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Acid–base equilibria of β-blockers in acetonitrile*

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Abstract: The acid–base equilibria of a series of β-adrenoceptor blocking drugs in acetonitrile have been studied, and pK_{HB^+} values determined. The theory of such titrations is discussed and simple potentiometric and visual methods in acetonitrile media are proposed for the assay of β-adrenoceptor blocking drugs.

Keywords: *Equilibrium constants; β-adrenoceptor blocking drugs; acetonitrile; non-aqueous titration.*

Introduction

β-Adrenoceptor blocking drugs are of therapeutic value in the treatment of various cardiovascular disorders, such as angina pectoris, cardiac arrthymia and hypertension. A great number of β-blockers are available, which differ not only in their specific β-adrenoceptor blocking effects, but also in their non-specific effects. The latter can result in a membrane-stabilizing effect, a local anaesthetic action as well as a cardiodepressant effect [1].

In addition to the pharmacological interest of such information, data are obtained which would be of importance for the control of the pH of a typical chromatographic system for the separation of antiarrhythmic drugs with acetonitrile as organic modifier.

Acetonitrile is one of the most important dipolar aprotic solvents and is used extensively as a reaction medium for mechanistic studies, as well as in electrochemistry and liquid chromatography. It owes its manifold applications in such diverse fields to its characteristics, as a much weaker electron donor than water and also a weak acceptor [2] and has a relatively high polarizability with solvatochromic parameter values of $\alpha = 0.19$, $\beta = 0.31$ and $\pi^* = 0.75$ [3]. The cumulative effect of these factors is that acetonitrile acts as a strongly differentiating solvent, as is reflected by its small autoprotolysis constant ($pK_{ap} = 33.6$) [4].

Although rapid methods for the determination of β-blockers in various biological fluids are required for chemical, toxicological and pharmaceutical studies [5], rapid and simple quality-control methods for their assay in formulations are also of interest. In this paper the acid–base equilibria in acetonitrile are discussed and simple potentiometric and visual titration methods are proposed for the assay of β-adrenoceptor blocking drugs.

Experimental

Apparatus

For potentiometric titrations, a Crison Digilab 517 pH-meter equipped with a Radiometer G 202 C glass electrode and the Pleskov (Ag/0.01 M $AgNO_3$ in acetonitrile) reference electrode with 0.1 M tetraethylammonium percholorate in acetonitrile as salt bridge, was used [6].

Reagents

Acetonitrile (Merck, for chromatography). Nitromethane (Fluka, analytical grade). Perchloric acid (Carlo Erba, RPE–ACS grade), 0.1 M solution in nitromethane. Picric acid (Doesder, analytical grade, vacuum dried). Tetraethylammonium perchlorate (Carlo Erba, RS grade). Tetrabutylammonium hydroxide TBAH, 0.1 M solution in propan-2-ol (Carlo Erba, RPE grade).

All β-blocker drugs studied are shown in Table 1 and were purified materials kindly supplied by pharmaceutical laboratories from Barcelona and Madrid.

Determination of the dissociation constants of the β-blockers

From the dissociation constant value of

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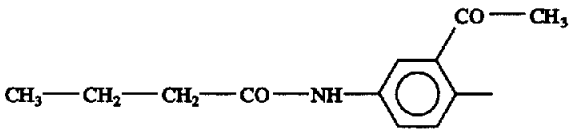
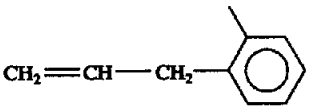
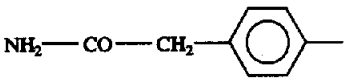
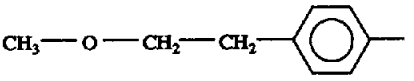
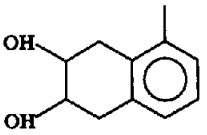
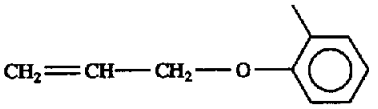
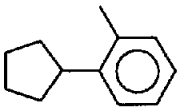
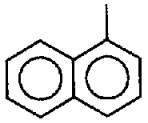
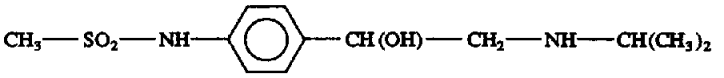
Table 1
Structure of β-adrenoceptor blocking agents

Substance	Ar—O—CH_2—CH(OH)—CH_2—NH—$C(CH_3)_2$R Ar	R
1. Acebutolol		—H
2. Alprenolol		—H
3. Atenolol		—H
4. Metoprolol		—H
5. Nadolol		—CH_3
6. Oxprenolol		—H
7. Penbutolol		—CH_3
8. Propranolol		—CH_3
9. Sotalol		

picric acid, pK_{HPi} = 11.0 [7], the standard potential of the cell was determined as reported previously [6, 8].

The dissociation constants of the β-blockers were determined by potentiometric titration of their 5×10^{-3} M solutions in acetonitrile with 0.1 M perchloric acid in nitromethane at 25.0 ± 0.2°C [4]. The dissociation constant, K_{HB^+}, of the protonated base is given by

$$K_{HB^+} = a_{HS^+} \frac{[B]}{[HB^+]} \frac{y_B}{y_{HB^+}} \qquad (1)$$

where a represents activity and y the molar activity coefficient.

Results and Discussion

The pK_{HB^+} values in acetonitrile for the β-

blockers were determined using equation (1) and are summarized in Table 2.

In solvents of relatively high dielectric constant, such as acetonitrile, in which perchlorate salts can be considered completely dissociated, the pH at 50% neutralization, pH_{HNP}, is equal to pK_{HB^+} if activity coefficients are neglected, even though homoconjugation species are present [9]. In our work, activity coefficients are considered and E_{HNP} and pH_{HNP} values are shown in Table 2.

All protonated bases studied [4, 6] are much weaker acids in acetonitrile than in water (Table 3). Although the solvent influence is complex, taking into account the availability of acetonitrile to solvate cations but not anions, the dominant factor must be that the proton acceptor power of acetonitrile is much lower than that of water.

The difference in pK_{HB^+} between acetonitrile and water in terms of transfer activity coefficients is expressed by equation (2) [10]:

$$^{AN\to W}pK_{HB^+} = (pK_{HB^+})_{AN} - (pK_{HB^+})_W = p\gamma^t_{AN\to W}(H^+) + p\gamma^t_{AN\to W}(B) - p\gamma^t_{AN\to W}(HB^+) \quad (2)$$

in which γ^t is the transfer activity coefficient.

In a recent review [11], the various extrathermodynamic assumptions which have been made to find transfer activity coefficients, have been discussed. In this work a $\log \gamma^t_{W\to AN}(H^+)$ value of 8.1 reported by Kolthoff and Chantooni [12] was used. A value of $\log \gamma^t_{W\to AN}(H^+)$ of 8.1 means that a solute given a hydrogen-ion activity of 1 in acetonitrile would give an activity of $10^{-8.1}$ in water.

Taking into account that ΔpK_{AN-H_2O} values [4] [13] [14] are close to 8.1, the difference in pK_{HB^+} between acetonitrile and water is mainly determined by the proton transfer activity coefficient. Thus assuming equation (2), the difference of $p\gamma^t_{aN-W}(B)$ and $p\gamma^t_{aN-W}(HB^+)$ is negligible.

In this paper the formation constants of BHB^+ complexes for the β-adrenoceptor blocker drugs were evaluated by the method of Coetzee *et al.* [15, 16] from plots of potential (E) versus $\log (c_b/c_s)$, where c_b and c_s are the analytical concentrations of the base and salt, respectively [5]. The plots for several β-blockers are shown in Fig. 1.

Figure 1 shows no evidence of the formation of BHB^+ complexes for β-blockers under the experimental conditions used, since in all cases linear plots with slopes close to 59 mV/decade were obtained. The curves for neutralization of

Table 2
Dissociation constants, pK_{HB^+}, and effective acidities, pK'_{HB^+}, for protonated β-adrenoceptor blockers in acetonitrile

Substance	E_{HNP}	pH_{HNP}	pK_{HB^+}	pK'_{HB^+}
Propranolol	−369.8	17.65	17.52 ± 0.08	9.42
Penbutolol	−373.4	17.69	17.59 ± 0.08	9.49
Metoprolol	−374.8	17.72	17.62 ± 0.09	9.52
Atenolol	−376.5	17.76	17.59 ± 0.08	9.49
Alprenolol	−373.5	17.72	17.66 ± 0.07	9.56
Nadolol	−382.7	17.86	17.73 ± 0.10	9.63
Oxprenolol	−387.3	17.95	17.85 ± 0.09	9.75
Acebutolol	−387.0	17.95	17.89 ± 0.08	9.79
Sotalol	−385.2	17.55	17.46 ± 0.04	9.36

Table 3
Equilibrium constants of β-adrenoceptor blockers in acetonitrile (pK_{HB^+}), acetic acid ($\log K_{f\,HAc}^{BHClO_4}$), and water ($pK_{H_2O}$)

Substance	pK_{HB^+}	pK_{H_2O}	ΔpK_{AN-H_2O}	$\log K_{f\,HAc}^{BHClO_4}$
Propranolol	17.52	9.5	8.02	8.72 ± 0.09
Penbutolol	17.59	9.3	8.29	8.26 ± 0.10
Metoprolol	17.62	9.7	7.92	8.47 ± 0.09
Atenolol	17.59	9.6	7.99	8.74 ± 0.08
Alprenolol	17.66	9.5	8.16	8.22 ± 0.09
Nadolol	17.73	9.7	8.03	8.81 ± 0.10
Oxprenolol	17.85	9.5	8.35	8.28 ± 0.09
Acebutolol	17.89	9.4	8.49	8.63 ± 0.10
Sotalol	17.46	9.8	7.66	8.36 ± 0.09

β-blockers with perchloric acid in acetonitrile can therefore be calculated in the same way as for water media, since homoconjugation is negligible in dilute solutions, as is usually the case for bases [9].

One of the main purposes of studies dealing with the influence of solvents on acid–base equilibria is to obtain a solvent-independent acidity or basicity scale [17]. For an aprotic solvent, such as acetonitrile, the dissociation constants are then translated to the absolute scale by the equation [18]:

$$pK'_{HB^+} = pK_{HB^+} + p\gamma^{t}_{W\rightarrow AN}(H^+).$$

The values of pK'_{HB^+} shown in Table 3 provide a measure of the effective acidity of the protonated β-blockers, irrespective of the medium.

On the other hand, the autoprotolysis constant defines the normal range of pH in the solvent and also has important bearings on acid–base titrations in non-aqueous media, where the "pH jump" at the equivalence point is larger, the greater the pK_{ap} value.

Although acetic acid has been a popular solvent for the titration of bases, the formation constants of HB^+ are much larger in acetonitrile ($K_f(HB^+) = = 1/K_{HB^+}$) than in acetic acid ($K_{f\ HAc}^{BHClO_4}$) [19, 20], as shown in Table 3. Hence the break in pH at the end-point is much greater for titration in acetonitrile than for titration in acetic acid [4, 6].

Titration curves with sharp and reproducible inflection points are obtained in acetonitrile for all the β-blockers studied.

On the other hand, organic bases employed in pharmaceutical preparations, which show a sharp break in the titration curve such as β-blockers, may be determined by the more rapid indicator method with the accuracy and precision obtainable by the potentiometric method.

The change in pH near the equivalence point can be calculated from the dissociation constants of the protonated β-blockers, so it is possible to predict which indicators (I) will give a sharp colour change in the equivalence range, since the pK_{HI^+} values and quality of colour change in acetonitrile are known [8]. The β-blockers were visually titrated with errors lower than 2% and the indicator selected on the basis of pK_{HI^+} and the quality colour change is Tropaeolin 00.

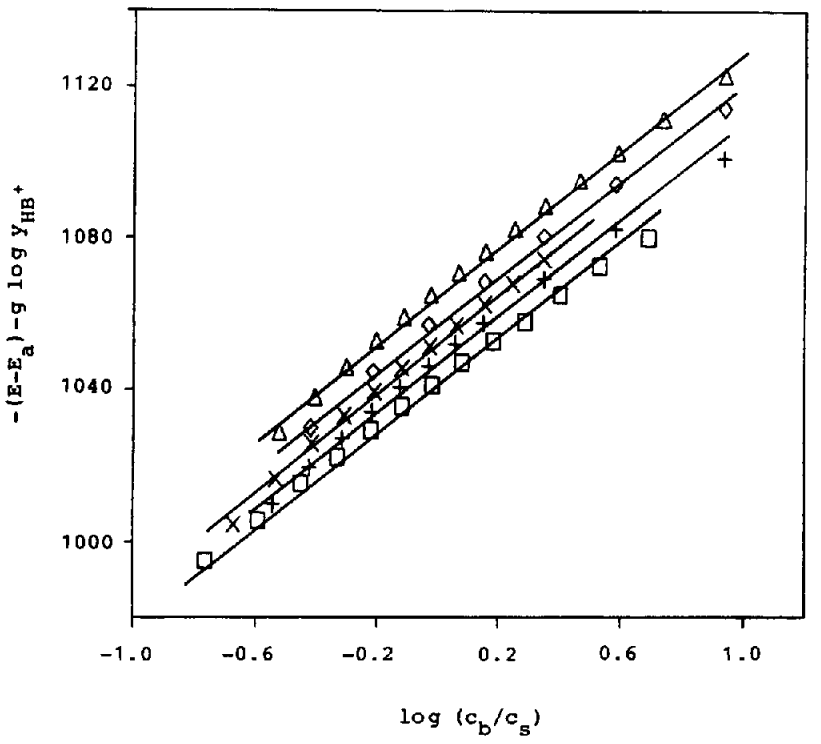


Figure 1
Potential versus log (c_b/c_s) for several β-blockers. □ Sotalol, △ oxprenolol, ◇ nadolol, × atenolol and + propranolol.

Conclusion

The study of acid–base equilibria for a selection of β-adrenoceptor blocking agents has demonstrated that titration of these compounds in acetonitrile with perchloric acid has potential as a method of assay.

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