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pH-Metric log *K* calculations of famotidine, naproxen, nizatidine, ranitidine and salicylic acid

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Abstract

The octanol/water partition coefficient (log *K*) is one of the most commonly used parameters in structure–activity relationships in many areas such as drug design (including pesticides), pharmacokinetics, anesthesiology, environmental sciences, toxicology, bioaccumulation and predicting skin permeability as a predictive parameter.

log *K* is generally determined using shake flask method, but the possibility of calculating log *K* using pH-metric titrations and half neutralization points is demonstrated in this study. The potentiometric pH titration technique has been developed as an automatic technique for log *K* determination but it can be achieved by manual titrations. This technique uses the pK_a of the substance. The pK_a of the substance shifts pK'_a when the titration is repeated in the presence of octanol. log *K* value of the substance can be determined using pK_a, pK'_a values and relevant equation.

The aim of the study was to determine the log *K* values of a series of compounds using pH-metric titrations and to compare pH-metric log *K* determination results with the other methods. The log *K* values of famotidine, naproxen, nizatidine, ranitidine and salicylic acid were determined using both shake flask method and potentiometric titrations. Their log *K* values were also calculated theoretically using computer program and all results were compared. The pH-metric log *K* values were found to be close to the shake flask method results. This method was found to be useful for the determination of log *K* values as it provides a high degree of accuracy even in the presence of titratable impurities in the solution.

Keywords: Octanol/water partition coefficient; pH-Metric log *K* calculations; Famotidine; Naproxen; Nizatidine; Ranitidine; Salicylic acid

1. Introduction

The partition coefficient is the equilibrium concentration of solute in a non-polar solvent divided by the concentration of the same compound in a polar solvent. In most applications, the polar solvent is water and octanol is generally used as a non-polar solvent. The octanol/water partition coefficient (*K*, often reported as log *K*) is a particularly useful parameter in quantitative–structure–activity–relationships (QSAR) [1] in following areas: drug design, pharmacokinetics [2], anesthesiology [3], environmental sciences, toxicology and bioaccumulation [4,5], skin research (such as predicting skin permeability) [6–8].

The log *K* is usually measured by the shake flask method, high performance liquid chromatography (HPLC) or filter probe technique, counter-current distribution, rotating diffusion cells [9,10] but there has been growing interest in determining the parameter by potentiometry with a pH electrode [11] The latest technique uses the pK_a of the substance to determine log *K*. The pH-metric technique typically consists of two linked titrations. The first titration is carried out in the aqueous phase over a pH range that encompasses the pK_a of the drug. The pK_a of the substance can be determined using the half neutralization point of the titration curve or it is particularly convenient to use the so-called 'difference curve' [12]. The difference curve (also called the formation curve or Bjerium plot) is a plot of n_H, the average number of bound protons

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(hydrogen ion binding capacity) versus $-\log H^+$ for a single substance 'X' in solution:

$$nH = \{[HCl] - [KOH] + nX - [H^+] + (K_w/[H^+])\}/X \quad (1)$$

where n is the number of dissociable protons introduced into the solution by the substance X, $K_w = [H^+]\,[OH^-] = 10^{-13.75}$ at 25°C and 0.2 M ionic strength.

The titration is repeated after the addition of the partition solvent, stirring vigorously throughout to ensure equilibrium partition between the phases. A shift in pK_a to pK'_a is seen, magnitude of which depends on the partition coefficient is given as follows [13,14]:

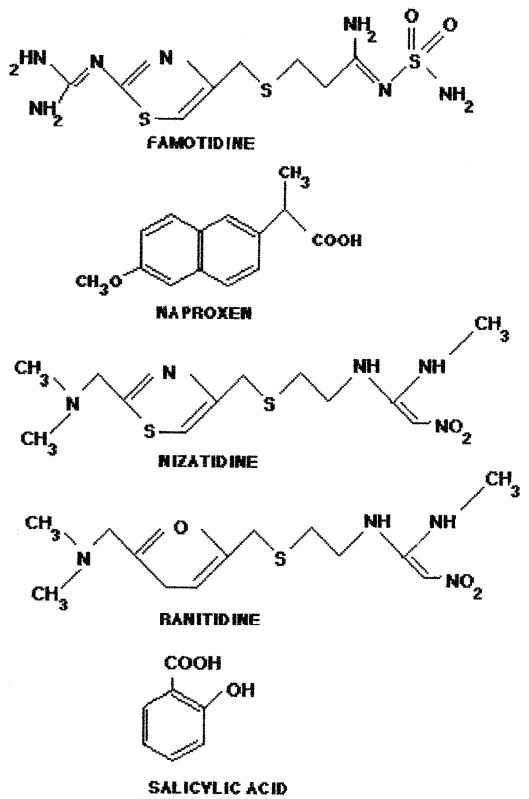

Fig. 1. The molecular structure of famotidine, naproxen, nizatidine, ranitidine and salicylic acid.

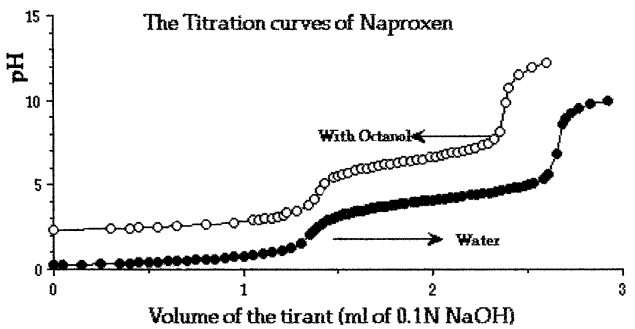

Fig. 2. The titration curves of naproxen with and without octanol.

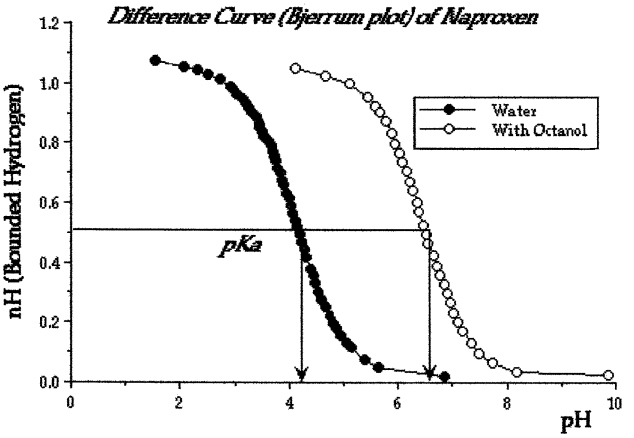

Fig. 3. The difference curves of the naproxen with and without octanol.

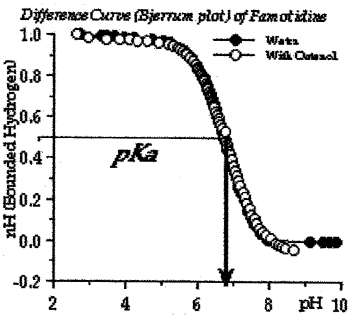

Fig. 4. The difference curves of the famotidine and nizatidine with octanol.

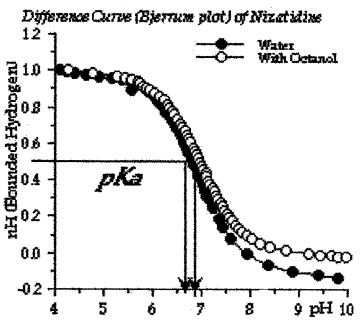

Fig. 5. The difference curves of the famotidine and nizatidine without octanol.

$$K = (10^{(pK'_a - pK_a)} - 1)/r \quad \text{(for acids)} \quad (2)$$

$$K = (10^{(pK_a - pK'_a)} - 1)/r \quad \text{(for bases)} \quad (3)$$

$$r = V_{org.}/V_{aqu.} \quad (4)$$

An automated pH-metric $\log K$ determination provides a high degree of accuracy [11] but it can also be done by manual titration and the manual titration method does not need complicated and expensive equipment. The aim of the present study was to determine $\log K$ values of compounds using manual pH-metric titration and to compare results with the other

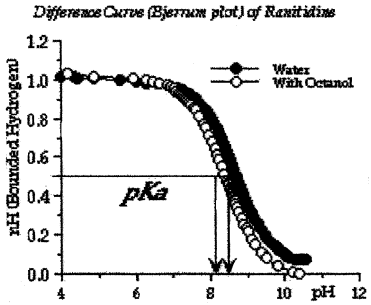

Fig. 6. The difference curves of the ranitidine and salicylic acid with octanol.

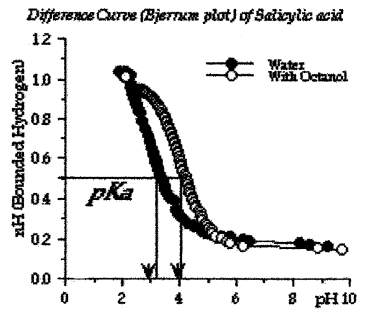

Fig. 7. The difference curves of the ranitidine and salicylic acid without octanol.

Table 1
The result of the pK_a of the substances

Compound	pK_a	pK'_a
Famotidine	6.780 ± 0.0609	6.785 ± 0.0639
Naproxen	4.151 ± 0.0265	6.512 ± 0.0135
Nizatidine	6.825 ± 1.158	6.998 ± 0.126
Ranitidine	8.657 ± 0.130	8.135 ± 0.0942
Salicylic acid	3.156 ± 0.164	4.325 ± 0.087

methods. This method was found to be useful and accurate.

2. Experimental

Famotidine was obtained from Ilsan Iltas Company, Turkey. Naproxen and salicylic acid were purchased from Sigma Chemical Co. Ltd, St. Louis, USA. Nizatidine was obtained from Elly Lilly, Illinois, USA. Ranitidine was obtained from Fako Drug Company, Turkey.

All other solvent and reagents were of analytical grade.

2.1. Apparatus

The titration instrument (digital pH meter Metrohm, model 654) that was used to perform pK_a and log K assays was equipped with a dosimeter (Metrohm model 665) and a magnetic stirrer. Titrations were performed at 25°C.

Titrations in the presence of octanol generally took longer to complete (45–90 min, depending on the sample and the requested pH range) than those in its absence (30–60 min). The pH was accepted as 'stable' when the magnitude of the change in pH after a titrant addition was less than 0.01/min. The actual pH readings were taken with the stirring turned off. The water-saturated octanol was used for the log K experiments.

2.2. pK_a and log K determination

The substance was dissolved in 10 ml of water; standardized 0.1 N HCl was added to lower the pH to 2–2.5 and the solution was titrated with 0.1 N KOH to about pH 11. After each titrant addition, the pH was measured. The pK_a of the substance was then determined using the Bjerium plot mentioned above.

The titration was repeated after adding partition solvent (octanol). The pK'_a was determined using the difference curve. The log K was calculated from the pK_a shifting (using Eqs. (2)–(4)).

2.3. log K determination using computer program

ACD-LogP computer program [15] was used to calculate log K of compounds. Each compound was created on the computer using the program and their log K values were calculated.

Table 2
log K values of the substances

Compound	log K (pH-metric)	log K (shake-flask)	log K (ACD-LogP)	log K (Literature)[16]
Famotidine	−0.982	-1.127 ± 0.0836	-1.020 ± 1.000	N.A.
Naproxen	3.313	3.297 ± 0.0718	3.000 ± 0.240	3.180
Nizatidine	0.644	0.820 ± 0.0224	1.046 ± 0.750	N.A.
Ranitidine	1.033	2.188 ± 0.0548	2.060 ± 0.250	N.A.
Salicylic acid	2.093	2.188 ± 0.0548	2.060 ± 0.0548	2.21

N.A.: values not available in the literature.

2.4. log K determination (shake-flask method)

Substances were dissolved in water and their HPLC chromatograms were obtained. A 10 ml volume of these solutions was mixed with 2 ml of octanol (octanol was mixed with the water previously and stirred for an overnight period at 25°C to obtain water saturated octanol) in a small capped bottle. All bottles were stirred for an overnight period at 25°C. The water phases were taken and their HPLC chromatograms were obtained. The peak areas were used to calculate the substance concentration and then log *K*. Mobile phase I was used for naproxen and salicylic acid analyses while mobile phase II was used for famotidine, nizatidine and ranitidine.

Mobile phase I. Acetonitrile (137.5 ml), water (112.5 ml), K_2HPO_4 (0.619 g), orthophosphoric acid (1 ml) (pH 3.5). Flow rate: 1 ml/min. UV detection was carried out at 230.9 nm.

Mobile phase II. Methanol (15 ml), water (69 ml), 0.05 M $NaH_2PO_4 \cdot H_2O$(16 ml) (pH 5.5). Flow rate: 1.5 ml/min. UV detection was carried out at 267 nm.

2.5. HPLC

Waters Millipore (510 pump, 717 plus auto sampler, 996 photo diode array detector, C_{18} ODS reverse phase column-25 × 0.4 cm, i.d.)

3. Results and discussion

Fig. 1 shows the molecular structures of the compounds. Fig. 2 shows the titration curves of naproxen with and without octanol presence. The pK_a of the substances were determined using 'difference curve' (Bjerium plot). Eq. (1) was used to obtain the 'difference curve'. Microsoft Excel computer package was used for the calculation. A typical 'difference curve' was shown in Fig. 3 for the naproxen. The value of 0.5 in 'difference curve' indicates the pK_a of the compound (Figs. 4–7).

Table 1 summarizes the result of the pK_a of the substances.

log *K* values of the substances were calculated using Eqs. (2)–(4). log *K* values of the compounds were also determined using shake-flask method. Their log *K* values were calculated from the changes of the peak areas when octanol is added. Table 2 summarizes the log *K* values of the substances using pH-metric titrations, using the shake-flask method and the computer program.

log *K* values obtained by pH-metric titration appear to be closer to the calculated log *K* values and the literature values of naproxen and salicylic acid. However, it should be noted that there are some variations for most pK_a results in the literature reflecting different experimental conditions. Similarly log *K* measurements have been performed in the literature using pH-metric titrations and ionization constants by curve fitting [14] for a series of 11 acids and bases, which spans the log *K* range from 0.63 to 5.33 and closer results were obtained comparing with the results of the shake-flask method. The author has indicated that the impurities of compounds could be effective but the method was found to be very accurate even in the presence of the titratable impurity.

It has been shown that the pH-metric method for pK_a determination can be useful to determine log *K* values of ionized drugs and it is easily adapted to the microcomputer. The method provides a high degree of accuracy even in the presence of impurities. The equilibrium is reached rapidly in emulsified aqueous-octanol mixtures that the titrant can be added continuously at a normal rate similar to any aqueous titration. Therefore the pH-metric log *K* measurement is found to be rapid, practical and convenient.

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