Genomics in Enzymology: Identifying new activities based on sequence alignments and an understanding of the chemistry.
Reviews: Raushel, Gerlt (2003) Current Opinion in Chemical Biology 252-264.
Walker Chemistry and Biology (2002) 9, 1287-96.
Thornton, (2002) J. Mol Biology 321, 41-65.

Definitions:
Homologous enzymes: enzymes that come from a common ancestor and are structurally related. In general structure outlives sequence therefore in many cases it is difficult to make connections by sequence comparisons alone.

Orthologs: Homologs in different species that catalyze the same reaction. (Ex. All the enzymes in the glycolysis pathway and most enzymes in primary metabolism have been evolutionarily conserved)

Paralogs: Homologs in the same species that have diverged from one another by gene duplication. These proteins have different specificity and different catalytic function.

Family: Group of homologous enzymes that share the same reaction and specificity. Most of the time these enzymes have > 30% sequence identity in BLAST comparisons.

Superfamily: Gourp of homologous enzymes that catalyze reactions with different substrate specificity and catalyze a different overall reaction. However, they share a common mechanistic attribute. The enolase superfamily members can stablize and a carbanion adjacent to a carboxylate.

Suprafamily: Homologous enzyme that catalyze different overall reactions with no common mechanistic attributes.

Ref Divergent Evolution of Enzymatic Function Gerlt and Babbitt Ann Rev Biochem 70, 209-46 (2001).

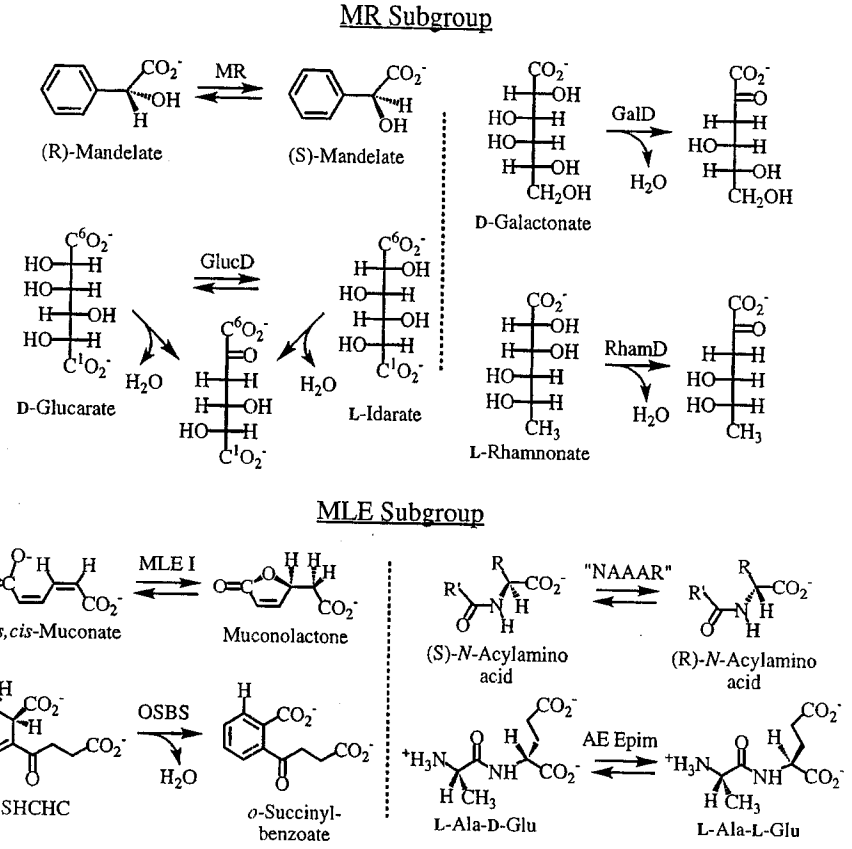


Figure 1 Reactions catalyzed by members of the enolase superfamily.

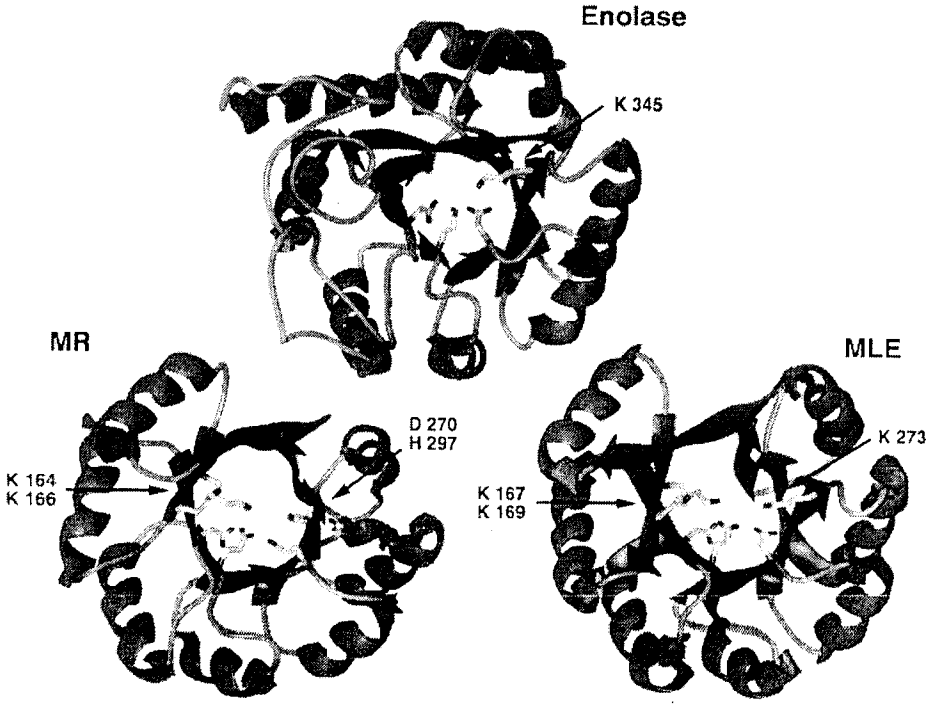
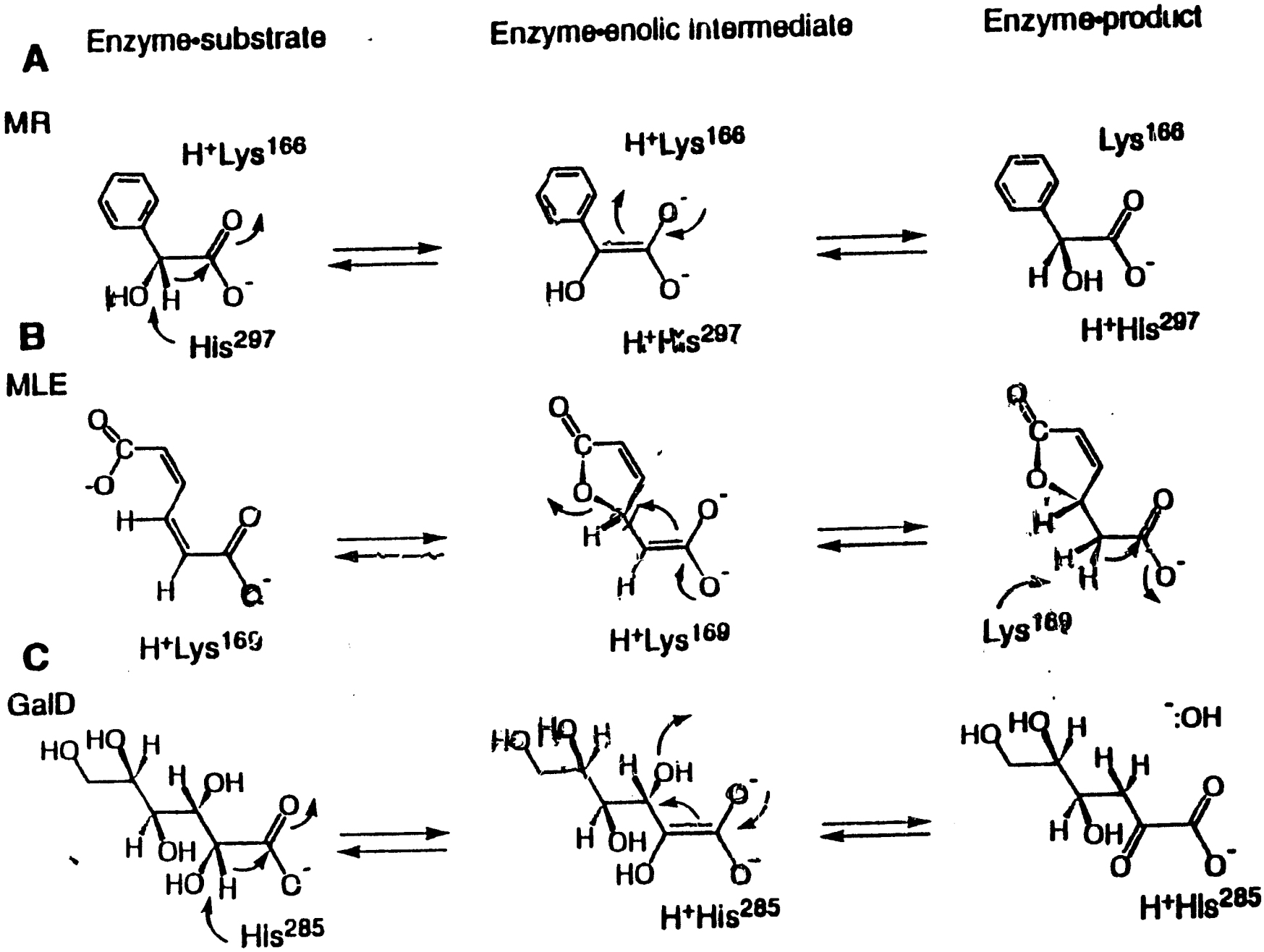
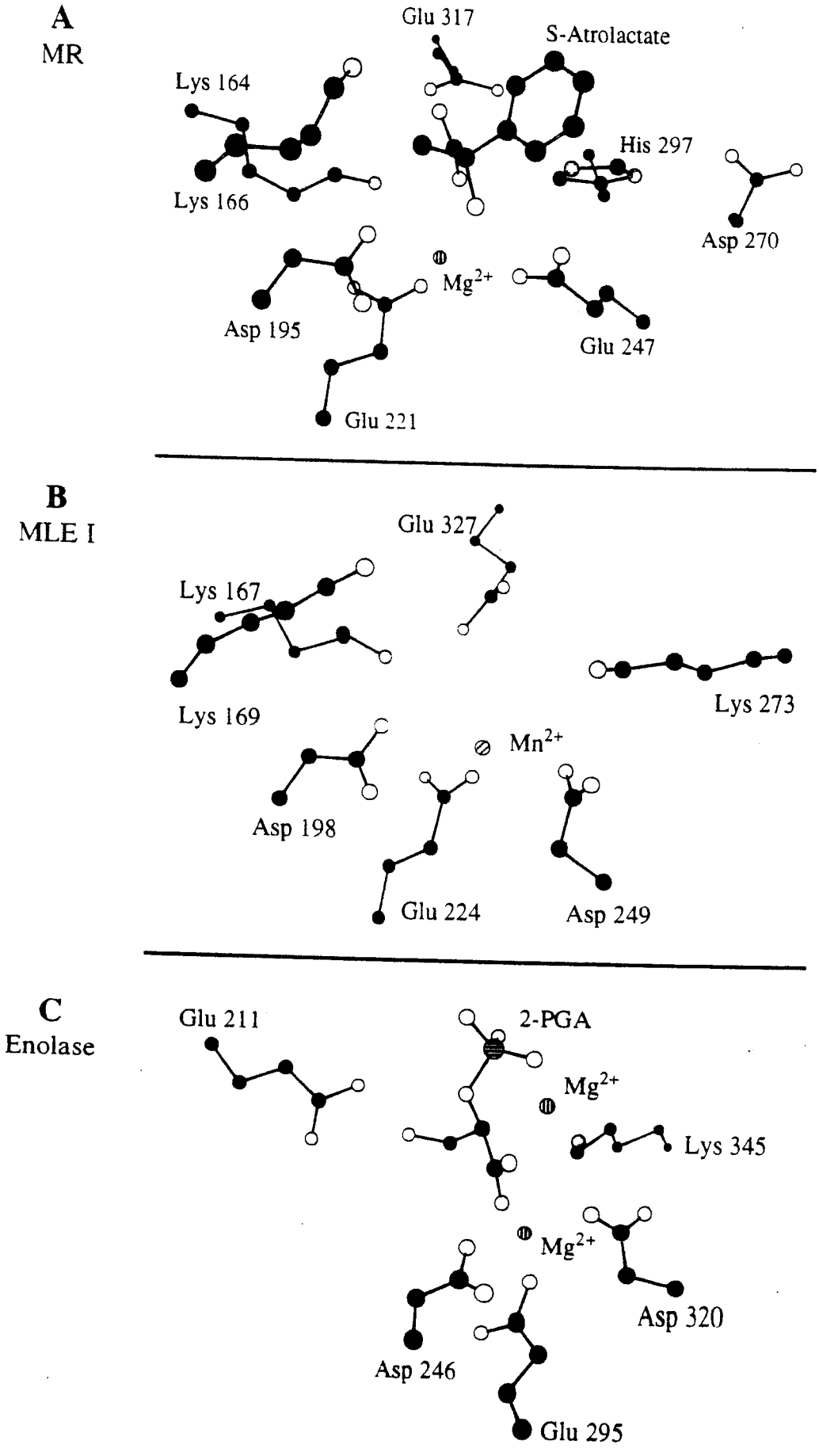


Figure 2 The $(\beta/\alpha)_8$ (TIM) barrel domains of enolase, MR, and MLE, showing the positions of the functional groups in the active site; the identities of the acid/base catalysts are given. β-Sheets are colored blue, α-helices are red.


A
Enzyme-substrate
Enzyme-enolic intermediate
Enzyme-product
MR
H+Lys166
His297
H+Lys166
H+His297
Lys166
H+His297
B
MLE
H+Lys169
H+Lys169
Lys169
C
GalD
His285
H+His285
:OH
H+His285


A
MR
Glu 317
S-Atrolactate
Lys 164
His 297
Lys 166
Asp 270
Mg2+
Asp 195
Glu 247
Glu 221
B
MLE I
Glu 327
Lys 167
Lys 273
Lys 169
Mn2+
Asp 198
Glu 224
Asp 249
C
Enolase
Glu 211
2-PGA
Mg2+
Lys 345
Mg2+
Asp 320
Asp 246
Glu 295

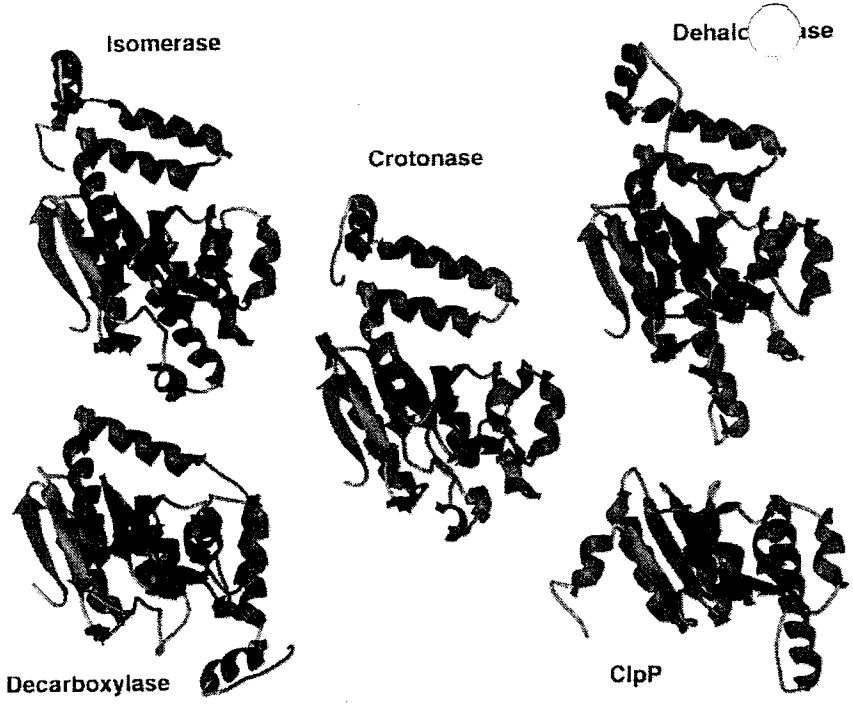


Figure 8 Structures of crotonase, dehalogenase, $\Delta^{3,5}$, $\Delta^{2,4}$-dienoyl CoA isomerase, methylmalonyl CoA decarboxylase, and ClpP protease.

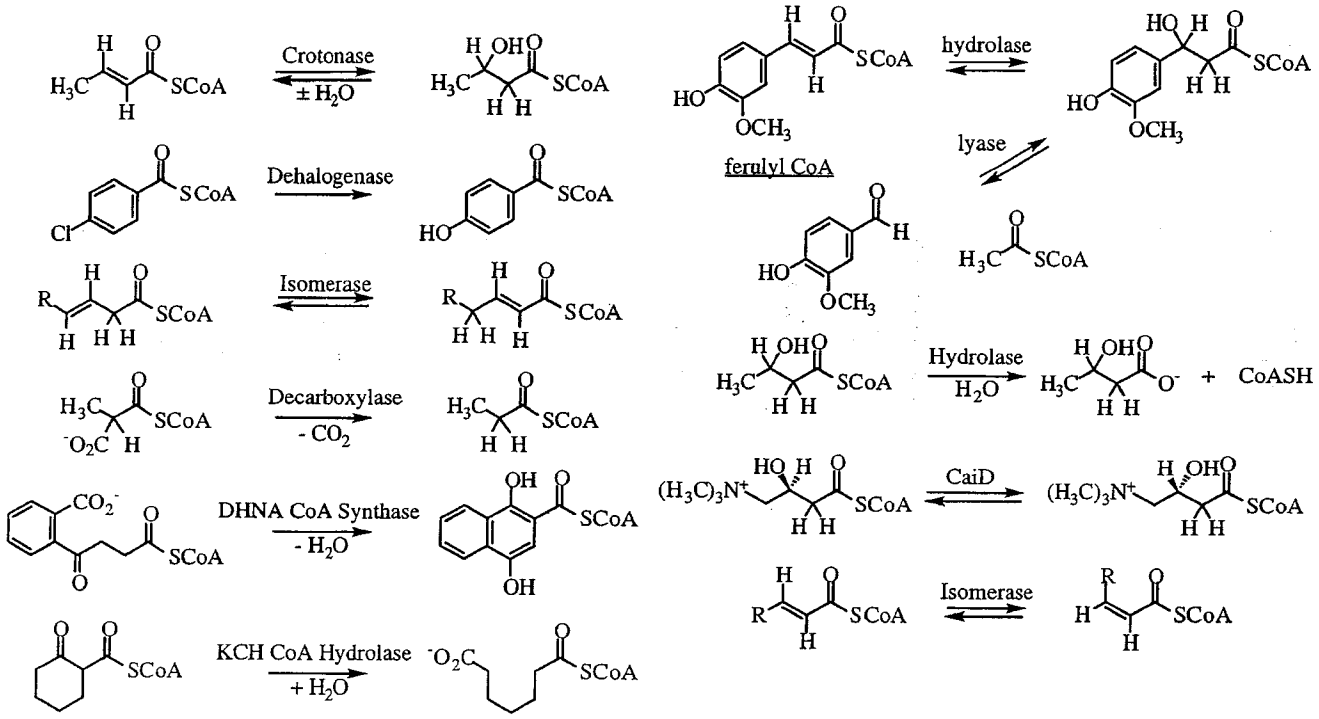


Figure 7 Reactions catalyzed by members of the crotonase superfamily. Dihydroxynaphthoate (DHNA); 2-ketocychlohexyl (KCH); carnitinyl CoA epimerase (CaiD).

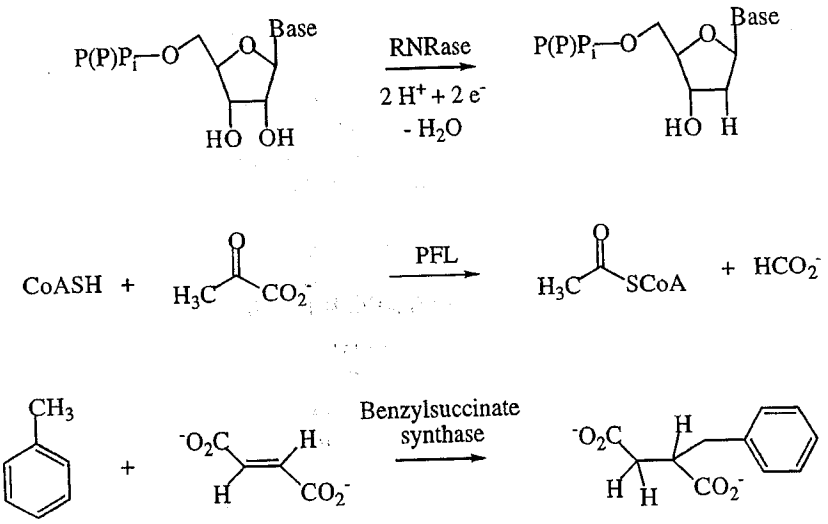


Figure 5 Reactions catalyzed by members of the thiyl radical superfamily.

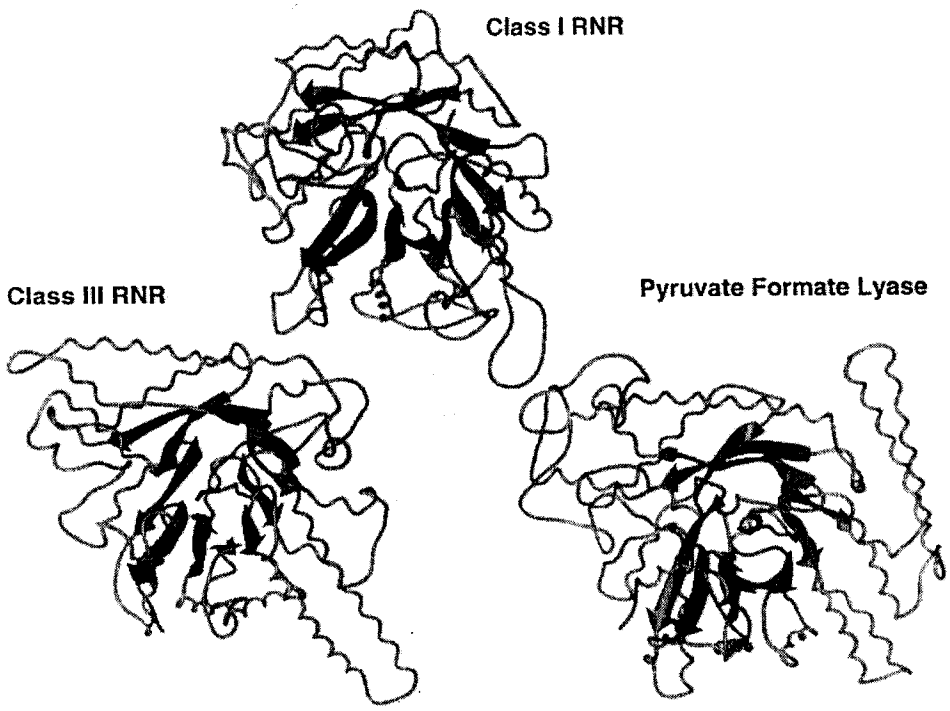


Figure 6 The $(\beta/\alpha)_{10}$ barrel domains of the class I and class III ribonucleotide reductases and PFL. The β-sheets of the two halves of the barrel are colored red and green; the active site cysteines are blue.

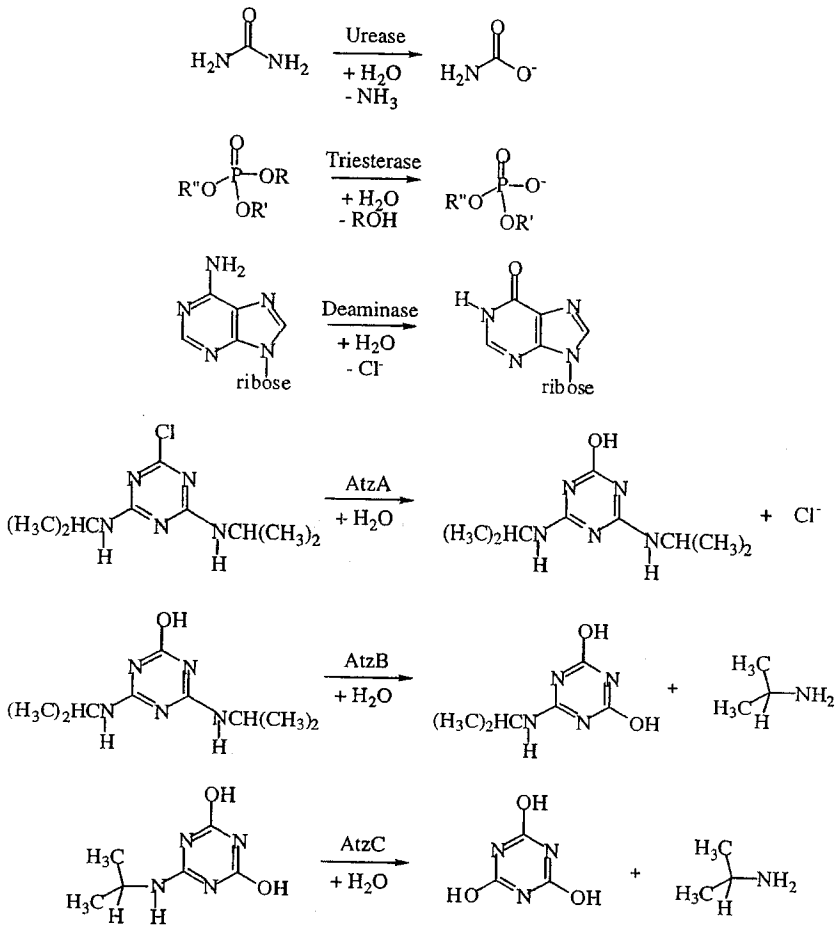


Figure 3 Reactions catalyzed by members of the amidohydrolase superfamily.

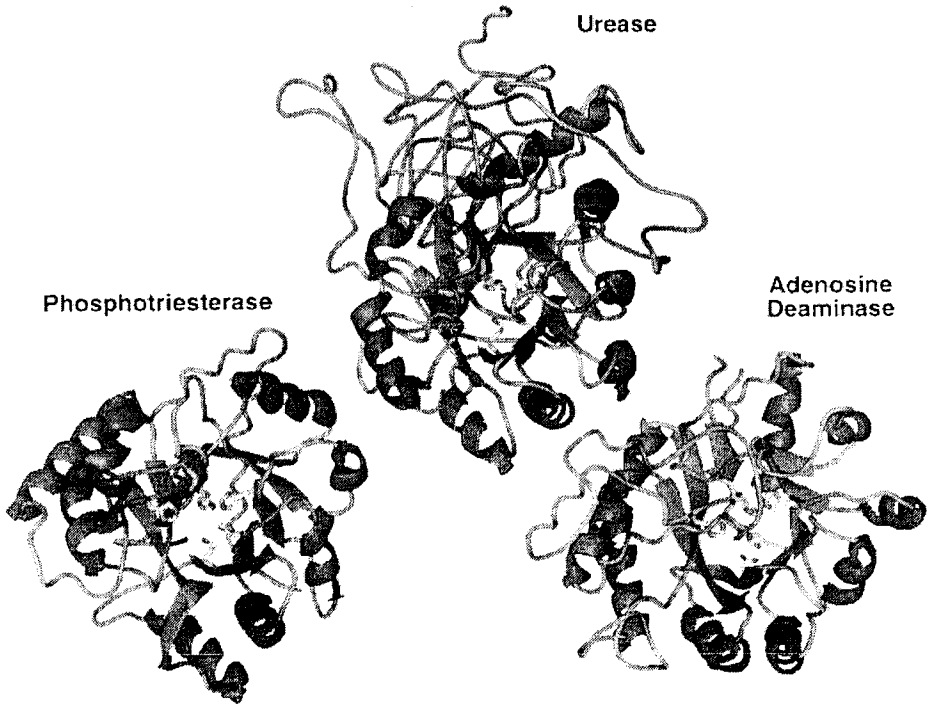


Figure 4 The $(\beta/\alpha)_8$ (TIM) barrel domains of urease, phosphotriesterase, and adenosine deaminase.