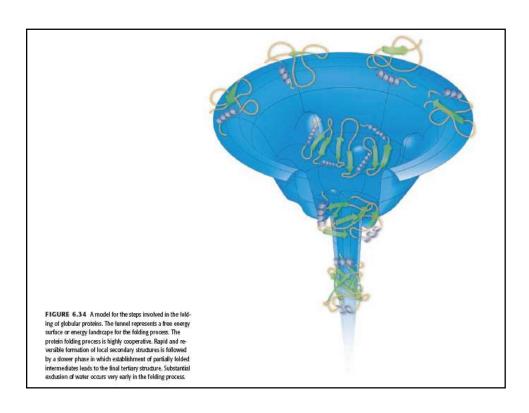
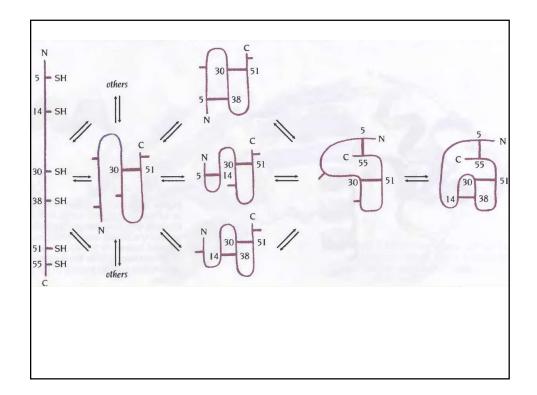


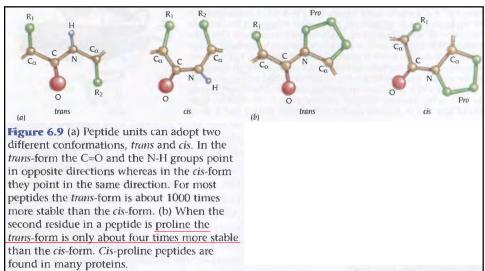
**Figure 6.3** The unfolded state is an ensemble of a large number of conformationally different molecules,  $U_1...U_m$ , which undergo rapid interconversions. The molten globule is an ensemble of structurally related molecules,  $M_1...M_m$ , which are rapidly interconverting and which slowly change to a single unique conformation, the folded state F. During the folding process the protein proceeds from a high energy unfolded state to a low energy native state. The conversion from the molten globule state to the folded state is slow and passes through a high energy transition state, T.



Many proteins can fold spontaneously *in vitro*, although some appear to fold more slowly/less accurately than they do *in vivo*. Although the primary sequence ultimately dictates tertiary structure, several obstacles to correct folding exist, including:

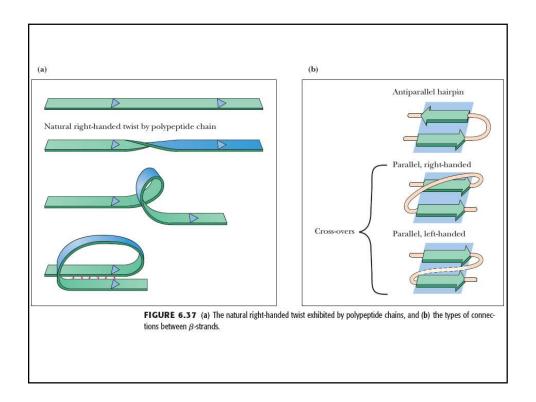
- aggregation of partially folded intermediates via intermolecular hydrophobic interactions;
- isomerization of proline residues;
- formation of disulfide linkages between incorrect pairs of cysteine residues.





Isomerization of proline residues can be a rate-limiting step in protein folding

Cis-trans isomerization of proline peptides is intrinsically a slow process and *in vitro* it is frequently the rate-limiting step in folding for those molecules that have been trapped in a folding intermediate with the wrong isomer.



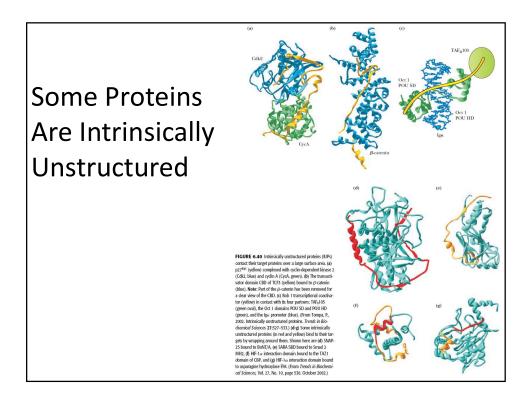


TABLE 6.3 Aggregation Sym of Globular Prote	
Protein	Number of Subunits
Alcohol dehydrogenase	2
Malate dehydrogenase	2
Superoxide dismutase	2
Triose phosphate isomerase	2
Glycogen phosphorylase	2
Aldolase	3
Bacteriochlorophyll protein	3
Concanavalin A	4
Glyceraldehyde-3-phosphate dehydrogenase	4
Immunoglobulin	4
Lactate dehydrogenase	4
Prealbumin	4
Pyruvate kinase	4
Phosphoglycerate mutase	4
Hemoglobin	2 + 2
msum	0
Aspartate transcarbamoylase	6+6
Glutamine synthetase	12
TMV protein disc	17
Apoferritin	24
Coat of tomato bushy stunt virus	180

