observed for CypB (endoplasmic reticulum), CypD (mitochondrial inner membrane), CypE (nucleus) and RanBP2 (nuclear pore).[13] Studies directed at the functional characterization of CypA, CypB, CypD and Cyp40 have been reported over the last 20 years; however, native roles for the majority of the family and potential roles in disease states have not yet been elucidated.

11.1.1.2 PPIase Activity of Cyclophilins

Several mechanisms by which Cyps catalyze the *cis–trans* isomerization of an Xaa–Pro bond have been proposed; however, the currently accepted mode of catalysis is based on distortion of the planar amide bond (Figure 11.2).[14] Binding of a proline-containing substrate in a manner that twists the amide bond leads to a lower barrier to rotation due to loss of amide resonance.[15] An important protonation of the prolyl amide by an active site residue (side chain of [Arg][55] in CypA) facilitates the formation of a pyramidal nitrogen, which is a key feature of the isomerization.[16] Notably, mutation of [Arg][55] results in a 'catalytically inactive' form of CypA, which has been extensively used as a mechanistic probe.[17] Crystal structure analysis of several proline-containing substrate peptides bound to human CypA revealed that all ligands evaluated bound with the Xaa–Pro bond in the *cis* configuration and with no distortion from planarity.[18] Since most Xaa–Pro amide bonds reside preferably (5–6-fold preference) in the *trans* configuration, Ke and Huai proposed that the principal role of Cyps is to facilitate a *trans* to *cis* isomerization.[18]

While the PPIase activity of Cyps has been well studied, several additional roles for Cyps have been described. Binding of CypA or CypB to CD-147/EMMPRIN (an extracellular receptor for CypA) leads to activation of MAP kinase pathways and induction of matrix metalloproteinase (MMP) production.[19] A role for CypA as an inflammatory chemotactic cytokine, acting through the CD-147/EMMPRIN receptor, was revealed using models of asthma in which blocking the CypA–CD-147 interaction with anti-CD-147 or CsA resulted in a significant decrease in neutrophil and eosinophil migration and improved lung pathology.[20] Further roles for extracellular Cyps in renal fibrosis and ischemia-reperfusion injury have been described with CD-147/EMMPRIN being a key activating receptor.[21]

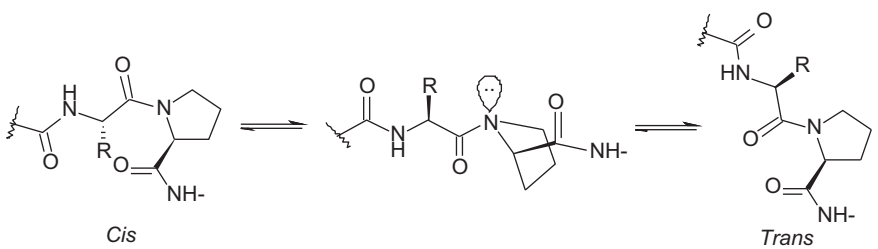

Figure 11.2 Proposed mechanism of PPIase action involving a twisted amide bond and a pyramidalized nitrogen.