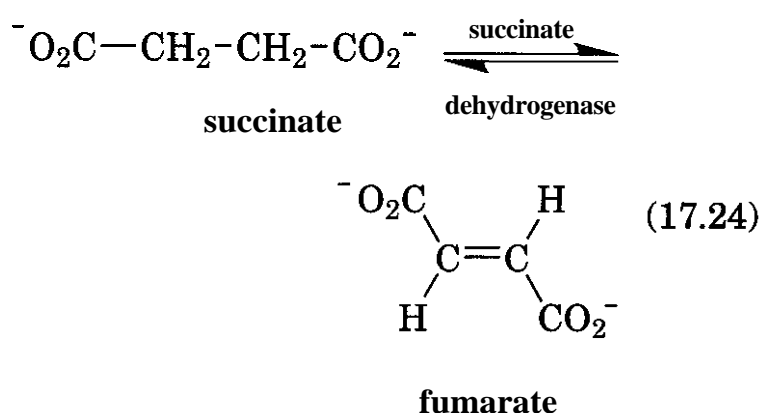


2.3.4 Examples of Rapid Reversible Inhibitors. Competitive inhibitors are often similar in structure to one of the substrates of the reaction they are inhibiting. Inhibitors of this type are sometimes called substrate analogs and their binding **affinity** (K_i) usually approximates that of the substrate. One of the first reactions inhibited by a substrate analog was that catalyzed by succinate dehydrogenase (Equation 17.24).



This reaction is competitively inhibited by malonate ($\text{}^{-}\text{OOCCH}_2\text{COO}^{-}$) that has, like succinate, two carboxylate groups. It is therefore able to bind to the enzyme's active site but, with only one carbon atom between the carboxylates, further reaction is impossible.

Substrate analogs are rarely useful as enzyme inhibitors, given that large concentra-

tions are required for inhibition, and their inhibition is readily overcome by any buildup of substrate. However, they are often useful probes for determining enzyme specificity and even mechanism. Phenylethanolamine *N*-methyltransferase (PNMT) catalyzes the terminal step in epinephrine (adrenaline) biosynthesis, the conversion of norepinephrine to epinephrine (Equation 17.25), with concomitant conversion of *S*-adenosyl-L-methionine (SAM, AdoMet) to *S*-adenosyl-L-homocysteine (SAH, AdoHcy).

S-Adenosyl-L-homocysteine (10) (Fig. 17.12), the product of the reaction, and 2-(2,5-dichlorophenyl)cyclopropylamine (11) are analogs of *S*-adenosyl-L-methionine and norepinephrine, respectively. Using these inhibitors it was possible to ascertain the binding order of the two substrates (75). Kinetic analyses showed that SAH was a competitive inhibitor of SAM and a noncompetitive inhibitor of norepinephrine, whereas (11) was a competitive inhibitor of norepinephrine and an uncompetitive inhibitor of SAM. This indicates that the binding of substrates is ordered, with SAM binding first. If norepinephrine bound first, it would be expected that SAH would be an uncompetitive inhibitor and (11) would be noncompetitive with respect to SAM. If a random

