## The Application of QSAR/QSSR Methods for Catalyst Evaluation and Development in Phase Transfer Catalysis

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A series of rigid, stereodefined quaternary ammonium ions, sharing common core scaffolds, were synthesized employing the tandem inter [4+2] / intra [3+2] cycloaddtion of nitroalkenes in the fused mode and were evaluated against a model PTC alkylation reaction. The studies revealed that the introduction of an alkoxy functionality beta to the quaternary nitrogen atom resulted in a profound rate increase in the alkylation reaction, which may be manifested through polarization of the positive potential encompassing the nitrogen atom. Furthermore, systematically modifying the accessibility of two of the four exposed faces of the tetrahedral space enclosing the nitrogen atom resulted in significant variation in both rate and selectivity. In an effort to gain quantifiable insight in relating the variation in the rate to the molecular properties of the catalysts, an 11 descriptor 2d QSAR model was developed. Additional insight on the rate was gained upon relation of the catalysts' overall 3-d structure through the development of a CoMFA model implementing simple steric and electronic fields (Lennard-Jones and coulombic potentials). Similarly, a CoMFA model representing preliminary efforts at relating enantioselectivity to catalyst structure was developed.

## A Structural Basis for Dynamics in OMPDC Catalysis

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Orotidine 5'-monophosphate decarboxylase (OMPDC) is a great model for studying enzyme catalysis because it carries out a difficult reaction, formation of UMP by decarboxylation of OMP, that involves formation of a vinyl carbanion intermediate without the use of any cofactors. In fact, the uncatalyzed rate is $2.8 \times 10^{-16}$ $s^{-1}$ at 25 °C. OMPDC accelerates this extremely slow reaction to the limits of diffusion making it the most proficient [$(k_{cat}/K_M)/\ k_{non} = 4.8 \times 10^{22}$ $M^{-1}s^{-1}$] pure protein catalyst known at physiological pH. It has been shown that 11.6 kcal/mol of the 22.4 kcal/mol reduction in the free energy of activation for OMP decarboxylation relative to the uncatalyzed rate is contributed by the binding energy associated with the phosphodianion group of the OMP substrate. We have obtained evidence that suggests that conformational changes accompany binding of the phosphodianion substituent of OMP. We hypothesize that binding of the phosphate group triggers a change from an open conformation to the closed, catalytically active conformation. The present studies are directed toward understanding the structural features in and around the active site that allow for this conformational change. Mutagenesis of residues that form a hydrophobic cluster proximal to the binding site for the phosphate group but remote from the active site have a specific effect on the value of $K_M$ but not of $k_{cat}$. Experiments utilizing an altered substrate indicate that the increase in $K_M$ is specifically caused by a decreased ability to form the active, closed conformation of the enzyme.