Thermochemical Properties of Diacetimide, N-Butyldiacetimid and N-Phenyldiacetimide

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Heats of hydrolysis have been determined calorimetrically at 25°C for three diacetimides, $RNAc_2$. For the idealized isothermal (25°C) reaction $RNAc_2(s/l) + H_2O \rightarrow RNHAc(s/l) + HOAc(l)$ the enthalpy change has been determined to be -4.33 ± 0.05, -9.68 ± 0.06, and -10.88 ± 0.08 kcal/mole for R = H, Bu, and Ph, respectively. Corresponding enthalpy values for the gaseous state reaction were derived as -1.1 ± 0.4, -4.9 ± 0.3, and -5.4 ± 1.0 kcal/mole, respectively. Heats of hydrolysis in dilute aqueous solution were determined to be -4.28 ± 0.06 and -12.04 ± 0.07 kcal/mole for R = H and R = Bu, respectively. (No ionization of reaction products.) Heats of hydrolysis values have been discussed and compared with corresponding enthalpy values for the hydrolysis of the parent amide compounds.

Diacylimides, $\begin{array}{c} R_1CO \\ \\ R_2CO \end{array}\Big\rangle N-R$, form a reactive group of carbonyl compounds which recently has attracted an increased interest. Diacylimides have been reported as intermediates in various types of acyl transfer reactions facilitated by a neighbouring amide group,[1] and it has in this connection been suggested that the reaction type might have a role in enzymatic reactions. Wieland and coworkers [2] demonstrated that intramolecular acyl transfer from a thiol ester to an amino group can proceed *via* acylation of a neighbouring peptide group. Behme and Cordes [3] observed spectrophotometrically formation of a diacylimide as an intermediate in the hydrolysis of O-acetyl-salicyl-amide. Other examples are provided by Shafer and Morawetz [4] and by Bernhard *et al.*[5] who identified cyclic imides as intermediates in enhanced ester hydrolysis and amide reactions.

No thermodynamic properties for diacylimides seem to have been reported and it was therefore felt of interest to undertake some basic thermochemical measurements on this group of compounds. In this paper are reported results

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from a calorimetric investigation on diacetimide, N-butyldiacetimide and N-phenyldiacetimide. Enthalpy values have been derived for the hydrolysis reactions (R = H, Bu, or Ph)

$$RNAc_2 + H_2O \rightarrow RNHAc + HOAc$$
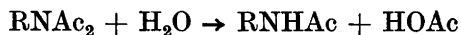
involving the pure compounds in their condensed states, and in their gaseous states as well as for dilute aqueous solution. The thermochemical properties of the imides have been compared with corresponding data for the parent monoacetyl compounds.

EXPERIMENTAL

Materials. Acetamide (Eastman Kodak) was recrystallized three times from chloroform. Crystals were crushed and dried in vacuum; m.p. 84.9°C.

Diacetimide, Ac_2NH, was prepared from acetamide by acetylation with acetic anhydride in the presence of bisacetamide hydrochloride.[6] The compound was recrystallized twice from ether followed by repeated sublimation in vacuum; m.p. 81.0°C. The equivalent weight, as determined by alkaline hydrolysis and back titration with standard hydrochloric acid, was equal to the theoretical.

N-Butylacetamide and acetanilide were from Ref. 7,

N-Butyldiacetimide was prepared from N-butylacetamide and acetic anhydride.[8] The compound was fractionally distilled until the equivalent weight was equal to the theoretical; $n_D^{25} = 1.4495$; $d_4^{25} = 0.9818$.

N-Phenyldiacetimide was prepared by acetylation of acetanilide with acetic anhydride (*cf.* Ref. 9). The reaction product was fractionally distilled through a simple column. The main fraction was purified by repeated fractionated crystallization. Equivalent weight was equal to the theoretical; m.p. 38.0°C.

Calorimetric measurements. Heats of hydrolysis and heats of solution measurements were performed with an "isothermal-jacket" glass calorimeter, described in detail elsewhere.[10,11] 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 were performed after the reaction had taken place. No significant correlation between amount and kind of reactant and the measured heat equivalent values was found and therefore derived mean values have been used in calculating the results.

Heats of vaporization measurements were carried out in a microcalorimeter recently described by Morawetz and Sunner.[12]

The acetyl compounds were hydrolysed in 0.8 N sodium hydroxide, water-ethanol solution (160 g NaOH, 2 l water, 3 l 96 % ethanol) to form acetate and the parent monoacetyl compound. Reaction periods were 2 to 6 min, and corrections for heat exchange were calculated by means of the Regnault-Pfaundler method. Normal K-values (K = the constant in Newton's cooling law) were obtained, which indicates that reactions slower than the main reaction were absent.

The hydrolysis experiments were supplemented by heats of solution measurements in the hydrolysis medium in order to arrive at enthalpy data for the "thermochemical state", $\Delta H°$, and in 0.2 M sodium chloride solution, to give data for the process in water solution. 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 earlier heats of solution measurements [13] 0.2 M NaCl was used as calorimetric liquid.

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.

Table 1. Results from heats of hydrolysis and heats of solution measurements performed in 0.8 M NaOH, water-ethanol solution. $\varepsilon = 7537 \pm 3$.

Reaction	Ampoule content		$10^4 \times \log R_i/R_f$	$-\Delta H$ kcal/mole
	Substance	mmoles		
Eqn. I	HNAc$_2$(s)	2.727	45.21	12.49
		3.004	49.63	12.48
		2.763	46.03	12.55
		2.635	43.64	12.48
			Mean	12.50 $\pm$ 0.03
Eqn. I	BuNAc$_2$(l)	2.709	75.30	20.95
		2.701	75.12	20.96
		2.743	75.87	20.85
		1.781	49.61	20.99
			Mean	20.94 $\pm$ 0.04
Eqn. I	PhNAc$_2$(s)	3.539	80.67	17.18
		2.914	66.19	17.12
		3.365	76.54	17.15
		2.995	67.71	17.04
			Mean	17.12 $\pm$ 0.04
Eqn. II	H$_2$NAc(s)	3.189	-13.66	-3.23
		3.593	-15.54	-3.26
		3.435	-14.93	-3.28
		2.005	-8.58	-3.23
		2.530	-10.89	-3.25
			Mean	-3.25 ± 0.01
Eqn. II	BuNHAc(l)	2.996	-0.52	-0.13
		2.850	-0.67	-0.18
		2.953	-0.62	-0.16
		2.780	-0.58	-0.16
			Mean	-0.16 ± 0.01
Eqn. II	PhNHAc(s)	1.793	-12.48	-5.24
		1.735	-11.69	-5.08
		1.577	-10.97	-5.24
		1.670	-11.31	-5.10
		1.692	-11.88	-5.29
		1.413	-9.69	-5.17
		1.424	-9.68	-5.13
			Mean	-5.18 ± 0.03

RESULTS

The experimental results of hydrolysis and solution experiments are summarized in Tables 1 and 2. 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

Table 2. Results from heats of solution measurements performed in 0.2 M aqueous NaCl solution. $\varepsilon = 8846 \pm 8$.

Substance	mmoles	$10^4 \times \log R_i/R_f$	$-\Delta H$ kcal/mole
H_2NAc	3.268	-8.50	-2.30
	3.619	-9.40	-2.30
	1.825	-4.72	-2.29
	1.275	-3.36	-2.33
		Mean	-2.31 ± 0.02
$HNAc_2$	1.708	-3.73	-1.94
	1.108	-2.39	-1.91
	1.120	-2.43	-1.93
	1.260	-2.74	-1.93
		Mean	-1.93 ± 0.01
$BuNAc_2$	1.399	2.18	1.38
	1.517	2.50	1.46
	1.435	2.46	1.52
	1.195	1.92	1.42
	1.276	2.13	1.48
		Mean	1.45 ± 0.03

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 deviation of the mean. Otherwise, they are the average deviation of the mean.

Corrections to standard state. The idealized isothermal hydrolysis reaction V is obtained from eqns. I—IV.
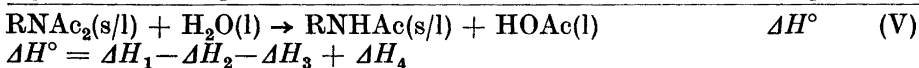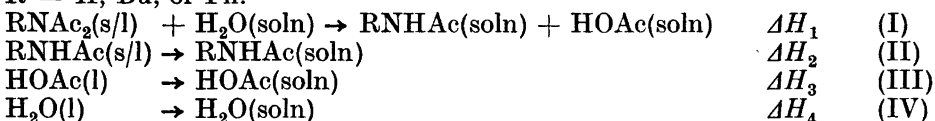
R = H, Bu, or Ph.

$RNAc_2(s/l) + H_2O(soln) \rightarrow RNHAc(soln) + HOAc(soln)$	ΔH_1	(I)
$RNHAc(s/l) \rightarrow RNHAc(soln)$	ΔH_2	(II)
$HOAc(l) \rightarrow HOAc(soln)$	ΔH_3	(III)
$H_2O(l) \rightarrow H_2O(soln)$	ΔH_4	(IV)
$RNAc_2(s/l) + H_2O(l) \rightarrow RNHAc(s/l) + HOAc(l)$	ΔH°	(V)

$\Delta H^\circ = \Delta H_1 - \Delta H_2 - \Delta H_3 + \Delta H_4$

Table 3. Summary of enthalpy values (kcal/mole) for reactions I—V.

R	ΔH_1	ΔH_2	$\Delta H_3{}^a$	$\Delta H_4{}^a$	ΔH°
H	-12.50	3.25	-11.62	-0.20	-4.33 ± 0.05
Bu	-20.94	0.16	-11.62	-0.20	-9.68 ± 0.06
Ph	-17.12	5.18	-11.62	-0.20	-10.88 ± 0.07

[a] Ref. 13.

Table 4. Summary of results from vaporization measurements performed * at 25°C.

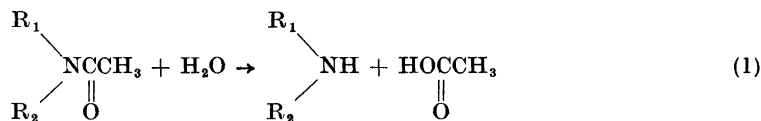| Substance	ΔH_v kcal/mole
Acetamide(s)	19.2 ± 0.3
Diacetimide(s)	17.5 ± 0.2
Butylacetamide(l)	18.2 ± 0.3
Butyldiacetimide(l)	15.4 ± 0.1
Phenyldiacetimide(s)	21.5 ± 0.2

* These measurements were made by Mr. E. Morawetz. Given uncertainties include estimates of systematic errors.

In Table 3 are summarized enthalpy values for reactions I—V, and Table 4 contains a summary of results from vaporization measurements. Uncertainties given in Tables 3 and 4 include estimates of possible systematic errors.

DISCUSSION

In Table 5 have been summarized heats of hydrolysis data for the N-acetyl compounds investigated here and, for the purpose of comparison, also for acetamide, butylacetamide and acetanilide. Data given refer to the "thermochemical standard state" ($\Delta H°$), to the ideal gaseous state ($\Delta H°_{gas}$), to the state of dilute (*ca.* 0.01 M) aqueous solution with all reaction components in nonionic state (ΔH_{aq}).

Heats of hydrolysis in the gaseous state. All reactions listed in Table 5 can be characterized by reaction (1).

$$\begin{array}{c} R_1 \\ \diagdown \\ \diagup \quad \text{NCCH}_3 + \text{H}_2\text{O} \rightarrow \\ R_2 \quad \underset{\text{O}}{\overset{\|}{}} \end{array} \quad \begin{array}{c} R_1 \\ \diagdown \\ \diagup \quad \text{NH} + \text{HOCCH}_3 \\ R_2 \quad\quad \underset{\text{O}}{\overset{\|}{}} \end{array} \quad (1)$$

where R_1 and R_2 = H, Bu, Ph, or Ac.

In the reaction C—N and O—H bonds are broken while N—H and C—O bonds are formed. If no changes other than breaking and formation of chemical bonds were influencing the energy of the reaction system one would expect $\Delta H°_{gas}$ to be about $+ 2$ kcal/mole [11] for all the compounds listed in Table 5. $\Delta H°_{gas}$ for the unsubstituted acetamide is close to this figure, $+ 1$ kcal/mole, from which can be concluded that the resonance energy of acetamide is nearly identical with that of acetic acid.*

The difference in gaseous heats of hydrolysis for the three monoacetyl compounds, HNHAc, BuNHAc, and PhNHAc, can be accounted for in terms of differences in resonance stabilization of the amide group, —NH—C—.

$$\underset{\text{O}}{\overset{\|}{}}$$

The main resonance forms for an N-acetyl compound can be written as

* This is in fair agreement with data in Wheland's compilation [23] (p. 99).

Table 5. Heats of hydrolysis of some N-acetyl compounds. Data are given in kcal/mole and refer to the iso-thermal reaction at 25° C for the standard state, $\Delta H°$, the gaseous standard state, $\Delta H°_{gas}$, for dilute aqueous solution (*ca.* 0.01 M. No ionozation), ΔH_{aq}. Given uncertainties include estimates of systematic errors.

Standard state reaction	$\Delta H°$	$\Delta H°_{gas}$ [a]	ΔH_{aq}
$HNAc_2(s) + H_2O(l) \rightarrow H_2NAc(s) + HOAc(l)$	-4.33 ± 0.05 [b,c]	-1.1 ± 0.4 [c]	-4.28 ± 0.06 [c]
$H_2NAc(s) + H_2O(l) \rightarrow H_3N(g) + HOAc(l)$	$+18.2 \pm 0.3$ [d]	$+1.4 \pm 0.4$ [d]	$+7.3 \pm 0.2$ [d]
$BuNAc_2(l) + H_2O(l) \rightarrow BuNHAc(l) + HOAc(l)$	-9.68 ± 0.06 [c]	-4.9 ± 0.3 [c]	-12.04 ± 0.07 [c,e]
$BuNHAc(l) + H_2O(l) \rightarrow BuNH_2(l) + HOAc(l)$	$+13.20 \pm 0.05$ [f]	$+5.3 \pm 0.3$ [c,f,g]	$+10.82 \pm 0.06$ [h]
$PhNAc_2(s) + H_2O(l) \rightarrow PhNHAc(s) + HOAc(l)$	-10.88 ± 0.07 [c]	-5.4 ± 1.0 [c,i]	—
$PhNHAc(s) + H_2O(l) \rightarrow PhNH_2(l) + HOAc(l)$	$+10.05 \pm 0.06$ [f]	-0.3 ± 1.0 [f,i,j]	$+4.8 \pm 0.3$ [f,k]

[a] Heats of vaporization of water and acetic acid (to give monomeric vapor) were taken to be 10.52 [14] and 12.49 [11] kcal/mole, respectively.

[b] $HNAc_2(s)$ refer to crystal form A, *cf.* Ref. 15.

[c] This work.

[d] $\Delta H°$ for the hydrolysis of acetamide was calculated from $\Delta H_f°$-values for acetamide, water and ammonia [14] and for acetic acid.[16] Heat of vaporization of acetamide was taken to 18.8 $\pm$ 0.3 kcal/mole. This is the mean between the calorimetric value reported in this work, 19.2 kcal/mole (Table 4) and a recent value derived from vapor pressure measurements,[17] 18.5 kcal/mole.

[e] Heat of solution of butylacetamide in water has been determined [10] to -3.51 kcal/mole.

[i] Ref. 7.

[g] Heat of vaporization of butylamine has been determined calorimetrically at 25°C, $\Delta H_v = 8.36 \pm 0.02$ kcal/mole.[18]

[h] Ref. 11.

[i] ΔH_v for acetanilide, 25 $\pm$ 1 kcal/mole, is an estinate.[19] The value reported by Aihara [20] (19.26 $\pm$ 0.11 kcal/mole) is judged to be by far too low.

[j] Heat of vaporization of aniline has recently been determined calorimetrically to 13.33 kcal/mole.[21]

[k] Heat of solution of acetanilide in water is calculated from solubility data [22] to be $\Delta H = 5.3 \pm 0.3$ kcal/mole. Heat of solution of aniline in water (to give 0.02 M solution) has been determined calorimetrically to be 0.42 $\pm$ 0.02 kcal/mole.[18]

a   b   c
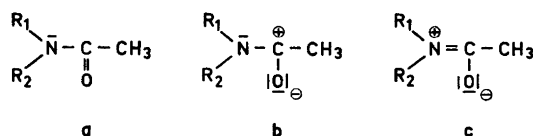
When the substituent group (R_1 or R_2) is electron attracting the ionic resonance forms will be opposed resulting in a decreased resonance stabilization of the amide group. Tafts [24] σ^*-values can be employed as a measure for the electron attracting power: $\sigma_{Ph}^* = +0.60$, $\sigma_H^* = +0.49$, $\sigma_{Bu}^* = -0.13$. The resonance stabilization of the amide group of BuNHAc is thus expected to be higher than that of HNHAc which again will not be as low as that of PhNHAc. For the latter compound there might also be another reason for a low resonance energy as compared with that of its hydrolysis products. In aniline, quinoide structures probably contribute to the resonance energy (Ref.23, p. 107) whereas in the amide, ionic quinoide structures like
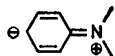
are opposing resonance forms b and c.

Table 6. Aqueous heats of solvation, kcal/mole.*

HNAc$_2$	-15.6	BuNAc$_2$	-16.9	PhNAc$_2$	$-$
H$_2$NAc	-16.9	BuNHAc	-21.7	PhNHAc	-20
H$_3$N	-8.28	BuNH$_2$	-13.92	PhNH$_2$	-12.91

* *Ca.* 0.01 M solution. For references see Table 5.

A decrease in the resonance stabilization of the amide will give rise to a negative increment in the ΔH°_{gas}-value. The above qualitative reasoning is thus in agreement with the experimental results being $\Delta H^{\circ}_{gas} = +5.3$ for BuNHAc, $+1.4$ for HNHAc, and -0.3 kcal/mole for PhNHAc.

ΔH°_{gas} for the first step of the hydrolysis of the diacetyl compounds is in all cases more negative than that for the following second step. This is believed to be partly caused by the release of a certain amount of "strain" energy when the acetyl group is substituted for by the small hydrogen atom. Further, ionic resonance forms b and, in particular, c will not be formed as readily when the nitrogen atom already is bound to an electron attracting acetyl group (R$_1$ or R$_2$). ΔH°_{gas} is therefore expected to contain a negative term due to an increased resonance energy in the reaction products.

ΔH°_{gas} for butyldiacetimide and phenyldiacetimide are more exothermal than that of diacetimide, which is believed to be caused mainly by steric factors. Inductive effects from H, Bu, or Ph will affect the ionic resonance forms both in di- and mono-acetyl compounds and are therefore expected to have only minor effects on the ΔH°_{gas} value for the diacetyl compounds.

Reaction heats in aqueous solution. Reactions listed in Table 5 all have in common that water is consumed and acetic acid is formed. ΔH_{solv}* for water is equal to its $-\Delta H_{vap}$ or -10.52 kcal/mole [14] while ΔH_{solv} for acetic acid is calculated to be -12.82 kcal/mole.[11] Substitution of acetic acid for water thus means a solvation-enthalpy contribution to the ΔH_{aq} values equal to -2.3 kcal/mole for all reactions listed in Table 5.
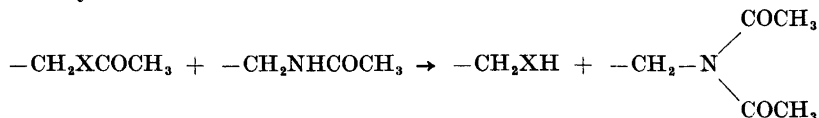
From the solvation enthalpies listed in Table 6 it may be seen that when one acetyl group in BuNAc$_2$ is substituted for by a hydrogen atom $-\Delta H_{solv}$ is increased by 4.8 kcal/mole. If the same comparison is made between diacetimide and acetamide, solvation stabilization is increased by 1.3 kcal/mole. However, when substituting acetyl groups of the monoacetyl compounds by hydrogen it is seen that the $-\Delta H_{solv}$ value is *decreased* by 7 to 8 kcal/mole.

The discussed differences in solvation enthalpies are of course reflected in the differences between the ΔH°_{gas} and ΔH_{aq} values for the hydrolysis reactions summarized in Table 5. Hydrolysis of a diacylimide to give the parent amide is more exothermal in aqueous solution than the same reaction in the gaseous state, whereas for the amide hydrolysis there are marked differences going in the other direction.

* ΔH_{solv} = heat of solvation. $\Delta H_{solv} = \Delta H_{solution} - \Delta H_{vaporization}$.

Biochemical considerations. Experimentally it has been demonstrated [1-5] that acyl transfer from esters, thiol esters and amides can be facilitated by neighbouring amide groups under the intermediate formation of diacylimides. The predominance of amide groups together with easily visualized steric requirements makes the suggestion of imide-intermediates in enzyme chemistry an attractive hypothesis.

Discussion of the energy requirements for imide formation in enzymatic reactions must be very limited as long as no information concerning entropy changes are available. As judged from the present enthalpy values, however, the energetics for imide formation seem to be rather unfavourable. ΔH_{aq} for the transacylation reaction

$$-CH_2XCOCH_3 + -CH_2NHCOCH_3 \rightarrow -CH_2XH + -CH_2-N \begin{array}{c} COCH_3 \\ \diagup \\ \diagdown \\ COCH_3 \end{array}$$

can be estimated (*cf.* Refs. 11, 25) to be $+ 13$ kcal/mole (X = O), $+ 11$ kcal/mole (X = S), and $+ 23$ kcal/mole (X = NH). When the acyl donor is an amide (X = NH), however, there will, in the physiological pH range, be a considerable decrease in the enthalpy value due to the highly exothermal protonation of the amino group formed. This will bring the enthalpy change close to that expected for esters and thiol esters.

The great differences in enthalpy values between gaseous and aqueous heats of hydrolysis for diacylimides indicate that medium factors have a pronounced influence on the energetics of these types of reactions. An extensive medium interaction (water, protein *etc.*) can give rise to a sizeable entropy effect which might effect very markedly the value for the free energy change ($\Delta G = \Delta H - T\Delta S$) and the equilibrium constant ($\Delta G° = - RT \ln K$).

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