Extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2, respectively) play a critical role in regulating cell division and have been implicated in cancer. In addition to activation by MAPK/ERK kinases 1 and 2, certain mutants of ERK2 can be activated by autophosphorylation. To identify the mechanism of autoactivation, we have performed a series of molecular dynamics simulations of ERK1 and ERK2 in various stages of activation as well as the constitutively active Q103A, I84A, L73P, and R65S ERK2 mutants. Our simulations indicate the importance of domain closure for autoactivation and activity regulation, with that event occurring prior to folding of the activation lip and of loop L16.