

# Cloe Select pK<sub>a</sub> and log P

**cyprotex**experts in **ADME**

## Background Information



'pK<sub>a</sub> affects solubility, permeability, log D and oral absorption by modulating the distribution of neutral and charged species.'

<sup>1</sup>Di L and Kerns EH. (2003)  
*Current Opinion in Chemical Biology*: 7, 402-408.

- The pK<sub>a</sub> of a molecule is the pH at which the molecule is 50 % protonated.
- Log P (or partition co-efficient) is a measure of the lipophilicity of a compound.
- Cloe Select pK<sub>a</sub> and log P determination uses a pH-metric GLpKa technology developed by Sirius. This is considered to be a 'gold standard' method for determining these properties.
- In pH-metric methods, pK<sub>a</sub> is measured by titrating a solution of the sample in water or solvent with acid and base, and calculating the pK<sub>a</sub> from comparing the shape of the titration curve with that of a blank titration, in the absence of test compound. Log P is also measured by a pH-metric method, based on a two-phase acid-base titration in the presence of octanol.
- GLpKa supports six partition solvents including octanol, and eight co-solvents including methanol and DMSO.

### Protocol

**Method**

Potentiometric titration

**Instrument**

GLpKa (Sirius Analytical Instruments Ltd)

**Compound Requirements**

10 mg solid compound

**Partition Solvent used for****Log P Determination**

n-Octanol (others available on request)

**Data Delivery**pK<sub>a</sub>

Log P (optional)

Standard error

Goodness of fit

Calculated log D at pH<sub>7.4</sub>(based on pK<sub>a</sub> and log P)

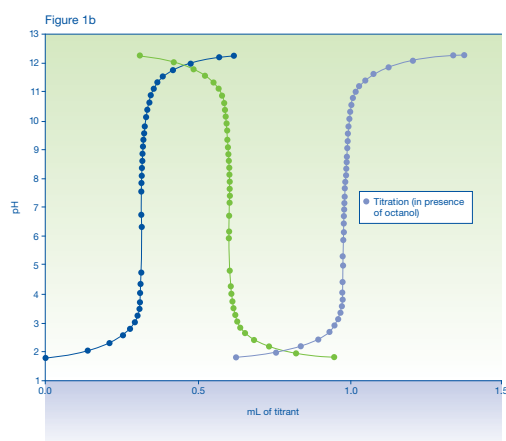
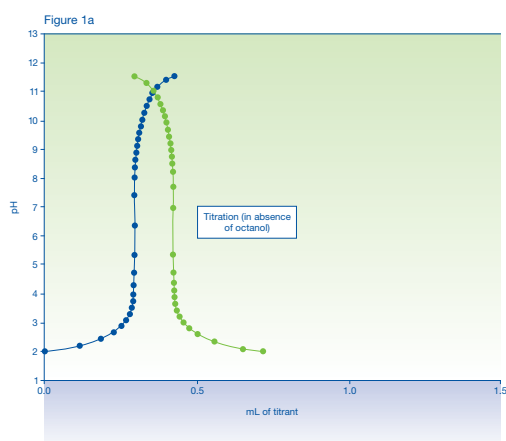
Log P is determined by measuring the  $pK_a$  in the presence of increasing concentrations of the partition solvent, octanol.



### Cloe Select GLpKa

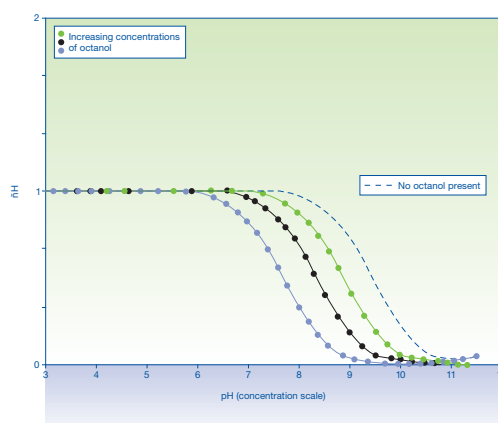
$pK_a$  measurements are determined using the GLpKa instrument from Sirius-Analytical.

**Figure 1**  
Titration curves for acebutolol in the absence (Figure 1a) and presence (Figure 1b) of octanol.



The GLpKa automatically performs pH-metric titrations. A blank acid-base titration is compared to a titration in the presence of the compound. A difference curve is produced from the volume of titrant required to reach a given pH with and without the compound.

**Figure 2**  
Bjerrum plot for acebutolol in the presence of increasing concentrations of octanol.



In this example, increasing the concentration of octanol reduces the  $pK_a$ , confirming the presence of a basic  $pK_a$  for acebutolol.

The titration curve is converted to a Bjerrum plot. The axes are reversed and the volume difference is converted to a unit of  $nH$ ; the average number of bound protons per molecule of compound. The  $pK_a$  is the pH at which the molecule is 50% protonated. Titrations are performed in the presence of increasing concentrations of the partition solvent (n-octanol). Log P is calculated from shifts in the apparent  $pK_a$  that occur in the presence of the partition solvent. From the measured  $pK_a$  and log P values, the log D value can be calculated as a function of pH.

### References

<sup>1</sup> Di L. and Kerns EH. (2003) *Current Opinion in Chemical Biology* 7; 402-408.