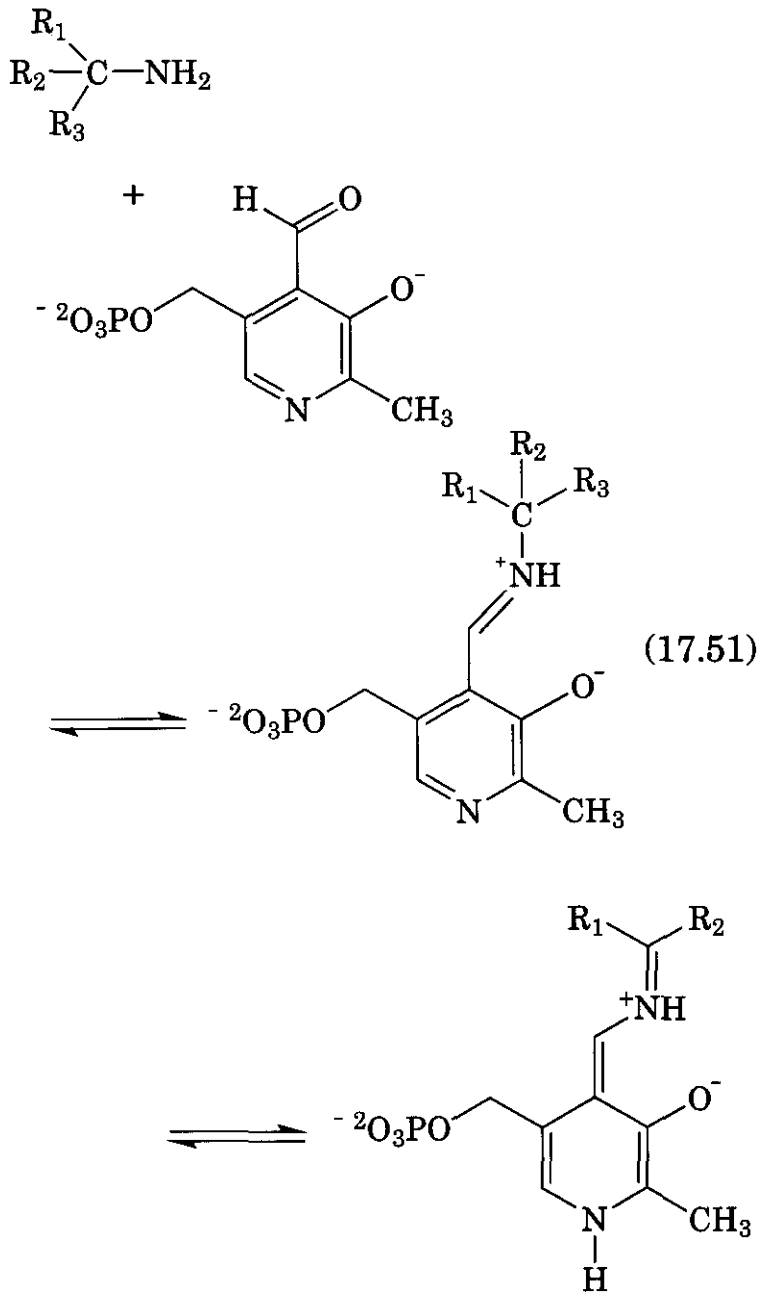
the PLP-dependent enzymes is extremely well characterized, making the design process somewhat easier. The initial steps in the mechanism for a PLP-dependent enzyme are shown in Equation 17.51.

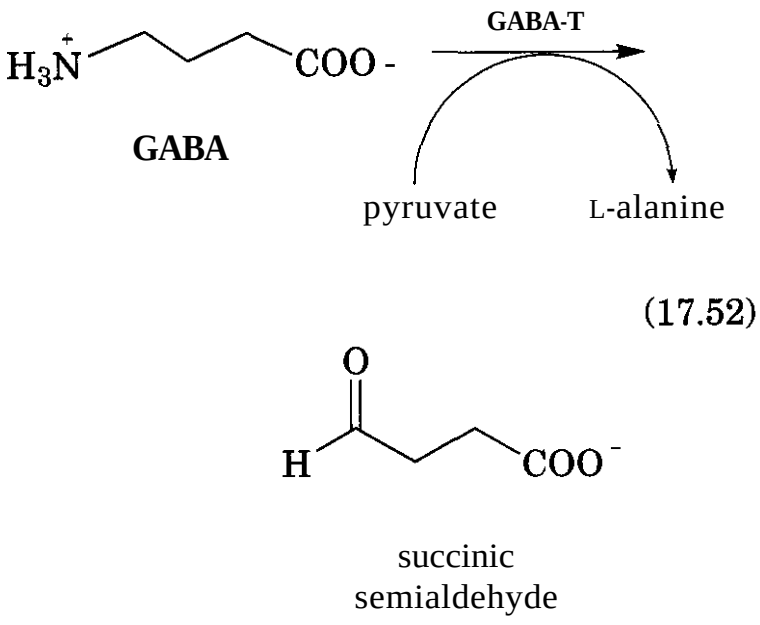


(17.51)

The first step involves Schiff base formation by the amino group of the substrate reading with pyridoxal phosphate to form an aldimine. This is followed by loss of a functional group (R_3, Equation 17.51), usually by abstraction by an active-site base, to form a resonance-stabilized carbocation.

y-Aminobutyric acid (GABA) is one of the major inhibitory neurotransmitters in the mammalian central nervous system. A decrease in the concentration of GABA had been shown to lead to convulsions. Therefore it was suggested that inhibitors of GABA transaminase, the enzyme responsible for the breakdown of GABA, may act as antiepileptic agents, by providing an increase in the concentration of GABA in the brain.

GABA aminotransferase (GABA transaminase, GABA-T) catalyzes the conversion of y-aminobutyric acid to succinic semialdehyde with the subsequent transfer of an amino group to pyruvate (Equation 17.52).



(17.52)

succinic
semialdehyde

GABA-T is a PLP-dependent enzyme and a wide variety of mechanism-based inhibitors have been described for this enzyme (202, 203). These include inhibitors bearing an unsaturated moiety, a leaving group, as well as those forming a stable complex with the cofactor (202, 203). Vigabatrin (8), currently used as an antiepileptic drug, provides an excellent example of this approach. The proposed mechanism is shown in Fig. 17.34.

As with the normal mechanism of the enzyme, the inactivation starts with Schiff base formation with the enzyme-bound pyridoxal phosphate, followed by removal of an a-proton by an active-site base to form the reactive electrophilic intermediate (82). This then partitions between hydrolysis of the Schiff base linkage, resulting in the keto product (83) and enzyme reactivation, and Michael-type addition of an enzyme active-site nucleophile, resulting in a stable covalently bonded enzyme adduct (84).

Ornithine decarboxylase (ODC), another PLP-dependent enzyme, catalyzes the rate-limiting step in the biosynthesis of polyamines, i.e., the conversion of ornithine to putrescine (Equation 17.53).

The enzyme is a target for drugs against African sleeping sickness caused by *Trypano-*