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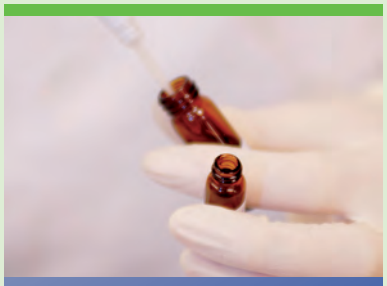
Cloe Select pK_a and log P

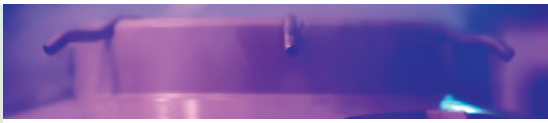
Background Information



'pK_a affects solubility, permeability, log D and oral absorption by modulating the distribution of neutral and charged species.'

[1]Di L and Kerns EH. (2003) *Current Opinion in Chemical Biology:* **7**, 402-408.

- The pK_a 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_a 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_a is measured by titrating a solution of the sample in water or solvent with acid and base, and calculating the pK_a 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_a
Log P (optional)
Standard error
Goodness of fit
Calculated log D at $pH_{7.4}$
(based on pK_a and log P)

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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.

Figure 1a

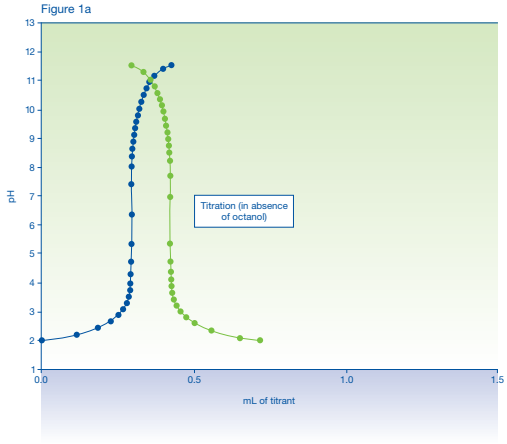
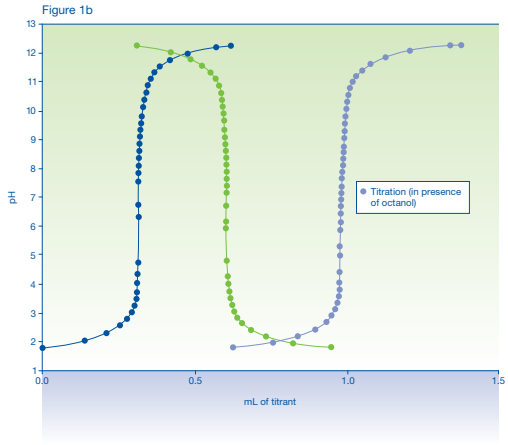
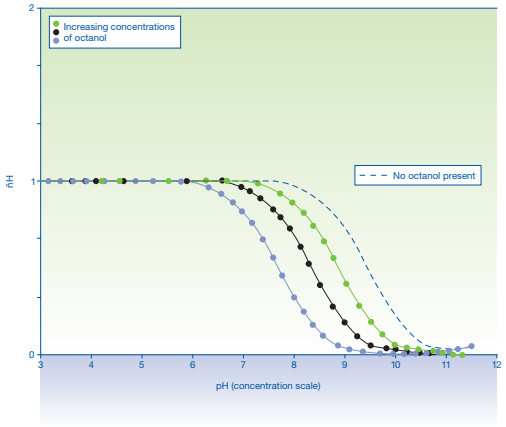


Figure 1b



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 ñH; 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

[1] Di L and Kerns EH. (2003) *Current Opinion in Chemical Biology* **7**; 402-408.