discovery group. The limitations faced by the preformulation group at this stage include the following:

- *Solubility of the compound*. There must be some solubility. The pK_a of poorly soluble compounds must be measured in aqueous methanol solution. If several titrations are carried out with different ratios of methanol:water, the Yesuda–Shedlovsky equation can reveal the theoretical pK_a in purely aqueous solution. Similarly, for poorly soluble compounds, provided the log P is high enough, the compound may be determined by titration, by the addition of the sample to the octanol first. The compound will then back partition into the aqueous layer. If this fails, spectroscopic methods have to be employed, as more dilute solutions may be used.
- *Stability of the compound*. The compound must be able to withstand the rigors of testing, such as not breaking down during the time it takes to establish equilibrium between the two phases.
- *Purity of the compound*. Substances submitted for pK_a and log P studies need to be pure, of accurately known composition, and be submitted as free bases or inorganic acid salts. In general, no reliable measurements can be made on organic acid salts.
- *Single compound*. It is preferred to prepare a series of compounds to validate methods of testing, to validate a trend, and to obviate many experimental problems.

Table 4.5 summarizes the advantages and disadvantages of the most commonly used methods to measure pK_a and log P. These are presented together, because in many instances, both parameters can be obtained from unified experimental runs, a strategy that is very useful when the quantity of the substance available is limited, as is the case in most instances.

Most companies would do well by studying the available equipment from Sirius (6). Table 4.6 lists the available equipment and their applications.

4.5.1 Ion Pair Log *P*

Ion pair log Ps might be determined by at least two or preferably three titrations in different ratios of octanol to water. The apparent pK_a in the presence of octanol, the poK_a, can be used to determine the presence of ion pair partitioning according to the equations:

$$P_{XH} = \frac{r_2(10^{P_aK_a(2) - pK_a} - r_1 10^{P_aK_a(1) - pK_a} - (r_2 - r_1) \times 10^{P_aK_a(1) + pK_a + P_aK_a(2) - 2pK}}{r_1 r_2 (10^{P_aK_a(1) - pK_a} - 10^{P_aK_a(2) - pK_a})} \quad (4.64)$$

$$P_X = \frac{r_1(10^{P_aK_a(2) - pK_a} - r_2 10^{P_aK_a(1) - pK_a} - r_2 - r_1}{r_1 r_2 (10^{P_aK_a(1) - pK_a} - 10^{P_aK_a(2) - pK_a})} \quad (4.65)$$

where r is the octanol:water ratio.