ELSEVIER

International Journal of Pharmaceutics 151 (1997) 193–199

international journal of pharmaceutics

Foaming activity and pK_a of some surface active compounds

F.A. Alvarez Núñez, S.H. Yalkowsky *

College of Pharmacy, The University of Arizona, Tucson, AZ 85721, USA

Received 10 November 1996; received in revised form 21 January 1997; accepted 22 January 1997

Abstract

A novel method to determine the pK_a of surface active compounds is presented. Since the ionized and unionized forms of amphiphiles have distinct surface and foaming properties, foamability as a function of pH can be used to obtain an approximate pK_a. Since foam is easily produced and measured, this method requires no specialized equipment. The foamability–pH profile is sigmoidal for both weak acids and bases, and a change of the foam activity is consistently observed in the region of their pK_a. The above relationship is confirmed using the following surface active compounds: amitriptyline, cyclohexylamine, dexverapamil, 3,5-diiodothyropropionic acid (DITPA), diphenhydramine, heptanoic acid, *n*-heptylamine, ibuprofen, laurylcarnitine, naphthoic acid, oleic acid and phenytoin. © 1997 Elsevier Science B.V.

Keywords: Amphiphile; Foam; pK_a

1. Introduction

There are many well known techniques for the determination of pK_a including: potentiometric titration, and the pH dependency of spectrophotometry, partition coefficient, electrophoresis and solubility (Perrin et al., 1981). Unfortunately, these methods require specialized equipment, as well as a significant amount of drug and/or time. In the case of ionizable amphiphiles, the change in surface activity, or interface affinity, as a function of the degree of ionization can also be used to determine the pK_a (Retzinger et al., 1986). In addition to the requirements of the above methods, surface tension measurements demand careful control of purity and surface temperature (Adamson, 1982). So although the surface tension method can be used to determine the pK_a of surface active compounds, it is inconvenient and time consuming.

Foam is a dispersed system of a gas in a continuous liquid phase (Shchramm and Wassmuth, 1994). Because foam has an extremely large interfacial area its stability is determined by a number of factors involving bulk solution as well as surface properties.

* Corresponding author.

PII S03 8-5173(97)04906-5

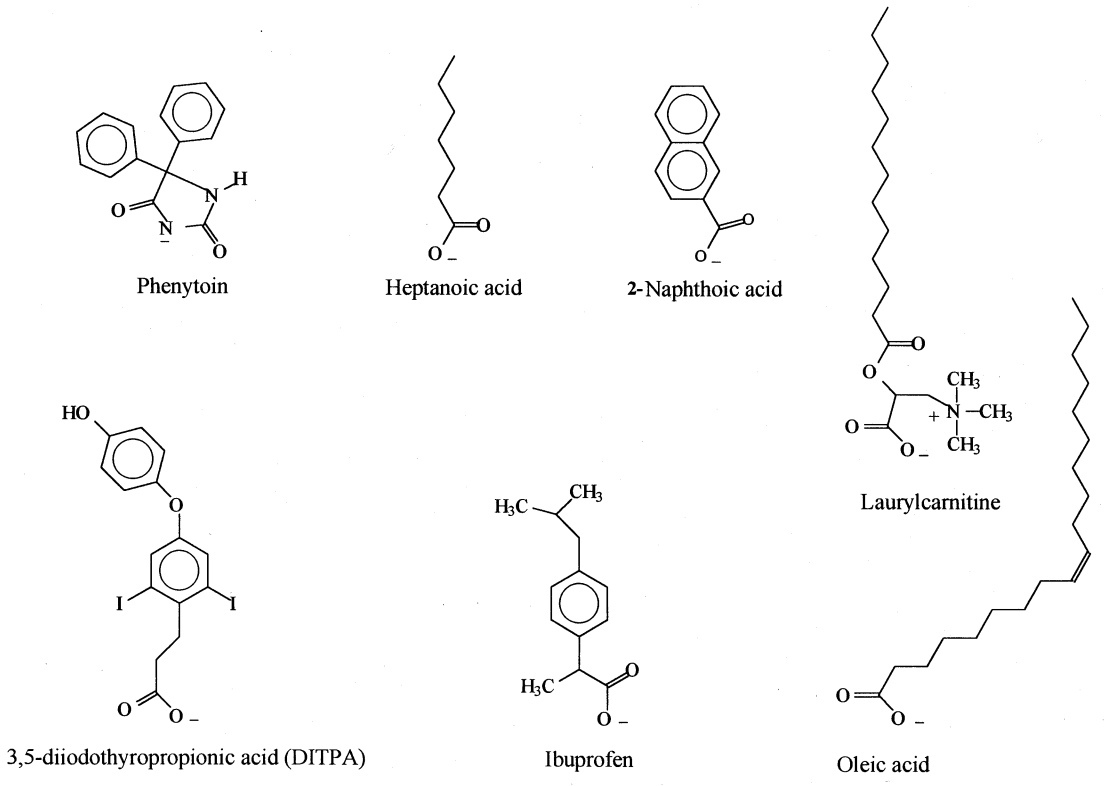

Fig. 1. Molecular structure of the experimented weak acids.

The presence of an amphiphile at the gas–liquid interface reduces the surface tension (which is the driving force for the reduction of surface area) and increases the foam stability. The degree of ionization of the compound can affect the foamability by affecting the strength of the interaction. Therefore, if the surface activity of a weak electrolyte changes as a function of its degree of ionization, these changes will be observed on a foam activity vs. pH profile. Although, the presence of foam upon agitation of an aqueous solution is usually an indication of surface activity, there are no reports correlating it with either the degree of ionization or the pK_a (Malysa et al., 1991). The goal of this investigation is to present the foamability as a tool in the pK_a estimation of some surface active compounds.

2. Materials and methods

2.1. Materials

Amitriptyline, cyclohexylamine, diphenhydramine, heptanoic acid, *n*-heptylamine, ibuprofen sodium salt, naphthoic acid, phenytoin sodium salt, and 3,5-diiodothyropropionic acid (DITPA) were used as obtained from Sigma. The potassium salt of oleic acid was obtained from TCI America. Dexverapamil was provided by Knoll Pharmaceutical. Laurylcarnitine was synthesized as is described by Yalkowsky and Zografi (1970). The buffer materials, phosphate salts and phosphoric acid were purchased from Sigma. The water used filtered through a double-deionized purification system (Milli-Q System from Millipore). The chemical structures of the weak

acids and bases studied are presented in Figs. 1 and 2. Notice that their polar heads are facing down. These figures show a variety of lipophilic and hydrophilic regions. Note that although laurylcarnitine is formally an acid it is cationic at low pH and zwitterionic at high pH.

2.2. Methods

2.2.1. Foam ratio (Fr)–pH profiles

Solutions of each amphiphilic were prepared by using phosphate buffers (5×10^{-2} M) at different pH. The pH of these solutions was measured with a corning pH meter (model 140) that was regularly calibrated with pH 4.00, 7.00 and 10.00 standard buffers (VWR Scientific). A set of at least nine test tubes (Pyrex® no.9826) containing 1 ml of solution each with different pH were placed on a test tube rack and secured with a rubber band. An extra tube containing 1 ml of water was placed on the rack and used as a reference. The rack was shaken (up and down) for approximately 30 s and the height of foam measured immediately. The foam ratio ($Fr = h/h_{max}$) was determined from h, which represents the height of foam observed on specific tube and h_{max}, the highest foam observed on the set. It should be noted that the effect of the dimensions of the test tubes and the degree of shaking are normalized in Fr. Each experiment was repeated at least three times using fresh solutions. All samples were independently evaluated by two individuals. No important differences were found among the values.

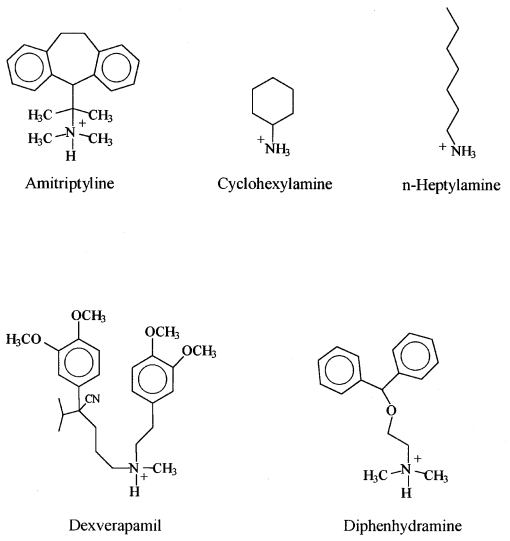

Fig. 2. Molecular structure of the experimented weak bases.

2.2.2. Initial foam height (h_i)

Solutions of the ionic form of the amphiphilies (10^{-3} M) were prepared by using phosphate buffers (5×10^{-2} M) at pH $\approx$ 3 for weak bases and pH $\approx$ 10 for weak acids. Two ml of each solution was transferred to a test tube ($\approx$ 8 mm of internal diameter). The tube was shaken for 15 s and the initial foam height (h_i) measured with a ruler. The experiment was repeated at least three times.

3. Results

The foam ratios (Fr) of the weak acids and bases studied are presented as a function of pH in Figs. 3 and 4, respectively. Note that in all cases the Fr–pH profile is sigmoidal and the inflection point (pH_i) is observed near to the reported pK_a value (vertical lines). The maximum Fr is observed at high pH for weak acids and at low pH for weak bases. Laurylcarnitine shows higher foamability in the pH range where the zwitterionic form dominates.

Table 1 shows the pK_a values reported in the literature, the inflection points of the Fr–pH profiles (pH_i) and the initial foam height (h_i) of the ionic form of the amphiphile solutions (10^{-3} M). In most of the cases the difference between pK_a and pH_i is less than one pH unit. Note that the literature reports more than one pK_a for the same ionizable group of some compounds.

Fig. 5 shows the relationship between the inflection point of the Fr–pH profile (pH_i) and pK_a. In general, pH_i is lower than the pK_a for weak bases and higher than pK_a for weak acids.

4. Discussion

When water is vigorously shaken, bubbles are produced. These bubbles quickly dissipate because of the combined effect of gravity (which pulls the liquid down) surface tension (which

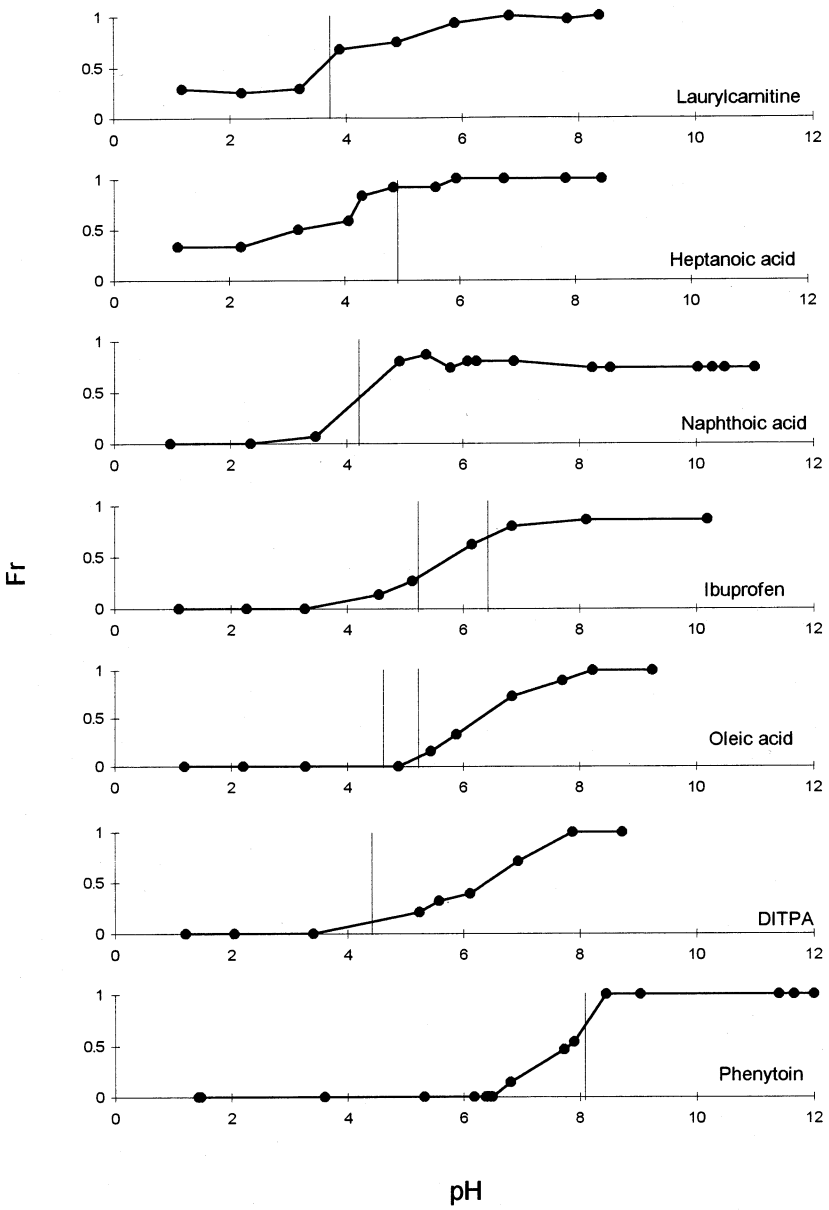

Fig. 3. Foam ratio (Fr) as a function of pH of laurylcarnitine (10^{-3} M), naphthoic acid (5×10^{-3} M), DITPA (10^{-4} M), oleic acid (10^{-3} M), ibuprofen (10^{-4} M), heptanoic acid (10^{-4} M), and phenytoin (10^{-3} M). The lines mark the pK_a reported in the literature.

pulls the liquid together and reduces surface area). The presence of amphiphilic molecules at the surface reduces the surface tension and therefore stabilizes the bubbles. The effectiveness of an amphiphile as a foam stabilizer is dependent upon its ability to accumulate and orient at the air–water interface. This ability is related to the normal (or perpendicular) interactions of its moiety with water, the squeezing out of the nonpolar moieties from water, and to the lateral interac-

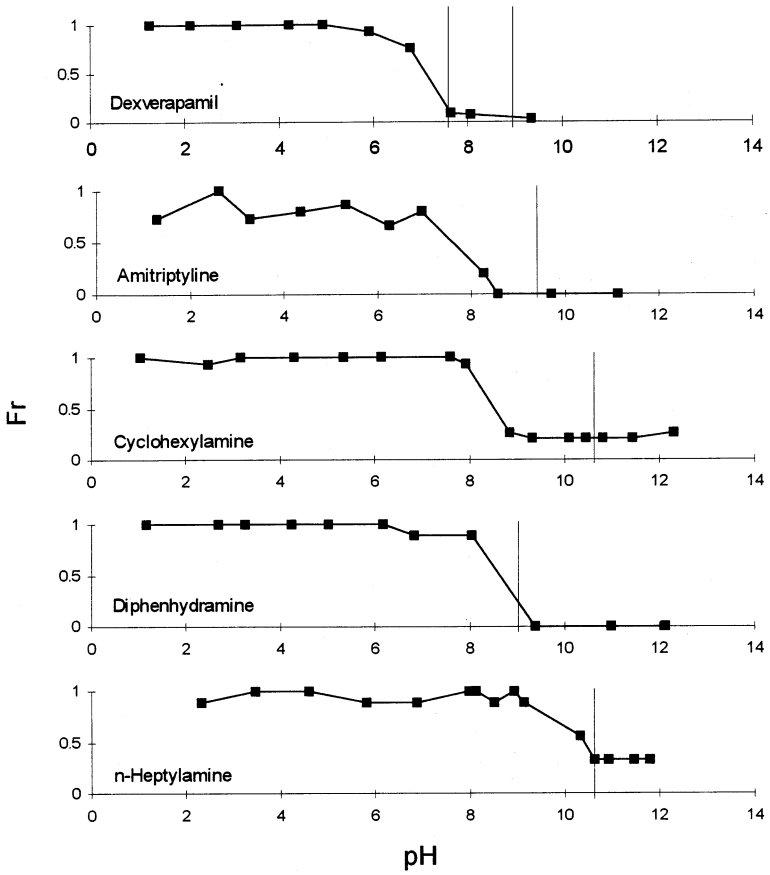

Fig. 4. Foam ratio as a function of pH of dexverapamil (10^{-3} M), diphenhydramine (10^{-3} M), amitriptyline HCl (10^{-3} M), cyclohexylamine (10^{-2} M), and $n-$heptylamine (10^{-3} M) (e). The lines mark the pK_a reported in the literature.

tions of the nonpolar and polar moieties with the corresponding moieties of neighboring molecules at the interface.

The molecular structures of the tested amphiphiles are presented in Figs. 1 and 2. The structural differences suggests different degrees of interaction once the molecules are either oriented at an interface or self associated in solution. The effect of these differences on the initial foam height (h_i) is observed on Table 1. For example, laurylcarnitine shows greater surface activity than ibuprofen, due to both its longer hydrophobic chain (van der Waals interactions) and its two ionic charges (electrostatic interactions), and therefore a higher foaming activity is observed and can be anticipated. In general, the larger the hydrophobic chain (laurylcarnitine and oleic acid), the higher the h_i. In addition, branching decreases the effective chain length, and reduces the ability of the amphiphile to act as a foaming agent (e.g. methyl groups in amitryptyline). This is consistent with the results of Varadaraj et al. (1990) who showed that hydrophobes with branches have weaker intermolecular cohesive forces than straight ones. The cyclic compounds in Table 1 have small hydrophobic surface areas and therefore low h_i values.

The primary indication of foamability is the solute–water interactions that are normal to the interface. Since ion–water interactions are stronger than dipole–water interactions, the ionized forms of amphiphiles can expected to interact more strongly with water than their uncharged counterparts. This is consistent with the

data in Figs. 3 and 4. All of the acids in Fig. 3 produce more foam at high pH where they are ionized than at low pH. For example, phenytoin produces the highest Fr above pH 9.1 and the lowest below pH 6.5 where the ionized form and the free acid are the prevailing species, respectively. For DITPA, oleic acid and ibuprofen the higher Fr is observed around pH 8 where the main species is the carboxylate ion. Similarly the cationic bases in Fig. 4 produce more foam than their uncharged counterparts. For example, amitriptyline (pK_a 9.4) and *n*-heptylamine (pK_a 10.6), the highest Fr is observed around pH 6–7 where the conjugated acid is present in more than 90%. These results are consistent with the data presented by Zhao et al. (1990) for *p*-hexadecylaniline in acidic and basic solutions. Their study shows that *p*-hexadecyl anilinium promotes higher surface pressure than *p*-hexadecyl aniline at the same concentration. It is interesting to note that laurylcarnitine is a more effective foaming agent as a zwitterion than as a cation. This is likely due to its greater lateral interactions as well as to the greater normal interactions that are produced by the two charged groups.

Table 1
pK_a values, pH values at the inflection point of the Fr–pH profiles (pH_i) and initial foam height (h_i) of the amphiphile solutions

Compound	Literature pK_a	pH_i	h_i (mm)[a]
Laurylcarnitine	3.7[b]	3.6	26
Naphthoic acid	4.2[c]	4.2	5
DITPA	4.4[d]	6.5	9
Heptanoic acid	4.9[c]	4.2	7
Oleic Acid	4.8[e], 5.0[f]	6.4	24
Ibuprofen	4.6[g], 5.2[h]	5.6	7
Phenytoin	8.1[i], 8.3[i]	8.2	4
Dexverapamil	8.0[j], 8.9[j]	7.7	7
Diphenhydramine	9.0[k]	8.7	5
Amitriptyline	9.4[l]	8.4	5
n-Heptylamine	10.6[c]	10.5	5
Cyclohexylamine	10.6[c]	8.4	4

[a]Standard deviations were between 0.6 and 1.0.
[b]Yalkowsky and Zografi, 1970.
[c]Albert and Serjeant, 1984.
[d]Heimbecher, S., Personal communication, 1996.
[e]Cistola et al., 1988.
[f]Somasundaran and Ananthapadmanabhan, 1978.
[g]Fini et al., 1995.
[h]Delgado and Remers, 1991.
[i]Schwartz et al., 1977.
[j]Surakitbanharn et al., 1995.
[k]Holcomb and Fusari, 1972.

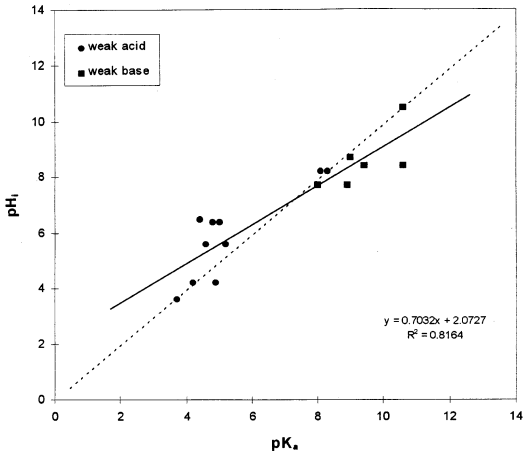

Fig. 5. Correlation between pH at the inflection point of the Fr–pH profile (pH_i) and pK_a. Compounds with two reported pK_a were plotted twice.

Because the pK_a of a weak electrolyte is the pH at which it is 50% ionized, a relationship between it and the inflection point (pH_i) of the Fr–pH profile can be anticipated. In fact, the Fr–pH profiles for both weak acids and bases (Figs. 3 and 4) have a sigmoidal shape where the inflection point is observed in the region of their pK_a (vertical lines). Fig. 5 shows the relationship between pH_i and pK_a of the studied compounds. The line of identity (dashed) systematically overestimates the pK_a of weak acids, and underestimates the pK_a for weak bases. This suggests that pH_i is not the best measure of the pK_a. On the other hand, the regression line (bold) predicts the pK_a with an standard error of 0.85. The difference between the regression line and the line of identity is likely the result of surface molecules having a different pK_a than the bulk molecules. Aggregation of acids at the surface will increase the effective pK_a because the anions present at half neutralization will inhibit further loss of protons. Similarly, aggregation of partially neutralized amines will result in a positive charge that repels protons. This cause, the pK_a of acids to fall above the identity line and the pK_a of bases to fall below it.

5. Conclusions

This study shows the feasibility for obtaining an approximate pK_a value for ionizable amphiphilic compounds by measuring the foam activity as a function of pH. The approximate pK_a value can be estimated in a very short time without the need for analytical instrumentation. This technique can be valuable for the formulator, especially when the time is an important factor, drug availability is limited, and high accuracy is not needed.

Acknowledgements

This work was supported by the National Cancer Institute (Contract # N01-CM-27757). We thank the Consejo Nacional de Ciencia y Tecnología de México and the DGAPA of Universidad Nacional Autónoma de México. The experimental work of Ms. Mi Jin Kim is appreciated.

References

Adamson, A.W., *Physical Chemistry of Surfaces*. 4th Edn, Wiley, New York, 1982.

Albert, A. and Serjeant, E.P. *The Determination of Ionization Constants*. 3th Ed., Chapman and Hall, New York, 1984.

Cistola, D.P, Hamilton, J.A., Jackson, D. and Small, D.M., Ionization and phase behavior of fatty acids in water: application of the Gibbs Phase Rule. *Biochemistry*, 27 (1988) 1881–1888.

Delgado, J.N. and Remers, W.A. (Eds.) *Wilson and Givold's Texbook of Organic Medicinal and Pharmaceutical Chemistry*, 9th Ed., Lippincott, Philadelphia, 1991.

Fini, A., Fazio, G., and Feroci, G., Solubility and solubilization properties of non-steroidal anti-inflammatory drugs. *Int. J. Pharm.*, 126 (1995) 95–102.

Holcomb, I.J. and Fusari, S.A., Diphenhydramine. In Florey, K. (Ed.), *Analytical Profiles of Drug Substances*, Vol. 3, Academic Press, New York, 1972.

Malysa, K., Miller, R. and Lunkenheimer, K., Relationship between foam and surface elasticity forces: fatty acid solutions. *Colloids Surfaces*, 53 (1991) 47–62.

Perrin, D.D., Body, D. and Serjeant, E.P. *pK_a Prediction for Organic Acids and Bases*. Chapman and Hall, London, 1981.

Retzinger, G.S., Cohen, L., Lau, S.H. and Kezdy, F.J., Ionization and surface properties of verapamil and several verapamil analogues. *J. Pharm. Sci.*, 75 (1986) 976–982.

Schwartz, P. A., Rhodes, C.T. and Cooper, J.W. Solubility and ionization characteristics of phenytoin. *J. Pharm. Sci.*, 66 (1977) 994–997.

Shchramm, L.L. and Wassmuth, F., Foams: basic principles. In Schramm, L.L. (Ed.), *Foams*, American Chemical Society, Washington, DC, 1994.

Somasundaran, P. and Ananthapadmanabhan, K.P., Solution chemistry of surfactants and the role of it in adsorption and froth flotation in mineral–water systems, In Mittal, K.L. (Ed.), *Solution Chemistry of Surfactants*, Vol. 2, Plenum Press, New York, 1978.

Surakitbanharn, Y, McCandless, R., Krzyzaniak, J. F., Dannenfelser, R. M. and Yalkowsky, S.H., Self-association of dexverapamil in aqueous solution. *J. Pharm. Sci.*, 84 (1995) 720–723.

Varadaraj, R., Bock, J., Valint, P., Zushma, S. and Brons, N. J., Relationship between fundamental interfacial properties and foaming in linear and branched sulfate, ethoxisulfate, and ethixylate surfactants. *J. Colloid Sci.*, 140 (1990) 31–34.

Yalkowsky, S. H. and Zografi, G., Some micellar properties of long-chain acylcarnitines. *J. Colloid Interface Sci.*, 34 (1970) 525–533.

Zhao, X., Subrahmanyan, S. and Eisenthal, K.B., Determination of pK_a at the air/water interface by second harmonic generation. *Chem. Phys. Lett.*, 171 (1990) 558–562.