HYDROGEN BOND NETWORKS FACILITATE THE CONVERSION OF ALIPHATIC ALDEHYDES IN THE CHARGED ACTIVE SITE OF S. CEREVISIAE TRANSKETOLASE

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Naturally, transketolase (TK, E.C. 2.2.1.1) catalyzes asymmetric C-C bond formation in glycolysis derived metabolites to afford carbohydrates for nucleotide synthesis and the production of essential aromatic amino acids.[1] While results obtained earlier in our group showed that a decrease in active site polarity in *S. cerevisiae* transketolase was beneficial for the conversion of non-phosphorylated substrates,[2] the charged mutation D469E was counterintuitively found to promote the conversion of aliphatic aldehydes in *E. coli* transketolase.[3] Here we present a comparative study of the most beneficial single and double point mutants obtained from both reports for the conversion of aliphatic aldehydes using *S. cerevisiae* transketolase.[4] It was confirmed that a complete change of active site polarity is not required for the successful conversion of aliphatic aldehydes and surprisingly was found more beneficial than charge neutral mutations. These results were rationalized in docking studies, where a molecule of water was identified at the center of a hydrogen bond network, essential for substrate binding and correct orientation towards the cofactor, thus allowing the conversion of aliphatic aldehydes in the charged active site of transketolase.

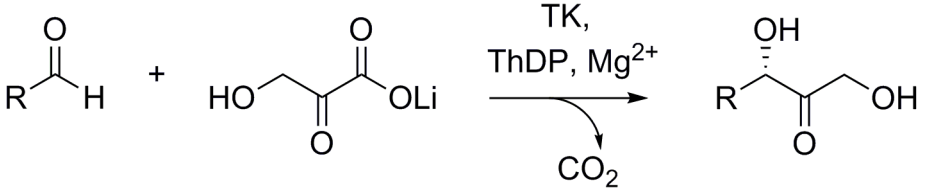

Figure 1: General scheme for the transketolase catalyzed coupling of aliphatic aldehydes with lithium hydroxypyruvate to afford chiral dihydroxyketones.

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