administered dexamethasone-21-sulfate provided essentially no parent dexamethasone in the plasma or urine, but was instead excreted unchanged in the urine (Miyabo et al., 1981). Oral administration of a prednisolone-21-sulfate prodrug as its sodium salt achieved colon-specific delivery of the parent glucocorticoid, in addition to improving its solubility in water (Doh et al., 2003). The prodrug proved to be chemically stable in pH 1.2 and 6.8 buffer, as well as in the contents of the stomach and small intestine. When incubated with cecal contents, the prodrug was reduced to 9.6% of its original amount in 10 h, presumably owing to the hydrolytic action of a sulfatase from a bacterial source that prompted release of prednisolone.

Two independent methods were used to prepare sulfonate prodrugs of Taxol (Zhao et al., 1991). As seen earlier with other Taxol prodrug reactions, the 2′-position was the preferred position at which to bind the promoiety. The first approach, then, was to prepare the amide derivative of the 2′-succinyl derivative with the organic-soluble tetrabutylammonium salt of taurine or its homolog 3-amino-1-sulfopropionic acid using the mixed anhydride method in tetrahydrofuran. The tetrabutylammonium salts were converted to the sodium salts by ion exchange. The second approach involved the preparation of 2′-acryloyltaxol by the mixed anhydride method and then taking advantage of the nucleophilicity of sodium bisulfite in a Michael reaction in aqueous isopropyl alcohol. Michael addition to the α,β-unsaturated ester occurred readily to yield the desired sodium sulfonate derivative.

A simple method to modify promoiety acidity or basicity is to select other more acidic or basic ionizable functional groups. Convenient solubilizing moieties for ester prodrugs where the formulation pH should be between 3.5 and 5 would be those containing either sulfonic acid ($pK_a < 2$) or tertiary amine ($pK_a > 8$) functionalities. Quaternary ammonium-containing moieties, such as the choline esters mentioned earlier, would also be excellent choices for water-soluble derivatives if solubility was the only consideration (Anderson and Conradi, 1987).

Morpholinoalkyl esters (see Figure 16.1 for chemical structures) of the potent nonsteroidal anti-inflammatory agent, diclofenac, were prepared and characterized regarding solubility and hydrolysis reaction rates (Tammara et al., 1994). The alkyl group provides a spacer between the carboxylic acid of diclofenac and the morpholine moiety, which is the site of protonation to yield an ionized prodrug. Alkyl groups consisting of two, three, and four methylene groups were included in the study, and it was found that increasing the chain length improved the stability in pH 7.4 phosphate buffer, but decreased the stability in simulated gastric fluid. In each case, the solubility was improved at least 2000-fold in simulated gastric fluid and in pH 7.4 phosphate buffer. Experimental partition coefficients between 1-octanol and pH 7.4 phosphate buffer demonstrated that the derivatization also markedly improved the lipophilicity. Although stable in the solid state, the hydrolysis rates in simulated gastric fluid or pH 7.4 phosphate buffer indicate that these prodrugs could be formulated only as dry mixtures to be reconstituted as solutions before use.

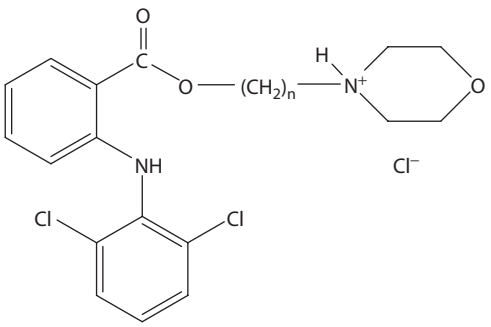

FIGURE 16.1 Chemical structure of water-soluble morpholinoalkyl ester prodrugs of diclofenac. The subscript *n* equals 2, 3, or 4.