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PH-metric log *P* 11. pK_a determination of water-insoluble drugs in organic solvent–water mixtures

A. Avdeef [a], K.J. Box [b], J.E.A Comer [b], M. Gilges [c], M. Hadley [c], C. Hibbert [b], W. Patterson [c], K.Y. Tam [b,*]

[a] *pION Inc., 142 Smith Place, Cambridge, MA 02138, USA*
[b] *Sirius Analytical Instruments Ltd., Riverside, Forest Row Business Park, Forest Row, East Sussex RH18 5DW, UK*
[c] *SmithKline Beecham Pharmaceuticals, Old Powder Mills, Leigh, Tonbridge, Kent TN11 9AN, UK*

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Abstract

The apparent acid dissociation constants (p$_s K_a$) of two water-insoluble drugs, ibuprofen and quinine, were determined pH-metrically in acetonitrile–water, dimethylformamide–water, dimethylsulfoxide–water, 1,4-dioxane–water, ethanol–water, ethylene glycol–water, methanol–water and tetrahydrofuran–water mixtures. A glass electrode calibration procedure based on a four-parameter equation ($pH = \alpha + Sp_cH + j_H[H^+] + j_{OH}[OH^-]$) was used to obtain pH readings based on the concentration scale (p$_c$H). We have called this four-parameter method the Four-Plus™ technique. The Yasuda–Shedlovsky extrapolation ($p_sK_a + \log[H_2O] = A/\varepsilon + B$) was used to derive acid dissociation constants in aqueous solution (pK_a). It has been demonstrated that the pK_a values extrapolated from such solvent–water mixtures are consistent with each other and with previously reported measurements. The suggested method has also been applied with success to determine the pK_a values of two pyridine derivatives of pharmaceutical interest.

Keywords: Acid dissociation constants; pK_a; pH-metric titration; Acetonitrile; Dimethylformamide; Dimethylsulfoxide; 1,4-Dioxane; Ethanol; Ethylene glycol; Methanol; Tetrahydrofuran

1. Introduction

Acid dissociation constants (pK_a values) are useful physico-chemical measurements describing the extent of ionization of functional groups with respect to pH. These parameters are important in research areas such as pharmaceutical drug discovery and development, where knowledge of the ionization state of a particular functional group is often vital in order to understand the pharmacokinetic and pharmacodynamic properties of new drug substances [1]. Traditionally, pH-metric titration was employed to determine the pK_a's of ionizable groups in aqueous solution. However, the success of this approach is sometimes hampered by poor aqueous solubility ($< 10^{-4}$ M). Spectrophotometric pK_a determination is an attractive alternative provided that the compound is

* Corresponding author.

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water soluble to the extent of 10^{-6} M and it contains chromophore(s) in proximity to the ionization centre(s) such that the protonated and deprotonated forms exhibit sufficient spectral dissimilarities [2,3]. If the compound is sufficiently soluble in a water-miscible organic solvent, it is possible to determine pH-metrically the apparent pK_a (p$_s K_a$) in co-solvent mixtures. Aqueous pK_a values can be determined by extrapolation of the p$_s K_a$ values to zero organic solvent content [2].

Knowledge of p$_s K_a$ values as a function of solvent composition is also useful in the application of reversed-phase HPLC for the separation of ionizable compounds [4]. Retention in such systems is influenced by the ionization state of functional groups present on the analytes [5]. Typically, acetonitrile or methanol are employed as co-solvents with water, often in the presence of buffers or other modifiers. In order to obtain satisfactory chromatographic resolution for individual components, the p$_s K_a$ values of the samples and the pH values of the eluents are useful parameters for consideration [5].

Methanol is widely accepted as a co-solvent in semi-aqueous work and its effect on pK_a has been investigated extensively [1,2]. In a previous study (part 3 of this series) [6], we presented a glass electrode calibration protocol based on a four-parameter equation which enabled reliable pH measurement and hence accurate p$_s K_a$ determination of water-insoluble samples in methanol–water mixtures. This approach, in conjunction with the Yasuda–Shedlovsky extrapolation method [7,8], was successfully applied to determine aqueous pK_a values from co-solvent measurements [6]. It has been demonstrated that the Yasuda–Shedlovsky extrapolation procedure for aqueous pK_a determinations using co-solvent data is generally more accurate than conventional method (p$_s$K$_a$ vs weight% organic solvent) as the latter often exhibits marked non-linearity [1,2,6]. Recently, this method was validated using a broad range of drug compounds [9].

In this report, we extend our investigations to include other commonly used solvents, namely acetonitrile, dimethylformamide, dimethylsulfoxide, 1,4-dioxane, ethanol, ethylene glycol and tetrahydrofuran. The four-parameter approach is referred to as the Four-Plus™ technique. The main aim of the investigation was to establish an accurate procedure to relate the operational pH scale to the concentration pH scale based on the Four-Plus™ technique, thus forming the basis for reliable p$_s K_a$ determinations in a variety of co-solvent systems. In the following discussion, we detail experimental procedures employed for such measurements. The accuracy of the technique is then illustrated by determination of pK_a values for several water-insoluble drug compounds in co-solvent solution by Yasuda–Shedlovsky extrapolations to zero percent organic content.

2. Experimental

2.1. Reagents and apparatus

Ibuprofen (sodium salt) and quinine (hydrochloride salt) were purchased from Sigma (Poole, England). Pharmaceutical intermediates SKF-75250 and SB-221789 (hydrochloride salt) were provided by SmithKline Beecham Pharmaceuticals. Acetonitrile (far UV grade) was supplied by Romil (Cambridge, UK). Dimethylformamide, dimethylsulfoxide, 1,4-dioxane, ethanol, ethylene glycol, tetrahydrofuran, hydrochloric acid, potassium hydroxide and potassium chloride (all AR grade) were obtained from Fisher (Loughborough, UK). The preparation and standardization of HCl and KOH solutions were described elsewhere [10]. Solutions were prepared in deionized water of resistivity $> 10^{14}$ Ω-cm. Potassium chloride was added to standardize the ionic strength of water and solvent–water mixtures. All titrations were performed by using either a PCA101 or a GLpK_a automatic titrator (Sirius, Forest Row, UK) [11,12]. The processing of the pH-metric data, computations of p$_s K_a$ values via a non-linear least squares procedure and Yasuda–Shedlovsky extrapolation treatments were performed using pK_aLOG P™ software (v5.01, Sirius).

2.2. Titrations in aqueous and semi-aqueous media

All titrations were performed in solutions of 0.15 M KCl under argon atmosphere at 25 ± 0.5°C using standardized 0.5 M HCl or 0.5 M KOH titrants. Sample solutions were prepared from 0.5 to 5 mM. For the semi-aqueous experiments, 8–40 wt.% acetonitrile, dimethylformamide, dimethylsulfoxide, 1,4-dioxane, ethanol, ethylene glycol, methanol or tetrahydrofuran were utilized. Sample solutions (between 10 and 20 ml) were pre-acidified to low pH (between 1.8 and 3.0) using 0.5 M HCl and titrated alkalimetrically to between 10.0 and 12.2. The pH change per titrant addition was limited to approximately 0.2 pH U. Data were acquired when the drift was less than 0.01 pH U min^{-1}. Typically, more than 30 pH readings were collected for each titration.

3. Results and discussion

3.1. Glass electrode standardization

The Four-Plus™ procedure was used for glass electrode calibrations in both aqueous and semi-aqueous media. Specifically, titrations were performed in a series of semi-aqueous HCl solutions of known concentration containing 0.15 M KCl and 0–40 wt.% of the aforementioned solvents, using 0.5 M KOH solution. Nine titrations with different solvent compositions were carried out for each co-solvent system. The operational pH scale was established by calibrating the pH measuring circuit with a single aqueous phosphate buffer (pH 7.0) and assuming the Nernst slope. All data reported in this study are based on the concentration scale with respect to an ionic strength of 0.15 M and 25°C. As the proton concentrations driving strong acid-strong base titrations can be readily calculated, the concentration pH value (p_cH ($= -\log[H^+]$)) is related to the operational pH reading by the equation as given below [13].

$$pH = \alpha + Sp_cH + j_H[H^+] + j_{OH}\frac{K_w}{[H^+]} \quad (1)$$

The intercept parameter α corresponds to the negative logarithm of the activity coefficient of H^+ at working temperature and ionic strength. The S term denotes the ratio between the actual slope and the Nernst slope. The j_H term corrects pH readings for the non-linear pH response due to liquid junction and asymmetry potentials in moderately acidic solution (pH 1.5–2.5), while the j_{OH} term corrects for any high-pH (pH > 11) non-linear effects. These parameters are determined by a weighted non-linear least squares procedure [13]. For aqueous titrations, the ionization constants of water (K_w) as a function of temperature and ionic strength, were taken from Sweeton et al. [14]. For semi-aqueous titrations, literature values of ${}_sK_w$ (the ionization constants of water in the solvent–water mixtures) were utilized [15–19]. In processing the titration data, contribution from carbonate was incorporated into the calculations. The acid dissociation constants of carbonic acid in solvent–water mixtures were determined iteratively in parallel with the the parameters as defined in Eq. (1).

Table 1 gives the parameters as a function of R (wt.% of organic solvent). The following polynomial function was employed to fit the results,

$$P = \sum_{i=0}^{n} P_i R^i \quad (2)$$

where P can be any one of the parameters ($= \alpha$, S, j_H or j_{OH}, see Eq. (1)) at a particular R value and n is the degree of the polynomial used. In general, $n \leq 4$ was sufficient to give reasonably good fits. With high quality glass electrodes, the variation in the polynomial coefficients, P_i ($1 \leq i \leq n$) as shown in Eq. (2) was insignificant. This indicated that the same set of coefficients should be applicable for other glass electrodes. Note that the first terms of the polynomials ($i = 0$) were numerically equivalent to the aqueous parameters (Eq. (1)), which therefore must be determined beforehand. To this end, the conversion of the operational pH reading to the p_cH value at any R value (0–40%) can be accomplished by the following steps:

1. deduce the aqueous parameters of the glass electrode from an aqueous calibration titration;

Table 1
Four-Plus™ parameters for acetonitrile–water, dimethylformamide–water, dimethylsulfoxide–water, 1,4-dioxane–water, ethanol–water, ethylene glycol–water and tetrahydrofuran–water mixtures at 25°C and an ionic strength of 0.15 M (data for methanol–water mixtures was given in ref. [6])

R (wt.%)	α	S	j_H	j_{OH}
Acetonitrile–water				
0	0.093	0.9992	0.8	−0.2
3.3	0.086	1.0015	0.4	−0.5
6.7	0.062	1.0039	0.7	−0.7
10.2	0.038	1.0060	0.7	−1.1
13.8	0.030	1.0066	0.6	−1.5
17.5	0.017	1.0066	0.7	−1.7
21.5	0.008	1.0060	0.8	−2.0
25.6	0.002	1.0032	0.5	−2.0
29.8	−0.015	1.0004	0.6	−1.4
34.2	−0.032	0.9959	0.4	−0.3
38.4	−0.025	0.9908	0.0	−1.4
Dimethylformamide–water				
0	0.099	0.9993	0.2	−0.7
4.8	0.085	1.0266	0.8	−2.3
10.0	0.094	1.0481	1.7	−4.2
15.0	0.293	1.0415	0.6	−3.3
20.0	0.239	1.0471	1.6	−6.5
24.5	0.337	1.0384	1.0	−7.3
30.9	0.421	1.0317	0.8	0.1
35.7	0.523	1.0161	−2.1	25.5
Dimethylsulfoxide–water				
0	0.084	1.0015	0.1	−1.3
6.1	0.078	1.0106	1.6	−1.1
9.7	0.125	1.0139	1.0	−2.0
18.0	0.141	1.0147	1.7	−1.8
23.8	0.206	1.0141	1.4	−3.3
29.5	0.266	1.0093	1.2	−2.4
41.1	0.403	1.0041	1.2	−14.4
1,4-Dioxane–water				
0	0.076	1.0005	0.6	−0.6
5.6	0.104	0.9987	−0.2	−0.3
11.4	0.119	0.9940	0.3	−0.3
17.1	0.119	0.9945	0.1	−0.5
22.8	0.141	0.9868	−0.2	−0.4
34.0	0.203	0.9768	−1.2	−0.4
39.5	0.193	0.9820	−0.9	−1.5
45.1	0.197	0.9710	−1.0	−0.8
Ethanol–water				
0	0.069	1.0009	0.7	−0.5
4.4	0.076	1.0026	1.6	−0.9
8.9	0.106	1.0008	1.2	−0.4
13.5	0.125	0.9985	0.7	0.1
18.1	0.147	0.9960	0.7	0.2
22.6	0.200	1.0009	0.7	−0.5
27.4	0.246	0.9930	0.1	−0.3
32.1	0.255	0.9913	0.9	1.7
36.4	0.348	0.9849	0.1	10.7
EthyleneGlycol–water				
0	0.073	1.0028	0.8	−1.2
6.6	0.055	1.0040	0.9	−0.3
11.9	0.054	1.0042	0.4	−0.3
17.8	0.024	1.0058	0.9	−0.1
23.8	0.023	1.0059	0.6	−0.2
29.3	0.018	1.0079	0.3	−0.3
35.0	0.003	1.0062	0.5	0.0
41.1	−0.008	1.0069	0.4	0.0
Tetrahydrofuran–water				
0	0.086	1.0002	0.4	0.3
4.9	0.103	0.9962	0.3	0.7
9.9	0.132	0.9930	0.1	2.7
14.8	0.171	0.9910	−0.4	1.0
20.5	0.206	0.9895	−0.6	0.5
25.5	0.236	0.9882	0.3	−1.0
30.7	0.264	0.9855	0.2	−1.1
37.1	0.313	0.9775	−0.1	0.5

2. calculate the co-solvent parameters by using Eq. (2) at a particular R value;

3. solve Eq. (1) by using the Newton–Raphson method [20].

Fig. 1 shows the change of α, S, j_H and j_{OH} as a function of R for the eight solvent–water systems calculated using Eq. (2) (experimental points as listed in Table 1 were omitted for clarity). The following aqueous parameters were utilized: $\alpha = 0.09$, $S = 1.001$, $j_H = 1.0$ and $j_{OH} = -1.0$ [6]. It is of interest to note that the variations in these parameters versus R are markedly different for various solvent–water systems. This implies that the calibration parameters for each system must be deduced independently. Fig. 2 shows plots of pH-p_cH as a function of pH and R generated using Eqs. (1) and (2) in conjunction with the best-fit polynomial coefficients of the eight solvent–water systems. The aqueous values of α, S, j_H and j_{OH} employed were as with as Fig. 1. The pH-p_cH values are comparable to α at $R = 0$ and pH values between 4 and 10. With solvent compositions and pH values outside these regions, the values are not comparable, suggesting that nonlinear glass electrode response is significant and

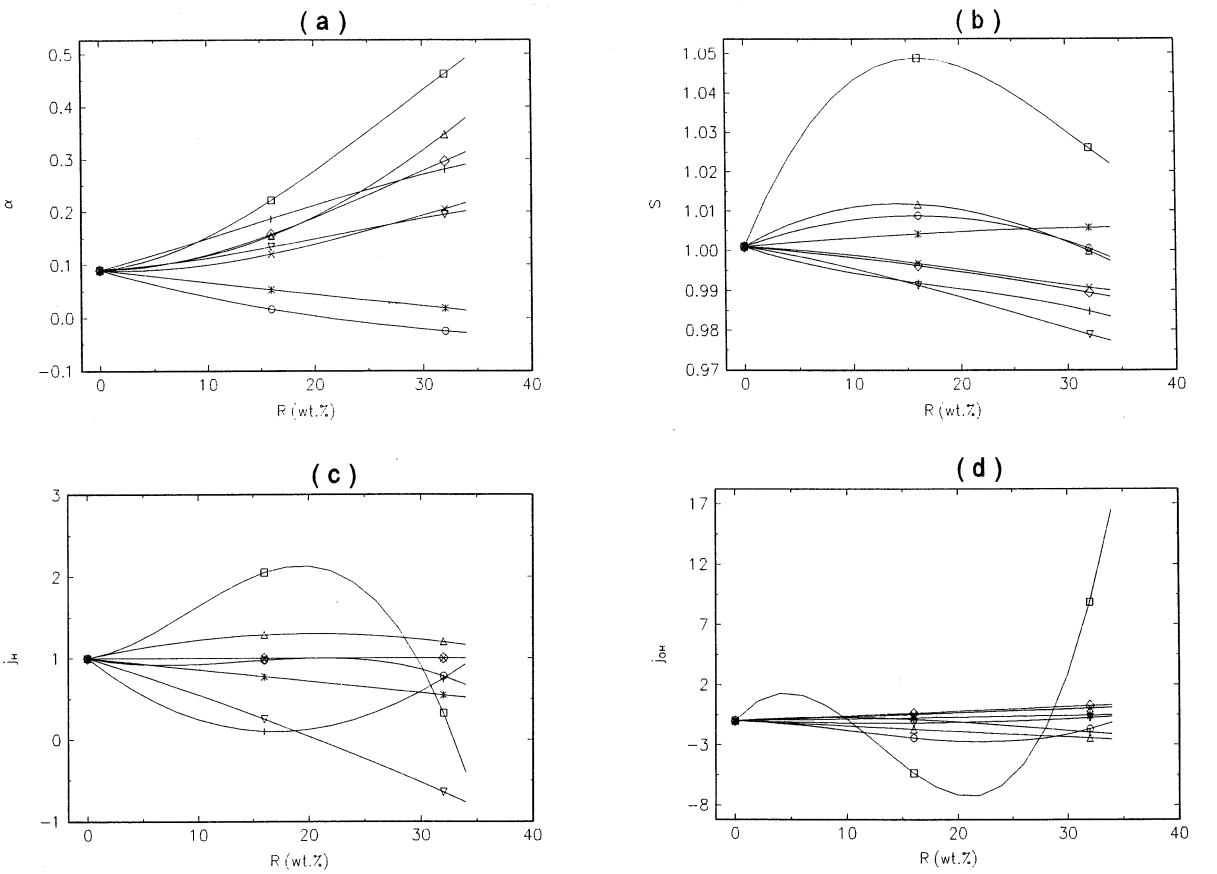

Fig. 1. Change of (a) α; (b) S; (c) j_H and (d) j_{OH} vs. the weight percent of acetonitrile (○), dimethylformamide (□), dimethylsulfoxide (△), 1,4-dioxane (▽), ethanol (◇), ethylene glycol (*), methanol (X) and tetrahydrofuran (|). (Calculated using Eq. (2) with the following aqueous parameters: $\alpha = 0.09$; $S = 1.001$; $j_H = 1.0$; $j_{OH} = -1.0$).

correct electrode calibration methodology as reported here is essential for reliable quantification of p_cH values. It is clear that for a particular set of aqueous α, S, j_H and j_{OH} values, conversion between pH and p_cH at differing pH and R values can be accomplished by use of Fig. 2.

3.2. Determination of pK_a using Yasuda–Shedlovsky extrapolation

Use of the method described above enabled pH-metric titrations for the determination of p_sK_a values of ibuprofen and quinine. Based on the Born electrostatic model and Bjerrum's theory of ion association, Yasuda [7] and Shedlovsky [8] independently derived a correlation whereby a plot of $p_sK_a + \log[H_2O]$ versus $A/\varepsilon + B$ produces a straight line, where $[H_2O]$ represents the molar water concentration and ε denotes the dielectric constant of the mixture. Terms A and B symbolize the slope and the intercept of the plot, respectively. It has previously been reported that when using solvent/aqueous mixtures with ε values greater than 50, the extrapolation to the purely aqueous domain is linear and produces relatively accurate pK_a values [1,6,9]. With this criterion in mind, aqueous pK_a was evaluated using log 55.5 and 1/78.3, the logarithm of the molar concentration and the inverse of the dielectric constant of pure water respectively. In the present work, dielectric con-

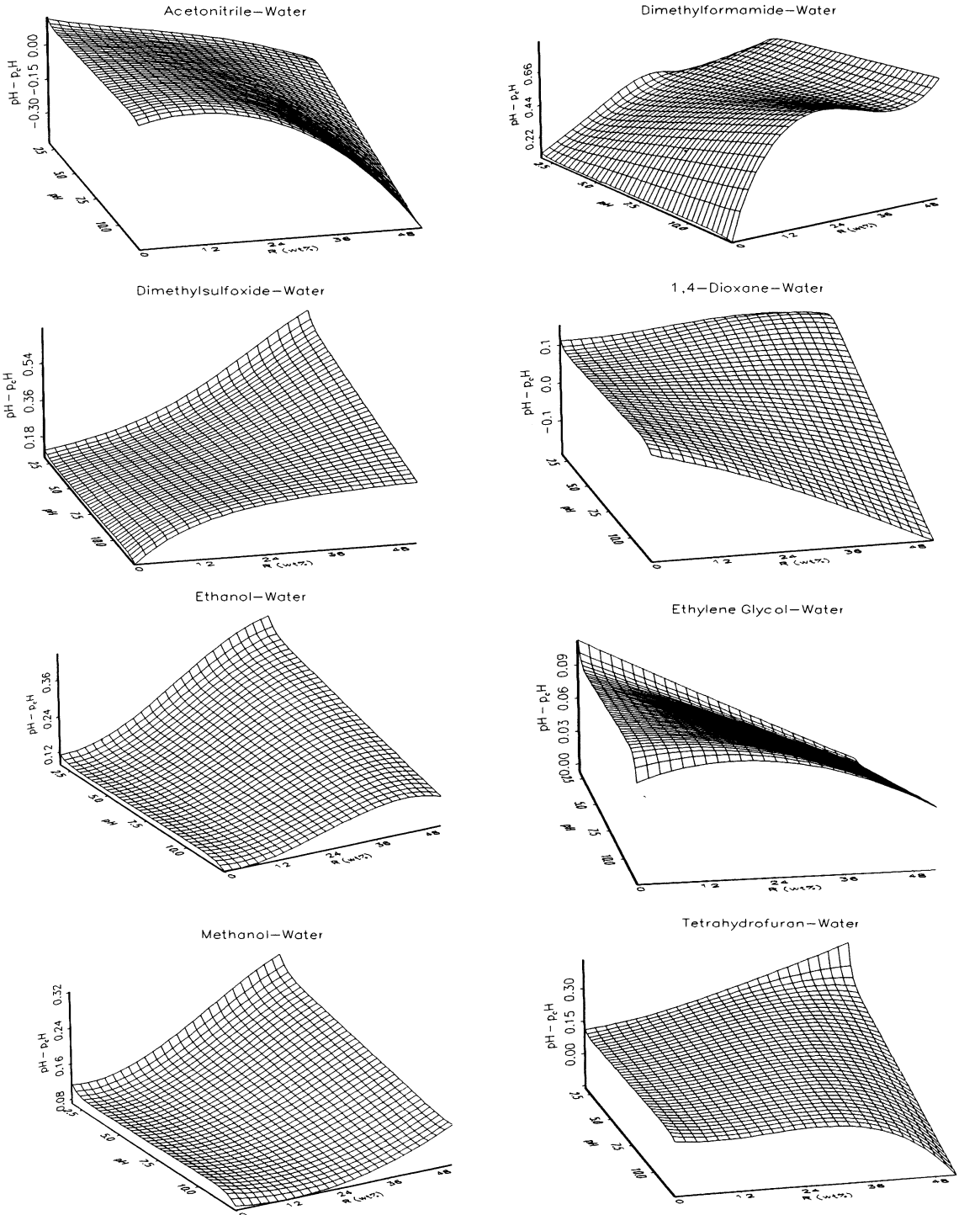

Fig. 2. Differences between the operational and concentration pH values as a function of operational pH values and weight percent of various solvent–water mixtures generated using Eqs. (1) and (2).

stants versus R for various solvent–water systems were taken from the literature [18,21–26].

Fig. 3 shows the structures of ibuprofen, quinine, SKF-75250 and SB-221789. In this preliminary investigation, we selected ibuprofen and quinine (two relatively water-insoluble compounds) to examine the feasibility of extending the Yasuda–Shedlovsky approach to several other commonly used organic solvent–water mixtures. It was found that extrapolation plots including the p_sK_a values from solvent rich compositions ($R > 35$ wt.%) usually exhibited sublinear behavior. However, for a few solvents, such as ethylene glycol and methanol, linearity could be extended to about 55 wt.%. This is in accordance with a recent observation indicating a change in the ionic diameter of solvated drugs at such solvent compositions, resulting in a shift of A (which is inversely proportional to the average ionic diameter of the solvated molecule) [8]. In view of this, some of the p_sK_a values obtained above 35 wt.% solvent were excluded from our extrapolation treatments. Figs. 4 and 5 show, respectively, the Yasuda–Shedlovsky extrapolations of ibuprofen and quinine in various solvent–water mixtures. As listed in Table 2, the agreement between the pK_a values of the samples

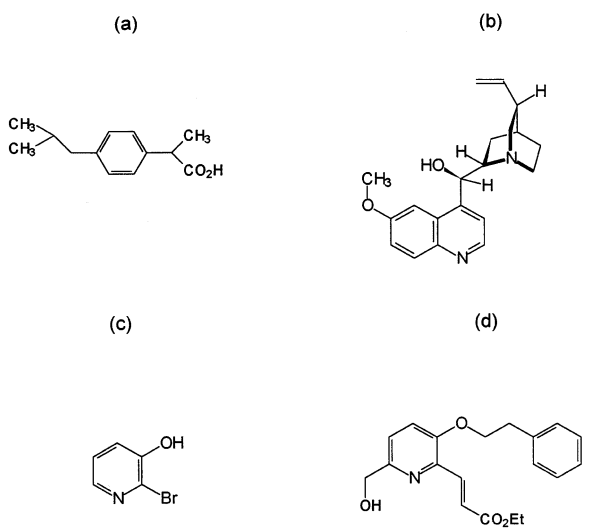

Fig. 3. Structures of (a) ibuprofen, (b) quinine, (c) SKF-75250 and (d) SB-221789.

Table 2
pK_a values of ibuprofen and quinine as determined from various solvent–water mixtures at 25°C with an ionic strength of 0.15 M, using the Yasuda–Shedlovsky extrapolation method (uncertainty represents the estimated standard deviation)

	Ibuprofen	Quinine
Acetonitrile–water	4.31 (±0.04)	4.13 (±0.01)
		8.52 (±0.03)
Dimethylformamide	4.30 (±0.05)	3.85 (±0.07)
–water		8.15 (±0.06)
Dimethylsulfoxide	4.35 (±0.03)	4.32 (±0.03)
–water		8.51 (±0.01)
1,4-Dioxane–water	4.46 (±0.10)	4.25 (±0.01)
		8.57 (±0.01)
Ethanol–water	4.33 (±0.01)	4.24 (±0.11)
		8.55 (±0.06)
Ethylene glycol–water	4.34 (±0.06)	4.21 (±0.06)
		8.54 (±0.04)
Methanol–Water	4.45 (±0.04)	4.24 (±0.09)
		8.55 (±0.04)
Tetrahydrofuran	5.16 (±0.07)	4.07 (±0.09)
–water		8.58 (±0.04)
Literature data	4.4[a]	4.1[a], 8.5[a]
	4.31 (±0.05)[b]	4.33 (±0.01)[d]
	4.61[c]	8.59 (±0.01)[d]

[a] Table 9.15 in ref. [2]; no estimated uncertainty and experimental conditions quoted.

[b] Spectrophotometric determination at 22°C and ionic strength of 0.2 M [27].

[c] Potentiometric determination in dimethylsulfoxide–water solutions at 25°C and a linear correlation method to obtain the pK_a value [28]; no estimated uncertainty quoted.

[d] Spectrophotometric determination in water at 25°C and ionic strength of 0.15 M [3].

obtained from various solvent–water mixtures and literature values is generally good.

The pharmaceutical intermediate SKF-75250 was found to be soluble in water and acetonitrile–water mixtures which permitted direct comparison between the pK_a values obtained from aqueous and co-solvent titrations. Fig. 6a,b depict, respectively, the Yasuda–Shedlovsky extrapolations of SKF-75250 and SB-221789. It is evident that even for low pK_a values (< 4), the Yasuda–Shedlovsky treatment generates essentially linear data. As shown in Table 3, the aqueous pK_a values of SKF-75250 are generally consistent with those determined using Fig. 6, suggesting the proposed electrode calibration method and the Yasuda–

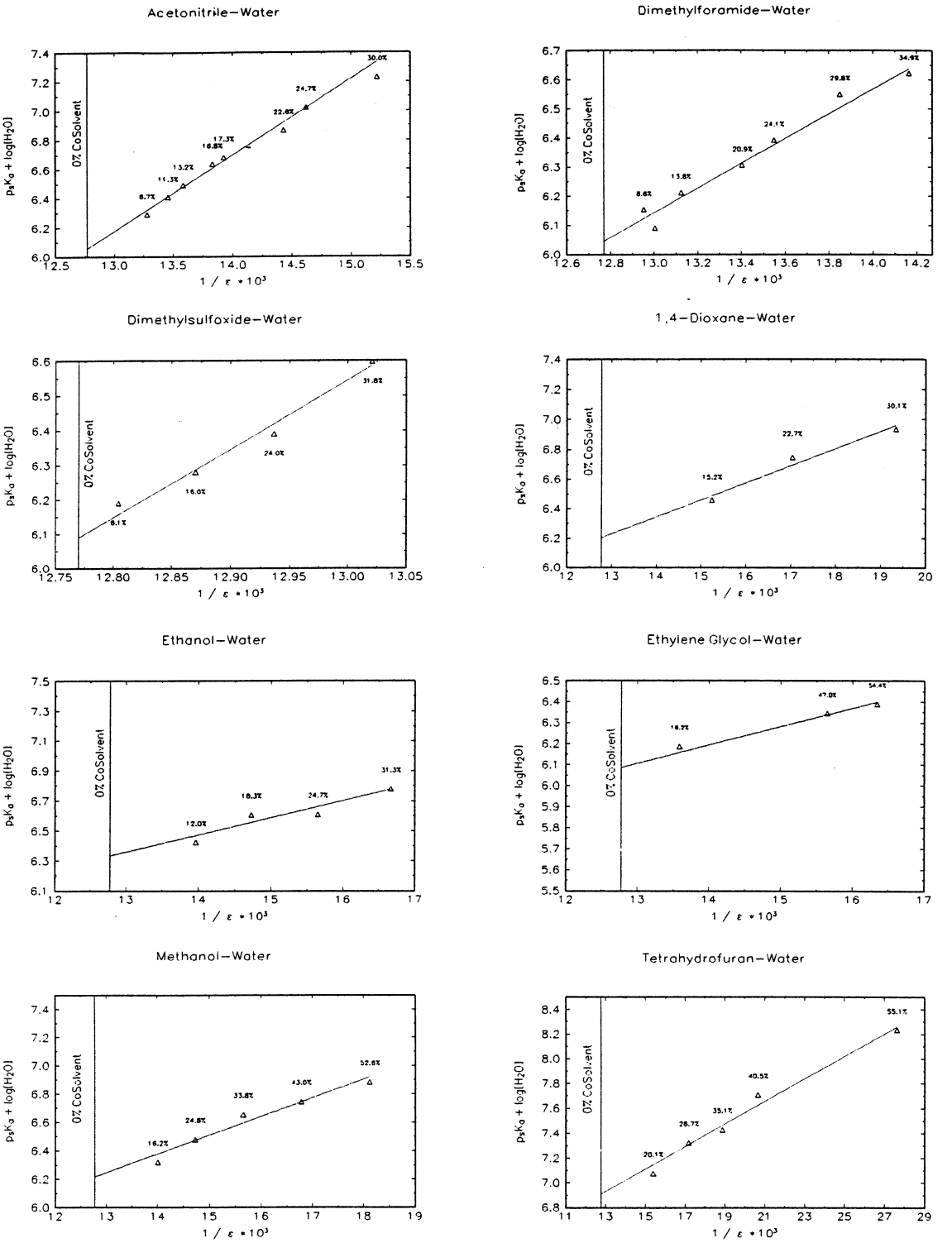

Fig. 4. Yasuda–Shedlovsky extrapolations of ibuprofen in various solvent–water mixtures at 25°C and an ionic strength of 0.15 M.

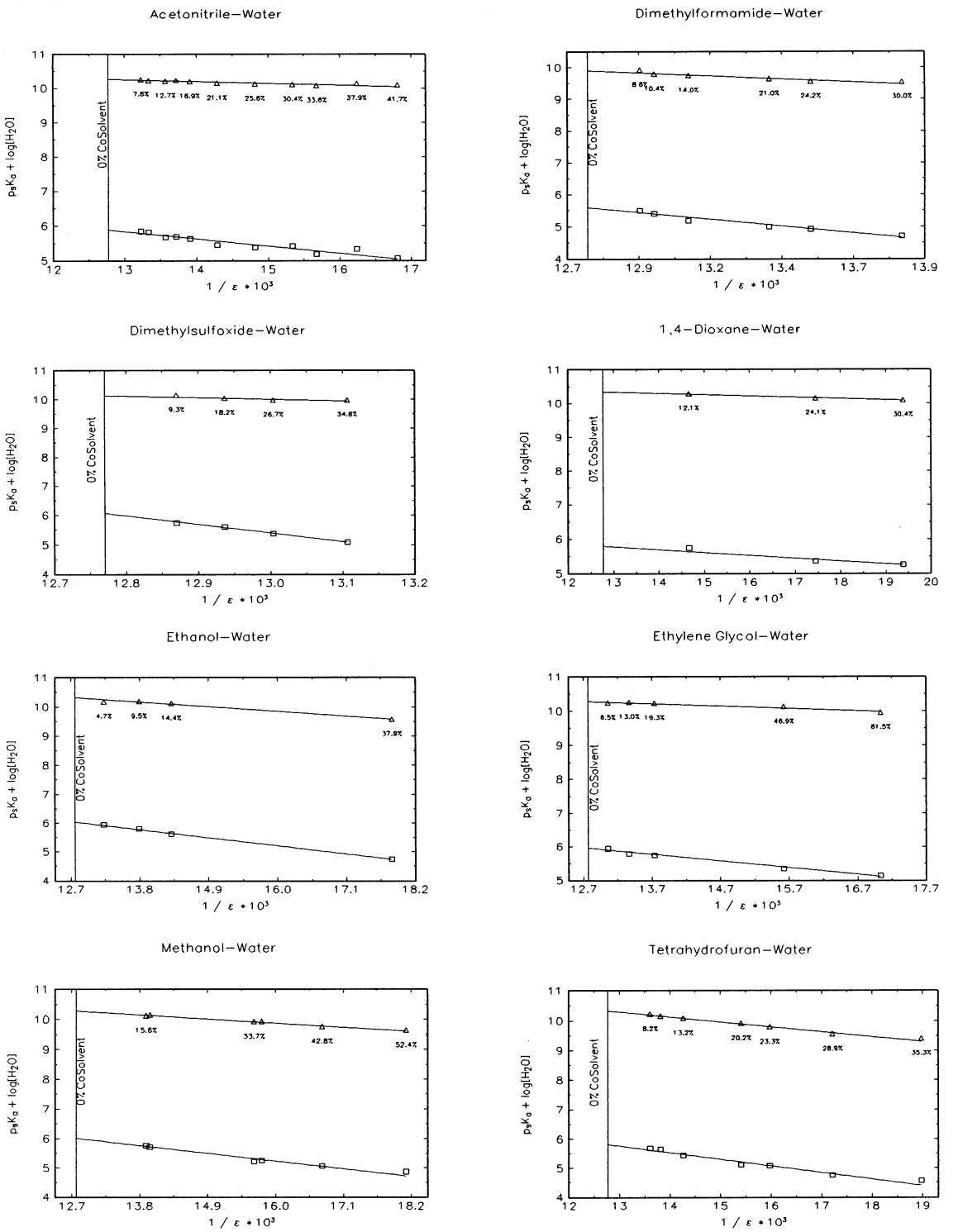

Fig. 5. Yasuda–Shedlovsky extrapolations of quinine in various solvent–water mixtures at 25°C and an ionic strength of 0.15 M.

Shedlovsky extrapolation are crucial for accurate pK_a determination in solvent–water mixtures. Note that the pK_a value of the pyridine group increases by approximately 1 pH U as the electron withdrawing bromo-substituent (SKF-75250) is replaced by an acrylic ester substituent (SB-221789).

4. Conclusions

We have applied the Four-Plus™ technique together with the Yasuda–Shedlovsky method for the pH-metric pK_a determination of water- insoluble substances in mixtures of water and eight

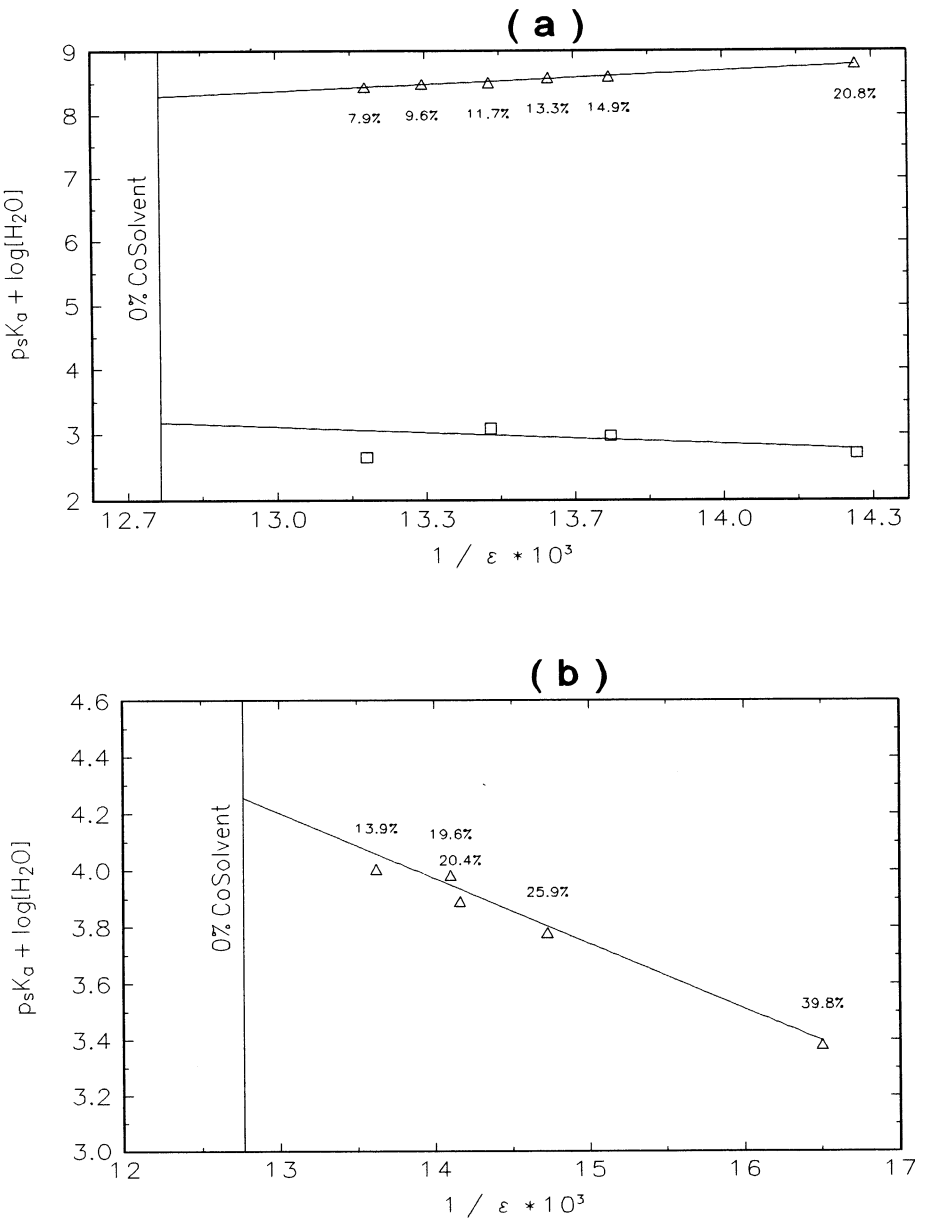

Fig. 6. Yasuda–Shedlovsky extrapolations of (a) SKF-75250 and (b) SB-221789 in acetonitrile–water mixtures at 25°C and an ionic strength of 0.15 M.

Table 3
pK_a values of SKF-75250 and SB-221789 as determined from acetonitrile–water mixtures at 25°C with an ionic strength of 0.15 M, using the Yasuda–Shedlovsky extrapolation method (uncertainty represents the estimated standard deviation)

	SKF-75250	SB-221789
Acetonitrile–Water	1.43 (± 0.32)	2.51 (± 0.07)
	6.54 (± 0.02)	
Aqueous	1.79 (± 0.02)	N.S.[a]
	6.56 (± 0.01)	

[a] Not soluble in water.

organic solvents, namely acetonitrile, dimethylformamide, dimethylsulfoxide, 1,4-dioxane, ethanol, ethylene glycol, methanol and tetrahydrofuran. It was demonstrated that the technique described allowed a robust calibration of glass electrodes in solvent–water mixtures such that the transformation between the operational pH scale and the concentration pH scale could be performed accurately. Based on this calibration, accurate values of apparent pK_a (p_sK_a) were obtained from titrations performed in these solvent–water mixtures. Yasuda–Shedlovsky extrapolation treatment was found to be useful, particularly in the water-rich region ($R < 35\%$), in order to evaluate aqueous pK_a values from the p_sK_a data. The method is exemplified by use of two water-insoluble drugs, namely ibuprofen and quinine, and two pyridine derivatives of pharmaceutical interest. pK_a data generated using this procedure with different solvent–water mixtures is generally comparable and also shows good correlation with reported literature values.

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