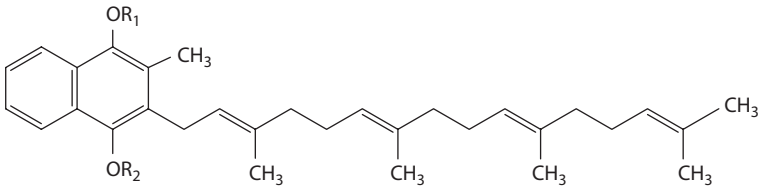
TABLE 16.4
Solubility, Partition Coefficients, and Regeneration Half-Lives for Menahydroquinone-4 Ester Prodrugs



Derivative	Solubility in Water (mM)[a]	Log *P*[b]	Hydrolysis Half-Life in Rat Plasma (min)	Hydrolysis Half-Life in Buffer[c] (min)
R_1: $(CH_3)_2NCH_2CO$– R_2: H–	24	4.56	3.01	3410
R_1: H– R_2: $(CH_3)_2NCH_2CO$–	5.7	4.67	2.90	2350
R_1: $(CH_3)_2NCH_2CO$– R_2: $(CH_3)_2NCH_2CO$–	~50	3.66	15.0	1390

Source: With kind permission from Springer Science + Business Media: *Pharm. Res.*, Vitamin K prodrugs. 1. Synthesis of amino acid esters of menahydroquinone-4 and enzymatic reconversion to an active form, 12, 1995a, 18–23, Takata, J.

[a] Solubility of the hydrochloride salt of the prodrug at room temperature.

[b] Log of the partition coefficient between 1-octanol and pH 7.4 phosphate buffer.

[c] Buffer is pH 7.4 phosphate buffer at 37°C.

Aminoalkanecarboxylic acid ester prodrugs of vitamins K (Takata et al., 1995a) and E (Takata et al., 1995b) exhibit considerable solubility in water and possess a high susceptibility to hydrolysis by liver esterase. Vitamin E prodrugs include primary (glycinate), secondary (sarcosinate), and tertiary aminoacetic acid (*N,N*-dimethylglycinate) ester derivatives. Monoesters and a diester of menahydroquinone-4 (Table 16.4) were prepared using *N,N*-dimethylglycine to improve the solubility and esterase lability of the parent drug (Takata et al., 1995a). Cleavage to regenerate menahydroquinone-4 under conditions similar to those found *in vivo*, which could be described by apparent first-order kinetics, confirms that they act as true prodrugs. The dramatic difference between the *in vitro* and *in vivo* rates of hydrolysis suggests that stable solution dosage forms could be prepared with rapid bioconversion possible on administration.

N-Acylation of amines to provide amide prodrugs has limited application because amides, in general, are relatively stable *in vivo* (Bundgaard, 1987). Certain amides formed with amino acids, however, may be susceptible to enzymatic cleavage. Examples are γ-glutamyl derivatives of dopamine, l-dopa, and sulfamethoxazole, which are hydrolyzed by γ-glutamyl transpeptidase. The use of γ-glutamyl derivatives as kidney-specific prodrugs has been recommended on the basis of their preferential bioactivation in the kidney (Wilk et al., 1978; Orlowski et al., 1979). Various amino acid derivatives of benzocaine have proved to be highly water soluble and were rapidly cleaved not only in the presence of enzymes found in human serum but also by certain proteolytic enzymes (Zlojkowska et al., 1982). Dipeptide prodrugs of 5-fluorouracil were prepared that allowed a comparison of the sensitivity to chemical and enzymatic hydrolysis (Nichifor and Schacht, 1997). It was found that the stability depended on the *N*-terminal amino acid, the configuration of the *C*-terminal substituted glycine (characterized by optical rotation), and the presence of substituents on the dipeptides. Chemical hydrolysis rates were decreased with an increase in the hydrophobicity of the *N*-terminal amino acid. Hydrolysis rates were much lower for dipeptides with free carboxyl end groups than for dipeptides in the ethyl ester form. The prodrug derivatives with the lowest