ACTA CHEMICA SCANDINAVICA 12 (1958) 635—640

# The Heats of Aminolysis of *n*-Butyl Thiolacetate and Acetic Anhydride

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The heat of aminolysis of *n*-butyl thiolacetate by *n*-butylamine was determined at 25°C. For the idealized, isothermal aminolysis reaction

*n*-BuSAc (l) + *n*-$BuNH_2$ (l) → *n*-BuSH (l) + *n*-BuNHAc (l)

the enthalpy change was found to be $-13.7 \pm 0.2$ kcal/mole. The heat of aminolysis of acetic anhydride was also determined and from the obtained value and known values of the heats of hydrolysis of acetic anhydride and *n*-butyl thiolacetate a value of $-13.80 \pm 0.15$ kcal/mole was derived for the heat of aminolysis of *n*-butyl thiolacetate.

The heat of hydrolysis of *n*-butyl acetamide was calculated to be $12.69 \pm 0.10$ kcal/mole.

Recently much interest has been directed towards S-acyl compounds as acetylating agents in biochemical systems. It is known that a thiolester of an aminoacid easily forms a peptide by aminolysis [1]. In connection with previous work [2] on energy relationships of S-acylated compounds it seemed of interest to determine the enthalpy change of the reaction

$$RCOSR' + R''NH_2 \longrightarrow R'SH + RCONHR''$$

The reaction can be looked upon as an model for peptide formation, where RCOSR' corresponds to a S-acyl activated amino acid and $R''NH_2$ to an amino acid.

In the simplified system investigated here, R was methyl and R', R'' were *n*-butyl. Thus the thiol ester was *n*-BuSAc and the amine was *n*-$BuNH_2$. However, the value obtained might be significantly in error. It was therefore checked by an indirect determination, by measuring the heat of aminolysis of acetic anhydride and combining this with known values for the heats of hydrolysis of $Ac_2O$ and *n*-BuSAc, from which the heat of aminolysis of *n*-BuSAc could then be calculated.

## PART I. AMINOLYSIS OF *n*-BUTYL THIOLACETATE

### Experimental

*Materials.* *n*-BuSAc was prepared and purified according to Ref.[2] The equivalent weight was determined by iodometric titration of the thiol formed by alkaline hydrolysis [2].

The equivalent weight indicated 100.0 % purity. $n^{25}_D = 1.4584$ $d_4^{25} = 0.9385$. $n$-$BuNH_2$ (purum grade) was dried by refluxing with NaOH-pellets. The amine was distilled through an efficient column and a fraction boiling at 76.2°C (760 mm Hg) was collected. Potentiometric titration gave an equivalent weight corresponding to 99.6 % purity.

*Auxiliary substances.* $n$-BuSH was freshly distilled and its purity as checked by iodometric titration was found to be 100.0 %. $n$-BuNHAc was prepared from $n$-BuSAc and $n$-$BuNH_2$. The synthesis and physical data of the substance are described below.

*Chemistry of the process.* In order to secure a rapid reaction and to avoid side reactions the aminolysis was carried out in butyl amine. However, the thiol formed was extremely rapidly oxidised by air in the alkaline medium. The rate of oxidation was studied by exposing to air solutions of $n$-BuSH in $n$-$BuNH_2$. After a given time the solution (5 ml of a 3 % solution in a 100 ml conical flask) was cooled with dry ice, acidified with glacial acetic acid and titrated with iodine. The experiments showed that *ca.* 10 % of the thiol was oxidised within 30 min.

In order to check that the reaction products of the aminolysis reaction were as expected, the following synthesis was carried out. 20.0 g of $n$-BuSAc were added rapidly to 150 ml of $n$-$BuNH_2$. After 30 min at room temperature the excess of amine and the thiol formed were driven off by distillation at atmospheric pressure. The presence of thiol in the distillate was confirmed by the nitroprusside reaction. The remaining product was distilled at reduced pressure. $n$-BuNHAc was collected at 140–141°C and 21 mm Hg. Yield 16.6 g or 95 %. After further distillation the physical data of the substance were in good agreement with those given in the literature [3]. B. p. 230°C at 760 mm Hg, $n_D^{25} = 1.4391$, $d_4^{25} = 0.8951$.

*Apparatus.* The reactions were carried out in an isothermal calorimeter which will be described in a forthcoming paper [4].

*Calibration.* The heat capacity of the system was determined electrically by passing a known current for a known time (20 min) through the heating element. Thermal leakage was calculated by the Regnault-Pfaundler's method. The calibration experiments was carried out after the aminolysis experiments. In the runs, corrections were made for the small differences in heat capacity of the ampoule and its content.

*Procedure.* As stated above, it was not possible to avoid air oxidation of the thiol formed during an experiment. In order to suppress the influence of this exothermic reaction a small amount of butanethiol was added to the solution prior to the reaction. The heat of oxidation increased much less than expected from the increase in thiol concentration due to aminolysis. However, a significant error was introduced, which could be seen from the values of the thermal leakage constant, $K$. If thiol was added prior to the reaction the value of $K$ was only 10 % lower than in calibration experiments whereas the value of $K$ was found to be negative when butanethiol was not added.

The calorimeter was charged with 90 ml of $n$-$BuNH_2$ to which 9 mmoles of $n$-BuSH were added. The sealed glass ampoule contained *ca.* 3 mmoles of $n$-BuSAc. After equilibration the reaction was started by breaking the ampoule. The duration of the reaction period was 45 min, so that the thermal leakage had to be calculated by the Regnault-Pfaundler method. As the $K$-values obtained from the runs were abnormally low, the mean of those from the calibration experiments was used in the calculations. The small systematic error introduced by the oxidation of the thiol formed during the aminolysis cancels out to a great extent by the error in the heat of solution experiment of butanethiol — the only difference between the two series of experiments being the slow appearance of thiol in the aminolysis and the momentary mixing of thiol and solvent in the solution experiment.

*Heat of solution measurements.* $n$-BuSH: In order to obtain a close similarity between the solution measurements and the aminolysis experiments, the reactino period was kept at 45 min. $n$-BuNHAc: The reaction period was 5 min and $R_i$ and $R_f$ were obtained graphically.

*Corrections to standard state.* The idealised aminolysis reaction IV is obtained from reactions I to III, which correspond to the actual experiments.

| | | |
|---|---|---|
| I | $n$-$BuNH_2$ (l) + $n$-BuSAc (l) → $n$-BuSH (soln) + $n$-BuNHAc (soln) | $\Delta H_1$ |
| II | $n$-BuSH (l) → $n$-BuSH (soln) | $\Delta H_2$ |
| III | $n$-BuNHAc (l) → $n$-BuNHAc (soln) | $\Delta H_3$ |
| IV | $n$-$BuNH_2$ (l) + $n$-BuSAc (l) → $n$-BuSH (l) + $n$-BuNHAc (l) | $\Delta H°_4$ |

$$\Delta H°_4 = \Delta H_1 - \Delta H_2 - \Delta H_3 \quad (1)$$

*Units of measurement.* 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. The molecular weights were computed from the 1951 Table of international atomic weights [5].

## Results

The experimental results are summarised in Tables 1 to 3. In Table 1 the results from the calibration experiments are given. The first column shows the input of electrical energy, the second the expression proportional to the temperature increase and the third the value of the heat capacity in calories per unit of log $(R_i/R_f)$. Uncertainties are given as the standard deviation of the mean.

*Table 1.* Calibration experiments.

| $q$, cal | $10^4 \times \log (R_i/R_f)$ | | $10^{-2} \times \varepsilon$ |
|---|---|---|---|
| 36.34 | 103.69 | | 35.05 |
| 36.43 | 104.09 | | 35.00 |
| 36.66 | 104.35 | | 35.13 |
| 36.56 | 104.39 | | 35.02 |
| | | Mean | 35.05 ± 0.03 |

Tables 2 and 3 give the results of the aminolysis experiments. The first column gives the amount of substance, the third the amount of heat evolved, and the last gives the enthalpy change in kcal/mole.

*Table 2.* Determination of the heat of aminolysis of *n*-butyl thiolacetate by *n*-butylamine.

| mmole | $10^4 \times \log (R_i/R_f)$ | $q$, cal | | $-\Delta H$, kcal/mole |
|---|---|---|---|---|
| 3.034 | 131.20 | 45.99 | | 15.16 |
| 2.823 | 121.01 | 42.41 | | 15.02 |
| 2.864 | 122.72 | 43.01 | | 15.02 |
| 3.080 | 133.27 | 46.71 | | 15.17 |
| 2.919 | 126.61 | 44.38 | | 15.20 |
| | | | Mean | 15.11 ± 0.04 |

*Table 3.* Heat of solution measurements.

| Substance | mmole | $10^4 \times \log (R_i/R_f)$ | $q$, cal | | $-\Delta H$, kcal/mole |
|---|---|---|---|---|---|
| *n*-BuSH | 2.915 | 1.02 | 0.36 | | 0.12 |
| | 2.778 | −1.77 | −0.62 | | −0.22 |
| | 3.112 | 0.11 | 0.04 | | 0.01 |
| | 3.429 | −0.56 | −0.20 | | −0.06 |
| | | | | Mean | −0.04 ± 0.07 |
| *n*-BuNHAc | 3.077 | 12.12 | 4.25 | | 1.38 |
| | 3.105 | 13.05 | 4.57 | | 1.47 |
| | | | | Mean | 1.42 ± 0.04 |

From eqn. (1) $\Delta H_4^0$ is calculated to be 13.73 ± 0.09 kcal/mole. However, uncertainty in the $K$-value used is estimated to be 2 %. This will cause an uncertainty in $\Delta H_1$ amounting to 0.1 kcal/mole. Therefore, the best value that can be obtained from these experiments is believed to be

$$\Delta H_4^0 = -13.7 \pm 0.2 \text{ kcal/mole.}$$

## PART II. AMINOLYSIS OF ACETIC ANHYDRIDE

*Materials.* $Ac_2O$ was freshly distilled immediately before the experiments. Its equivalent weight (determined by potentiometric titration of the acetic acid formed by hydrolysis) indicated 99.9 % purity. $n$-$BuNH_2$ was treated as given in part I.

*Auxiliary substances.* HOAc was purified by freezing out 4 times. The equivalent weight corresponded to 100.0 % purity. $n$-BuNHAc was prepared from $Ac_2O$ and $n$-$BuNH_2$. Details of the method of synthesis and physical data of the substance are given below. Benzene, free from thiophene was dried with KOH-pellets and distilled.

*Chemistry of the process.* $Ac_2O$ reacts vigorously with pure $n$-$BuNH_2$. In the calorimetric experiments the reaction rate was moderated by performing the aminolysis in benzene solution. The reaction products were soluble in this medium at the concentrations used. To confirm that $n$-BuNHAc was obtained in the reaction, the following experiment was carried out.

0.3 mole of $Ac_2O$ was added rapidly to a solution of 1.2 moles of $n$-$BuNH_2$ in 150 ml benzene. The temperature of the mixture was kept below 30°C by cooling with ice water. After *ca.* 10 min the benzene and the excess of amine was distilled off. To the residue, 50 ml of water were added and the solution was extracted three times with ether. The product was dried with anhydrous $CaCl_2$ and the ether distilled off. The residue was distilled under reduced pressure through an efficient column. 28.6 g (83 %) $n$-BuNHAc was collected at 92.5°C (1 mm Hg). The physical data of the substance were in good agreement with those given in the literature [3]. B.p. 230°C at 760 mm Hg, $n_D^{25} = 1.4393$, $d_4^{25} = 0.8950$.

*Apparatus.* See Part I.

*Calibration experiments.* The calorimeter was calibrated as in Part I, except that the heat was supplied for 4 min only. The main period lasted for 7 min and $R_i$ and $R_f$ were obtained graphically.

*Correction to standard state.* The idealized aminolysis reaction IX is obtained from reactions V to VIII which correspond to the reactions taken place under actual experimental conditions.

| | | |
|---|---|---|
| V | $Ac_2O$ (l) + $n$-$BuNH_2$ (soln) → $n$-BuNHAc (soln) + HOAc (soln) | $\Delta H_5$ |
| VI | HOAc (l) → HOAc (soln) | $\Delta H_6$ |
| VII | $n$-BuNHAc (l) → $n$-BuNHAc (soln) | $\Delta H_7$ |
| VIII | $n$-$BuNH_2$ (l) → $n$-$BuNH_2$ (soln) | $\Delta H_8$ |
| IX | $Ac_2O$ (l) + $n$-$BuNH_2$ (l) → $n$-BuNHAc (l) + HOAc (l) | $\Delta H_9^0$ |

$$\Delta H_9^0 = \Delta H_5 - \Delta H_6 - \Delta H_7 + \Delta H_8 \quad (2)$$

The experimental results are summarized in Tables 4 to 6.

*Table 4.* Calibration experiments.

| $q$ cal | $10^4 \times \log (R_i/R_f)$ | $10^{-2} \times \varepsilon$ |
|---|---|---|
| 35.62 | 123.35 | 28.88 |
| 35.49 | 121.02 | 29.32 |
| 35.10 | 120.94 | 29.02 |
| 35.58 | 123.42 | 28.83 |
| 35.43 | 121.71 | 29.11 |
| 32.62 | 112.64 | 28.96 |
| | Mean | 29.02 ± 0.08 |

*Table 5.* Heat of aminolysis of acetic anhydride by *n*-butylamine.

| mmole | $10^4 \times \log (R_i/R_f)$ | $q$ cal | $-\Delta H$, kcal/mole |
|---|---|---|---|
| 1.073 | 144.13 | 41.83 | 38.98 |
| 0.983 | 132.57 | 38.47 | 39.14 |
| 1.102 | 148.43 | 43.07 | 39.08 |
| 1.038 | 140.18 | 40.68 | 39.19 |
| 1.207 | 163.38 | 47.41 | 39.28 |
| | | Mean | 39.13 ± 0.06 |

*Table 6.* Heat of solution measurements.

| Substance | mmole | $10^4 \times \log (R_f/R_i)$ | $q$, cal | $-\Delta H$, kcal/mole |
|---|---|---|---|---|
| HOAc | 1.389 | 64.77 | 18.79 | 13.53 |
| | 1.376 | 64.11 | 18.60 | 13.52 |
| | 1.041 | 48.25 | 14.00 | 13.45 |
| | | | Mean | 13.50 ± 0.02 |
| *n*-BuNHAc | 1.202 | −6.40 | −1.86 | −1.55 |
| | 1.115 | −5.82 | −1.69 | −1.52 |
| | 1.027 | −5.62 | −1.63 | −1.59 |
| | | | Mean | −1.55 ± 0.04 |
| *n*-$BuNH_2$ | 0.827 | −1.46 | −0.42 | −0.51 |
| | 0.710 | −1.21 | −0.35 | −0.49 |
| | 1.073 | −2.13 | −0.62 | −0.58 |
| | | | Mean | −0.53 ±0.03 |

From eqn. (2) is obtained $\Delta H_9^0 = -26.65 \pm 0.08$ kcal/mole.

## Calculation of the heat of aminolysis of *n*-BuSAc

The heat of aminolysis of *n*-BuSAc (reaction IV) can be obtained from $\Delta H_9^0$ and the known heats of hydrolysis of *n*-BuSAc[2] and $Ac_2O$[6], $\Delta H°$ equals −1.09 ± 0.06 kcal/mole and −13.92 ± 0.05 * kcal/mole, respectively.

IX $Ac_2O$ (l) + *n*-$BuNH_2$ (l) → *n*-BuNHAc (l) + HOAc (l) $\Delta H_9^0$

X *n*-BuSAc (l) + $H_2O$ (l) → *n*-BuSH (l) + HOAc (l) $\Delta H_{10}^0$

XI $Ac_2O$ (l) + $H_2O$ (l) → 2 HOAc (l) $\Delta H_{11}^0$

IV *n*-BuSAc (l) + *n*-$BuNH_2$ (l) → *n*-BuNHAc (l) + *n*-BuSH (l) $\Delta H_4^0$

$$\Delta H_4^0 = \Delta H_9^0 + \Delta H_{10}^0 - \Delta H_{11}^0 \quad (3)$$

Thus we find $\Delta H_4^0$ to be −13.82 ± 0.11 kcal/mole. This value is in good agreement with the value given in Part I. Taken into consideration the more favourable experimental conditions of the indirect determination $\Delta H_4^0 =$ −13.80 ± 0.15 kcal/mole seems at present to be the best value that can be given.

### Calculation of the heat of hydrolysis of *n*-BuNHAc

It is well known that N-alkyl acetamides do not easily hydrolyze at room temperature. It is therefore difficult to obtain a good value for the heat of hydrolysis from direct measurements. However, by subtracting reaction IX from reaction XI we get the idealized hydrolysis reaction XII

XII $\quad n\text{-BuNHAc(l)} + H_2O(l) \rightarrow n\text{-BuNH}_2(l) + HOAc(l) \qquad \Delta H_{12}^0$

$$\Delta H_{12}^0 = \Delta H_{11}^0 - \Delta H_9^0 \qquad (4)$$

Thus the heat of hydrolysis of *n*-BuNHAc is calculated to be $12.73 \pm 0.10$ kcal/mole.

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* The value has been recalculated to 25°C. The uncertainty is an estimate.

Received January 24, 1958.