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Enzyme promiscuity is defined as the ability of enzymes to catalyze alternate substrate or catalytic reactions apart from their native physiological relevant enzymatic activity. These promiscuous activities usually have low catalytic efficiency and are considered futile in metabolism. However, these secondary adventitious reactions become essential under environmental or genetic perturbation wherein they serve as precursors for evolving new enzymatic activities. Owing to the significance of promiscuous enzymes as a source of novel reactions, we investigated various binding and catalytic site features of substrate promiscuous enzymes and contrasted these with specialist enzymes, which are known to catalyze a single substrate. Moreover, the insights into the structural basis of substrate promiscuity would greatly benefit the rational design of an enzyme to catalyze desired substrate(s). Previous anecdotal studies on some enzymes have suggested that flexibility, hydrophobicity, and protonation states of active site residues play an important role in enzyme promiscuity. However, general structural characteristics of substrate promiscuous enzymes have not been studied in detail yet. In this study, we have systematically studied the structural attributes that influence the binding/catalytic residues of known promiscuous and specialist enzymes. The flexibility of substrate binding sites as measured using B-factor, dynamic flexibility index, and graph theoretical approaches showed that these are similar between specialist and generalist enzymes. Further, our analysis coherently indicates structural invariability of the enzymes, which are functionally different in terms of their ability to catalyze alternate substrates. This coherence over a range of structural features suggests that promiscuous enzymes and specialist enzymes broadly share similar attributes. Based on these observed similarities in the structural attributes and known functional plasticity of proteins, we argue that enzyme’s substrate preference or its selectivity is a continuum, which would range from highly specific to multi-specificity.