In polar solvents such as DMSO, water or THF charged with LiCl, this intramolecular hydrogen-bonding network is disrupted and at least in the latter case (THF–LiCl), the amide bond between [MeLeu]^{9} and [MeLeu]^{10} is now *trans*.[30] CsA also resides in this conformation when bound to Cyp. In addition, it has been shown that temperature can influence CsA conformational structure in polar solvent.[31]

11.1.2.2 Binding Pharmacophores

CsA exerts its immunosuppressive activity by binding to two proteins sequentially to form a ternary complex (Figure 11.3).[32] The first of these is a Cyp, which is a *cis–trans* proline isomerase, with the most predominant of the human Cyps being CypA.[33,34] The binary CsA–CypA complex binds to and is a potent inhibitor of the phosphatase activity of CaN, a calcium-dependent, serine/threonine phosphatase that promotes the synthesis of T-cell lymphokines such as interleukin-2 (IL-2). Thus, CaN inhibition ultimately suppresses the immune response.

X-ray crystallography has revealed which residues of CsA bind to CypA and CaN.[35–37] Figure 11.3 shows that residues 9, 10, 11, 1 and 2 form the 'Cyp binding domain' that binds to CypA, whereas residues 4, 5, 6 and 7 comprise the 'CaN binding domain' that binds to CaN. Residues 3 and 8 are at interfaces between these two binding domains and can potentially have an impact on both CypA and CaN binding.

In addition to various autoimmune diseases that can be addressed by CaN inhibition, there are a variety of diseases that are treated by Cyp inhibition alone, most notably the infectious diseases caused by human immunodeficiency virus-1 (HIV-1)[38] and HCV,[39] both of which are addressed in Section 11.2. In such cases in which Cyp inhibition alone is sought, it is preferred to use a drug that does not bind CaN and is therefore non-immunosuppressive, particularly when combating a viral disease in which a functional immune response is needed. In such cases, it is necessary to modify the cyclosporine synthetically such that CaN binding is inhibited.

11.2 Cyclophilins Involved in Viral Replication

11.2.1 Human Immunodeficiency Virus

HIV-1, the parasitic virus causing AIDS, depends heavily on host cellular machinery for its survival, replication and infectivity. CypA is the first cellular protein ever found to be incorporated into HIV-1 virions. Subsequently, a significant number of publications have suggested several roles of CypA in the HIV life cycle,[38] all of which are independent of CaN and the NFAT pathway.

Initial reports of CsA inhibiting HIV-1 surfaced in 1988,[40] although the first report specifically implicating CypA involvement in the HIV-1 life cycle was published 5 years later, when it was reported that endogenous CypA colocalizes with the HIV-1 Gag protein in the cytoplasm, binding specifically to