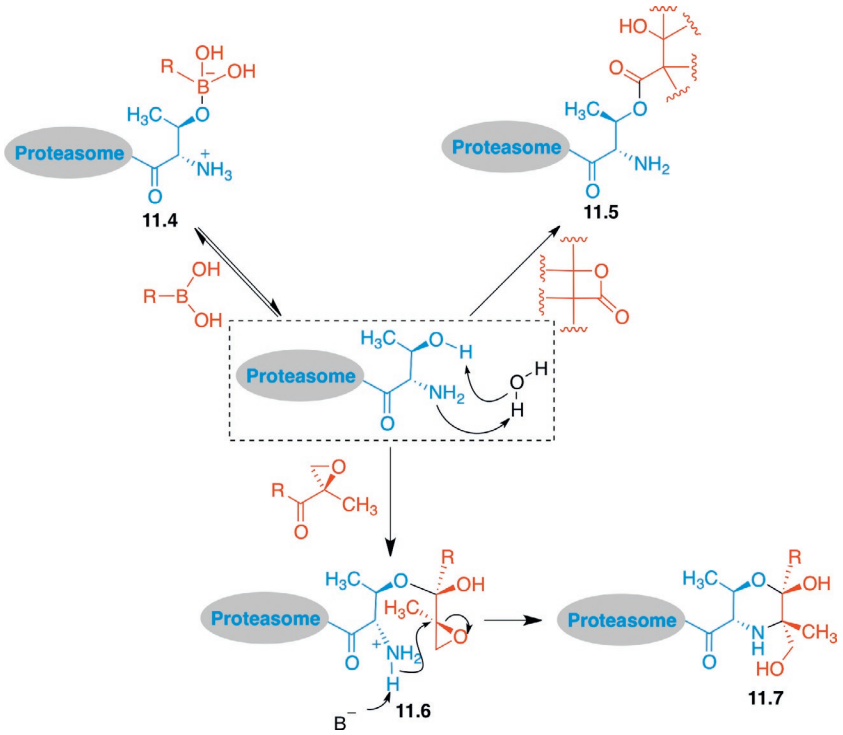

FIGURE 11.9

Mechanisms of proteasome inhibition by boronic acids, β-lactones, and α,β-epoxy ketones.

The interaction of peptide boronic acids is due to the availability of an empty *p*-orbital on boron atoms that can accept the oxygen lone pair of N-terminal threonine residues to form stable tetrahedral intermediates **11.4**,[16] whereas fused β-lactone derivatives are probably opened by the Thr oxygen to give esters **11.5**. Finally, α,β-epoxy ketones generate hemiacetals **11.6** by addition of the Thr oxygen to the carbonyl group, and this is followed by nucleophilic attack of the amino group onto the more hindered epoxide carbon atom with inversion of its configuration to form morfoline derivatives **11.7**. This mechanism has been confirmed by X-ray crystal diffraction and spectrometric analysis of the complex formed by natural proteasome inhibitor epoxomycin and the yeast *Saccharomyces cerevisiae* 20S proteasome (Figure 11.9).[17]

2.1.2 NEDD8-Activating Enzyme Inhibitors

There are several proteins related to ubiquitin that have their own ligases and are known as ubiquitin-like (UbL) proteins. One UbL pathway of particular interest is NEDD8, whose E1-activating enzyme is known as NEDD8-activating enzyme (NAE). In the first step of the activation process, MgATP and NEDD8 yield NEDD8–AMP, which reacts with the thiol of a cysteine residue in the NAE active site to form the NAE–NEDD8 thioester and release AMP. A second NEDD8–AMP is