chemical stability possessed dipeptides with amino and ethyl ester end groups, owing to their internal cyclization to the very chemically labile diketopiperazines. The sensitivity of these prodrugs to aminopeptidase and endopeptidase activity was also tested. Aminopeptidase-catalyzed hydrolysis rates were higher for dextrorotatory dipeptides and decreased in the order Ala > Leu > Phe > Gly as the *N*-terminal amino acid. Endopeptidase activity was higher toward levorotatory dipeptides and decreased in the order Ala > Gly > Phe ≈ Leu at the *N*-terminus. The presence of a free carboxyl instead of an ethyl ester end group at the *C*-terminus had little influence on aminopeptidase activity, but suppressed the endopeptidase activity.

MODIFICATIONS EMPLOYING HYDROPHOBIC FUNCTIONAL GROUPS

A high melting point reflects high crystal lattice energy in a solid. A high melting point and a high enthalpy of fusion lead to poor solubility in any solvent. In particular, preferential hydrogen bonding is responsible for high melting points and can actually fix the spatial configuration in the crystalline state. One prodrug approach to improve solubility is to reduce the melting point and enthalpy of fusion by interfering with the stronger interactions that can exist between drug molecules in the crystal framework.

An application of this approach was employed in the preparation of prodrugs of vidarabine. Vidarabine has a solubility of only 0.5 mg/mL, which is due at least in part to a melting point of about 260°C (Windholz et al., 1983) that is attributed to intermolecular hydrogen bonding in the crystalline lattice. When esterification at the 5′-hydroxyl group eliminated the potential for this intermolecular interaction, the melting point was lowered (Repta et al., 1975). By employing an acyl group that is only slightly lipophilic, the formyl group, a vidarabine prodrug with greatly enhanced solubility was obtained. The 5′-formate ester is rapidly hydrolyzed in human blood and has the potential for use in parenteral administrations (Repta et al., 1975). The ethyl ester of levodopa proved to be a highly water-soluble prodrug of levodopa and provided more rapid absorption across biological membranes (Djaldetti et al., 2002), presumably by offering both a higher concentration gradient and a higher partition coefficient. A longer alkyl chain length can lead to a lower melting point (Stinchcomb et al., 1995), but likely also a higher lipophilicity that counters any improvement in solubility achieved by the lower melting point.

Diester and triester prodrugs of the antiviral agent, 6-methoxypurine arabinoside, were prepared because the parent drug has an unfavorable metabolic profile (Jones et al., 1992). The triacetate was able to enhance bioavailability in the rat, as measured by the appearance of the parent drug in the urine. The lower solubility of the longer chain aliphatic or the aromatic triesters was assumed to be the underlying cause of the reduced bioavailability of those derivatives. In contrast, the diesters, in particular the diacetates, significantly enhanced systemic availability, probably resulting from the higher solubility and enhanced partition coefficient found with these prodrugs. These, then, are examples of the phenomenon of improved solubility and improved lipophilicity present in the same prodrug. It would have been worthwhile to conduct an investigation of the melting points and enthalpies of fusion to confirm that the improvements were a result of reduced crystal lattice energy brought about by blocking hydrogen bonding in the crystal state.

With 5-fluorouracil, the N_1 and N_3 sites are each available for acylation reactions. When various N_1- or N_3-acyl derivatives were prepared, they proved to be readily hydrolyzed in aqueous buffer solutions to quantitatively yield the parent drug (Buur and Bundgaard, 1984a, 1984b). The N_1-acyl derivatives were found to be highly unstable; the N_3-derivatives proved to be more stable. Blocking the N_3-position diminished the opportunities for hydrogen bonding in the crystal lattice, resulting in a lower melting point and higher solubility (Table 16.5). The selection of the acyl group influenced the hydrolysis rate under conditions approaching those found *in vivo*, as well as the physicochemical properties of the derivative, such as solubility and lipophilicity. Preparation of the 1-alkylcarbonyloxymethyl prodrugs of 5-fluorouracil was accomplished by reacting the appropriate alkylcarboxymethyl chloride with 5-fluorouracil in 1-methylpyrrolidine and acetonitrile (Taylor and Sloan,