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Quantitative assay of 3,4-diaminopyridine in water by thermometric titrimetry

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Abstract

Thermometric titrimetry allows the quantitative assay of pure 3,4-diaminopyridine or in pharmaceutical capsules by titration in water by hydrochloric acid. Satisfactory titrations with 99 p 100 recovery and 1 p 100 precision were obtained with amounts of about 4.5×10^{-4} mol. Lactose and starch used as excipients in the capsules as well as gelatin which constitutes their matrix, did not interfere in the titration. © 1998 Elsevier Science B.V.

Keywords: Thermometric titrimetry; Diaminopyridines; Pharmaceutical analysis

1. Introduction

4-Aminopyridine and 3,4-diaminopyridine are compounds of interest for the treatment of some neurological diseases such as Lambert-Eaton myasthenic syndrome [1]. Since 4-aminopyridine is now almost forsaken because of its side effects [2], current studies are focused on 3,4-diaminopyridine. Its clinical use requires one to perform quality control which is not, so far, covered by any pharmacopoeia. In current practice, 3,4-diaminopyridine is quantitatively assayed by potentiometric titration in anhydrous acetic acid by perchloric acid [1].

We describe, here, the quantitative assay of pure 3,4-diaminopyridine or in dosage forms (gelatin capsules) by thermometric titrimetry in water with hydrochloric acid.

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2. Experimental

2.1. Reagents and chemicals

3,4-Diaminopyridine was obtained in the best grade available (ACS certified grade) from Acros and was used without purification.

2.2. Apparatus

Thermometric titrations were performed with the apparatus already described [3], which enclosed a motor-driven syringe pump, a glass Dewar flask, a stirring motor, a thermistor incorporated in an arm of a simple wheatstone bridge, an amplifier, and a recorder. The Dewar flask was covered with a PTFE cap through which holes just large enough to house the thermistor, stirring device and titrant tip have been drilled. The Dewar flask and the cap have been built according to the description of Christensen and Izatt [4]. Initial sample volume was 92 cm^3 and the titrant was deliv-

ered at a nominal constant rate of 0.0085 $cm^3\ s^{-1}$. Titration vessel and titrant were enclosed in a constant temperature bath. For analytical purposes, corrections for heat losses were not performed, since at any rate they did not preclude the good localization of the end point. However, the temperatures of the titrand and titrant solutions were carefully matched at the beginning of the titration. All experiments were performed at 25°C.

2.3. Procedures

For pure 3,4-diaminopyridine, a known amount (from 4.6×10^{-5} to 4.6×10^{-3} mol) was put into the titration vessel together with 92 cm^3 of pure water. The solution was mechanically stirred at constant speed until thermal equilibrium was achieved. Then, it was titrated with a hydrochloric solution about one hundred times more concentrated than the titrand solution, since it is well known that thermometric titrations are more accurate and precise if this concentration condition is fulfilled. End-points were indicated on thermograms by a break between the titration and post periods. Precision and accuracy were noted versus amounts of sample analyzed.

For the analysis of the dosage forms, the content of one, two and three capsules was assayed after dispersion, together with the gelatine matrix, into the 92 cm^3 of water enclosed in the calorimeter. Before the beginning of the titration, the mixture was stirred to ensure the complete dispersion of the form, the dissolution of 3,4-diaminopyridine and also to achieve thermal equilibrium. In order to study the influence of the presence of ingredients, the effect on the titration

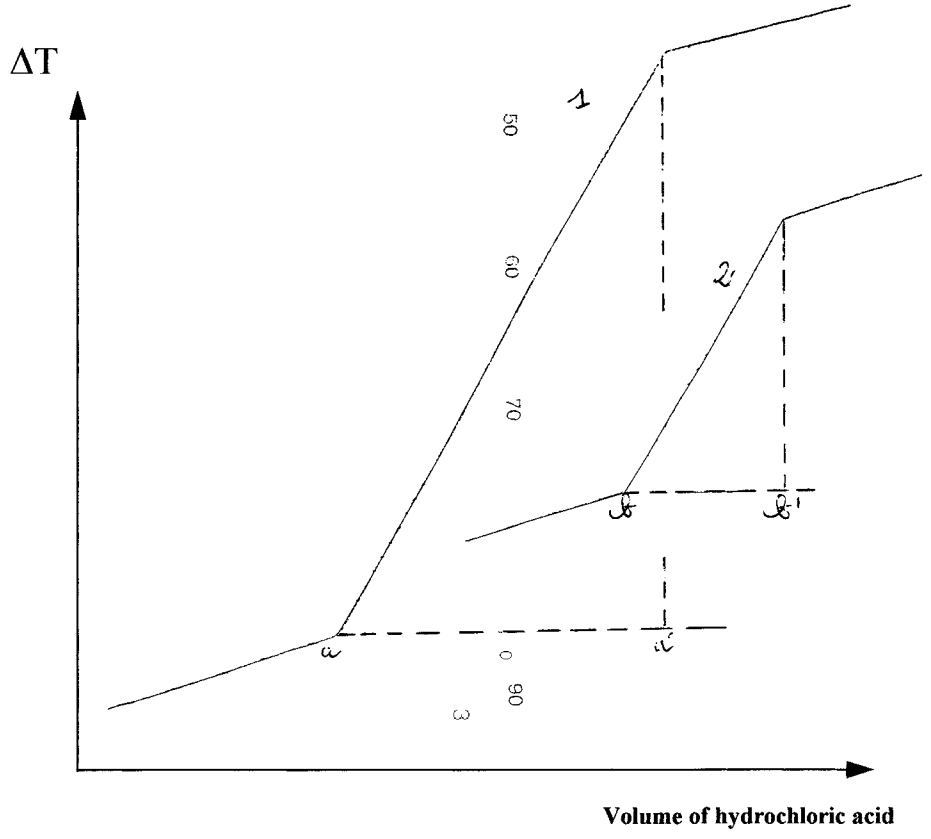

Fig. 1. Typical thermograms registered by thermometric titration of variable amounts of pure 3,4-diaminopyridine by hydrochloric acid. 1. Thermogram obtained with 10^{-3} moles (aa'=58 mm or 1 ml of hydrochloric acid 1 $mol.l^{-1}$) 2. Thermogram obtained with 5×10^{-4} moles (bb'=29 mm or 0.5 ml of hydrochloric acid 1 $mol.l^{-1}$).

accuracy and precision of the addition of starch and lactose to a pure sample of diamine was also noted.

3. Results and discussion

Fig. 1 reproduces some typical titration curves. The first point to note is that end points appeared on thermograms of 3,4-diaminopyridine for one added equivalent of hydrochloric acid. This is in agreement with the pK_a values ($pK_{A1}=-10.7\pm0.20$, $pK_{A2}=0.80\pm0.10$, $pK_{A3}=9.19\pm0.06$ [5]). Only the acidity endowed with the value 9.19 can be titrated with hydrochloric acid in water (likewise 2,3–2,6- and 2,5-aminopyridines exhibited only one sharp end point corresponding to one added equivalent of hydrochloric acid, in agreement with their pK_A values).

Table 1 shows that the results were satisfactory till a limiting lower content of the order of 50 mg, i.e. for a concentration in the calorimeter of 5×10^{-3} mol l^{-1} since accuracies and precisions were of the order of 1% or less. It is interesting to note that for large amounts, the precision can be considered as constant. With weak amounts, it is dependent with the titrand concentrations. Such behaviour of precisions are often encountered in thermometry titrimetry. With large amounts, the precision is constant and dependent only on the apparatus. With weak amounts of analyte, it is dependent mainly of its concentration C and of the value of the titration reaction enthalpy ΔH i.e. of the product $C\Delta H$ [6]. This is at the origin of the concept of 'enthalpimetric index' which is the minimum concentration which can be titrated by thermometric titrimetry at a given precision level [7]. Values obtained in this work allow to admit that a concentration of 5×10^{-3} mol l^{-1} can be titrated with a precision of about 1 p 100. Owing to the enthalpy of protonation of 3,4-diaminopyridine ($\Delta H_p\cong-45300$ J mol^{-1}) that we have determined independently, the 'enthalpimetric index' found $(ESI)_{1\%}=200$ J l^{-1} is in good agreement with that already found with our apparatus ($(ESI)_{1,82\%}=55.8$ J l^{-1}) [8]. A weak thermal effect, indeed, is at the origin of a poorer precision than a greater one.

Table 1
Precisions and accuracies of thermometric titration of pure 3,4-diaminopyridine in water (titrant: hydrochloric acid 1 mol l^{-1})

Mass of drug (mg)		Recovery (%) [b]	Precision [c]
Taken	Found [a]		
109	109.29	100.26	0.29
54.5	54.20	99.45	0.86
20	19.56	97.8	3.18
10	9.38	93.8	3.80
5	3.27	65.46	15.00

[a] Mean of 6 independent titrations.
[b] (Found/Taken)×100.
[c] S.D.

Table 2
Effect of addition of starch and lactose to pure samples of 3,4-diaminopyridine [a]

Excipient (mg)	Mass of drug found [b]	Recovery (%)
Starch (100)	50.11	100.22
Lactose (100)	49.48	98.95

[a] 50 mg – Titrant: hydrochloric acid 1 mol l^{-1}.
[b] Mean of 4 independent titrations.

Mixtures of lactose or starch and 3,4-diaminopyridine have been assayed (Table 2). In all determinations, 100 mg of excipient were added to 50 mg of diamine. Results were satisfactory. Consequently, at this concentrations which are quite representative of reality, lactose and starch did not interfere in the titration. The content of 'home-made' capsules have also been quantitated. Each capsule contained 20 mg of diamine and 150 mg of lactose. When three capsules were analyzed together, results were satisfactory (accuracy; 2.8 p 100 – precision (standard deviation); 2.73 p 100 – (4 replicates of titration of 3 gelatine capsules together)). However, results were quite unsatisfactory when only one capsule was assayed (accuracy; 11 p 100 – precision 7.3 p 100). This confirms, on one hand, preceeding results obtained with pure 3,4-diamine showing that amounts weaker than 50 mg cannot be titrated. On the other hand, this confirms that lactose does not disturb the titration nor does gelatin. It is interesting to note that before and after titration the system was not homogeneous, owing to the presence of gelatine. Undoubtly, here lies one of the great advantages of thermometric titrimetry which does not necessitate the existence of a homogeneous medium to allow satisfactory titrations. This is due to the use of thermistors as temperature sensors, which are indifferent to the medium into which they are dipping. This possibility has been already exploited by different authors [9–11].

4. Conclusions

As a result, the proposed method provides a simple, precise, and rapid means for the determination of 3,4-diaminopyridine either in the pure form or in gelatin capsules. Moreover, there is a lower cost than non aqueous titrations.

It is, therefore, suitable for routine quality control.

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