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Dissociation constants and assay of weak bases in non-aqueous solvents*

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Abstract: A method is described for evaluating standard cell potentials of specific electrode pair systems in anhydrous acetic acid and acetonitrile. The dissociation constants (K_{HB^+}) in acetonitrile and the overall dissociation constants (K_B) and (K_{BHClO_4}) in anhydrous acetic acid of a series of bases of pharmaceutical interest have been determined. Simple potentiometric and visual titration methods are proposed for the assay of bases and their mixtures.

Keywords: *Standard potentials; dissociation constants; non-aqueous titration.*

Introduction

For many years, acetic acid has been a popular solvent for the titration of weak bases because of the high purity of the commercial product, its physical characteristics, low basicity and good solvating power. However, the dielectric constant of the solvent is low (6.13) and its high acidity renders it unsuitable for the assay of mixtures of bases [1, 2]. In contrast, acetonitrile has weak solvating power [3] and has a relatively high dielectric constant (36) and very low autoprotolysis constant ($K_{HS} < 10^{-33}$) [2]. Therefore, it offers a wide pH range (0–33), which allows measurement of large changes in pH that can occur during an acid–base titration, even for very weak bases which usually cannot be determined in acetic acid medium [4]. It also allows the observation of a greater number of and steeper potential inflections in titrations of mixtures of bases owing to their different base strengths in acetonitrile [5].

The precise interpretation of potentiometric titration curves for acid–base reactions in anhydrous acetic acid requires a knowledge of the overall dissociation constants of the base, (K_B) and base perchlorate (K_{BHClO_4}). The Kolthoff and Bruckenstein notation [6, 7] shows:

$$B + HAcO \rightleftharpoons BH^+AcO^- \rightleftharpoons BH^+ + AcO^-$$

$$K_B = \frac{a_{BH^+}\, a_{AcO^-}}{a_B + a_{BH^+AcO^-}} \qquad (1)$$

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$$BHClO_4 \rightleftharpoons BH^+ClO_4^- \rightleftharpoons BH^+ + ClO_4^-$$

$$K_{BHClO_4} = \frac{a_{BH^+}\, a_{ClO_4^-}}{a_{BHClO_4} + a_{BH^+ClO_4^-}} \tag{2}$$

For a solution of base alone, equation 3 gives the potential

$$E_B = E^0_{GC} + E_j + RT/F \ln K_s - RT/2F \ln K_B c_B \tag{3}$$

E^0_{gC} is the standard potential of the cell, E_j is the liquid junction potential, K_s is the autoprotolysis constant of the solvent and c_i is the stoichiometric concentration (mol l^{-1}) for the particular solute, i.

For a solution of a base and its perchlorate in acetic acid the hydrogen ion activity is given by equation 4 [7].

$$a_{H^+} = K_s \left[\frac{K_B c_B + K_{BHClO_4}\, c_{BHClO_4}}{K_B c_B\, (K_S + K_B c_B)}\right]^{1/2} \tag{4}$$

For moderately dilute solutions of bases having $K_B > 10^{-10}$, the term $(K_s + K_B c_B)$ becomes $K_B c_B$ [7] and the Nernst relationship assumes the form [6, 8, 9]:

$$E_{B,BHClO_4} = E^0_{gC} + E_j + RT/F \ln K_s - RT/F \ln K_B c_B + RT/2F \ln (K_B c_B + K_{BHClO_4} c_{BHClO_4}) \tag{5}$$

Equations 3 and 5 permit the determination of K_B and K_{BHClO_4} if the quantity $(E^0_{gC} + E_j)$ for an electrode pair system has been determined.

Although acetonitrile is a solvent with good resolving power for acids, it is not very suitable for the differentiating titration of acids in mixtures because of homo- and heteroconjugation [2, 3]. However, solvation of anions is less than that of cations and from an analytical viewpoint, conjugation is negligible for bases [10]. Thus, acetonitrile is a very suitable solvent for titration of bases, especially of very weak bases and their mixtures [5].

For the dissociation constant of a protonated base in acetonitrile [11]:

$$K_{HB^+} = a_{HS^+} \frac{[B]\, y_B}{[HB^+]\, y_{HB^+}} \tag{6}$$

[X] denotes the molar concentration, a_x the activity and y_x the molar activity coefficient of species X. If the electrode system is calibrated, K_{HB^+} can be evaluated from the Nernst equation [5].

In the present work, a reliable method is used for evaluating standard cell potentials for specific electrode pair systems in both anhydrous acetic acid [9] and acetonitrile [12]. The dissociation constants (K_{HB^+}) in acetonitrile and the overall dissociation constants (K_B) and (K_{BHClO_4}) in anhydrous acetic acid of a series of bases have been determined. The bases studied were 1,3-diphenylguanidine, trimethoprim, pyridine, nicotinamide, pyridinolcarbamate, nicotinic acid, urea, and sulphamethoxazole. From the dissociation constants in both media it is possible to calculate the change of pH near the end-point of the titration and it is also possible to predict the indicator that will give a sharp colour

change at the end-point [12, 13]. The theoretical principles have been tested and simple potentiometric and visual titration methods are proposed for the assay of bases and their mixtures.

Experimental

Apparatus

For titrations in acetonitrile, a CRISON micropH 2002 pH-meter equipped with a Radiometer G 202C glass electrode and a Pleskov [Ag/(0.01 M) $AgNO_3$ in acetonitrile] electrode as reference with a 0.1 M solution of tetraethylammonium perchlorate in acetonitrile serving as double salt bridge (Fig. 1), was used [14, 15].

For titrations in acetic acid medium, a CRISON 517 pH-meter with a Radiometer G 202B glass electrode and K 401 calomel electrode was used.

Reagents

Anhydrous acetic acid (Carlo Erba; RS grade). The water content was less than 0.005% as determined by the Karl–Fisher method.

Acetonitrile for chromatography (Merck); nitromethane (Fluka; A.R. grade); perchloric acid (Carlo Erba, RPE–ACS grade). 0.1 M solutions in acetic acid and in nitromethane were prepared.

Sodium acetate anhydrous (Carlo Erba; RPE–ACS grade); picric acid (Doesder; R.A. grade; vacuum dried); tetraethylammonium perchlorate (Carlo Erba; RS grade);

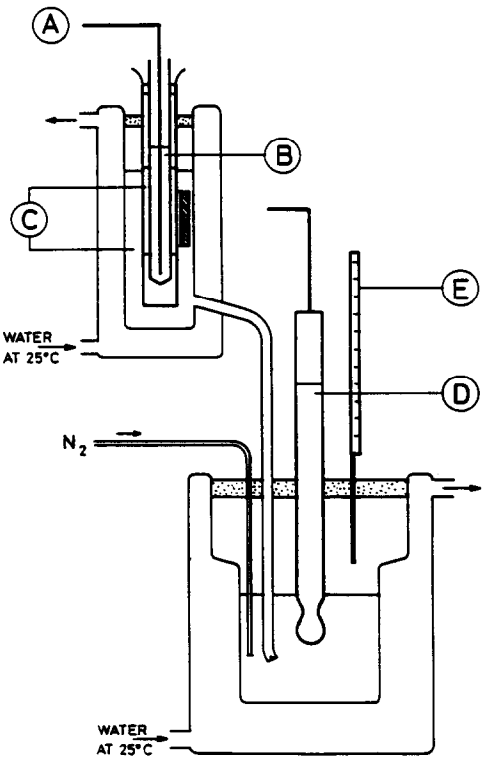

Figure 1
Potentiometric cell for titrations in acetonitrile with the reference electrode and salt bridge. A, Silver electrode; B, $AgNO_3$ 0.01 M in acetonitrile; C, tetraethylammonium perchlorate 0.1 M in acetonitrile; D, glass electrode; E, burette with titrant.

tetrabutylammonium hydroxide (TBAH). A 0.1 M solution in propan-2-ol (Carlo Erba; RPE grade) was prepared.

Nicotinic acid (Carlo Erba; RS grade); pyridine (Fluka; A.R. grade); 1,3-diphenylguanidine (Fluka; purum). Recrystallized from ether.

Urea (Merck; A.R. grade). Purified by Kolthoff's method [16]. Nicotinamide, trimethoprim, pyridinolcarbamate and sulphamethoxazole, were purified materials of Laboratorios Almirall, Barcelona, Spain.

Determination of the standard potential

The glass electrode in acetonitrile was calibrated by titration of a 5×10^{-5}M picric acid solution in acetonitrile with TBAH as reported previously [12].

The glass electrode in acetic acid medium was calibrated by titration of a 1×10^{-3}M sodium acetate solution in glacial acetic acid, with 0.1 M perchloric acid solution in the same solvent [9].

A computer program written in Basic, ACETERISO [17], was used to calculate the standard potentials in acidic and basic medium. Table 1 shows standard potential values for each titration in both acetic acid and acetonitrile media.

From the acidic and basic potential values in acetonitrile, the autoprotolysis constant of the medium was calculated. The average value ($pK_{HS} = 33.25$) agrees with the value reported previously [12].

Determination of constants

The determination of dissociation constants of bases in both solvents, was carried out by means of potentiometric measurements at 25 ± 0.02°C.

In acetonitrile, 5×10^{-3}M solutions of base were titrated with a 0.1025 M solution of perchloric acid in nitromethane whereas in acetic acid 1×10^{-3}M solutions of base were titrated with a 0.1005 M solution of perchloric acid in acetic acid.

The computer program ACETERISO was used for calculation of K_{HB^+} in acetonitrile, using equation 6. a_{H^+} was calculated from the experimental potential values and the standard potential of the cell, $[HB^+]$, taking into account the total dissociation of the salt [11], and activity coefficients were calculated from the reduced Debye-Hückel equations [15]. From these values, the pK of the base is computed for each point of titration.

Table 1
Standard potentials in acidic and basic media in anhydrous acetic acid and in acetonitrile

Titration	Acetic acid E_a^0	Acetic acid E_b^0	Acetonitrile E_a^0	Acetonitrile E_b^0
1	81.8	880.42	652.7	−1302.2
2	79.1	877.72	654.4	−1305.9
3	81.6	880.22	654.8	−1305.2
4	81.9	880.52	651.4	−1332.7
5	81.4	880.02	655.1	−1318.1
6	84.6	883.22	650.8	−1315.5
7	83.5	882.12	653.5	−1317.4
8	84.0	882.62	654.1	−1312.0
9	82.2	880.82	652.2	−1315.1
Average	82.23	880.85	653.2	−1313.8

A computer program, ACETIC (in Pascal), was written to calculate both overall dissociation constants (K_B and K_{BHClO_4}), by means of equation 3 using the standard potential values obtained. When the K_B for the base had been obtained, potentiometric data for base–base perchlorate mixtures of known composition were used to compute the K_{BHClO_4} constant using equation 5.

Results and Discussion

The bases selected for study were of general pharmaceutical interest and widespread use.

Equation 3 was used to determine the overall dissociation constant (K_B) of the bases. In acetic acid medium the activity coefficient term has an insignificant influence in the data obtained [9, 16]. The results obtained for a titration of nicotinamide are shown in Table 2, and for all bases in Table 3.

K_B can also be calculated theoretically, from the a_{H^+} of a solution of pure perchlorate [7], but these solutions are extremely sensitive to minute traces of acids or bases

Table 2
Overall dissociation constant of nicotinamide and nicotinamide perchlorate

Volume of titrant (ml)	E (mV)	C_B (mM)	C_{BHClO_4} (mM)	pK_B	pK_{BHClO_4}
0.20	394.9	3.63	0.80	7.40	6.09
0.30	402.2	3.22	1.19		6.09
0.40	408.8	2.81	1.58		6.09
0.50	415.7	2.40	1.97		6.08
0.60	422.5	2.00	2.36		6.08
0.70	430.4	1.60	2.74		6.06
0.80	438.8	1.21	3.12		6.08
0.85	444.8	1.01	3.31		6.05
0.90	450.2	0.81	3.49		6.08
0.95	458.0	0.62	3.68		6.08
0.98	463.9	0.50	3.79		6.07
1.00	467.8	0.42	3.87		6.09
1.02	473.7	0.35	3.94		6.08
1.04	480.4	0.27	4.01		6.08
Average				7.40 ± 0.02	6.08 ± 0.01

Table 3
Overall dissociation constants for bases and base perchlorates in acetic acid and dissociation constants for protonated bases in acetonitrile

Base	Acetic acid pK_B	pK_{BHClO_4}	Acetonitrile pK_{BH^+}
1,3-Diphenylguanidine	6.21 ± 0.02	6.06 ± 0.04	18.34 ± 0.06
Trimethoprim	6.52 ± 0.02	6.05 ± 0.05	16.12 ± 0.05
Pyridine	6.50 ± 0.02	6.10 ± 0.10	12.57 ± 0.05
Nicotinamide	7.40 ± 0.02	6.08 ± 0.04	10.93 ± 0.05
Pyridinolcarbamate	7.39 ± 0.05	6.07 ± 0.05	10.42 ± 0.06
Nicotinic acid	7.59 ± 0.03	5.95 ± 0.05	—
Urea	9.69 ± 0.24	4.99 ± 0.09	8.52 ± 0.29
Sulphamethoxazole	8.65 ± 0.03	5.55 ± 0.15	7.19 ± 0.05

(especially water), since they are completely unbuffered [7, 18]. In fact, determination of a_{H^+} at the equivalence point should give more accurate K_B results when the base is very weak. This has been tested and in the case of the very weak base urea, the value of K_B given in Table 3 corresponds to the value obtained from measurements made at the end-point of its titration. The pK_B values of trimethoprim, nicotinamide, pyridinolcarbamate and sulphamethoxazole have not been reported previously. For the other substances studied the literature pK_B values differ.

To determine K_{BHClO_4} values, two different approaches were used, i.e. from the a_{H^+} in a mixture of perchloric acid and the perchlorate salt, and after the K_B has been obtained from potentiometric data of a base–base perchlorate mixture of known composition. The conclusion from these studies is that the second method is the more suitable owing to the extreme sensitivity of the perchlorate salt–perchloric acid system to traces of impurities including water [18].

Equation 5 permits the determination of K_{BHClO_4} of the bases. The results obtained during a titration of nicotinamide are shown in Table 2, and Table 3 gives the average values of K_{BHClO_4} for the series of bases. Because of the very weak basicity of urea equation 4 was used. The data obtained are in good agreement with the only two reported values for pyridine and urea [8].

The pK_{HB^+} values were determined in acetonitrile by using equation 6. The results obtained from one titration of nicotinamide solution are shown in Table 4 and are summarized for all the bases in Table 3. The constant for nicotinic acid cannot be evaluated since it is not soluble in acetonitrile. Only two of the bases in Table 3 were included in a previous investigation in which acetonitrile was used [10]. The literature data for pyridine (12.33) and 1,3-diphenylguanidine (17.90) are slightly lower than the data in Table 3.

From the dissociation constants obtained it is possible to predict if the solvents are suitable for use in the titration of the base. To confirm this the bases were titrated with both potentiometric and visual detection of the end-point. A solution of perchloric acid in anhydrous acetic acid was used as the titrant in both media. However this solution shows a smaller potential inflection in acetontrile, especially on the basic side, and is not suitable for titrations of mixtures of bases because acetic acid levels the difference in basic strength [5]. The solution of perchloric acid in nitromethane, is a suitable titrant for use in acetonitrile and can be used for assaying mixtures of bases. Titrations of bases in acetonitrile with perchloric acid in nitromethane give a greater break of potential at the

Table 4
Dissociation constant of protonated nicotinamide in acetonitrile as solvent

Volume of titrant (ml)	E (mV)	[B] (mM)	[BH^+] (mM)	y_{BH^+}	pH	pK_{BH^+}
0.20	−34.2	4.36	1.01	0.887	11.62	10.99
0.30	−20.0	8.84	1.51	0.863	11.38	10.91
0.40	−8.6	3.32	2.01	0.844	11.19	10.90
0.50	1.6	2.80	2.50	0.828	11.01	10.88
0.60	11.6	2.29	2.99	0.814	10.85	10.88
0.70	21.7	1.78	3.47	0.801	10.67	10.86
0.80	32.9	1.28	3.94	0.789	10.49	10.87
0.90	50.8	0.78	4.41	0.778	10.18	10.82
Average						10.88 ± 0.03

Table 5
Indicators for titrations in acetic acid and in acetonitrile

	Acetic acid	Acetonitrile
1,3-Diphenylguanidine	*TR*(0.47)* CV(1.70) BG(1.42)	NR(1.51) *MG*(1.21) BG(1.30) pNB(1.28) *TR*(0.90) QR(1.55)
Trimethoprim	CV(3.36) BG(3.35) *pNB*(−1.32) MG(−1.32)	NR−1 *MG*(0.97) pNB *TR*(−0.37) QR BG
Pyridine	CV(−2.37) BG(−1.98) pNB(−1.98) *MG*(−1.22)	NR−1(1.27) MG(1.31) pNB(0.81) *TR*(0.64) QR(0.82) BG(1.12)
Nicotinamide	MG(−2.50) *NB*(−0.54)	NR−1 *MG*(1.01) pNB(0.81) *TR*(−0.16) QR BG
Pyridinolcarbamate	*MG*(−2.20) NB(2.40)	NR−1 *MG*(0.22) pNB(0.37) TR(−1.60) QR(−0.38) BG
Nicotinic acid	*MG*(0.30) NB(1.20)	—
Urea	—	NR−1(1.67)
Sulphamethoxazole	—	NR−1(1.12)

TR = Tropeolin 00, CV = crystal violet, BG = brilliant green, pNB = *p*-naphtholbenzein, MG = Malachite green, NR = neutral red, QR = quinaldine red, NB = Nile Blue.

* % Error average of five determinations. The titrations were carried out using 5 to 50 mg of substance.

end-point than those with perchloric acid in acetic acid medium. For example the titration of trimethoprim gives a break of about 600 mV in acetonitrile whereas in acetic acid the break is about 200 mV. Acetonitrile also permits the titration of all bases studied in this investigation, with errors less than 2%, whereas in acetic acid the weaker bases such as sulphamethoxazole and urea cannot be determined.

By using the pKa values and the transition ranges of indicators in acetic acid [13] and in acetonitrile [12], the indicator that gives the best colour change at the equivalence point in a titration of a base can be predicted. The proposed indicators for the titration of each base in both solvents are shown in Table 5.

In order to test the usefulness of acetonitrile for titrations of mixtures of bases, the binary mixture of tetramethylguanidine and pyridine was titrated using neutral red or a mixture of bromocresol green and tropeolin 00 as indicators [12]. In this work, binary mixtures of 1,3-diphenylguanidine and pyridine or other weak bases were successfully titrated in acetonitrile with perchloric acid in nitromethane with potentiometric detection of the end-point. The potentiometric titration of a mixture of trimethoprim and sulphamethoxazole (1:5), permits the differentiating assay of these substances with errors less than 2%.

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