formulations. The counterion, therefore, affects the solubility, but could also affect the chemical stability of the salt form. In preformulation studies, the stability and potential formulation issues must be considered before the final salt selection is made.

The phosphate ion and various sulfonates have proved useful for basic drugs. However, hydrochloride salts are by far the most common choice for basic drugs, far outweighing the sulfates, the nearest in frequency (Berge et al., 1977). Bromide and iodide salts of drugs are not as common because their halide counterions are not pharmacologically inert and because they are more expensive. Ionic fluorine appears only in its inorganic form as a prophylactic against dental caries (Miller and Heller, 1975).

Due to the weakening of the crystal lattice strength by the use of a hydrophobic organic counterion, there is an increased chance of formation of amorphous forms. Black et al. reported 25 different salts of ephedrine using organic and inorganic acids. Most of the salts formed using organic acids were either temporarily or permanently amorphous in nature. The recrystallization of certain organic salts is definitely an issue of physical stability and is not ideal for pharmaceutical applications (Black et al., 2007). Therefore, the use of a polymer to stabilize such amorphous forms has been suggested to overcome the problems associated with recrystallization (Kesisoglou and Wu, 2008).

ORGANIC SALTS

At one time, it was believed that the solubility of a salt form could be enhanced by selecting a counterion that is itself more hydrophilic. For diclofenac, an increase in the number of hydroxyl groups in the counterion failed to support this relationship between solubility and the hydrophilicity of the counterion (Fini et al., 1996; Parshad et al., 2004). Indeed, a reduction in the polarity of the counterion was able to enhance the solubility of benzylamine derivatives by reducing the strength of the lattice energy, reflected by a decrease in the melting point (Parshad et al., 2004). Choosing an organic species to react with a drug to develop an organic salt has the potential to provide advantages including lower toxicities and, perhaps surprisingly, a higher aqueous solubility than an inorganic counterion can provide. Triamterene (2,4,7-triamino-6-phenylpteridine) is a diuretic that, despite three amino groups (Figure 15.1), is only weakly monobasic. Most attempts to form classic salts have failed. Acetic acid, however, was shown to form a salt with triamterene that has a higher solubility than the phosphoric, sulfuric, nitric, or hydrochloric acid salts (Dittert et al., 1964). The ammonium and ethanolamine salts of para-aminosalicylic acid were each shown to have a higher aqueous solubility than the potassium, sodium, calcium, or magnesium salts of the same drug (Forbes et al., 1995).

Formation of the hydrochloride salt of the antimalarial agent α-(2-piperidyl)β-3,6-*bis*(trifluoromethyl)-9-phenanthrenemethanol approximately doubles its solubility in water, as shown in Table 15.1. To investigate the ability of an organic counterion to improve the aqueous solubility, various organic acid salts of the antimalarial agent were prepared. Results suggest that a significant increase in solubility can be achieved with the proper choice of the salt form. For example, the lactate salt is approximately 200 times as soluble as the hydrochloride salt (Agharkar et al., 1976).

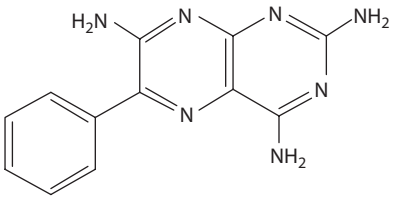

FIGURE 15.1 The chemical structure of triamterene.