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Ionization constants of an amino acid as a function of temperature

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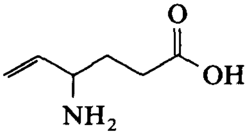
The ionization constants of compound I (MDL 71754, 4-amino-5-hexenoic acid) have been determined over the temperature range 25–60 °C using a potentiometric titration procedure. The procedure was the same as that used previously (Streng et al., 1976) with the following modifications: Combination electrode (Radiometry GK2402B), pH meter (Radiometry PHM85), water bath to control the temperature of the solution (RMS-20 Lauda circulating constant temperature bath; ±0.01 °C). Knowing the ionization constants as a function of temperature, the values for the thermodynamic properties ΔH and ΔS were determined.



Compound I

Potentiometric titrations were run in triplicate on Compound I at 30, 45, 50 and 60 °C. Solutions were prepared by dissolving approx. 30 mg of MDL 71754 in 50 ml of deionized water. To these solutions, an excess (approx. 6 ml) of standardized HCl (~0.05 M) was added to doubly protonate the compound. These solutions were placed in the water bath and titrated with standardized NaOH (~0.05 M) solution. The solution pH values were measured as a function of the amount of NaOH added. The solutions were stirred by bubbling nitrogen saturated with water into the beaker.

The titration data were input into a computer program which determines the equilibrium constants of diprotic compounds [*]. The average values of these calculations are listed in Table 1 where the standard deviations of the listed K_a values are between 1 and 5%. These data were treated according to the van't Hoff equation (Eqn 1) to determine ΔH. Knowing ΔH, ΔS could then be calculated (Eqn 2):

$$\frac{d\ln(K)}{d(1/T)} = -\frac{\Delta H}{R} \tag{1}$$

where K is the equilibrium constant, T is the temperature (in K), ΔH is the enthalpy and R is

TABLE 1

Average K_a values

T (°C)	K_1 ($\times 10^5$)	K_2 ($\times 10^{10}$)
25	9.600 ± 0.159	1.833 ± 0.076
30	9.113 ± 0.361	2.399 ± 0.035
45	9.618 ± 0.387	5.920 ± 0.325
50	9.221 ± 0.394	7.503 ± 0.155
60	9.051 ± 0.342	12.02 ± 0.058

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[a] The program includes corrections for activity coefficients using Davies approximation. A copy of the program is avialable on request from the author.

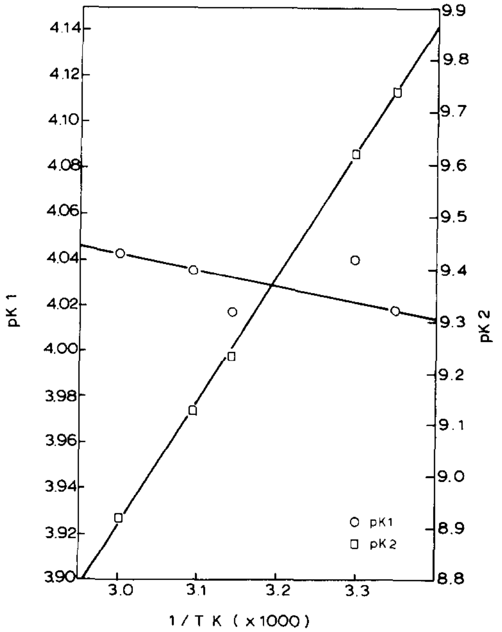

Fig. 1. Van't Hoff plot.

TABLE 2

Predicted pK_a values

T (°C)	pK_1		ΔpK_1	pK_2		ΔpK_2
	Pred.	Meas.		Pred.	Meas.	
25	4.018	4.018	0.000	9.739	9.737	0.002
30	4.022	4.040	−0.018	9.609	9.620	−0.011
45	4.032	4.017	0.015	9.243	9.228	0.015
50	4.036	4.035	0.001	9.129	9.125	0.004
60	4.042	4.043	−0.001	8.910	8.920	−0.010

ΔpK = predicted − measured.

TABLE 3

ΔH and ΔS values [a]

K	ΔH	ΔS
1	−1.34	−81.2
2	45.2	−34.7

[a] ΔH, kJ/mol; ΔS, J degree^{-1} mol^{-1}.

the gas law constant (8.315 J degree^{-1} mol^{-1}; 1.987 cal degree^{-1} mol^{-1}).

$$\Delta S = \frac{RT\ \ln(K) + \Delta H}{T} \qquad (2)$$

where ΔS is the entropy.

From the van't Hoff equation, the slope of the line of a graph of pK vs $1/T$ will equal $\Delta H/2.303R$. In Table 2 the measured, predicted and difference in the pK_a values are given. There is good correlation between the calculated and measured values. Comparison with pK_a values for similar compounds indicates that these trends would be expected (Kortum et al., 1961; Perrin, 1965, 1972). Fig. 1 is a plot of these data and the calculated curves. Based on the literature values, pK_1 can be assigned to the carboxylic acid group and pK_2 to the amino group. It can be seen that there is little change in pK_1 over this temperature range (becoming a slightly weaker acid) while pK_2 changes by a factor of five (becoming a weaker base). The slope of these lines will equal ΔH and ΔS can be determined using Eqn 2. The results of these calculations are given in Table 3. These values are consistent with those found in the literature where ΔH values are in the range 1.7 to −0.8 kJ/mol for pK_1 and between 46 and 54 kJ/mol for pK_2 and ΔS values are in the range −67 to −88 J degree^{-1} mol^{-1} for pK_1 and −17 to −38 J degree^{-1} mol^{-1} for pK_2 (Martell and Smith, 1974, 1982).

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