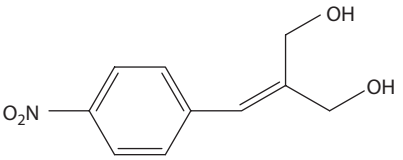

FIGURE 16.7 Double release nitrodiol as the base for prodrug dendrimer development.

course of the 48 h evaluation. In the plasma system, naproxen was released from each of the ester prodrugs through pseudo-first-order kinetics. It was released slowly from the lactic acid ester, with only 25% released in 24 h, and quickly from the diethylene glycol ester, with a half-life of 51 min. It is not surprising that the direct amide linkage to naproxen resulted in a product that was considered unsuitable as a prodrug owing to high stability against enzyme-catalyzed hydrolysis.

Two issues with typical dendrimer prodrugs have been presented by De Groot et al. (2003). First, each single drug molecule must be independently cleaved from the end group in order to be released. Second, the dendrimer itself is not usually completely degraded. To circumvent these issues, they developed a *cascade-release dendrimer* wherein the dendrimer completely and rapidly dissociates into its building blocks when it experiences a single triggering event, and this process also induces release of the drug molecules that were bound to the end groups. The triggering can even be tuned to provide site-specific release. These cascade-release dendrimers possess two or more generations of branched self-elimination linkers, each of which releases multiple leaving groups on activation. Cleavage of the bond between the dendrimer and any linker moiety also results in release of the parent drug with its regained activity. Proof of concept was provided using a double release nitrodiol (Figure 16.7) wherein the nitro group acts as a masked amine group. Reduction of the nitro group to an amine would act as the trigger for the self-eliminations. The nitrodiol was activated using 4-nitrophenyl chloroformate to produce the *bis*(4-nitrophenyl carbonate) derivative, which was then coupled to two equivalents of poorly soluble paclitaxel to yield the desired dendron. At 0°C, paclitaxel reacts with the carbonates at its most reactive 2′-hydroxy group. When the nitro function was reduced under mild conditions, using zinc and acetic acid, complete disappearance of the starting dendron and release of the paclitaxel were observed, and these results were supported by thin layer chromatography studies. Proton-NMR confirmed these results and demonstrated complete release of the paclitaxel molecules. NMR spectra of paclitaxel derivatives can be complicated, but the 2′-H signal of the paclitaxel in the dendron, representing a hydroxyl group bound to an alkyloxy-carbonyl group, is a distinguishable signal ($\delta = 5.46$ ppm). This signal disappears completely and the corresponding 2′-H signal of paclitaxel itself ($\delta = 4.74$ ppm) appears over the course of the decomposition of the dendron.

CHEMICAL AND ENZYMATIC LABILITY OF THE PROMOIETY

Most prodrugs are biologically inactive (Sinkula and Yalkowsky, 1975), and therefore, an important feature in the design of a prodrug is the sensitivity of the modification to cleavage through chemical or enzymatic means to release the promoiety and return the pharmacologically active agent. It should be possible to predict the *in vitro* lability because suitable models for nonenzymatic hydrolysis have been developed for many promoieties of interest (Charton, 1977). A method for predicting *in vitro* reactivity by energy measurements has been recommended (Charton, 1977), although it might not be possible to predict the actual hydrolysis rate, even under *in vitro* conditions, since drugs are generally too complex to allow accurate calculations of rates. Nevertheless, the method could be useful in preliminary screening of potential promoieties meant to undergo rapid enzymatic hydrolysis in blood (Notari, 1985), and in interpolations of chemical or enzymatic labilities within a homologous series of chemicals. Unless one conducts exhaustive animal or human pharmacokinetic studies, however, it is difficult to prove conclusively that a prodrug is indeed rapidly and