NMR and small molecule directed studies of enzyme dynamics

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Protein dynamics is an essential component of protein folding and stability, ligand binding, enzyme catalysis, and allosteric transmission. Given this broad range of influence, it is expected that dynamics plays a role in essentially any protein-mediated process. Relatively few experimental studies have investigated how protein dynamics interplay with small molecule drugs. To address this problem, we have characterized how the dynamics of dihydrofolate reductase (DHFR) responds to a series of structurally related inhibitors. Using relaxation dispersion NMR, we observed an overall correlation between rates of DHFR conformational switching and inhibitor dissociation, although conformational switching was faster. Based on this finding, we propose that internal protein motion serves as a mechanical initiator for dissociation in DHFR, and potentially for other receptor-ligand complexes. In addition, we found that one inhibitor induces widespread apparent motion in the enzyme. Interestingly, much of this motion is due to large-scale conformational switching of the inhibitor itself.