Under the mounting threat of climate change, increasing atmospheric methane concentrations are a constant source of concern and debate. Conversion of methane to desirable fuels and chemicals could simultaneously mitigate global warming and meet increasing energy demands. Industrial catalysts that can selectively activate the 105 kcal mol⁻¹ C-H bond in methane require high temperatures and pressures, along with significant capital expenses. The use of biocatalysts produced by methane-consuming (methanotrophic) bacteria provides an environmentally friendly alternative. The primary biocatalyst in methanotrophic bacteria is the copper-dependent, membrane-bound enzyme particulate methane monooxygenase (pMMO). Any use of methanotrophs for biological gas-to-liquids conversion or for bioremediation requires a detailed understanding of pMMO structure and function. Despite extensive research, the molecular details of the pMMO copper active site remain controversial, in part because the enzyme loses activity upon isolation from methanotroph membranes. Thus, it is critical to structurally characterize pMMO in its native cellular environment. Our quest to achieve molecular characterization of pMMO in situ will be discussed.