteins (bottom) and ultimately proceeds through multiple intermediates to form the final cross- β -sheet amyloid fibril.

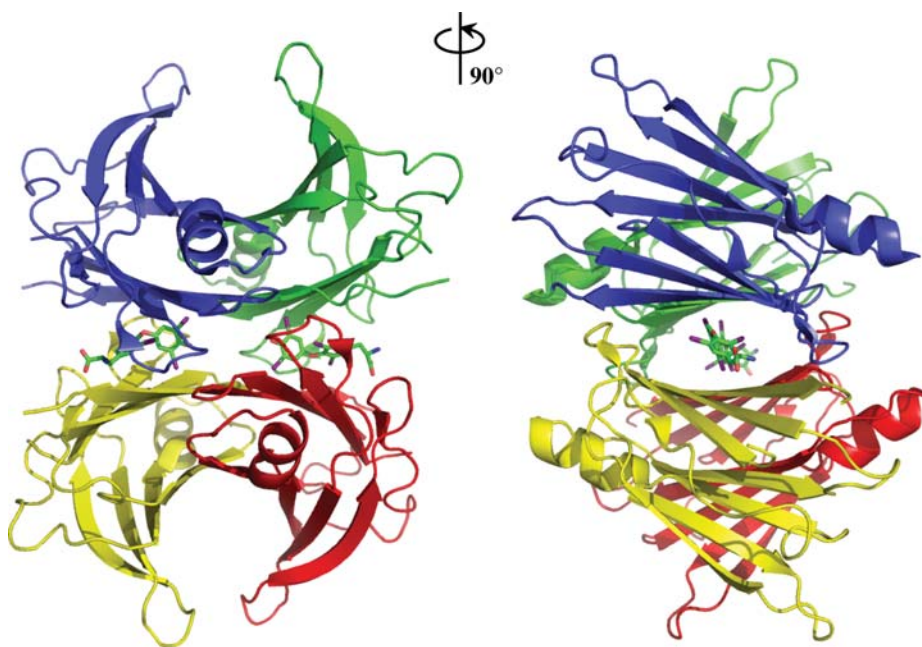


FIGURE 45.2 Structure of the TTR tetramer, with each monomer depicted in a different color, with thyroxine bound along the crystallographic two fold axis in each of two symmetry related thyroxine-binding sites. (From [162], with permission. Copyright © 2008 American Chemical Society.)

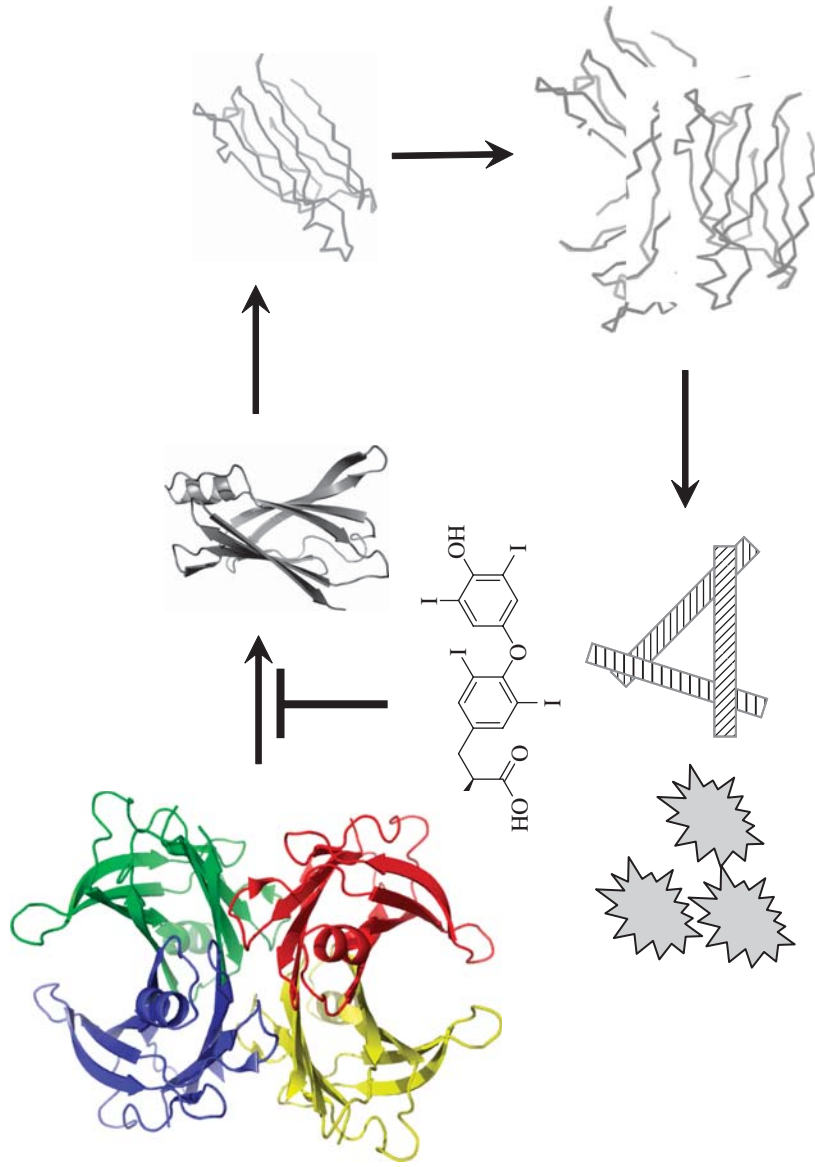


FIGURE 45.3 TTR amyloidogenesis cascade. The TTR tetramer dissociates into four folded monomers which must undergo partial denaturation in order, subsequently, to misassemble into a spectrum of aggregate structures, including protofibrils, cross- β -sheet amyloid fibrils, and amorphous aggregates.

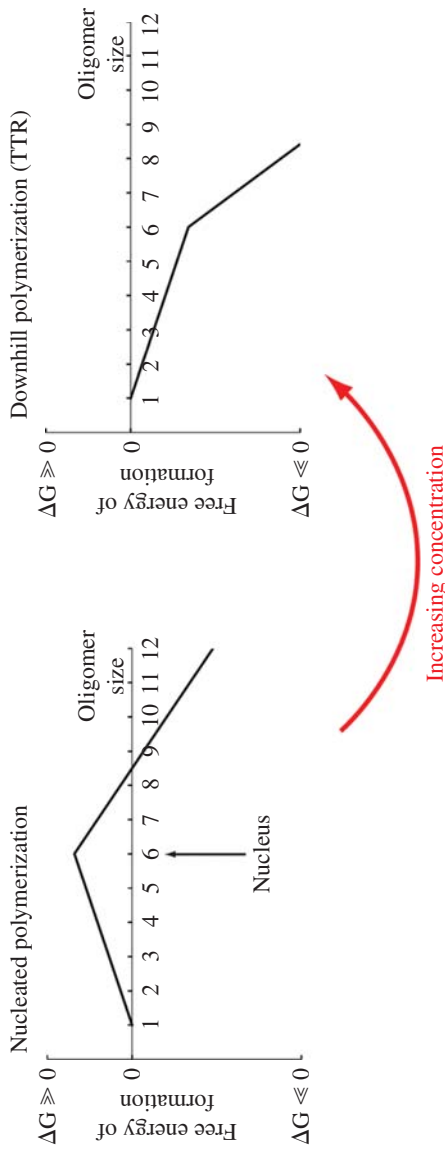


FIGURE 45.4 Amyloidogenesis can occur by way of a nucleated polymerization or through a downhill polymerization mechanism. TTR always appears to aggregate through a downhill mechanism, whereas A β fibrillization proceeds through a high-energy nucleus at relatively low concentration ($< \mu\text{M}$) and can become a downhill polymerization at high concentration.

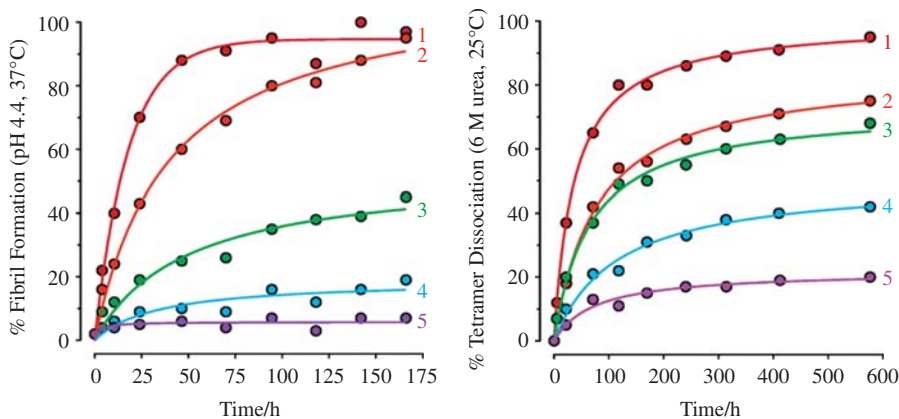
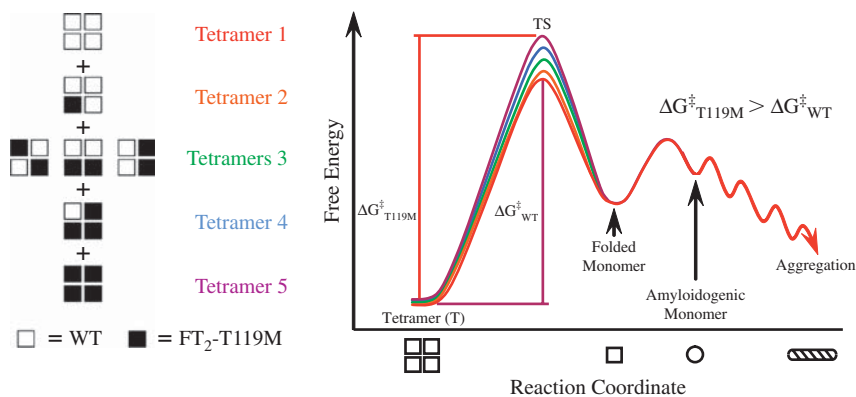


FIGURE 45.5 Interallelic trans-suppression ameliorates TTR amyloid disease by making the TTR dissociation barrier increase proportional to the number of T119M TTR suppressor subunits in the tetramer otherwise composed of subunits that can engage in amyloidogenesis. (From [71], with permission. Copyright © 2005 American Chemical Society.)

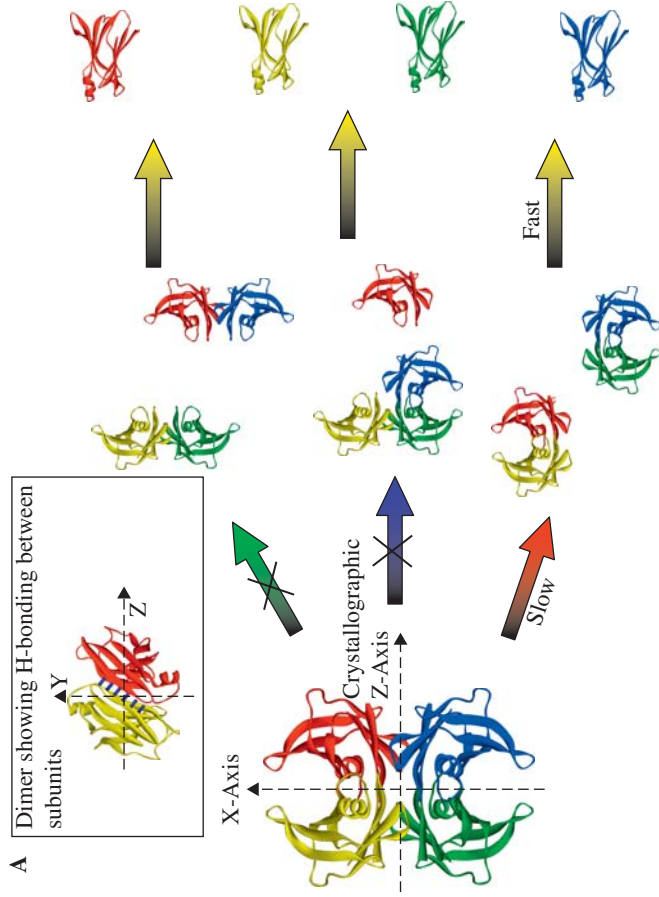


FIGURE 45.6 (A) The TTR tetramer could dissociate through numerous mechanisms, many of which are shown. The operational mechanism is shown at the bottom, wherein the dimers dissociate from the tetramer about the interface incorporating the crystallographic Z-axis.

B

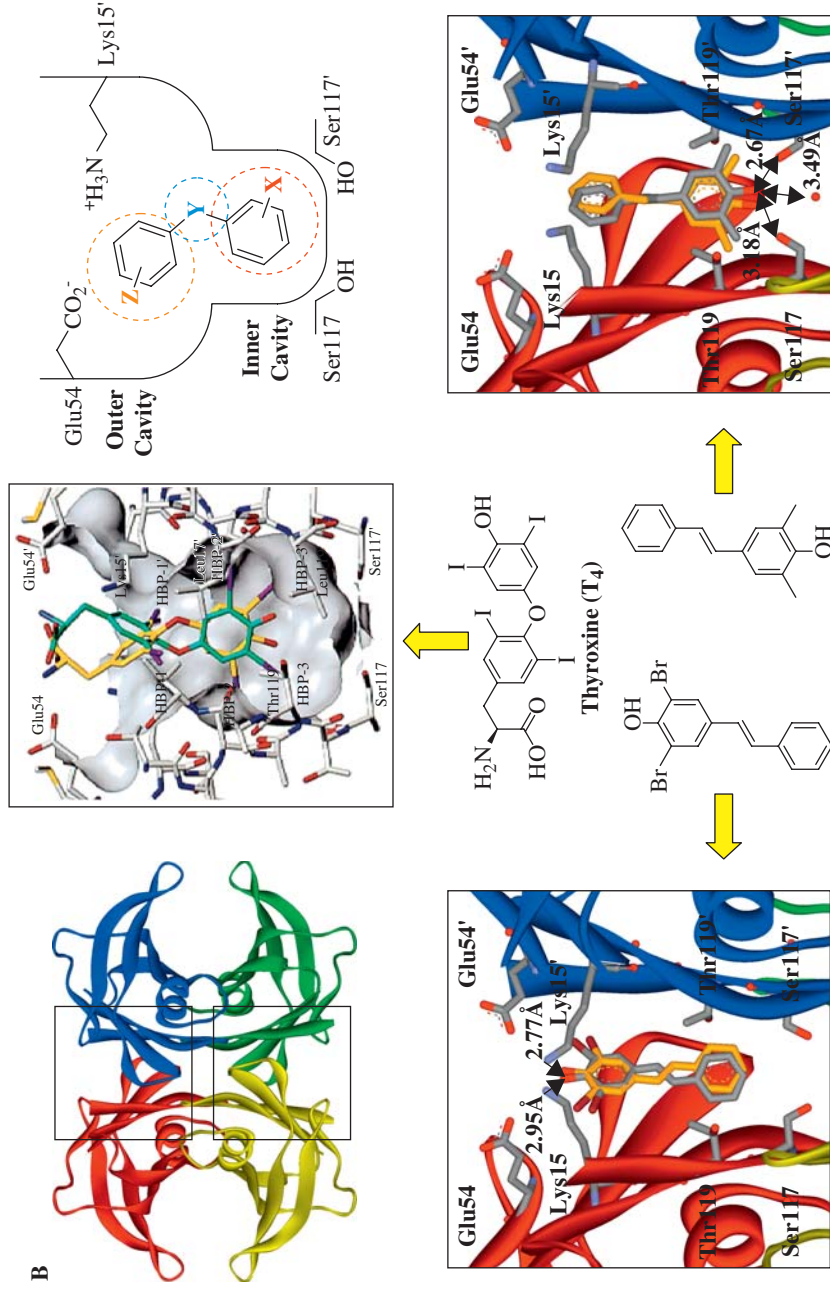


FIGURE 45.6 (B) Dissociation through this mechanism is prevented through kinetic stabilization of the tetramer by binding of at least one ligand to one of the two thyroxine-binding sites. (From [162], with permission. Copyright © 2008 American Chemical Society.)

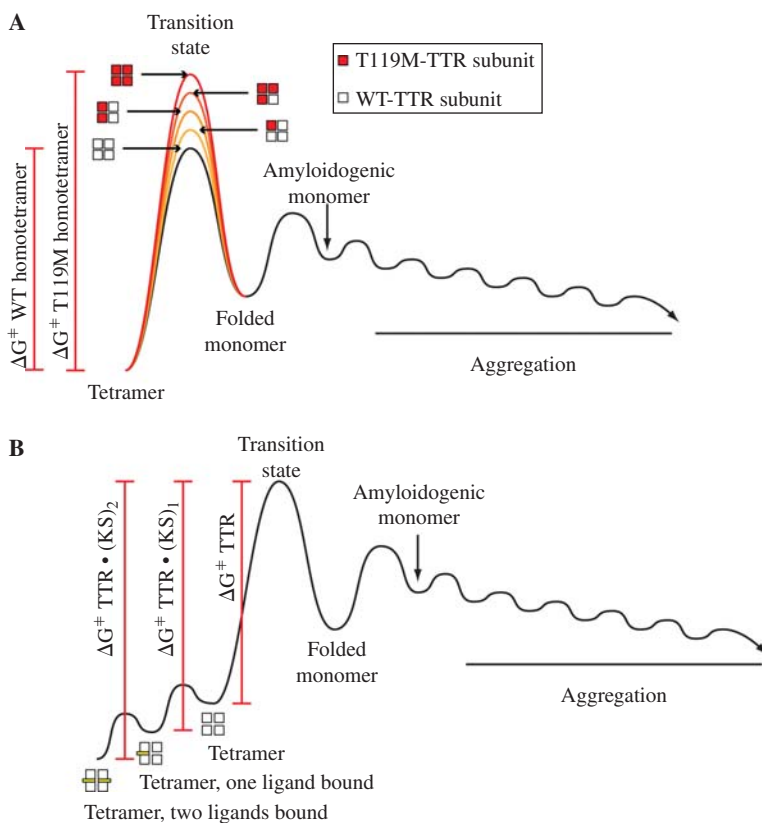


FIGURE 45.8 Kinetic stabilization of TTR by way of interallelic trans-suppression through T119M subunit incorporation into the tetramer (A) or small-molecule binding (B) equivalently increase the tetramer dissociation barrier preventing amyloidogenesis and pathology. (From [71], with permission. Copyright © 2005 American Chemical Society.)

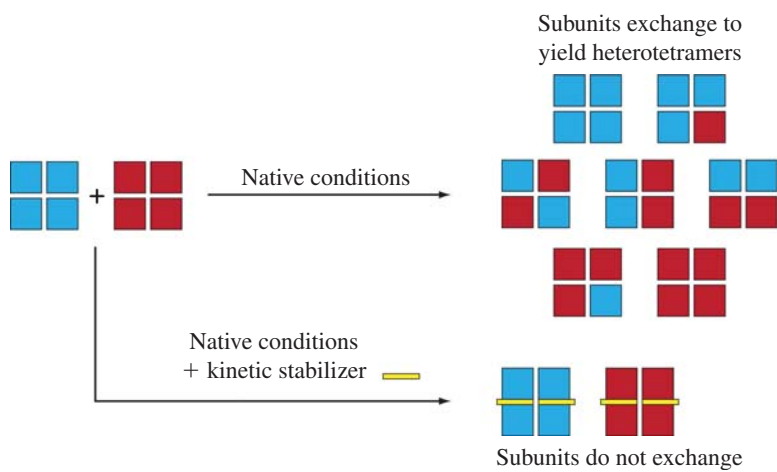


FIGURE 45.9 Subunit exchange method to demonstrate that TTR kinetic stabilizers prevent TTR subunit exchange under physiological conditions.

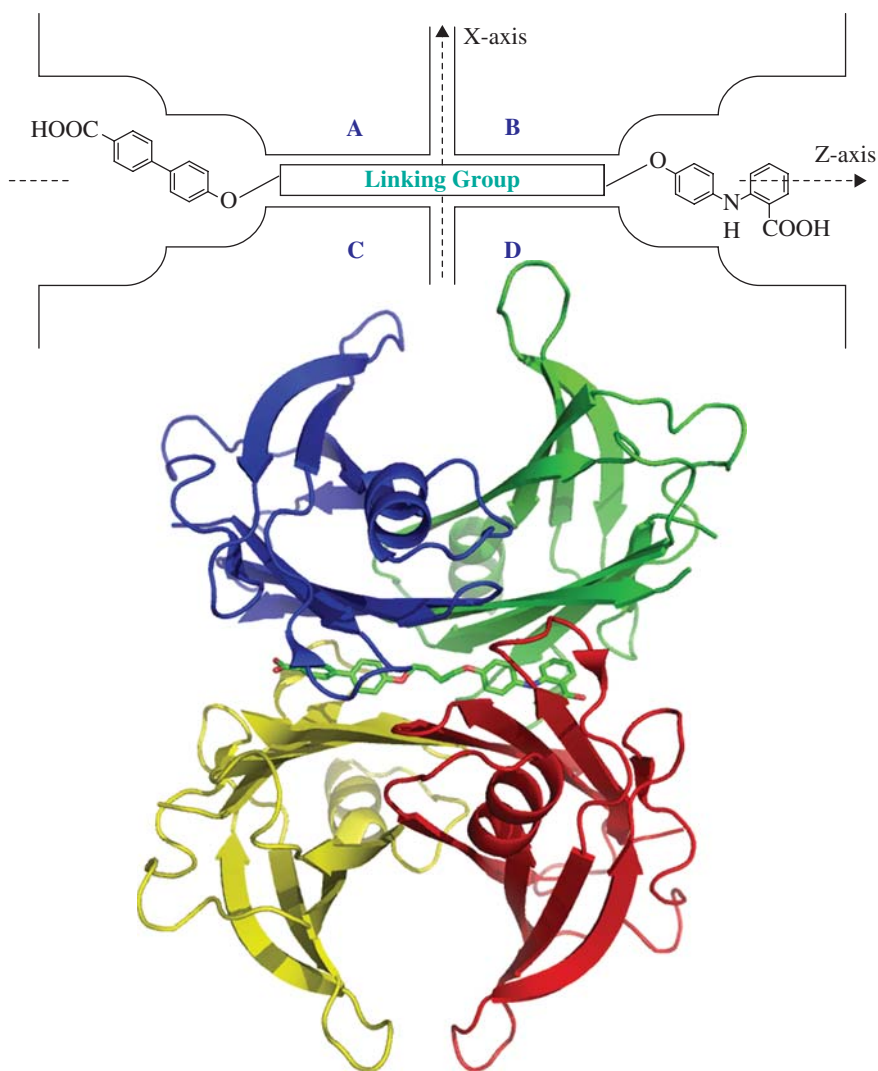


FIGURE 45.10 Kinetic stabilization of the TTR tetramer can be accomplished by the design and synthesis of ligands that template TTR tetramer formation within the endoplasmic reticulum by simultaneously occupying both thyroxine-binding sites. (From [162], with permission. Copyright © 2008 American Chemical Society.)