be oxidized to form the corresponding hydroxyl amines, sulfoxides and sulfones. Ether cleavage and deamination reactions are also possible, as enzymatic oxidation of carbon atoms with alpha heteroatom substitution leads to structures that are chemically unstable and decompose to the corresponding by-products.

Initial processing of compounds through phase 1 metabolism generally establishes new nucleophilic sites on a substrate, either via direct functionalization as observed in hydroxylation pathways or via decomposition of unstable compounds such as those generated in oxidative deamination reactions. These new functional groups, most often alcohols and amines, provide an opportunity for further metabolic processing in phase 2 metabolic pathways (conjugation reactions). Of course, if these groups are present in a molecule to start with, then phase 1 metabolism is not necessary for phase 2 conversions to occur. The enzymes that comprise the phase 2 metabolic pathways append groups onto the new sites, generally producing compounds of increased polarity that are more readily excreted into the urine. UDP-glucuronosyl transferases (UGTs),[53] for example, appends glucuronic acid onto compounds with a suitable functional group such as an alcohol or amine (Figure 6.29(a)). This process is often referred to as glucuronidation, while the products are referred to as glucuronides. In a similar fashion, sulfotransferases[54] increase the polarity of phase 2 substrates via sulfation of a suitable functional group. The resulting compounds are substantially more polar and significantly more susceptible to excretion in the urine (Figure 6.29(b)).

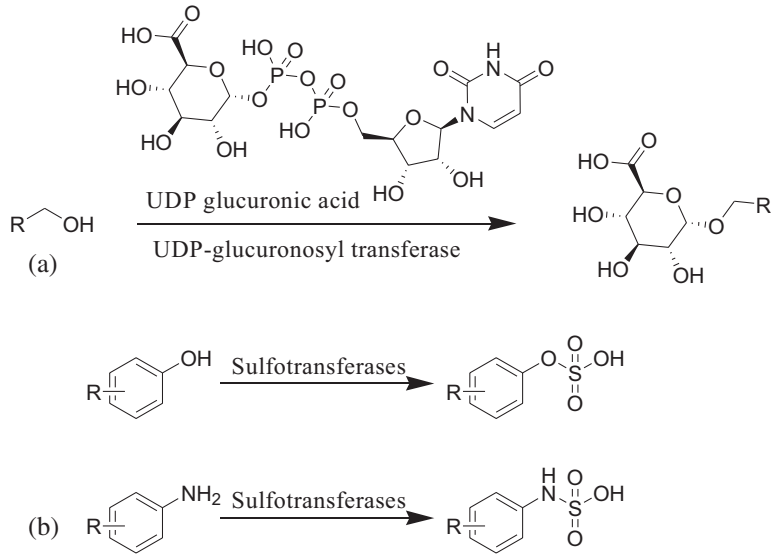

FIGURE 6.29 (a) Glucuronidation of an alcohol. (b) Sulfonylation of an alcohol or amine.