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Thermoanalytical study of cyclocondensation of some derivatives of nitrosouracil

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Abstract

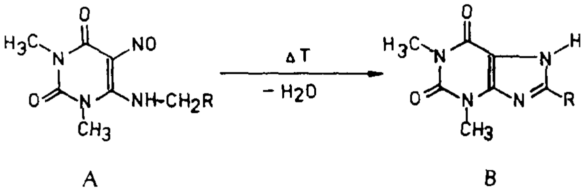
The exothermic conversion of 1,3-dimethyl-4-alkylamino-5-nitrosouracils into theophylline or its 8-substituted derivatives was investigated. The conversion was carried out in the solid phase. The course of this reaction is affected by steric and electronic properties of the substituents present in proximity to the reaction centre of the starting substance. The values of molar reaction enthalpies (ΔH_r) of 19 derivatives of 1,3-dimethyl-4-alkylamino-5-nitrosouracils were determined. The relationship between these values and the structure of the substituent was examined.

Keywords: DSC; Nitrosouracil; Solid-state reactions

1. Introduction

The methods of thermal analysis are frequently used to determine the basic physicochemical properties of organic compounds as well as for investigating their reactions and thermal behaviour [1,2]. An interesting use for these methods is to study the decomposition of organic substances in the solid phase.

The cyclization reaction of 1,3-dimethyl-4-alkylamino-5-nitrosouracils (A) yielding 8-alkyltheophyllines (B), has been previously studied using differential scanning calorimetry (DSC) [3–6]. The general course of the reaction is described in Scheme 1. This reaction is interesting for two reasons. The reaction products, theophylline and its derivatives, are applied in medical practice. At the same time, it is a rare case of an organic synthesis being carried out in solid phase and producing high yields (over 96%).



Scheme 1.

The subjects of this paper are the thermochemical study of this reaction and an elucidation of the influence of different substituents on the course of the cyclocondensation in the solid phase.

2. Experimental

The 1,3-dimethyl-4-alkylamino-5-nitrosouracils (Table 1) were prepared by modification of previously

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Table 1
Values of reaction enthalpies (ΔH_r) of the cyclocondensation of the derivatives of 1,3-dimethyl-4-alkylamino-5-nitrosouracil as a function of the type of substituent R (heating rate 2.5 K min^{-1})

Compound		ΔH_r	ΔH_r	T[a]	T[b]
No.	R	(J g^{-1})	(kJ mol^{-1})	(K)	(K)
I	H	1138.1±18.4	225.5±3.6	415	388–424
II	CH_3	1169.6±15.7	248.2±3.3	397	364–405
III	C_2H_5	1135.1±29.2	256.8±6.6	398	356–403
IV	C_3H_7	1092.9±32.4	262.6±7.8	376	363–386
V	C_4H_9	1042.8±32.9	265.2±8.4	372	363–384
VI	C_5H_{11}	998.6±30.9	267.9±8.3	356	336–384
VII	C_6H_{13}	981.9±30.6	277.2±8.6	373	367–388
VIII	C_7H_{15}	886.4±15.9	262.7±4.7	370	352–383
IX	$C_{11}H_{23}$[d]	690.2±7.3	243.3±2.6	370	367–374
X	$C_{13}H_{27}$[d]	607.5±15.9	231.2±6.1	369	366–373
XI	$C_{15}H_{31}$	673.2±11.4	275.4±4.6	366	352–383
XII	$C_{17}H_{35}$	490.2±9.8	214.1±4.3	371	356–381
XIII	CH_2OH	896.6±30.2	204.6±6.9	415	393–422
XIV	$(CH_2)_2OH$	933.9±14.5	226.2±3.5	391	364–399
XV	$CH_2C_6H_5$[c]	857.1±17.5	247.1±5.1	413	385–420
XVI	$(CH_2)_2C_6H_5$[c]	872.4±28.7	250.2±8.7	382	362–392
XVII	$CH(OH)C_6H_5$[c]	617.0±7.1	187.8±2.2	378	353–393
XVIII	$C(CH_3)_3$[c]	995.4±7.7	253.1±1.9	383	349–406
XIX	$CH(CH_3)_2$	1006.2±33.7	241.8±8.1	391	383–396

[a] Temperature of peak maximum.
[b] Temperature interval of the reaction.
[c] Multistep course of the reaction under given conditions.
[d] Heating rate 0.625 K min^{-1}.

described methods [7]. After repeated crystallization in methanol, the structures of the synthesized compounds were confirmed by elemental analysis as well as IR, UV, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The samples were the same as those used for the earlier determination of molar heat capacities and kinetics [4,6].

The reaction enthalpies were determined using a DSC-2C differential scanning calorimeter (Perkin–Elmer) in a dynamic nitrogen atmosphere with a flow rate of 20 ml min^{-1}. The samples (0.9–2 mg) were placed in sealed aluminium sample pans as used for volatile substances with perforated lids. Different sealing techniques were also used to study the influence of sample encapsulation on the shape of the reaction exotherm, for example, open sample pan, sealed sample pan, sealed sample pan with a pinhole, sample pan covered with punctured lid. The reference aluminium sample pan was empty. The heating rates were 20, 5, 2.5 and 0.625 K min^{-1}. Indium was used as standard for enthalpies.

3. Results and discussion

The preliminary DSC scans obtained for the 19 substituted nitrosouracils in the region 320–600 K consisted of two peaks. For example Fig. 1 shows the DSC scan of 1,3-dimethyl-4-methylamino-5-nitrosouracil (Compound I, Table 1). The first exothermic peak corresponds to the cyclization reaction while the second endothermic peak is to be attributed to melting or sublimation of the products, that is, the 8-substituted theophyllines [5]. The exothermic process was observed in the temperature interval 350–440 K depending on the type of reactant. The rate of heating and the composition of the atmosphere are among the important parameters which can influence the rate and mechanism of processes investigated by thermal analysis [8,9]. The phase transitions, for example, melting or sublimation accompanying the thermal decomposition of solid substances [10] can be considered as another factor. The preliminary DSC curves were obtained at a higher rate of heating (20 K min^{-1}) since

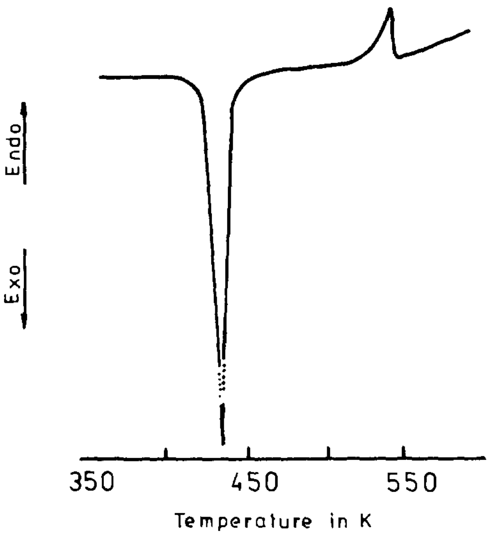

Fig. 1. DSC curve of 1,3-dimethyl-4-methylamino-5-nitrosouracil (Compound I, heating rate 20 K min^{-1}).

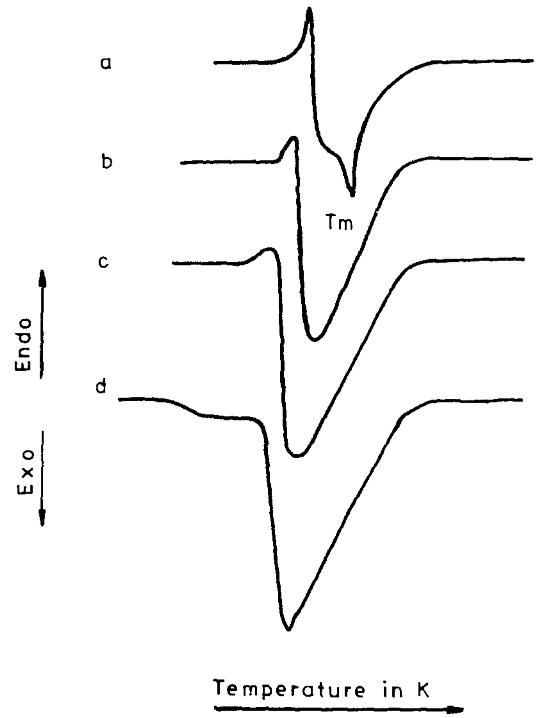

Fig. 2. Influence of the heating rate on position and form of the reaction curve of 1,3-dimethyl-4–dodecylamino-5-nitrosouracil (IX, Table 1). The heating rate and temperature corresponding to peak maximum (T_m) for individual records are: a – 20 K min^{-1}, T_m=387 K, b – 5 K min^{-1}, T_m=374 K, c – 2.5 K min^{-1}, T_m=372 K, d – 0.625 K min^{-1}, T_m=370 K.

some processes are not always detectable at slow heating [11]. The DSC scans showed that the course of reaction was affected, in some cases, by melting of the starting substance. Melting was observed with the *n*-alkyl-substituted derivatives of nitrosouracil with a long alkyl chain. For these substances, fusion (the endothermic effect in Fig. 2a) is simultaneously accompanied by cyclocondensation. Under these conditions the reaction proceeded in the melt. It was not possible to separate these processes, but it was possible to either completely or partially eliminate the influence of the interfering melting by appropriate selection of the experimental conditions. The results in Fig. 2(d) show that the reaction may proceed in a quasi-solid state provided the rate of heating is reduced.

The reaction was also accompanied by partial melting in the case of the R=$CH(OH)C_6H_5$ derivative of nitrosouracil (XVII) at high heating rate (Fig. 3).

In case of the methyl-substituted derivative of nitrosouracil (I), if the rate of heating was equal to 20 K min^{-1}, the cyclocondensation reaction proceeded simultaneously with melting, which increased the rate several times. It was also observed that the reaction character was affected by the mass of sample. If a certain critical value of weighed material (under equal experimental conditions) was exceeded, the reaction proceeded with an immeasurable rate in an explosive manner. The sealed sample pans distorted and ruptured and the sample holder in calorimeter was soiled by sublimed reaction product.

The method applied for testing the thermal stability of explosives [12] was based on the determination of both the critical mass of sample and the critical heating rate at which the decomposition or explosion occurs. Such a reaction course of the methyl derivative of nitrosouracil (I) is comparable with the thermal explosion of explosives [9,12,13]. Similar behaviour was found for some other compounds in this study, for example, compounds XIV, XIX in Table 1.

A weak endotherm at the end of reaction occurred for substances with R=C_4H_9 (V), C_6H_{13} (VII), $C_{17}H_{35}$ (XII), overlapped the reaction exotherm (e.g. Fig. 4). This endothermic effect disappeared at lower heating rate. Its origin is presently obscure.

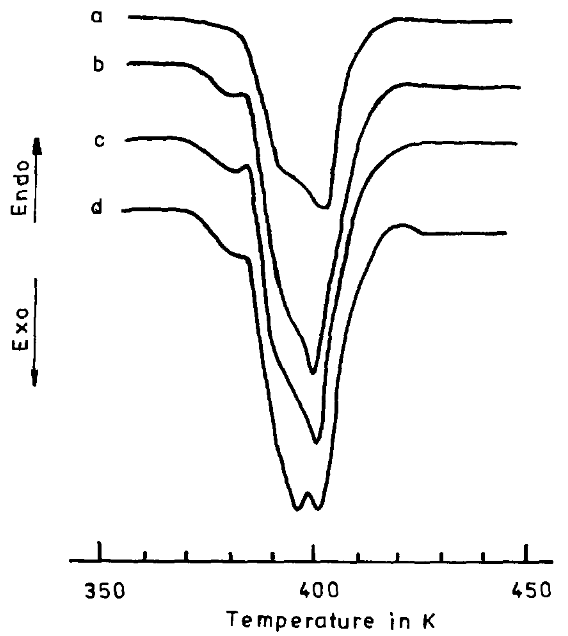

Fig. 3. Influence of sample sealing on form of the reaction exotherm for derivative XVII (heating rate 20 K min^{-1}). a – open sample pan, b – sealed sample pan, c – sealed sample pan with a pin-hole, d – sample pan covered with punctured lid.

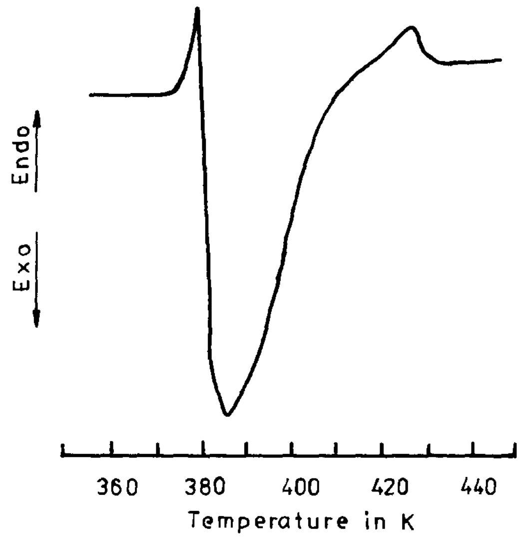

Fig. 4. The DSC curve of cyclization reaction for 1,3-dimethyl-4-pentylamino-5-nitrosouracil (V), heating rate 20 K min^{-1}.

The shape of the reaction exotherm allows the multistep course of the process to be considered. This applies to the derivatives of uracil with R=C_2H_5 (III), $CH_2C_6H_5$ (XV), $(CH_2)_2C_6H_5$ (XVI), $CH(OH)C_6H_5$ (XVII) and $C(CH_3)_3$ (XVIII). The records of composite peaks of these compounds are represented in Fig. 5. Two or three exothermic peaks may overlap and these may characterize the individual reaction steps. In the case of these compounds, the reaction took place under the given heating rates in the solid phase. For the derivative with R=$CH(OH)C_6H_5$ (XVII) the composite peak vanished at a heating rate of 2.5 K min^{-1}. The derivative of nitrosouracil with R=$CH_2C_6H_5$ (XV) exhibited the form of reaction peak analogous to that of the derivative with R=$(CH_2)_2C_6H_5$ (XVI) in Fig. 5(a).

The influence of the atmosphere surrounding the sample on the shape of DSC curve is represented in Fig. 3. As mentioned, the reaction of this derivative was accompanied by melting of the reactant and moreover the chemical process exhibited a complex character. The results from Fig. 3 indicate that the atmosphere surrounding the reactant can be regulated by different sealing of the sample pan. If the sample was placed in a sealed aluminium sample pan with perforated lid, the partial pressure of the water vapour liberated during the course of reaction at a given rate of heating increased. This manifested itself by a different shape of the reaction exotherm. A lower rate of heating, for example, 5 K min^{-1}, was responsible for a decrease in the pressure of the gaseous component in proximity to the sample. This produced an analogous form of the DSC curve as represented in Fig. 3(a).

In order to compare the values of reaction enthalpy found for all 19 derivatives, the reaction was investigated under equal experimental conditions. A heating rate of 2.5 K min^{-1} was chosen so that the reaction took place in the solid phase without melting of the reactant. However, two derivatives of nitrosouracil containing 12 and 14 carbon atoms in the side alkyl chain (Compounds IX, X) were exceptions. In these cases the reaction was accompanied by partial melting even at the low heating rate of 0.625 K min^{-1}. This fact was evidenced by the slightly fused reaction products in the sealed sample pan with punctured lid observed at opening the sample pan after completion of the reaction.

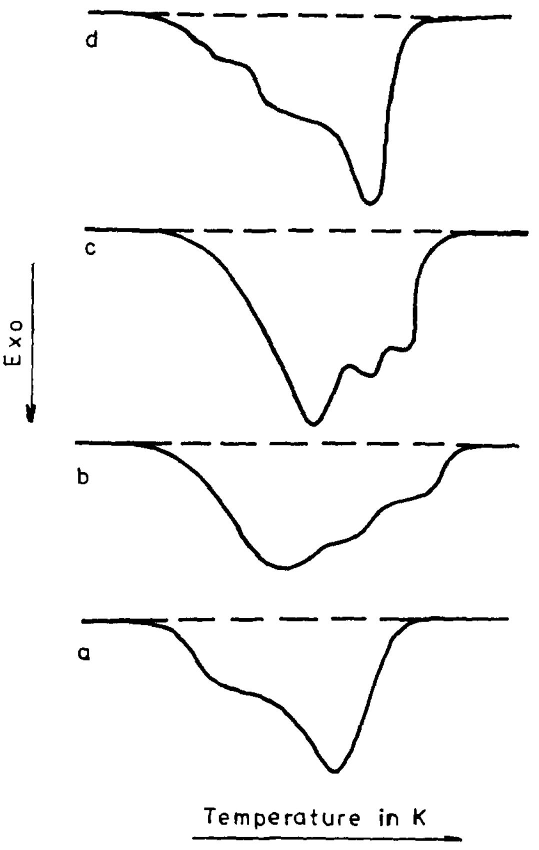

Fig. 5. The DSC records of cyclocondensation reaction of some derivatives of nitrosouracil a – $R=(CH_2)_2C_6H_5$ (XVI), heating rate 2.5 K min^{-1}, b – $R=C(CH_3)_3$ (XVIII), heating rate 5 K min^{-1}, c – $R=C(CH_3)_3$ (XVIII), heating rate 2.5 K min^{-1}, d – $R=C_2H_5$ (III), heating rate 2.5 K min^{-1}.

Additionally, the samples were placed in aluminium sample pans with sealed lids. The lids were punctured with a hole through which the liberated gaseous product escaped.

The values of reaction enthalpy (ΔH_r), as well as the thermometric data characterizing the cyclocondensation reaction of the derivatives of 1,3-dimethyl-4-alkylamino-5-nitrosouracil are given in Table 1. In all cases the values are averages of between five and nine experiments.

The results indicate that the investigated reactions belong to intense exothermic processes. The molar reaction enthalpies vary in the range 188–277 kJ mol^{-1} according to the type of substituent. Analogously, the calculated values of reaction enthalpy expressed in J g^{-1} varied in the range 490–1170 J g^{-1}. Differences with the previous published data of six derivatives of nitrosouracil [3] may be due to different heating rates.

When the thermometric data on *n*-alkyl-substituted derivatives presented in Table 1 are compared, it may be seen that the reaction proceeds (except for derivatives I, II and III) under given experimental conditions, in approximately equal temperature intervals. Similarly, the temperatures of the peak maximum of these compounds varied around 370 K. The values of molar reaction enthalpies of the *n*-alkyl-substituted derivatives of reactant increase with extending chain of the alkyl group in the order $C_1 < C_2 < C_3 < C_7$.

Since the values of the standard deviations are almost equal, the values of ΔH_r determined for the alkyl derivatives of nitrosouracil containing 4, 5 and 6 carbon atoms on the NH group were very similar. The molar reaction enthalpies of these compounds (IV, V and VI) were 263 kJ mol^{-1}, 265 kJ mol^{-1} and 268 kJ mol^{-1}, respectively.

On the other hand, it was observed that the values of ΔH_r decreased with extending chain of the alkyl group for $n > 7$ in the order $C_7 > C_8 > C_{12} > C_{14} > C_{18}$. An exception to this relationship was the derivative XI ($R=C_{15}H_{31}$). The value of its molar reaction enthalpy (275 kJ mol^{-1}) was higher than those of both similar derivatives (X and XII).

A comparison of the values of molar reaction enthalpies of the alkyl derivatives of uracil with branched chains with those of the analogous derivatives with linear chains is interesting. In both cases, that is, isobutyl (XIX) and *n*-butyl (IV) or neopentyl (XVIII) and *n*-pentyl (V), the value of ΔH_r of the branched alkyl derivatives was approximately 10 kJ mol^{-1} lower when compared with the value of the corresponding derivative containing the linear chain of the alkyl group. This fact may be explained by more compact and symmetrical molecular arrangement of the alkyl derivatives with branched chain.

If the derivatives of nitrosouracil which contained the alkyl group with a branched chain, that is, neopentyl (XVIII) and isobutyl (XIX), were compared with each other, the value of ΔH_r obtained for the first was in accordance with the expectation that its value would be higher owing to the activity of the electronic (i.e. induction) and steric effects. The value of ΔH_r

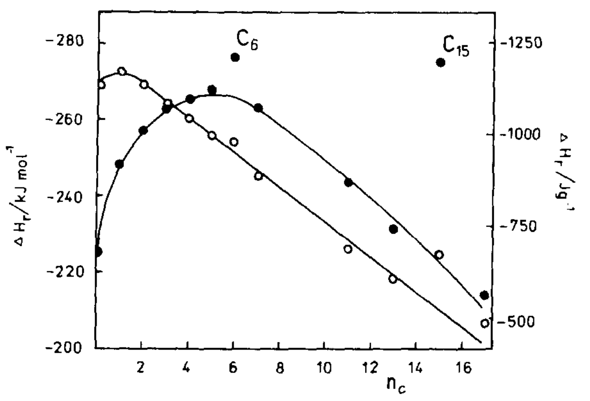

Fig. 6. Dependence of reaction enthalpy ΔH_r expressed in kJ mol^{-1} (•) and J g^{-1} (o) on the number of carbon atoms n_C in the NH group of side chain of substituted nitrosouracils.

obtained for Compound XVIII was 253 kJ mol^{-1} and that for Compound XIX was 242 kJ mol^{-1}..

The dependence of ΔH_r (J g^{-1}) on the logarithm of the number of carbon atoms in alkyl chain of the NH group was parabolic (Fig. 6). The value of ΔH_r (J g^{-1}) decreased with increasing numbers of carbon atoms in the chain.

On the basis of an analogous relationship for molar reaction enthalpy ΔH_r (kJ mol^{-1}), it may be assumed that the decreasing exothermic effect of the reaction of *n*-alkyl substituted derivatives of nitrosouracil are due to increasing number of carbon atoms at $n_C > 7$ and are probably caused by an increased mobility of the side chain as a consequence of more favourable conformation structures. As for these compounds, the possible influence of local melting on the flexibility of the side chain of the alkyl group cannot be excluded.

In order to appreciate the influence of substituents on the course of the investigated reaction in a more complex manner, some derivatives of nitrosouracil were prepared which contained a group of polar character in proximity to the reaction centre. The lowest values of molar reaction enthalpies (Table 1) were found for derivatives XIII and XVII, namely, 205 kJ mol-1 and 188 kJ mol^{-1}, respectively. In the case of these compounds, the values of ΔH_r were significantly lower than the values found in the case of substitution of the corresponding *n*-alkyl derivative in the NH group of the reactant. This fact indicates that the progress of the reaction in the solid phase as well as in the solution state was significantly promoted by the presence of groups with strong electron-acceptor effects (in this case it is the hydroxyl or phenyl group). The considerable influence of these substituents having strong electronic effects on the course of the reaction was confirmed by the fact that the derivatives of nitrosouracil containing the groups of type $CH_2C_6H_5$, $CH_2CH{=}CH_2$, CH_2CN etc. in the NH group could not be synthesised. This was caused by the enormous reaction rate of the cyclization of the reactants to products. The effect of these groups decreased with increasing distance from the reaction centre. Thus the derivatives XIII and XIV can be given as example. The value of ΔH_r found for derivative XIII was 205 kJ mol^{-1} and was rather lower when compared with 226 kJ mol^{-1} found for derivative XIV. This difference may be explained by a decrease in polar character of the OH group due to the homologous $-CH_2-$ increment in the chain. The analogous behaviour was also observed in the case of the phenyl-substituted derivatives of nitrosouracil.

In conclusion, on the basis of the results obtained by investigating the thermally initiated cyclocondensation reaction in solid phase, the value of molar reaction enthalpy and the course of reaction were influenced by the structure of the reactants (including different conformations) as well as by electronic and steric effects of the substituent in the NH group of starting substance.

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