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The calorimetric study of some guanidine derivatives involved in living bodies nitrogen metabolism

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Abstract The energies of combustion of creatine (anhydrous and monohydrate), creatinine, and arginine were measured in a static bomb adiabatic calorimeter, in pure oxygen at 3,040 kPa. The derived standard enthalpies of formation in solid state of the above-mentioned compounds are, respectively, −520.4 ± 4.3, −809.7 ± 1.3, −204.2 ± 7.0, and −634.8 ± 2.3 kJ mol^{-1}. The data of enthalpy of formation are compared with literature values and with estimated values by means of group additivity. The dehydration of creatine monohydrate and the processes occurring in the three guanidine derivatives at temperatures exceeding 200 °C were investigated by means of DSC.

Keywords Combustion · Formation · Dehydration · Enthalpy · Guanidine derivatives · DSC

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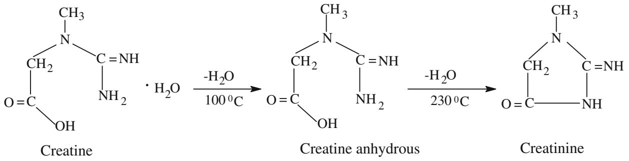
Introduction

This study deals with the thermochemistry of three important nitrogen-containing biochemical compounds: creatine, creatinine, and arginine. All three molecules contain the guanidine moiety.

Creatine is an amino acid produced in small amounts by some organs and stored in muscles. It is a nutritional supplement used to enhance an individual's ability to maintain power output during high intensity exercise. It forms a stable hydrate, for which there are no thermochemical data in literature and which is investigated too, in this work.

The monohydrate dehydrates at about 100 °C turning into the anhydrous form. Creatine eliminates a water molecule at a temperature around 230 °C and undergoes simultaneously an intramolecular cyclization, turning into creatinine.

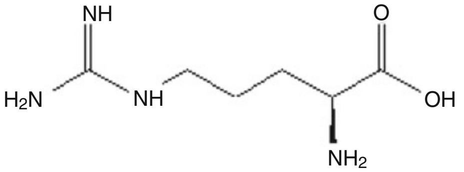


Creatinine is biochemically important because it is involved in the removal of creatine from the body.

For anhydrous creatine, only an old (1936) value of the enthalpy of formation was found [1]. Although we have found two close values for the enthalpy of formation of creatinine in literature [1, 2], we decided to make new measurements, because we considered them to be too negative.

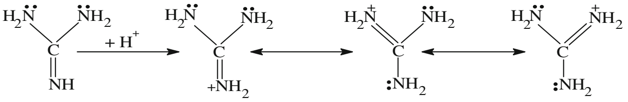
Arginine is involved in the urea cycle, by which ammonia is removed from the body.

The L-enantiomer of arginine is one of the 20 basic natural α-amino acids.



For arginine, two divergent values of the enthalpy of formation were found [3, 4].

Both arginine and creatine molecules are stabilized by means of the transfer of the carboxyl proton to the guanidine group, with formation of the corresponding zwitterions. In the guanidinium cation, the three carbon–nitrogen bonds become identical by resonance between equivalent structures:



The need for accurate thermal data measurements and for reliable prediction methods was renewed during the last years [5, 6].

Experimental

Materials

Anhydrous creatine [CAS 57-00-1], creatine monohydrate [CAS 6020-87-7], arginine [CAS 74-79-3], and creatinine [CAS 60-27-5] studied in this work were obtained commercially from Fluka, the first two, and from Merck, the later two, respectively. The compounds have the following assessed mass fraction purities: anhydrous creatine >99%, creatine monohydrate >99%, arginine >99%, and creatinine ≥99%. The four compounds were used without further purification.

Apparatus and experimental details

The combustion experiments were performed with a calorimeter of the Parr Instruments type, locally built. It is provided with an electronic system, which allows it to work in adiabatic conditions, with a difference of 0.002 °C, between the temperature of the calorimeter vessel and that of the shield. The temperature rise, following the combustion, was measured by means of a Beckmann thermometer. A difference between stable temperature values within 0.002 K was accepted.

In all measurements, the start temperature was lower than 25.0 °C by about one half of the expected temperature rise and the initial pressure was 3,040 kPa.

The calorimeter constant was measured by means of benzoic acid combustion (standard reference material 39I from NIST). The considered certified value of energy of combustion of benzoic acid is 26,454 ± 3.7 J g^{-1}. The calorimeter constant was calculated from the results of at least ten combustion runs, resulting in a value of 9,097 ± 3 J K^{-1}. The bomb was repaired and suffered some modifications. Some measurements, especially for arginine were done some time ago, with the old bomb, having a constant of 9,420 ± 4 J K^{-1}.

The final solution from the bomb was analyzed for the presence of nitric acid (about 20% from the total nitrogen). The heat due to nitric acid formation was obtained using the value of the enthalpy of formation of nitric acid ($\Delta_f H_{HNO_3}, aq = -58.8$ kJ mol^{-1}).

A Perkin Elmer 1B DSC was used for the measurement of the enthalpies of the processes occurring during heating (dehydration, fusion, and decomposition). The calorimeter was calibrated with indium ($\Delta_{fus}H = 28.46$ J g^{-1}). In all measurements, the calorimeter was operated at 4 mcal K^{-1} sensitivity and 4 K min^{-1} heating rate. The acquisition of experimental data was performed by means of a multimeter HP 34812A, serving as an interface with the computer, provided with the Benchlink data acquisition software. The acquired data were transferred to the Origin software for graphical processing. The area of the picks corresponding to the processes from the standard and studied substances allowed the calculation of the thermal effects in the later. The calibration constant of the calorimeter, for the above-mentioned operating conditions, determined by means of the indium standard amounts 1.622 J/unit area. The samples were weighed after the runs in order to obtain information about the nature of the evolved reaction products.

Results

Combustion energy

At least four runs were retained for each compound. Some runs were rejected because of doubt about combustion completeness. In runs used in data calculation, there was no evidence of soot formation in the bomb. The results of the combustion measurements for the four compounds are given in Tables 1, 2, 3, 4. The results of the combustion experiments are given according to actual standards for correct presentation of combustion experiments [7, 8].

ΔU(fuse) and ΔU(ign) were calculated from the mass of cotton and $\Delta_c h$(cotton) = 16,240 J g^{-1} [9] and from the mass of the fire and $\Delta_f h(Fe_2O_3) = 5.17$ kJ g^{-1} [10],

Table 1 Combustion data for creatine monohydrate

Experiment	1	2	3	4	5
m(cpd)/g	0.95350	0.98590	0.88720	0.90100	0.99862
m(fuse)/mg	12.32	14.41	16.81	12.50	12.13
ΔT_{ad}/K	1.883	1.880	1.668	1.660	1.851
$-\Delta U$(IBP)/J	17,130	17,101	15,173	15,098	16,839
$-\Delta U$(fuse)/J	200	234	273	203	197
$-\Delta U$(HNO_3)/J	54	51	51	43	61
$-\Delta U$(ign)/J	25	27	28	11	16
$-\Delta U$(ba)/J	1,907	1,354	916	735	923
$-\Delta_c u$/J g^{-1}	15,673	15,656	15,673	15656	15,664
$-\Delta_c u^0$/J g^{-1}	15,671	15,654	15,672	15,654	15,662
$\langle\Delta_c u^0\rangle = -15{,}663$ J g^{-1}					

m(cpd) mass of compound burned in each experiment, *m*(fuse) mass of the cotton thread fuse, ΔT_{ad} adiabatic temperature rise, ΔU(IBP) energy change for the isothermal combustion reaction under actual bomb conditions, ΔU(fuse) energy of combustion of the fuse, ΔU(HNO_3) energy correction for the nitric acid formation, ΔU(ign) energy used to ignite the sample by means of an iron fire, ΔU(ba) energy of combustion of a small pellet of benzoic acid (it was necessary in order to insure complete combustion of hydrated creatine), $\Delta_c u$ noncorrected massic energy of combustion of compound, $\Delta_c u^0$ standard massic energy of combustion

Table 2 Combustion data for anhydrous creatine

Experiment	1	2	3	4
m(cpd)/g	0.89458	1.04870	0.88283	0.75725
m(fuse)/mg	23.83	24.01	30.17	21.00
ΔT_{ad}/K	1.807	2.108	1.795	1.533
$-\Delta U$(IBP)/J	16,438	19,175	16,324	13,944
$-\Delta U$(fuse)/J	387	390	490	341
$-\Delta U$(HNO_3)/J	57	66	58	51
$-\Delta U$(ign)/J	28	32	26	28
$-\Delta_c u$/J g^{-1}	17,847	17,819	17,840	17,859
$-\Delta_c u^0$/J g^{-1}	17,844	17,816	17,837	17,857
$\langle\Delta_c u^0\rangle = -17{,}839$ J g^{-1}				

For key see footnote of Table 1

Table 3 Combustion data for creatinine

Experiment	1	2	3	4
m(cpd)/g	1.06195	1.08830	1.18685	1.14831
m(fuse)/mg	19.03	16.01	14.10	13.36
ΔT_{ad}/K	2.497	2.546	2.781	2.688
$-\Delta U$(IBP)/J	22,714	23,158	25,301	24,456
$-\Delta U$(fuse)/J	309	260	229	217
$-\Delta U$(HNO_3)/J	93	94	108	104
$-\Delta U$(ign)/J	44	42	41	35
$-\Delta_c u$/J g^{-1}	20,970	20,915	20,999	20,987
$-\Delta_c u^0$/J g^{-1}	20,968	20913	20,997	20,985
$\langle\Delta_c u^0\rangle = -20{,}966$ J g^{-1}				

For key see footnote of Table 1

Table 4 Combustion data for arginine

Experiment	1	2	3	4	5
m(cpd)/g	0.79905	0.91515	0.91945	0.75350	0.76055
m(fuse)/mg	34.98	30.97	37.99	40.02	31.96
ΔT_{ad}/K	1.885	2.217	2.161	1.855	1.857
$-\Delta U$(IBP)/J	17,757	20,168	20,356	16,874	16,901
$-\Delta U$(fuse)/J	568	503	617	650	519
$-\Delta U$(HNO_3)/J	72	51	43	73	82
$-\Delta U$(ign)/J	37	34	37	33	33
$-\Delta_c u$/J g^{-1}	21,375	21,395	21,381	21,391	21,388
$-\Delta_c u^0$/J g^{-1}	21,374	21,393	21,380	21,389	21,387
$\langle\Delta_c u^0\rangle = -21{,}385$ J g^{-1}					

For key see footnote of Table 1

respectively. In order to bring the experimental values of energy of combustion to the standard state ($T = 298.15$ K and $p = 101.325$ kPa) corrections were made with the Washburn approximate equation, recommended in the case of compounds with carbon, hydrogen, and oxygen of $C_aH_bO_c$ general formula [11]:

$$\Pi\% = \frac{-0.3ap_{\mathrm{init}}}{-\Delta U^{\mathrm{exp}}}\left[1-\frac{1.1\,(b-2c)}{4a}+\frac{2}{p_{\mathrm{init}}}\right]$$

where p stands for the initial oxygen pressure and $-\Delta U^{\mathrm{exp}}$ for the experimental energy of combustion, a, b, and c being the numbers of carbon, hydrogen, and oxygen atoms from the chemical formula of the compound, respectively. Π is calculated in percents from the experimental value. The above equation applies fairly in the case of nitrogen compounds as well [12].

The relative error in the determination of the heats of combustion was less than 2‰.

For calculating the enthalpies of formation, the following values were considered: $\Delta_f H^0_{CO_2}(g) = -393.151 \pm 0.013$ kJ mol^{-1}, $\Delta_f H^0_{H_2O}(l) = -285.83 \pm 0.042$ kJ mol^{-1} [13].

Our data of solid state enthalpies of formation are shown in Table 5, together with literature values [1–4, 14]. The uncertainties represent two standard deviations of the mean.

DSC runs

DSC runs in open crucible for monohydrated creatine showed three peaks (Fig. 1). The dehydration process occurring between 55 − 110 °C is confirmed by the weight loss of about 12%, observed by us, weighing the crucible after heating to 120 °C.

The peak starting at about 230 °C is attributed to the transformation of creatine into creatinine (Figs. 1, 2). This was proved by a complex investigation by Dash et al. [15]. The peaks recorded beyond 260 °C for creatine, as well as

Table 5 Enthalpies of combustion and formation in solid state

Compound	Our value			Literature value	
	$-\Delta_c U^0$/kJ mol^{-1}	$-\Delta_c H^0$/kJ mol^{-1}	$-\Delta_f H^0$/kJ mol^{-1}	$-\Delta_c H^0$/kJ mol^{-1}	$-\Delta_f H^0$/kJ mol^{-1}
Arginine	3725.2 ± 2.6	3726.4 ± 2.6	635.5 ± 2.9	3724.2 ± 3.1 [3]	3724.2 ± 3.1 [4]
				3724.2 ± 3.1 [4]	623.5 ± 1.4
Anhydrous creatine	2339.2 ± 4.5	2338.6 ± 4.5	520.2 ± 4.7	2323.1 ± 0.8 [1]	537.2 ± 0.8
Creatine monohydrate	2336.1 ± 2.6	2335.5 ± 2.6	809.2 ± 2.7	–	–
Creatinine	2371.6 ± 8.4	2371.6 ± 8.4	204.3 ± 8.5	2336.0 ± 0.4 [2]	239.9 ± 0.5
				2334.0 ± 0.9 [1]	238.5 ± 0.9

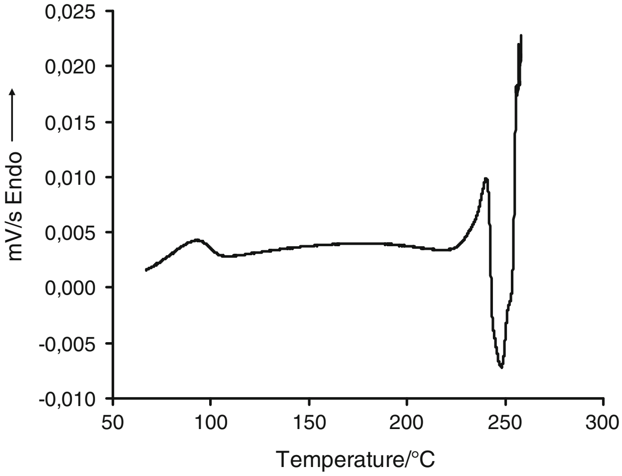


Fig. 1 DSC creatine monohydrate

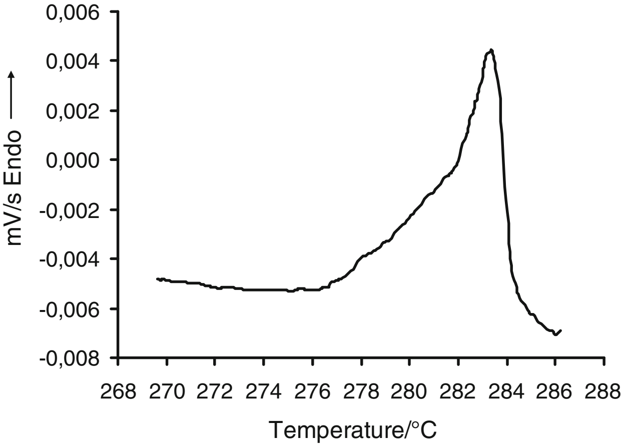


Fig. 3 DSC creatinine

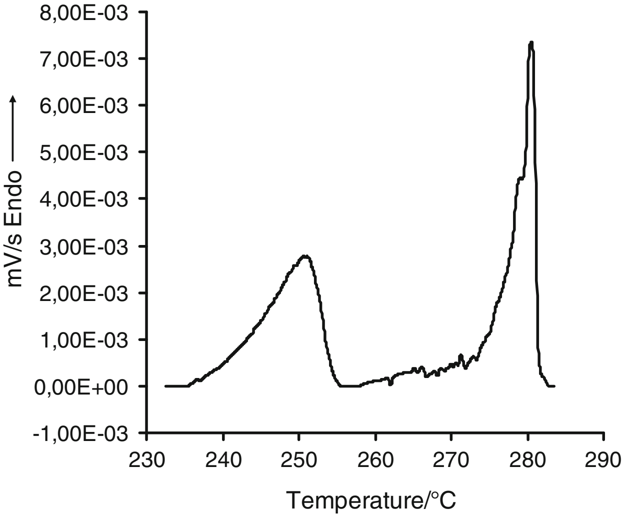


Fig. 2 DSC creatine anhydrous

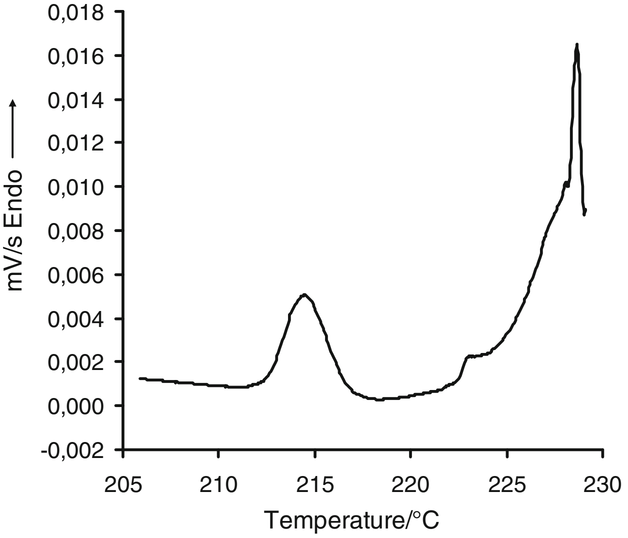


Fig. 4 DSC arginine

for creatinine (Figs. 1, 2, 3) correspond to the melting of the later, accompanied by decomposition (a weight loss was observed in this temperature range, too). The peak starts at a lower temperature in the case of creatine monohydrate probably because of a different morphology of creatine resulting from the dehydration process. A similar behavior was met for other organic compounds which form hydrates, as well [16].

Arginine melts and starts to decompose beyond 210 °C (Fig. 4). A sharp slope of the TGA curve in the range

Table 6 DSC data

Compound	T_{deh}/°C	T_{transf1}/°C	T_{transf2}/°C	ΔH_{deh}/kJ mol^{-1}	$\Delta H_{\mathrm{transf1}}$/kJ mol^{-1}
Arginine		214	228		11.2
Creatine anhydrous		234	276		55.4
Creatine monohydrate	55–110	228	254	37.5	72.6
Creatinine		277			33.6

220–250 °C was reported by Malik et al. [17], in their study about arginine dihydrate. This weight loss is equivalent with the weight of two ammonia molecules (one coming from the α-carbon atom and the other from the guanidyl group). Decomposition of the main carbon chain starts above 250 °C with the evolution of carbon dioxide. Kofler and Sitte [18] reported divergent values of the melting temperature of arginine, obtained by different methods, due to decomposition, as well.

The values of temperatures and enthalpies of the processes occurring in the four compounds on heating are synthesized in Table 6.

Estimation of enthalpies of formation

In this study, the method based on group contributions, with values recommended by Domalski and Hearing [19] was used. The guanidine groups were considered as a whole. The values of these group contributions with different substitution of the nitrogen atoms of guanidine were missing in literature as confirmed by Roux et al. [20] and were evaluated starting from the enthalpy of formation of guanidine and the effect of methyl substitution to urea (see Table 7, footnote) [21]. Urea is isoelectronic with guanidine; both are symmetric 6 Π molecules. The contributions of the mono- and 1,1-di-substituted guanidine groups were found to be −8 and 53 kJ mol^{-1}, respectively. Roux et al. [20], starting from the pK$_a$'s of the guanidinium and ammonium zwitterions of arginine, estimate an energy of about 6 kJ mol^{-1} for the transfer of a proton between the two cations. Consequently, the correction for the formation of a guanidinium zwitterion, within the group additivity scheme [19] would be −61 kJ mol^{-1}.

Salmon and Dalmazzone [22] have introduced new values for group parameters in solid state, which were taken into account too. The experimental and calculated values of the standard enthalpies of formation, of the four investigated compounds are shown in Table 7. The values estimated using the guanidine group contributions are marked by "a" in this table, while those obtained with parameters from reference [22] by "b".

In creatinine, one of the nitrogen atoms from the heterocycle is bound to two aliphatic carbon atoms, outside of the plane of the guanidine moiety (like in creatine), while the other nitrogen is bound to a carbonyl group (instead of a hydrogen atom). The contribution of the guanidine group in creatinine should be more positive (+65 kJ mol^{-1}) than that from creatine, if one takes into account the difference between the values of the group parameters N–(H)(C)(CO) (5.50 kJ mol^{-1} in amino acids) and N–$(H)_2$(C) (−6.30 kJ mol^{-1}).

Table 7 Experimental and calculated enthalpies of formation

Compound	$-\Delta_f H$ (exp, cr)/kJ mol^{-1}	$-\Delta_f H$ (calcd, cr)^a/kJ mol^{-1}	$-\Delta_f H$ (calcd, cr)^b/kJ mol^{-1}
Anhydrous creatine	520.2 (our value)	516	521.3 (650.1)
	537.2 [1]		
Creatine monohydrate	809.2	802	807.1 (935.9)
Creatinine	204.3 (our value)	~207	238.5 (380.3)
	239.9 [2]		
	238.5 [1]		
Arginine	635.5 (our value)	651	639.4 (768.9)
	637.7 [3]		
	623.5 [3], [14]		

Compound	Urea	Guanidine	Methyl-urea	1,1-Dimethyl-urea	1,3-Dimethyl-urea
$\Delta_f H^0$(cr)	333	56	331	319	314

[a] Values calculated by means of group parameters recommended by [19] and the estimated value of $\Delta_f H^0$ of methyl-guanidines [20], calculated from data for methyl ureas [21] (see below, all values in kJ mol^{-1})

[b] Values calculated by means of group parameters recommended by [22]. The values in parentheses from the last column include no correction

Discussion

The molar enthalpy of combustion is, as expected, greater in the case of anhydrous creatine than in that of the monohydrate. The consequence is a difference between the corresponding enthalpies of formation, which exceeds the value of the enthalpy of formation of water, by 3–4 kJ mol^{-1}. This value must be associated with the interaction energy between creatine and water molecules. The value of about 37 kJ mol^{-1}, for the dehydration enthalpy obtained by DSC, is lower than the latent heat of vaporization of water. The dehydration process occurring between 55 and 110 °C is confirmed by the weight loss of about 12%, observed both by us and by Dash et al. [15] by TGA. The interaction between creatine and water molecules is much weaker than that between asparagine and water molecules, in asparagine monohydrate (7–8 kJ mol^{-1}), observed by us in a previous study [23]. This observation is consistent with the low value of the dehydration heat and with the dehydration process starting at a lower temperature in the case of the former hydrate (55 °C compared to 82 °C).

We calculate a thermal effect in standard conditions of about 74 kJ mol^{-1}, for the reaction by which creatine transforms into creatinine, in good agreement with the value of 72.6 kJ mol^{-1}, obtained from the peak area.

The agreement between experimental and estimated values (method "a") of enthalpies of formation for creatines falls in the limits of the experimental errors. The experimental value for the monohydrate is more negative than the estimated one because the later does not contain the interaction energy between creatine and water molecules. The structure of creatine is stabilized by the transfer of the proton from the carboxyle group to the imine nitrogen, with formation of a zwitterion. This is not the case of creatinine, so that in the estimated value no zwitterion correction was considered.

A greater discrepancy is obtained in the case of arginine. We consider that the larger negative estimated value is due to the value of the group parameter N–$(H)_2$(C) taken into account, i.e., that for the second amino group in amino acids (−46.00 kJ mol^{-1}). It is possible that an amino group added to a zwitterion structure with guanidinium cation brings a smaller negative contribution.

Salmon and Dalmazzone [22] obtain by simple addition of group contributions very large negative values (last column of Table 7) of estimated enthalpies of formation of the four compounds. Their corrected values are calculated by adding a parameter for "aliphatic zwitterion" formation, excepting creatinine. Surprisingly, this parameter is a large positive value (128.8 kJ mol^{-1}). As regards creatinine, the correction is much more positive (142 kJ mol^{-1}) and it is not clear what it accounts for. The corrected estimated values of enthalpies of formation by method "2" are in good agreement with our experimental data, except for creatinine.

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