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**Dynamics and intramolecular ligand binding of DtxR studied by MD simulations and NMR spectroscopy** MYUNGGI YI, Inst. of Mol. Biophys. and Dept. of Phys., NILAKSHEE BHATTACHARYA, TIMOTHY LOGAN, Inst. of Mol. Biophys. and Dept. of Chem. and Biochem., HUAN-XIANG ZHOU, Inst. of Mol. Biophys. and Dept. of Phys. Florida State Univ. — Diphtheria toxin repressor (DtxR) regulates the expression of the diphtheria toxin gene through intramolecular ligand binding (Wylie et al., Biochemistry 2005, 44:40-51). Protein dynamics is essential to the binding process of the Pro-rich (Pr) ligand to the C-terminal SH3 domain. We present MD and NMR results on the dynamics and ligand interactions of a Pr-SH3 construct of DtxR. NMR relaxation data (T1, T2, and NOE) showed that the Pr ligand is very flexible, suggesting that it undergoes binding/unbinding transitions. A 50-ns MD trajectory of the protein was used to calculate T1, T2, and NOE, reproducing the NMR results for the SH3 domain but not for the Pr segment. During the MD simulation, the ligand stayed bound to the SH3 domain; thus the simulation represented the bound state. The NMR data for the Pr-segment could be explained by assuming that they represented the average behavior of a fast binding/unbinding exchange. Though unbinding was not observed in the MD simulation, the simulation did show large fluctuations of a loop which forms part of the wall of the binding pocket. The fluctuations led to opening up of the binding pocket, thus weakening the interaction with the Pr segment and perhaps ultimately leading to ligand unbinding.

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