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THERMODYNAMIC PROPERTIES OF THE DISSOCIATION OF 2-MERCAPTOPYRIDINE, 2-MERCAPTOPYRIMIDINE AND 2-THIOBARBITURIC ACID

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ABSTRACT

The changes in free energy, enthalpy and entropy for the dissociation and neutralization of 2-mercaptopyridine, 2-mercaptopyrimidine and 2-thiobarbituric acid have been determined at 25 ° C in aqueous potassium nitrate medium of 0 1 M ionic strength The changes in dissociation free energy were calculated from dissociation constants determined potentiometrically and refined using the program MINIGLASS The neutralization enthalpy changes were determined by direct thermometric titration, using linearization methods and the least-squares program MINITERM

INTRODUCTION

Pyrimidines are compounds of biological and industrial interest They have antithyroidal activity and frequently act as bactericides or fungicides They have also been used in vulcanization processes, as corrosion inhibitors and in emulsions for photothermographic processes

The dissociation constants of many pyridine and pyrimidine derivatives are found in the literature, but there is no concordance in the temperatures and ionic strengths at which they have been determined, which makes it impossible to compare the results However, the available data are sometimes affected by relatively high uncertainties, as is the case of the pK of 2-mercaptopyrimidine [1], or there may even be important differences between the values reported by several authors, as in the case of 2-thiobarbituric acid [1,2] In order to use either the linearization methods or the program MINITERM to calculate the neutralization enthalpies, the dissociation constants must be exactly known, for this reason they were determined by a potentiometric method, in the same experimental conditions

Dissociation free energies (ΔG_d) were calculated from the dissociation constants Neutralization enthalpies (ΔH_n) were determined by thermometric titration, using two calculation procedures the method of linearization by linear regression, developed by Mongay et al [3], including a correction

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parameter to compensate for the thermal loss caused by the imperfect adiabatic properties of the titration cell [4] and the least-squares refinement program, MINITERM, developped by Cerdà et al [5] and written in BASIC

From the free energies and enthalpies, the corresponding entropies were calculated

EXPERIMENTAL

Apparatus

Potentiometric measurements

Radiometer pHM84 pH Meter, with a Radiometer G202B glass electrode and a Radiometer K401 saturated calomel electrode

Metrohm Multidisomat E415 automatic burette, with a 10 cm^3 cylinder

Tectron S 473 100 circulation thermostat

Automatic titration assembly, composed of

Hewlett Packard 3421A Data acquisition unit

Hewlett Packard 9816 computer

Hewlett Packard 7475 plotter

Thermometric measurements

The thermometric titration assembly, built in this department, has been described in previous papers [6,7]

Thermometric data were processed using a IBM PC

Reagents

2-Mercaptopyridine (Fluka purum) was purified by recrystallization from benzene

2-Mercaptopyrimidine and 2-thiobarbituric acid (Fluka purum) were purified by recrystallization from water

1 M HCl, standardized against recrystallized sodium tetraborate decahydrate, and 1 M NaOH, standardized against potassium hydrogen phthalate, were used for thermometric titrations

Solutions of 0 01 M HNO_3, at 0 1 M ionic strength (potassium nitrate), standardized against sodium tetraborate decahydrate, and 0 06 M KOH, at 0 1 M ionic strength (potassium nitrate), standardized against potassium hydrogen phthalate, were used for potentiometric titrations Carbonate-free potassium hydroxide solution was prepared by precipitating carbonate ions by the addition of an excess of barium hydroxide, filtering, and later passing the solution through a cation exchanger (Amberlite IRA-120, K^+ form)

Potassium nitrate was also purified by recrystallization

All reagents were of analytical grade quality, and boiled bidistilled water was used throughout

Procedures

Dissociation constants

The dissociation constants of the compounds were determined by potentiometric titration [8] in a jacketed vessel, thermostated at 25 ± 0 1° C by circulating water Acidic solutions (T S) containing nitric acid–ligand mixtures were titrated with potassium hydroxide solution, and during the titration pure nitrogen [9] was bubbled through the solution to remove dissolved oxygen

The variation of free hydrogen ion concentration was measured using the cell calomel electrode / T S / glass electrode

The electrode system was calibrated in terms of hydrogen ion concentration by the Gran method [10]

In the experimental conditions used, the value found for pK_w was 13 782 ± 0 007

In the study of dissociation equilibria, the data pairs (V_t, pH) were transformed to ($\bar{J}$, pH), where $\bar{J}$ is the average number of protons bound to each ligand molecule [11] as defined by the following equation

$$\bar{J}=\frac{H_t-(h-K_w/h)}{L_t}=\frac{h\beta_1+2h^2\beta_2}{1+h\beta_1+h^2\beta_2}$$

where β_1 and β_2 are overall protonation constants, H_t is the total concentration of dissociable H^+, L_t is the total concentration of ligand and h is the free hydrogen ion concentration

From the values of ($\bar{J}$, pH), the protonation curves of the ligands were obtained (Figs 1 and 2)

Neutralization enthalpies

The calorific capacity of the titration vessel was determined, using the method of chemical calibration The neutralization of sodium hydroxide with hydrochloric acid, whose neutralization enthalpy is known at any temperature [12] was selected as a suitable calibration reaction Several aliquots of sodium hydroxide were placed in the titration vessel, potassium nitrate was added to obtain a 0 1 M final ionic strength and the solution was diluted to 40 cm^3 After allowing it to reach thermal stability, it was titrated with 1 M hydrochloric acid solution

The calorific capacity can be determined from the increment of temperature recorded at any point of the titration (usually the end-point) using the equation

$$\Delta T=\frac{\Delta H_n V_a M}{C_c+V_a}$$

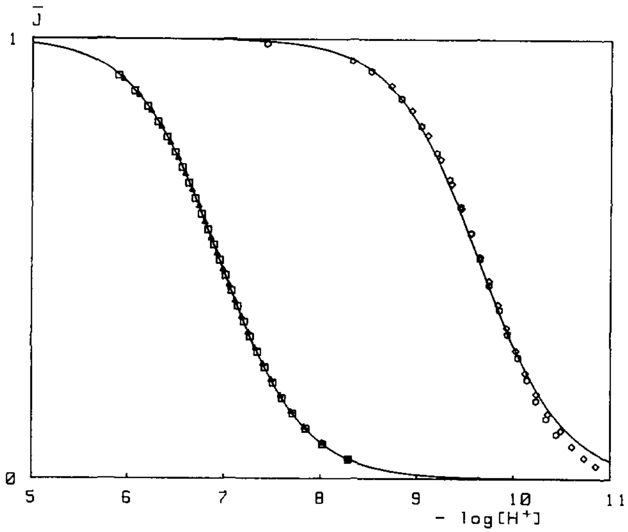

Fig 1 Protonation curves for 2-mercaptopyrimidine (C_1 □ = 7 107 mM, △ = 6 903 mM) and 2-mercaptopyridine (C_1 ◇ = 8 366 mM, ○ = 3 718 mM) Solid lines are calculated for pK_1 = 6 933 and 9 648, respectively

where C_c is the initial calorific capacity, V_a is the volume of titrant, ΔT is the recorded temperature increment, M is the concentration of titrant (in mol l^{-1}) and ΔH_n is the neutralization enthalpy of the reaction (in cal mol^{-1})

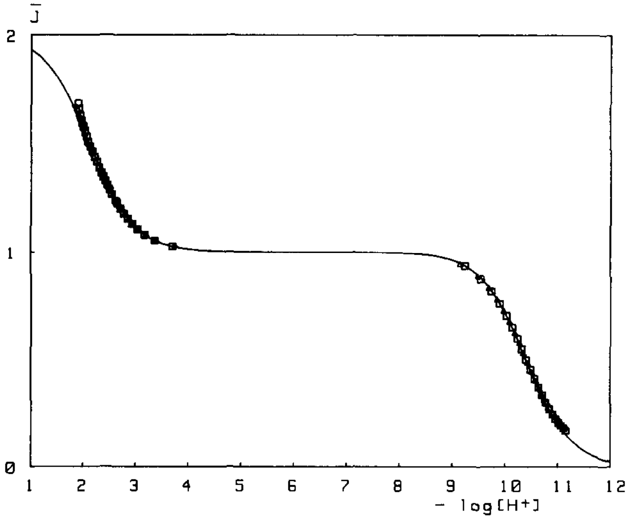

Fig 2 Protonation curves of thiobarbituric acid (C_1 □ = 7 634 mM, △ = 8 230 mM) Solid line is calculated for pK_1 = 2 124 and pK_2 = 10 405

When this equation was used with the temperature increments recorded at several points of the same titration, the calculated initial calorific capacity increased as the titration proceeded This could be attributed to heat losses originated by imperfect adiabatic properties of the titration vessel In order to compensate for this effect, a least-squares heat-leak correction method was used, making use of the linear equation

$$Y = a + bX$$

where

$$a = -C_c - V_a$$

and

$$b = -K_n/k$$

X and Y, expressed as

$$Y = \frac{MV_a \Delta H_n}{\Delta T_i} \qquad X = \frac{\Delta V_a}{\Delta T_i} \sum \frac{\Delta T_i + \Delta T_{i-1}}{2}$$

were calculated for several points of the titration k, the rate of titrant addition (ml min^{-1}), is a constant and K_n, the heat-leak coefficient in Newton's law ($dQ = -K_n \, dt(T_i - T_{ex})$), (which remained almost invariant during the titration)

An initial calorific capacity of 45 4 ± 0 2 cal K^{-1} (mean of five determinations) was obtained for an initial volume of 40 cm^3

Neutralization enthalpies were determined by thermometric titration with 1 M NaOH of 40 cm^3 of approximately $1\ 5 \times 10^{-2}$ M solutions (at 0.1 M ionic strength) of the three compounds studied

As is generally the case, the titration vessel was not perfectly adiabatic For this reason the equations developed by Mongay et al [3] for the determination of the enthalpy at several points of the titration, after compensating for the heat leak [4], were used

For 2-mercaptopyridine and 2-mercaptopyrimidine, weak monoprotic acids, experimental data were adjusted to the linear equation $Y = a + bX$, where

$$Y = \frac{\Delta T_i (C_c + V_a)}{C_0 V_0 \left[\dfrac{1}{1 + \beta h} - \dfrac{1}{1 + \beta_0 h_0} \right]}$$

$$X = \frac{\Delta V_a}{C_0 V_0 \left[\dfrac{1}{1 + \beta h} - \dfrac{1}{1 + \beta_0 h_0} \right]} \sum \left[\frac{\Delta T_i + \Delta T_{i-1}}{2} \right]$$

where $a = \Delta H_n$, $b = -K_n/k$, β_0 is the initial value of the protonation constant and h_0 is the initial free hydrogen ion concentration

For 2-thiobarbituric acid, a diprotic acid, experimental data were adjusted to the equation $Y = a + bX + cZ$, where

$$X = B/A$$

$$Y = \frac{\Delta T(C_c + V_a) - \left[\dfrac{C_0V_0(2 + \beta_{01}h_0)}{1 + \beta_{01}h_0 + \beta_{02}h_0^2} - h(V_0 + V_a) + \dfrac{V_0K_w}{h_0}\right]\Delta H_w}{C_0V_0A}$$

$$Z = \frac{\Delta V_a}{A}\sum\left[\frac{\Delta T_i + \Delta T_{i-1}}{2}\right]$$

$$A = \frac{1 + \beta_1 h}{1 + \beta_1 h + \beta_2 h^2} - \frac{1 + \beta_{01}h_0}{1 + \beta_{01}h_0 + \beta_{02}h_0^2}$$

$$B = \frac{1}{1 + \beta_1 h + \beta_2 h^2} - \frac{1}{1 + \beta_{01}h_0 + \beta_{02}h_0^2}$$

where $a = \Delta H_{n_2}$, $b = \Delta H_{n_1}$, $c = -K_n/k$

Recently, the program MINITERM, for the refinement of enthalpies from data obtained in thermometric titrations, was published [5] This program was also used to process our data and the results were compared with those obtained by the methods of regression

RESULTS AND DISCUSSION

Approximate values of the protonation constants were obtained by comparison of the experimental protonation curves with a series of normalized curves [13], and then these values were refined using the program MINIGLASS [14] in pK_a mode The function minimized by this program, U, was defined in terms of $-\log[\mathrm{H}^+]$

$$U = \sum_{i=1}^{n}\left[-\log[\mathrm{H}^+]_{\mathrm{exp},i} + \log[\mathrm{H}^+]_{\mathrm{calc},i}\right]^2$$

The dissociation constants were calculated from the values obtained for the protonation constants, which are listed in Table 1

Neutralization enthalpies were calculated using the procedures previously mentioned Their values are also shown in Table 1 In Fig 3 typical enthalpograms are represented

It can be observed that for 2-mercaptopyridine and 2-mercaptopyrimidine, weak monoprotic acids with moderate pK values, both MINITERM and linear regression methods with heat-leak correction gave comparable results, although deviations were slightly less using MINITERM For acids of this kind, the method of regression, which can be carried out with a relatively simple pocket calculator, is a valid procedure

TABLE 1

Compound	pK_a	ΔH_n [a]	ΔH_n [b]
2-Mercaptopyrimidine	6 948 ± 0 004	−7 9 ± 0 1	−7 85 ± 0 05
2-Mercaptopyridine	9 633 ± 0 007	−4 7 ± 0 1	−4 52 ± 0 05
2-Thiobarbituric acid	2 124 ± 0 006	−10 3 ± 0 3	−12 4 ± 0 2
	10 405 ± 0 003	−6 3 ± 0 3	−3 3 ± 0 3

[a] Linearization method [b] MINITERM results ΔH, kcal mol^{-1}

2-Thiobarbituric acid, however, is a diprotic acid with a low pK for its first dissociation and a very high pK for its second dissociation. This means a high enthalpy for the first neutralization and a low one, much affected by heat leakage originated by imperfect adiabatic character, for the second neutralization. In this case, results obtained using MINITERM differed from those obtained by the method of regression, and they had lower deviations The results offered by MINITERM were in better agreement with those that could be expected from the dissociation constants and the recorded enthalpograms.

From the data of Table 1, free energies, enthalpies and entropies of neutralization, dissociation and protonation were calculated, taking into account the following relations

Dissociation

$$HA \rightleftarrows H^+ + A^- \qquad K_d = \frac{[H^+][A^-]}{[HA]} \qquad \Delta G_d,\ \Delta H_d,\ \Delta S_d$$

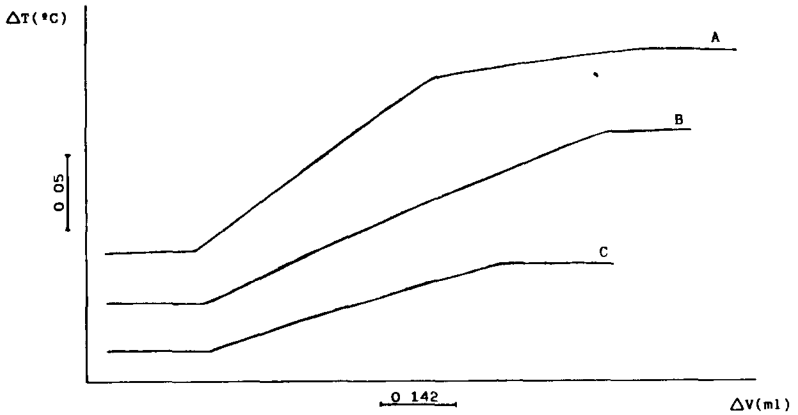

Fig 3 Sample thermometric titrations of A, 2-thiobarbituric acid, B, 2-mercaptopyrimidine, C, 2-mercaptopyridine

TABLE 2

Compound	pK_d	ΔG_d	ΔH_d	ΔS_d	pK_n	ΔG_n	ΔH_n	ΔS_n
2-Mercaptopyrimidine	6 948	9 48	5 12	−14 6	−6 834	−9 32	−7 85	4 9
2-Mercaptopyridine	9 633	13 14	8 45	−15 7	−4 149	−5 66	−4 52	3 8
2-Thiobarbituric acid	2 124	2 90	0 57	−7 8	−11 658	−15 90	−12 4	11 7
	10 405	14 19	9 67	−15 2	−3 377	−4 61	−3 3	4 4

Units ΔG and ΔH, kcal mol^{-1}, ΔS, cal (K mol)$^{-1}$

Neutralization

$$HA + OH^- \rightleftarrows A^- + H_2O \qquad K_n = \frac{[A^-]}{[HA][OH^-]} = \frac{K_d}{K_w}$$

$$\Delta G_n = \Delta G_d + \Delta G_w \qquad \Delta H_n = \Delta H_d + \Delta H_w \qquad \Delta S_n = \Delta S_d + \Delta S_w$$

Protonation

$$A^- + H^+ \rightleftarrows HA$$

$$K_p = \frac{[HA]}{[A^-][H^+]} = \frac{1}{K_d} \qquad K_{p_1} = \beta_1 \qquad K_{p_2} = \beta_2/\beta_1$$

$$\Delta G_p = -\Delta G_d \qquad \Delta H_p = -\Delta H_d \qquad \Delta S_p = -\Delta S_d$$

In Table 2 the values of neutralization and dissociation free energies, enthalpies and entropies are shown The change in entropy for the second neutralization of 2-thiobarbituric acid is higher than could be expected considering the value of its pK and the changes in entropies for the other compounds This can probably be attributed to the uncertainty in the determination of its neutralization enthalpy

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