Separations consume an estimated 10-15% of global energy. With the expectation that energy consumption will increase with population growth and the implementation of large-scale carbon capture efforts, there is intensive focus on developing new adsorbents. This feat is difficult, as the differences in the molecules of interest, such as CO₂ and N₂—the main components in post-combustion flue gas, are minimal. As such, separations require tailor-made adsorbents with molecule specific chemical interactions on their internal surface. One such solution, metal-organic frameworks (MOFs), are constructed by metal-ions or metal-ion clusters that are interlinked by organic ligands. Their unprecedented internal surface areas promote the adsorption of large quantities of guests. Further, the molecular nature of the organic ligands allows structural tunability, the introduction of multifunctional properties, and a modular approach to their design. As such, MOFs offer unmatched opportunities to achieve optimal efficiencies in many separations. New MOFs are regularly reported; however, to develop better materials in a timely manner, the interactions between guests and the internal MOF surface must first be understood. In this presentation, studies focused on understanding the structure-derived function of MOFs will be presented. Particular emphasis will be placed on applying in-situ x-ray and neutron diffraction techniques to elucidate small-molecule interactions in several MOF families that undergo extensive chemical substitution. The latter can provide a platform to test the efficacy and accuracy of developing computational methodologies in slightly varying chemical environments, a task that is necessary for their evolution into viable, robust tools for screening hypothetical materials.