Heats of Hydrolysis of Acetates and Thiolacetates

in Aqueous Solution

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Enthalpy changes, $\Delta H°$, for the idealized isothermal (25°C) reaction RXAc(s/l) + H_2O(l) → RXH(l) + HOAc(l) have been determined calorimetrically. $\Delta H°$ was found to be + 0.53 ± 0.06 and + 1.75 ± 0.07 kcal/mole for RXAc equal to β-acetylaminoethyl acetate (l) and β-acetylaminoethyl thiolacetate (s), respectively. By heat of solution measurements the enthalpy changes for the hydrolysis reactions in aqueous media (solute concentration *ca.* 0.01 M, no ionization of reaction products), were found to be + 0.47 ± 0.07, − 0.91 ± 0.08 and + 0.43 ± 0.06 kcal/mole for RX-Ac equal to $AcNHCH_2CH_2O$-Ac, $AcNHCH_2CH_2S$-Ac and C_2H_5O-Ac, respectively. The heats of hydrolysis of O- and S-acetates and the energetics of the acyl shift O → S in the gaseous state and in aqueous solution are discussed.

In a series of papers [1-3] enthalpy data for heats of hydrolysis of acetates and thiolacetates have been presented. The goal has been to provide some basic experimental data for these classes of compounds, with a special reference to their biochemical significance.

Of the biochemically important thiol esters acetyl coenzyme A is the most studied, and it was therefore felt desirable to determine the heat of hydrolysis of a comparatively simple, but still adequate model compound. In the present investigation β-acetylaminoethyl thiolacetate, $CH_3CONHCH_2CH_2S$-$COCH_3$, has been studied. This compound has been used earlier as a model for acetyl coenzyme A in kinetic studies of the hydrolysis process [4]. To enable a close comparison with the thiol ester, the heat of hydrolysis of the oxygen analogue β-acetylaminoethyl acetate, $CH_3CONHCH_2CH_2O$-$COCH_3$, has been determined. The S- and O-acetyl groups are easily split off in aqueous alkali, while the N-acetyl group is stable under the experimental conditions. Both esters are readily soluble in water and the determined standard enthalpy changes, $\Delta H°$ **

** Referring to the hypothetical process of the pure compounds in their condensed state, at 25°C.

for the processes have been recalculated to be valid for aqueous solution. For this purpose heats of solution in water (*ca*. 0.01 M solute concentration, ionic strength = 0.2) have been determined for the reaction components, as well as for ethyl acetate and ethanol. Unfortunately, the thiol acetates studied [1],[3] earlier are not sufficiently soluble in water to allow measurements of the heat of solution with the calorimetric equipment available.

EXPERIMENTAL

Materials. β-Acetylaminoethanol was prepared[5] from β-aminoethanol (Eastman Kodak, m.p. 9 – 10°C) and acetic anhydride (Merck, analytical grade). The preparation obtained was fractionally distilled at *ca*. 2 mm Hg, b.p. 140°C, and then left for some weeks, after which one of the fractions slowly crystallized. A water solution of the very hygroscopic crystals showed an alkaline reaction. The solution was neutralized to pH 7 and then treated with standard sodium hydroxide (to make a 0.05 M solution) for 20 min. Titration back to pH 7 with hydrochloric acid showed a consumption of alkali corresponding to *ca*. 2 % hydrolyzable acetate. The crystalline preparation was treated with 2 N aqueous potassium hydroxide at room temperature for 5 min followed by neutralization with hydrochloric acid. The water was removed in vacuum at 40°C and the precipitated potassium chloride was filtered off. The residue was distilled quickly through a short Vigreux column at *ca*. 2 mm Hg. The resultant compound reacted weakly alkaline and titrations indicated 0.2 % hydrolyzable acetate.

A sample of this preparation was kept at 200°C, under nitrogen, for one hour. When dissolved in water it showed a strong alkaline reaction. Titration to pH 7 consumed 17 mmoles of HCl per mole of N-acetate. When treated with alkali there was a net consumption equal to 19 mmoles. It thus seems as the N-acetate isomerizes to some extent to the O-ester at high temperatures (*cf*. Ref.[6]) The β-acetylaminoethanol, therefore, cannot be purified by distillation at reasonably high pressures especially as the O-ester would be expected to have a considerably higher vapor pressure.

The alkali-treated and quickly distilled preparation was inoculated with a minute quantity of impure crystals. When two thirds had crystallized the mother liquor was rejected. After the process had been repeated, no O-ester could be detected; $n_D^{25} = 1.4728$; $d_4^{25} = 1.1124$, m.p. 28.0 – 28.8°C.

Acetylation of the hydroxyl group of β-acetylaminoethanol with acetic anhydride according to Roe *et al.*[7] gave a product essentially neutral in water solution. However, the equivalent weight, as determined by alkaline hydrolysis and back titration, was too low, suggesting an extensive formation of N,N,O-triacetate, *ca*. 50 % when the reaction time was as long as 6 h at *ca*. 90°C. The N,O-diacetyl compound could not be purified by careful distillation as the compound was not stable at higher temperatures (an intense odor developed resembling that of pyridine).

To avoid the formation of triacetate, the N,O-diacetate was prepared from the N-acetate by acetylation with an equivalent amount of acetyl chloride in tetrahydrofuran solution at room temperature. Most of the hydrochloride formed was absorbed by the reaction mixture and was removed by ammonia. After filtering off the precipitated ammonium chloride, the excess of ammonia and the solvent was removed in vacuum, at room temperature. The residue was distilled quickly through a 30 cm Vigreux column, yield 83 %. Titration data indicated the product to contain 98 % N,O-diacetate. Attempts to purify the compound by fractional distillation in efficient columns at pressures between 5 and 10 mm Hg were unsuccessful; *ca*. 5 % too low equivalent weights were obtained. However, by repeated fractionation in a 30 cm Vigreux column, at *ca*. 1 mm Hg, an odor-less product giving the theoretical equivalent weight was obtained; $n_D^{25} = 1.4510$; $d_4^{25} = 1.1053$.

β-Acetylaminoethane thiol was prepared [8] from freshly distilled ethylenimine [9] and thiolacetic acid [10] (99.5 % according to iodine titration). After repeated fractional distillation at *ca*. 1 mm Hg the substance had the theoretical equivalent weight as determined by iodine titration in acetic acid [11]. $n_D^{25} = 1.5120$.

β-Acetylaminoethyl thiolacetate was prepared [8] from β-acetylaminoethane thiol by acetylation with ketene and purified by repeated fractional distillation at *ca.* 2 mm Hg followed by freezing out. Iodine titrations after alkaline hydrolysis [1] indicated 99.7 % purity. In calculating the enthalpy change it was assumed that 0.3 % inactive impurities were present; m.p. 30−32°C.

Ethyl acetate of analytical grade (Merck) was purified by fractional distillation. The equivalent weight, determined by alkaline hydrolysis and back titration, was equal to the theoretical. Ethyl alcohol of a commercial absolute grade was treated with magnesium [12] and distilled. The acetic acid was that described in Ref. [13].

Apparatus. The measurements were performed with an "isothermal-jacket" glass calorimeter, described in detail elsewhere [14,15]. The calorimeter was charged with 100 ml of liquid and the substance was contained in a sealed glass ampoule. The heat equivalent of the calorimeter including its content was determined by passing a known current for a given time (360 sec) through the heating element. The calibration experiments, at least five for each system, were performed after the reaction had taken place. No significant correlation between amount and kind of reactant and the measured heat capacity values was found and therefore derived mean values have been used in calculating the results.

Procedure. β-Acetylaminoethyl acetate was hydrolyzed in a 0.1 M aqueous solution of sodium hydroxide to which sodium chloride was added to give a total ionic strength of 0.2. The sodium hydroxide concentration was the same as was used in determining the equivalent weight of the ester. As in the analytical experiments, care was taken to avoid absorption of carbon dioxide in the calorimetric liquid. The reaction period was *ca.* 7 min and corrections for heat exchange were calculated by means of the Regnault-Pfaundler method [16]. Normal K-values (K = the constant in Newton's cooling law) were obtained, which indicates that side reactions slower than the main reaction were absent.

The thiol ester was hydrolyzed in 0.8 M sodium hydroxide solution (the same as was used in the analytical experiments). The reaction periods for the calorimetric hydrolysis experiments were 3−7 min; the length of the reaction period was mainly due to the slow dissolution of the crystalline thiol ester. Thiols, formed in an alkaline medium, are rapidly oxidized in the presence of oxygen. Most oxygen could be removed from the calorimetric system, but in order completely to cancel the small unavoidable heat effects due to oxidation the same technique as before [1,3] was used. Thus, 0.5 ml β-acetylaminoethane thiol was substituted for the sodium hydroxide solution. In doing so, normal K-values were obtained. Heat exchange corrections were calculated by means of the Regnault-Pfaundler method.

The hydrolysis experiments were supplemented by heats of solution measurements in the hydrolysis media in order to arrive at enthalpy data for the standard state, $\Delta H°$, and in 0.2 M sodium chloride solution *, to give data for the processes in water solution. These processes were all very rapid, and initial and final thermistor values were evaluated graphically.

Units of measurements. The results of the calorimetric experiments are expressed in terms of the defined calorie, equal to 4.1840 abs. joules, and refer to the isothermal process at 25°C and to the true mass.

RESULTS

The experimental results are summarized in Tables 1−3. In the tables the symbol log R_i/R_f means the expression proportional to the temperature change: R_i and R_f are the corrected thermistor resistance values at the start and the end, respectively, of the main period. ε is the heat equivalent of the calorimetric system expressed in cal/unit of log R_i/R_f. When five or more determinations were performed given uncertainties are standard deviations of the means. Otherwise, they are the average deviation of the mean.

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* Here, with only uncharged species present, heats of solution are not expected to be dependent on small differences in the ionic strength. However, to reach conformity with other heats of solution measurements 0.2 M NaCl was used as calorimetric liquid.

The heat of solution of β-acetylaminoethanol was found to be 0.1 kcal/mole more exothermal in aqueous alkali than in water at neutral pH, ionic strengths being the same. The difference is small but seems to be significant.

Corrections to standard states. The ideal isothermal hydrolysis reaction V is obtained from eqns. I—IV, which correspond to the reactions taking place under actual experimental conditions.

X = O, S.   R = AcNHCH$_2$CH$_2$—

RXAc(l/s) + H$_2$O(soln) → RXH(soln) + HOAc(soln)	ΔH_1	(I)
RXH(l) → RXH(soln)	ΔH_2	(II)
HOAc(l) → HOAc(soln)	ΔH_3	(III)
H$_2$O(l) → H$_2$O(soln)	ΔH_4	(IV)

$$\text{RXAc(l/s)} + \text{H}_2\text{O(l)} \rightarrow \text{RXH(l)} + \text{HOAc(l)} \qquad \Delta H° \qquad \text{(V)}$$
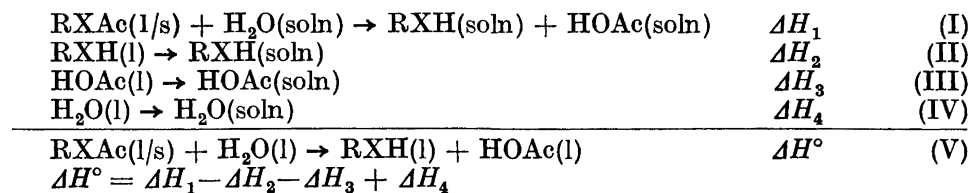$$\Delta H° = \Delta H_1 - \Delta H_2 - \Delta H_3 + \Delta H_4$$

Table 1. Results from heat of hydrolysis and heats of solution measurements performed in aqueous solution containing 0.1 mole NaOH and 0.1 mole NaCl per liter. $\varepsilon = 8882 \pm 7$ cal/unit of log R_i/R_f.

Substance	mmoles	$10^4 \cdot \log R_i/R_f$	$-\Delta H$, kcal/mole
AcNHCH$_2$CH$_2$OAc	3.266	58.87	16.01
	2.746	49.29	15.94
	2.398	43.21	16.00
	2.897	52.19	16.00
		Mean	15.99 ± 0.03
AcNHCH$_2$CH$_2$OH	3.387	10.78	2.83
	3.494	11.04	2.81
	2.752	8.80	2.84
		Mean	2.83 ± 0.01
HOAc	3.611	55.73	13.71
	4.306	66.29	13.67
	3.705	57.14	13.70
	3.167	48.73	13.67
	4.353	67.47	13.77
	3.181	48.81	13.63
		Mean	13.69 ± 0.02

Table 2. Results from heat of hydrolysis and heat of solution measurements performed in 0.8 M aqueous NaOH solution. $\varepsilon = 8858 \pm 4$ cal/unit of log R_i/R_f.

Substance	mmoles	$10^4 \cdot \log R_i/R_f$	$-\Delta H$, kcal/mole
AcNHCH$_2$CH$_2$SAc	2.605	59.79	20.33
	2.416	55.32	20.28
	2.967	68.25	20.38
	2.427	55.73	20.34
		Mean	20.33 ± 0.03
AcNHCH$_2$CH$_2$SH	2.595	24.60	8.40
	2.550	24.45	8.49
	2.616	24.96	8.45
	3.315	31.84	8.51
		Mean	8.46 ± 0.04

Table 3. Results from heats of solution measurements performed in 0.2 M aqueous solution of NaCl. $\varepsilon = 8878 \pm 7$ cal/unit of log R_i/R_f.

Substance	mmoles	$10^4 \cdot$ log R_i/R_f	$-\varDelta H$, kcal/mole
AcNHCH$_2$CH$_2$OAc	1.572	5.32	3.00
	1.180	3.98	2.99
	2.139	7.11	2.95
		Mean	2.98 $\pm$ 0.02
EtOAc	1.262	3.32	2.34
	1.211	3.09	2.27
	0.691	1.74	2.24
	0.950	2.40	2.24
		Mean	2.27 $\pm$ 0.03
AcNHCH$_2$CH$_2$SAc	1.449	-1.42	-0.87
	1.358	-1.43	-0.94
	0.900	-0.91	-0.90
	2.308	-2.46	-0.95
		Mean	-0.92 ± 0.03
AcNHCH$_2$CH$_2$OH	2.035	6.15	2.68
	2.393	7.36	2.73
	1.399	4.29	2.72
		Mean	2.71 $\pm$ 0.02
EtOH	1.405	3.82	2.41
	0.994	2.69	2.40
	1.650	4.47	2.40
	1.573	4.21	2.38
		Mean	2.40 $\pm$ 0.01
AcNHCH$_2$CH$_2$SH	1.654	2.71	1.45
	2.492	3.94	1.40
	3.310	5.31	1.42
	1.404	2.18	1.38
		Mean	1.41 $\pm$ 0.02

Table 4.

RXAc	$\varDelta H_1$	$\varDelta H_2$	$\varDelta H_3$	$\varDelta H_4$	$\varDelta H°$
AcNHCH$_2$CH$_2$OAc [a]	-15.99	-2.83	-13.69	0.00 [b]	0.53 $\pm$ 0.06
AcNHCH$_2$CH$_2$SAc	-20.33	-8.46	-13.64 [c]	-0.02 [c]	1.75 $\pm$ 0.07

[a] $\varDelta H_2$ refers to the heat of solution of liquid AcNHCH$_2$CH$_2$OH.
[b] Ref.[17]
[c] Ref.[18]
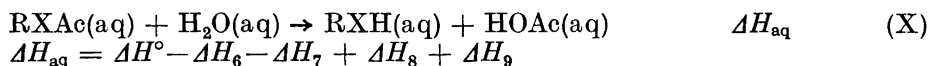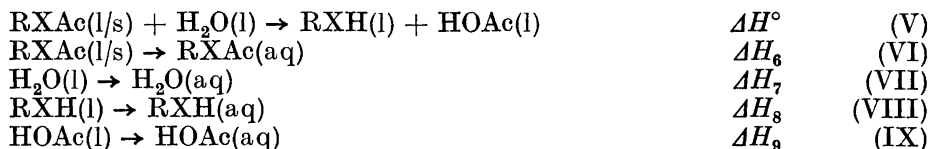
In Table 4 is given a summary of the data in connection with the heats of hydrolysis measurements. The uncertainties assigned for the $\varDelta H°$-values include possible systematic errors in the analysis and in the ε-values. All enthalpy values are expressed in kcal/mole.

Heats of hydrolysis in aqueous solution. Enthalpy changes for the hydrolysis reactions in aqueous solution (eqn. X) are derived according to the reaction scheme below.

$R = AcNHCH_2CH_2-,\ C_2H_5-$
$X = O,\ S$

(aq) symbolizes the aqueous medium, ionic strength = 0.2, solute concentration *ca.* 0.01 M.

$$RXAc(l/s) + H_2O(l) \rightarrow RXH(l) + HOAc(l) \qquad \Delta H° \qquad (V)$$
$$RXAc(l/s) \rightarrow RXAc(aq) \qquad \Delta H_6 \qquad (VI)$$
$$H_2O(l) \rightarrow H_2O(aq) \qquad \Delta H_7 \qquad (VII)$$
$$RXH(l) \rightarrow RXH(aq) \qquad \Delta H_8 \qquad (VIII)$$
$$HOAc(l) \rightarrow HOAc(aq) \qquad \Delta H_9 \qquad (IX)$$

$$RXAc(aq) + H_2O(aq) \rightarrow RXH(aq) + HOAc(aq) \qquad \Delta H_{aq} \qquad (X)$$
$$\Delta H_{aq} = \Delta H° - \Delta H_6 - \Delta H_7 + \Delta H_8 + \Delta H_9$$

In Table 5 are summarized data for reactions V—X. ΔH_7 is taken equal to zero [17]. All enthalpy values are expressed in kcal/mole.

Table 5.

RXAc	$\Delta H°$	ΔH_6	ΔH_8	ΔH_9	ΔH_{aq}
AcNHCH₂CH₂OAc	0.53	−2.98	−2.71	−0.33 [d]	0.47 ± 0.07
AcNHCH₂CH₂SAc	1.75	0.92	−1.41	−0.33 [d]	−0.91 ± 0.08
EtOAc	0.89 [e]	−2.27	−2.40	−0.33 [d]	0.43 ± 0.06

[d] Ref.[14]
[e] Ref.[2]

From the heat of solution of AcNHCH₂CH₂SH in 0.2 M NaCl (−1.41 kcal/mole) and in 0.8 M NaOH (−8.46 kcal/mole) and from the heat of ionization of water (*ca.* + 13.5 kcal/mole) the heat of ionization of the SH-group is calculated to approximately + 6.5 kcal/mole. pK_a' for AcNHCH₂CH₂SH has been reported [19] to be 9.2, which means that ionization of the thiol group will contribute + 0.04 kcal/mole to the heat of hydrolysis of the thiol ester at pH 7. At this pH acetic acid is dissociated almost completely. Using the value + 0.18 ± 0.05 kcal/mole for the heat of ionization of acetic acid, the heats of hydrolysis, at pH 7 and at an ionic strength of 0.2, will be + 0.65 ± 0.09, −0.69 ± 0.09 and + 0.61 ± 0.08 kcal/mole for β-acetylaminoethyl acetate, β-acetylaminoethyl thiolacetate and ethyl acetate, respectively.

DISCUSSION

When an ester is hydrolyzed in aqueous solution, the resulting enthalpy change is a gross effect, which tentatively can be divided into two parts: (*a*) The enthalpy change for the hypothetical hydrolysis reaction where no intermolecular interactions occur, *e.g.* in the ideal gaseous state. (*b*) Enthalpy

changes due to interactions with the solvent. These two enthalpy terms are again gross effects, and further, they cannot be expected to be completely independent of each other. However, in an attempt to analyze the obtained ΔH_{aq}-data the separation is useful.

Heats of vaporization data are not available to allow an accurate calculation of the heats of hydrolysis in the gaseous phase for β-acetylaminoethyl acetate and for the S-analogue. However, for studying enthalpy changes according to (a) the gas phase hydrolysis of ethyl acetate and ethyl thiolacetate should serve.

Heats of vaporization, ΔH_v, have been determined calorimetrically at 25°C for ethyl acetate and ethyl thiolacetate and found to be 8.40 ± 0.03 and 9.56 ± 0.05 kcal/mole [20], respectively. For water [17], ethanol [17]* and ethanethiol [21], ΔH_v were taken as 10.52 ± 0.00, 10.17 ± 0.04 and 6.58 ± 0.01 kcal/mole, respectively. Heat of vaporization of acetic acid to the monomer form has been derived to be 12.49 ± 0.07 kcal/mole [14].

From ΔH-data determined [1,2,3] earlier and from the given ΔH_v-data, heats of hydrolysis in the gaseous phase, $\Delta H°_{gas}$, are calculated to be + 4.63 ± 0.11 and − 1.82 ± 0.10 kcal/mole for ethyl acetate and ethyl thiolacetate, respectively.

Heats of reaction data for the gaseous state include enthalpy terms due to the formation and breaking of chemical bonds, changes in resonance energies and steric effects. In the hydrolysis of an O-acetate the same type of bonds broken are also formed. Thus, if there is no change in resonance energies, and if steric factors do not contribute to the energy change of the system, the heat of reaction should be zero. The experimentally derived value is + 4.6 kcal/mole, and, therefore, ethyl acetate seems to be more resonance stabilized ** than acetic acid by this amount. In the hydrolysis of a thiol ester, C−S and O−H bonds are broken while S−H and C−O bonds are formed. Using the thermochemical bond energies given in Table 6, $\Delta H°_{gas}$ for the hydrolysis reaction would be expected to be + 7 kcal/mole, neglecting changes in resonance energy.

Table 6. Thermochemical bond energies, E [22]

Bond	E, kcal
C−S	65
O−H	110.6
S−H	83
C−O	85.5

The $\Delta H°_{gas}$-value actually obtained is *ca.* −2 kcal/mole and a simple thiol acetate, therefore, is 9 kcal less stabilized by resonance than acetic acid or 13−14 kcal/mole less than the corresponding O-ester.

When a simple O-acetate is hydrolyzed in aqueous medium to form unionized acetic acid, the reaction was found to be accompanied by an enthalpy uptake of *ca.* 0.5 kcal/mole, or 4 kcal/mole less than in the gas phase reaction.

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* Gas imperfection estimated to 0.05 kcal/mole.
** Here, resonance energy of a compound refers to the difference between the heat of formation value calculated from thermochemical bond energies and that arrived at experimentally.

Apparently, stabilization due to solvation is more pronounced for the reaction products than for the reactants. In case of the thiol ester system the enthalpy change in going from the gaseous state to dilute aqueous solution is $+ 1$ kcal/mole which means that solvation enthalpies are stabilizing the starting system slightly more than the reaction products.

Energetics of acyl shift $O \rightarrow S$. Recently, Jencks and co-workers [23] measured the equilibrium, at 39°C, for the isomerization reaction

$$HSCH_2CH_2CH_2OAc(aq) \rightleftharpoons AcSCH_2CH_2CH_2OH(aq)$$
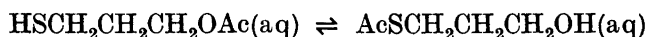
and obtained the standard free energy change, $\Delta G° = -RT \ln \dfrac{[AcSR]}{[AcOR']}$ to be $+ 2.50$ kcal/mole. As judged from the present calorimetric results the enthalpy change at an acyl shift $O \rightarrow S$ in aqueous medium will be $+ 1.3$ kcal/mole. Using these values, $\Delta G°$ is calculated to be $+ 2.3$ kcal/mole at 25°C. From these data, the entropy term, $T\Delta S$, for a simple transacetylation $O \rightarrow S$ in aqueous solution is derived to be -1.0 kcal/mole at 25°C. The $\Delta H°_{gas}$-value for the transacetylation reaction above is estimated to be about $+ 6.5$ kcal/mole and, thus, in the ΔH_{aq}-value of $+ 1.3$ kcal/mole about -5 kcal/mole is due to differences in the heats of solvation of the S-ester (with its OH-group) and the O-ester.

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