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Complete Reaction Cycle of a Cocaine Catalytic Antibody at Atomic Resolution. Xueyong Zhu¹, Tobin J. Dickerson^{2,3}, Claude J. Rogers^{2,3}, Gunnar F. Kaufmann^{2,3}, Jenny M. Mee^{2,3}, Kathleen M. McKenzie^{2,3}, Kim D. Janda^{2,3,4,*}, Ian A. Wilson^{1,4}, Depts. of Molecular Biology¹ & Chemistry² & Immunology³, The Skaggs Inst. for Chemical Biology⁴, The Scripps Research Inst., 10550 North Torrey Pines Rd., La Jolla, CA 92037, USA.

Abuse of cocaine is a major public health problem, and has been a significant social problem since the late 70's and early 80's when crack-cocaine was first introduced. Unfortunately, FDA-approved treatments do not exist for cocaine abuse, addiction, and overdose. Immunopharmacotherapy has been proposed as a promising means to treat cocaine abuse. The murine cocaine catalytic antibody 7A1 hydrolyzes of the benzoate ester of cocaine to produce the nonpsychoactive metabolites ecgonine methyl ester and benzoic acid. 7A1 Fab' fragment and six complexes with substrate cocaine, transition state analog, both products (ecgonine methyl ester and benzoate), one product ecgonine methyl ester, and finally the other product benzoate, as well as heptaethylene glycol were determined at 1.5-2.3 Å resolution. Here, we present the snapshots of the complete cycle of the cocaine antibody catalytic reaction at atomic resolution. Significant conformational changes occur along the 7A1-catalyzed cocaine hydrolysis pathway, but are generally limited to the active site, including some key residues and ligands themselves. Antibody CDR loop movements (up to 2.3 Å) and substantial side-chain rearrangements (up to 9 Å) alter the shape and size (~ 320 - 500 Å³) of the antibody active site from "open" to "closed" to "open" for the substrate, transition state and product states, respectively. From this comprehensive series of crystal structures, the catalytic mechanism is discussed, and the possible mutations have been proposed to explore how to improve catalytic proficiency.