TABLE 4.5

Advantages and Disadvantages of pK_a and Log *P* Measurement Techniques

Method	Measures	Advantage	Disadvantage	Concentration Required	Sample Size
Sirius Potentiometric pKa/log *P*	pKa, log *P*, log *P* app	Rapid, convenient	Insoluble or neutral samples cannot be measured	0.0001 M (0.1 mM)	1–5 mg
Sirius Yesuda-Shedlovsky	pKa	pKa for insoluble samples	Takes three or more titrations	0.0005 M (0.5 mM)	5 mg
Sirius ion-pair log *P*	log *P*, log *P* (ip)	Predict log D more accurately	Takes three or more titrations	0.0001 M (0.1 mM)	3–15 mg
Manual potentiometric pKa	pKa	Simple, rapid	Not for low or overlapping pKas; precipitation when titrated to neutral species; multiple experiments required	>0.0025 M (2.5 mM)	50 mg
pKa by UV	pKa	pKa for poorly soluble or scarce compounds	Slow	0.000025 M (25 µM)	6 mg
pKa by solubility	pKa	pKa for highly insoluble compounds	Slow, low accuracy	Below 0.0005 M (0.5 mM)	10 mg
Log *P* by filter probe	Log *P*	Log *P* for poorly soluble compounds, reliable > log *P* of 0.2	Messy, slow to set up, requires care. Inaccurate below log *P* of 0.2	0.000025 M (25 µM)	6 mg
Log D by filter probe	pKa, log *P*, log D	Can determine log *P*app at any pH	Only possible with compounds possessing isosbestic point	0.000025 M (25 µM)	6 mg
Log *P* by shake flask	Log *P*, log D at chosen pH	Low log *P* values. Can investigate surface effects	Slow, tedious, messy	0.000025 M (25 µM)	6 mg
Log *P* by HPLC	Log D at pH 7	Many compounds can be measured at once. Small sample size	Inaccurate, generally only carried out at pH 7	~2.5 mM	0.5 mg

[a] A wavelength, wavenumber, or frequency at which the total absorbance of a sample does not change during a chemical reaction, or a physical change of the sample, such as when one molecular entity is converted into another, which has the same molar absorption coefficient at a given wavelength.

Abbreviations: HPLC, high-performance liquid chromatography; UV, ultraviolet.