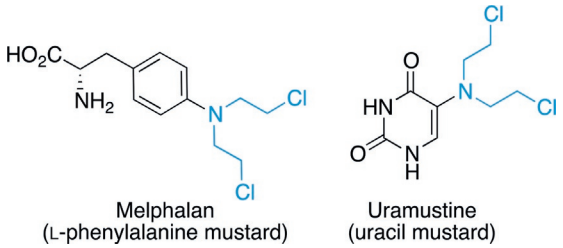
2.4 SITE-DIRECTED NITROGEN MUSTARDS

Due to their high toxicity, considerable effort has been devoted to the development of site-directed mustards. Initial strategies were based on the incorporation of moieties that were expected to accumulate preferentially in tumor cells. Thus, melphalan (Alkeran®), which contains an L-phenylalanine unit, was postulated to concentrate in melanomas because melanine is a product of phenylalanine metabolism. Although this original rationale was not correct, melphalan is used in certain types of bone marrow tumors such as multiple myeloma and ovarian or breast cancers. In addition, because of its myeloablative properties and broad antitumor effects as a DNA alkylating agent, melphalan remains the most widely used agent in preparative regimes for hematopoietic stem cell transplant.[12] The main role of its side chain is to facilitate drug uptake by employing two amino acid transport systems to enter tumor cells: the sodium-independent L-amino acid system and the sodium-dependent transporter for alanine, serine, and cysteine (ASC carrier). Other compounds designed on similar principles are uramustine (uracil mustard) and estramustine (see later).



In contrast to chlorambucil, the bioavailability of orally administered melphalan is highly variable, which can be attributed to its very rapid chemical degradation to the mono- and dihydroxy derivatives **5.14** and **5.15**.[13] *In vitro* studies have shown that this hydrolysis is pH dependent and takes place preferentially under neutral or basic conditions,[14] suggesting that the electron-withdrawing effect of the protonated amino group hampers aziridinium ion generation and its subsequent hydrolysis (Figure 5.6).

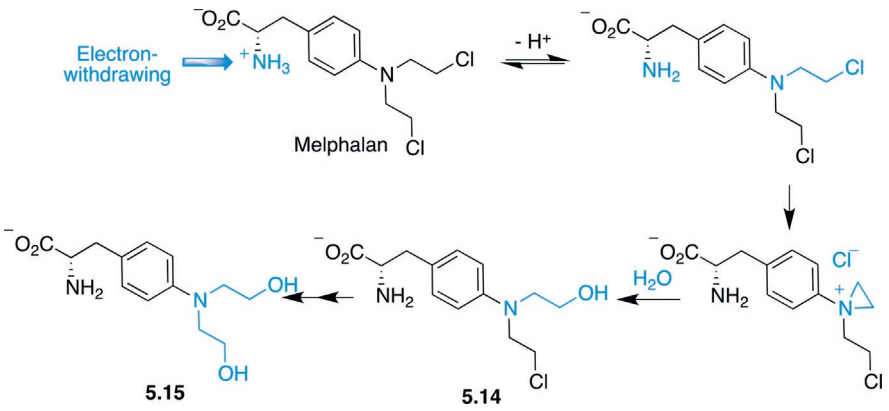


FIGURE 5.6

Chemical degradation of melphalan.