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Protometric thermometric titrations of sparingly soluble compounds in water in the presence of *n*-octanol

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Abstract

Thermometric titrimetry permits titration of acido–basic compounds in water in the presence of *n*-octanol. *n*-Octanol permits the solubilization of protolytes and moreover may also displace the equilibria of the titration reactions. Hydrochlorides of highly insoluble derivatives such as phenothiazine derivatives can be titrated with satisfactory accuracy and precision by sodium hydroxide despite their high pK_a values. Likewise barbiturate salts can be titrated by hydrochloric acid. In the case of some salts, the methodology may permit the sequential titration of the ion and counter ion.

Keywords: Thermometric titrimetry; Calorimetry; *n*-Octanol; Non-aqueous titration

1. Introduction

Organic acids and bases cannot usually be titrated in water because of their very weak solubility. This is the reason why non aqueous solvents are recommended quasi systematically for the titration of organic compounds [1]. Nevertheless, a first drawback of their use is their handling which is often cumbersome. A second one is that, in the case of some kinds of salts, they may not permit the titration of the solute of interest but instead that of the counter ion. Other solvent alternatives have been proposed to overcome the aqueous solubility problem such as using mixed solvents [1], micellar and two-phase systems [2–6]. Protometric titrations in the presence of two immiscible solvents have been performed for physico-chemical rather than analytical purposes especially in order to determine partition coefficients between two solvents [7,8].

We present here a study devoted to two-phase protometric thermometric titrations of poorly water-soluble compounds. Such titrations take into account the somewhat underestimated fact that the response of the thermistance, the temperature sensor used in thermometric titrimetry, does not depend on the medium it is dipped in [9–11]. The presence of two phases warrants good solubilization of all species and may also make titration reactions sufficiently quantitative by displacement of equilibria and, hence, more accurate than those

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in water. The latter possibility may moreover be helpful in the case of the titration of salts by permitting possibly the sequential titration of the different acido–basic species of the medium including the counter ions of the salt. To our knowledge, no two-phase thermometric titrations have been performed so far except for physicochemical purposes [10,11].

2. Experimental

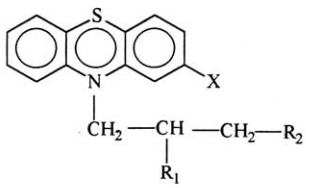
2.1. Chemicals

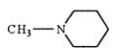
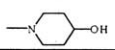
The pharmaceutical field provides numerous examples of titration of poorly water soluble compounds [12,13]. Purity of all chemicals was warranted by the suppliers:

- propericiazine base: Rhône-Poulenc Rorer Laboratory
- chlorpromazine and levomepromazine hydrochlorides: Rhône-Poulenc Rorer Laboratory
- thioridazine hydrochloride: Sandoz Laboratory
- phenobarbital sodium: Coopération pharmaceutique française
- barbital sodium: Merck Laboratory
- amobarbital: I.S.H. Laboratory
- secobarbital sodium: Coopération Pharmaceutique Française
- mepyramine maleate (pyrilamine): Sigma Laboratory
- sodium maleate acid: Acros Laboratory
- quinidine sulfate: Sigma Laboratory
- alimemazine tartrate or trimeprazine hemitartrate: Sigma Laboratory
- Théralène® drops (alimemazine tartrate): Medeva pharma Laboratory
- Largactil® tablets (chlorpromazine): Rhône-Poulenc Rorer Laboratory.

Amobarbital sodium was prepared by mixing one equivalent of barbituric and one equivalent of sodium hydroxide. Propericiazine hydrochloride was prepared by mixing one equivalent of propericiazine with one equivalent of hydrochloric acid. Structures, pK_a and water/*n*-octanol log *P* values are given in Tables 1–3.

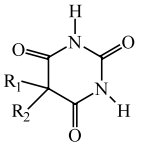
Table 1
Structure, pK_a, log *P*, $pK_{a_{app}}$ of some phénothiazines



compounds	log P	pK_a	pKa_{app}*	X	R_1	R_2
Chlorpromazine	5.35 [14]	9.30 [15]	4.86	Cl	H	$N(CH_3)_2$
Levomepromazine	4.68 [14]	9.15 [15]	5.38	OCH_3	CH_3	$N(CH_3)_2$
Thioridazine	6.51 [14]	9.50 [15]	3.90	SCH_3	H	
Propericiazine	3.90 [14]	8.10 [16]	5.11	CN	H	

* with V_w=82cm^3 and V_{org}=10cm^3

Table 2
Structure, pK_a, log P, p$K_{a_{app}}$ of some barbiturates



compounds	log P	pK_a	pKa_{app}*	R_1	R_2
Phénobarbital	1.42 [17]	7.41 [18]	7.92	$-CH_2-CH_3$	$-C_6H_5$
Barbital	4.47 [17]	7.91 [18]	11.51	$-CH_2-CH_3$	$-CH_2-CH_3$
Amobarbital	1.95 [17]	7.94 [18]	9.03	$-CH_2-CH_3$	$-(CH_2)_2-CH(CH_3)_2$
Secobarbital	2.15 [17]	7.92 [18]	9.18	$-CH_2-CH=CH_2$	$-CH-(CH_2)_2-CH_3$ CH_3

*with V_w=82cm^3 and V_{org}=10cm^3

2.2. Equipment

Thermometric titrations were performed with the help of an isoperibol calorimeter which consisted of 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 P.F.T.E. cap through which holes just large enough to house the thermistor, stirring device and titrant tip were made according to the description of Christensen and Izatt [23]. The performances of the whole assembly have been given elsewhere [24].

2.3. Experimental conditions

n-Octanol was chosen as non miscible solvent. Its solvent properties are now very well documented [25]. Water/*n*-octanol partition coefficients of numerous solutes are known and can even be calculated with fair accuracy [14,26]. This solvent does not favorize ion-pairs formation. In addition, some water/*n*-octanol transfer enthalpies, from which the thermometric titrimetry end point indication depends (see below) are sometimes known or approached [27]. The knowledge of both partition coefficients and transfer enthalpies is helpful to explain the obtained results as well as for the judicious choice of experi-

Table 3
pK_a and log P of other compounds

Compounds	pK_a	log P
Mepyramine maleate	4.00 [18] 8.90 [18]	2.85 [16]
Quinidine sulfate	4.20 [18] or 5.40 [19] 8.80 [18] or 10.00 [19]	2.64 [20]
Maleic acid	1.92 [21] 6.23 [21]	– –
Citric acid	3.13 [21] 4.76 [21] 6.40 [21]	– – –
Tartaric acid	3.03 [21] 4.37 [21]	– –
Alimemazine tartrate	8.60 [22]	–

mental conditions providing the most accurate titrations.

2.4. Procedures

The total initial volume in the calorimeter was 92 cm^3. Usually, volumes $V_w = 82$ and $V_{org} = 10$ cm^3 were chosen for the aqueous and organic phases respectively, but satisfactory results were obtained with different values. An amount of titrand in the range 5×10^{-4}–5×10^{-3} mole was introduced into the aqueous phase depending on the solubility of the derivatives studied. (Of course, solutes highly soluble in organic solvents were dissolved initially in *n*-octanol.) The titrant (1 mol l^{-1}) was delivered at a normal constant rate of 0.0085 ± 0.00006 cm^3 s^{-1}. Titration vessel and titrand were enclosed in a constant temperature bath. Care was taken to exactly match the temperatures of titrand and titrant solutions at the beginning of titrant addition. These last two conditions were fulfilled in order to minimize non-chemical thermal effects.

n-Octanol and water mutually saturated were systematically used. In this work, activities are assimilated to concentrations because of the low concentrations. For the same reason, thermal effects resulting from the possible salting out of *n*-octanol from water or conversely are also neglected.

3. Theory

In a thermometric titration where the reaction,

$$BH^+ + OH^- \rightarrow B + H_2O \quad (1)$$

takes place, the chemical heat q_r evolved is,

$$q_r = -\{(V+v)[B] - V[B]_o\}\Delta_r H, \quad (2)$$

where $\Delta_r H$ stands for the molar enthalpy change of the reaction, [B] and $[B]_o$ for the concentrations of B after the addition of the volume v of titrant solution and at the beginning of the titration when the volume in the calorimeter is V. Actually, the second term in brackets is negligible and Eq. (2) reduces to,

$$q_r = -(V+v)[B]\Delta_r H. \quad (3)$$

If the titration is performed in the presence of an immiscible solvent and if it is assumed that the only species to partition is B, the partitioning thermal effect q_{tr} must also be taken into account. It is given by the relation:

$$q_{tr} = -\{[B_{org}] - [B_{org}]_o\} V_{org} \Delta_{tr} H \quad (4)$$

where $\Delta_{tr} H$ is the molar transfer enthalpy according to the scheme: $B_w \rightarrow B_{org}$. $[B_{org}]$ and $[B_{org}]_o$ are concentrations of B in the organic phase during the titration and at the beginning. Actually $[B_{org}]_o$ is negligible since in this work the titrand is introduced as a salt and the aqueous phase is acidic. We have already demonstrated that the partitioning rate of a species from water to *n*-octanol during a thermometric titration can be considered as being immediate when an usual titrant addition rate is used [28]. This implies that for each titration point the partitioning equilibrium condition (5) is verified

$$P = \frac{[B_{org}]}{[Bw]}, \quad (5)$$

where P is the partition coefficient of B. Introducing Eq. (5) into Eq. (4) gives for the transfer thermal effect,

$$q_{tr} = -P[B_w] V_{org} \Delta_{tr} H. \quad (6)$$

The thermal effect involving the chemical and the partitioning effect, but excluding all the other effects (which can be classically corrected [29]), is:

$$q_{tot} = -[B_w](V_w + v)\left(\Delta_r H + P\frac{V_{org}}{V_w + v}\Delta_{tr} H\right). \quad (7)$$

Comparison of Eqs. (3) and (7) shows that titration in the presence of an immiscible solvent can be assimilated to a purely aqueous one the apparent molal reaction enthalpy of which is given by the linear combination: $\Delta_r H + P(V_{org}/(V_{w+v}))\Delta_{tr} H$. In thermometric titrimetry the condition $v \ll V_w$ is quasi-systematically fulfilled to minimize thermal capacity variations [30]. Hence, the apparent molal enthalpy can be considered as being constant during the titration.

Table 4
Accuracy and precision of thermometric titrations by sodium hydroxyde 1 M of 10^{-3} mol phenothiazine hydrochlorides

Compounds	Taken (mg)	Initial concentration (mol l^{-1})	Found (mg)[a]	Recovery (%)
Chlorpromazine hydrochloride	355.3	1.2×10^{-2}	357.8 (0.8%)	100.7
Levomepromazine hydrochloride	364.9	1.2×10^{-2}	366.0 (1.6%)	100.3
Propericiazine hydrochloride	365.5	1.2×10^{-2}	368.0 (1.6%)	100.7
Thioridazine hydrochloride	407.0	1.2×10^{-2}	402.5 (0.8%)	98.9

[a] Mean of seven replicates with standard errors in parentheses.

It results from the relevance of relation (7) that all considerations concerning analytical features of thermometric titrimetry previously developed for one-phase titrations can be extended to two-phase ones. It is interesting to note that relation (7) is also relevant when the species which partitions is the product of protonation of a weak monocharged base but this is no longer true when it is the titrand or the titrant which partitions. However, appropriate relations analogous to Eq. (7) can be written in these cases [10,31].

4. Results and discussion

Results obtained in the determination of some phenothiazine hydrochlorides are mentioned in Tables 4 and 5. Fig. 1 reproduces a typical thermogram obtained during the titration by sodium hydroxide solution of a solution of chlorpromazine hydrochloride.

Table 4 shows that for an initial concentration in the range of 10^{-2} mol l^{-1}, accuracy and precision were quite satisfactory. The sensitivity and selectivity is in a same order as non-aqueous titration using in pharmacopeias procedure. Table 5 shows, however, that for lower concentrations both fell abruptly and the final point became spurious. It systematically lay beyond the theoretical end point. It is interesting to note that by addition of octanol not only does the titration of phenothiazines become possible from the solubility standpoint but also from that of the displacement of the chemical reaction equilibrium. This can be explained by recalling the concept of end point sharpness in thermometric titrimetry introduced by Tyrrell [32]. When the titration reaction (1) is complete, the proportion α of the added hydroxide ions which are converted is always unity for a fraction titrated β such as $0<\beta<1$. When $\beta\geq1$ the concentration [B] and hence q_r remain constant. As a result, the end point is marked by a sudden change in the slope dq/dv. This is not true when the reaction is incomplete. α is then a function of β. It deviates from unity before and beyond the end point. The enthalpogram becomes a portion of the branch of a hyperbola [33]. Tyrrell has shown that the sharpness of the end point depends on the factor $\zeta=1/KC_o$, where K is the equilibrium constant of the titration reaction and C_o the analytical concentration of the titrand for the considered fraction titrated. For values $\zeta<10^{-3}$, a reasonably accurate location of the end point is found by linear extrapolation of the initial and final portions of the hyperbola where the proportion α does not appreciably deviate from unity. The end point is located at the intersection of the two

Table 5
Percentage recovery as a function of the sample mass of chlorpromazine hydrochloride

Taken in		Found in (mg)[a]	Recovery (%)
mg	mol l^{-1}		
44.6	1.5×10^{-3}	51.5 (11%)	116.0
88.8	3×10^{-3}	93.8 (9.9%)	105.6
142.1	4.9×10^{-3}	156.3 (3.5%)	110.0
159.9	5.5×10^{-3}	165.7 (1.5%)	103.7
177.6	6.1×10^{-3}	177.6 (1.9%)	100.0
355.3	1.2×10^{-2}	357.8 (0.8%)	100.7
532.9	1.8×10^{-2}	531.8 (1.2%)	99.8
710.6	2.4×10^{-2}	708.8 (1.1%)	99.8

[a] Mean of seven replicates with relate standard errors in parentheses.

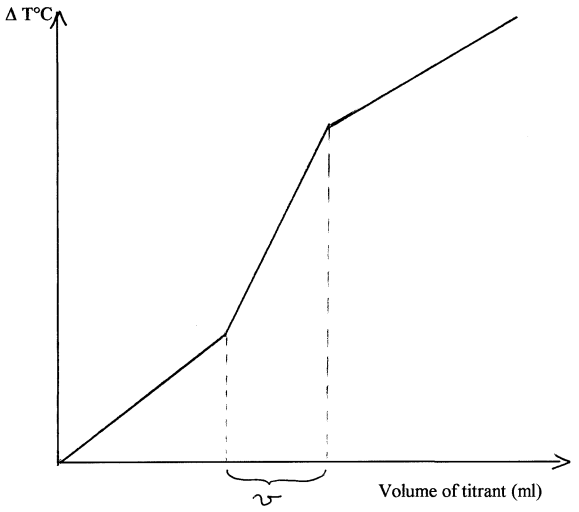


Fig. 1. Thermogram obtained by titration of chlorpromazine hydrochloride (1.2×10^{-2} mol l^{-1}) by sodium hydroxide (1 mol l^{-1}) ($V_w = 82$ ml, $V_{org} = 10$ ml).

straight lines. For larger ζ values, the curvature is too marked to obtain an accurate end point in this way. The intersection lies systematically beyond the theoretical end point. Concerning the titration of phenothiazines hydrochlorides, the equilibrium constant of the reaction (1) is,

$$K = \frac{[B]}{[BH^+][OH^-]},$$

and hence

$$K = \frac{K_a}{K_w},$$

where K_a is the dissociation constant of the acid BH^+ and K_w the ionic product of water. In the case of chlorpromazine ($K_a = 10^{-9,30}$) and at the initial concentration $C_o = 10^{-2}$ mol l^{-1}, $\zeta = 10^{-2,70}$. Even if the solubility problem had not occurred, the accurate titration in water would not be possible. This assertion is exemplified by the case of the thermometric titration in water of ephedrine hydrochloride [34], whose pK_a is the same as that of chlorpromazine hydrochloride but whose solubility in water is sufficient to preclude any precipitation during the protometric titration. The recorded enthalpogram did not exhibit a sudden change in the slope at the end point but instead a curvature which besides was sufficient to permit the determination of the pK_a value. Hence in the case of chlorpromazine *n*-octanol also intervenes by inducing displacement of the equilibrium of the titration reaction. In the presence of an immiscible solvent, it is easily demonstrated [35] that the behavior of an acid BH^+ can be assimilated to that of a hypothetical one in pure water. Its dissociation constant K'_a is given by the relation:

$$K'_a = K_a\left(1 + P\frac{V_{org}}{V_w}\right). \quad (8)$$

In the experimental conditions of the titration of chlorpromazine hydrochloride, $K'_a = 10^{-4,86}$ (Table 1) and the sharpness index was $\zeta \cong 10^{-7}$. The end point became accurate. With slightly lower initial concentrations, the final point should remain accurate but inspection of Table 5 shows that this was not the case. Actually the other factor which played a part is the magnitude of the thermal effect which became too weak for the following two reasons: first the titrand concentration was too low and secondly the signs of enthalpies $\Delta_r H$ and $\Delta_{tr} H$ were opposite. This last point may appear as being a limitation of the procedure but it must be noted that according to the species to be titrated this is not necessarily the case. Let us recall that chlorpromazine hydrochloride has been thermometrically titrated by sodium hydroxide in a purely aqueous medium [36]. The end point was sharp owing to the precipitation of the very insoluble chlorpromazine base. However, this procedure has not been extended to other salts of very insoluble organic bases probably because of the unpredictable precipitation of the liberated base. One major advantage of the procedure proposed here is that it involves the titration of solutes of interest. This is not the case with the procedure of pharmacopeias where it is the chloride ion of the phenothiazine hydrochloride which is titrated [12,13].

Another interesting example was provided by the thermometric titration of quinidine sulfate by sodium hydroxide in the presence of *n*-octanol.

Table 6
Accuracy and precision of thermometric titrations by hydrochloric acid 1 M of 10^{-3} mole sodium barbiturates salts

Compounds	Taken (mg)	Initial concentration, $\times 10^{-2}$ (mol l^{-1})	Found (mg)[a]	Recovery (%)
Sodium phénobarbital salt	254.2	1.2	258.4 (0.9%)	101.7
Sodium barbital salt	206.2	1.2	207.83 (1.4%)	100.8
Sodium amobarbital salt	248.3	1.2	250.0 (2.2%)	100.7
Sodium secobarbital salt	260.3	1.2	265.5 (1.7%)	102.0

[a] Mean of seven replicates with standard errors in parentheses.

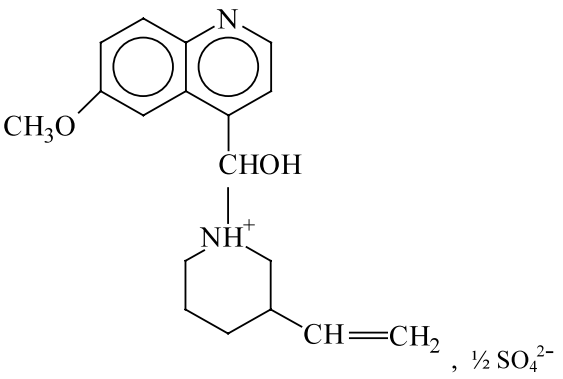


Table 7
Percentage recovery as a function of the sample mass of phenobarbital sodium salt

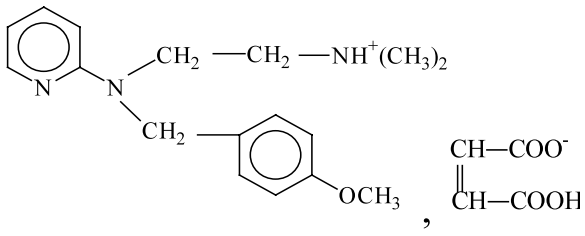
Taken in		Found (mg)[a]	Recovery (%)
mg	mol l^{-1}		
190.7	9.1×10^{-3}	188.1 (3.3%)	98.7
203.4	9.7×10^{-3}	206.5 (1.6%)	101.5
228.8	1.1×10^{-2}	231.8 (1.7%)	101.3
254.2	1.2×10^{-2}	258.4 (0.9%)	101.7
508.4	2.4×10^{-2}	515.0 (0.6%)	101.3

[a] Mean of seven replicates with standard errors in parentheses.

Owing to the pK_a values of the conjugated acids of quinidine ($pK_a = 4.20$ or 5.40 and 8.80 or 10.0) [18,19] it was the protonated quinuclidine that was neutralized. *n*-Octanol played here the same part than in the case of the titration of phenothiazines hydrochlorides i.e. it solubilized the free base and displaced the equilibrium of the titration reaction. Precisions and accuracies are given in Table 6. In this case, again, it was the organic part that was titrated by this procedure, while according to the recommendations of the pharmacopeias [12,13] titration in anhydrous acetic acid gives only the sum of three acidities.

In the titration of barbiburate salts by hydrochloric acid (Tables 7 and 8) using *n*-octanol ensured good solubilization of the product of the titration reaction. The fact that in the presence of *n*-octanol the apparent pK_a was enhanced [$K'_a = K_a/(1 + P(V_{org}/V_w))$] is of no practical interest since even in pure water pK_a values of barbiturics are sufficiently far from that of the pair H_3O^+/H_2O to ensure accurate titrations. As in the case of phenothiazines, transfer and titration enthalpies are of opposite signs, but this does not preclude the obtention of satisfactory results. The procedure described here appears to be simpler than those described in pharmacopeias [12,13].

The titration of mepyramine maleate



provides a good example of a sequential titration of both the pharmacologically active part and the counter ion (Fig. 2).

The thermogram exhibits two linear portions. The first one corresponds to the neutralization of the monomaleate ion as proved by addition of sodium maleate to the titrand solution. This is in

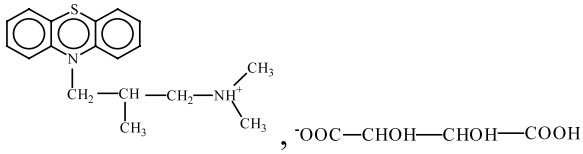
Table 8
Accuracy and precision of thermometric titration of 10^{-3} mol mepyramine maleate by hydroxyde sodium 1 M

	Taken, $\times 10^{-2}$ (mol l^{-1})	Found, $\times 10^{-2}$ (mol l^{-1})[a]	Recovery (%)
Maleate	1.2	1.16 (2.4%)	97.2
Mepyramine	1.2	1.19 (1.6%)	99.5

[a] Mean of seven replicates with standard errors in parentheses.

perfect agreement with the pK_a values of maleic acid (1.92–6.23) [21] and with those of the conjugated acids of mepyramine ($pK_a = 4.00$ and 8.90) [18]. Beyond its solubility effect, the presence of octanol induces also a shift in its apparent K_a value according to relation (8). The conjugated acid of mepyramine is stronger than in pure water. This could have been a drawback because with a sufficiently high volume V_{org} the pK'_a value would have been too close to that of monomaleate and as a result it would have been impossible to discriminate the two acidities. This is the reason why titration was performed with only 0.5 ml of *n*-octanol giving the value $pK'_a = 8.21$. The possibility of regulation of acidity dissociation constants is another advantage of the methodology described here but this possibility is actually limited by solubility considerations. It is worth noting that despite the small difference between $pK'_a = 8.21$ and the value $pK_a = 6.23$ of the monomaleate ion, an accurate titration was still possible. The origin and the justification of this possibility offered by thermometric titration has been discussed in the literature [37]. Precisions and accuracies obtained for both the monomaleate ion and mepyramine are given in Table 8. In the European pharmacopeia [12] it is recommended to perform titration of mepyramine maleate by potentiometric titration in acetic acid by perchloric acid. In these conditions the monomaleate ion and mepyramine are titrated simultaneously.

The method proposed was also used for the assay of a pharmaceutical preparation of 100 mg of chlorpromazine hydrochloride by sodium hydroxide without any detectable variation of the accuracy and recovery found with the pure hydrochloride (Table 9). Starch, gelatin, silice, magnesium stearate and lactose did not, indeed, interfere in assays. The method failed in our hands in the case of alimemazine tartrate.



If the titration of the pure salt by sodium hydroxide was satisfactory, giving only one final point corresponding to two equivalents per mole of salt

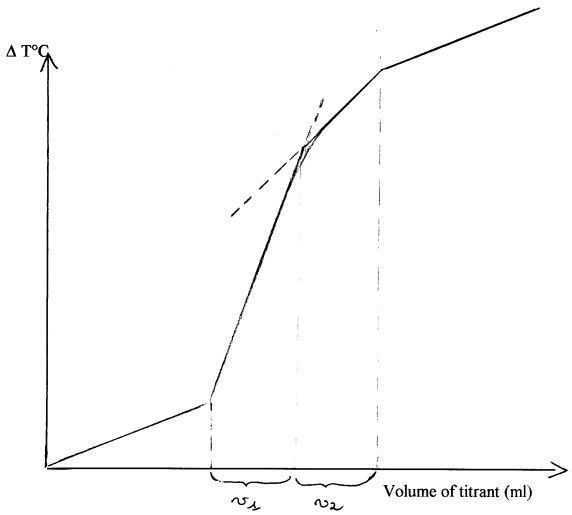


Fig. 2. Thermogram obtained by titration of mepyramine maleate (0.011 mol l^{-1}) by sodium hydroxide solution (1 mol l^{-1}) ($V_w = 91.5$ ml, $V_{org} = 0.5$ ml) v_1 corresponds to the neutralization of the monomaleate ion and v_2 to the conjugated acid of mepyramine.

Table 9
Accuracy and precision of thermometric titration of tablets of chlorpromazine hydrochloride 100 mg by hydroxyde sodium 1 M

Taken (mg)[a]	Found (mg)[b]	Recovery (%)
200	196.17 (2.1%)	98.1

[a] Two tablets of 100 mg.
[b] Mean of seven replicates with standard errors in parentheses.

of the conjugated acid (Table 10) it was not the case for a pharmaceutical preparation which contained citric acid. Because of this interference the thermogram exhibited no break, although the pK_a values of the citric acid (3.13–4.76–6.40) [21] and the tartaric acid (3.03 – 4.37) [21] differed notably from that of the conjugated acid of alimemazine (8.60) [22]. This was very likely due to the fact that the enthalpy of neutralization of citric acid did not differ substantially from the apparent one of the conjugated acid of alimemazine.

5. Conclusion

In conclusion, such a methodology is promising owing to the practical and theoretical possibilities it offers and also because it is easily handled avoiding the use of mercury salts, perchloric acid, glacial acetic acid which are commonly required in 70% of analytical methods of bulk drug in pharmacopeias.

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Table 10
Accuracy and precision of thermometric titration of 10^{-3} mole alimemazine tartrate by hydroxyde sodium 1 M

Taken		Volume octanol (ml)	Found[a]		Recovery (%)
mg	mol l^{-1}		mg	mol l^{-1}	
373.5	5×10^{-4}	5	366	4.9 10^{-4} (1%)	98
373.5	5×10^{-4}	10	362.3	4.85 (2.2%)	97

[a] Mean of four replicates with standard errors in parentheses.

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