

Kinetic study of the cyclization of 2-(3-phenylthioureido)benzotrile to 3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline-2-thione

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The rate of the cyclization of 2-(3-phenylthioureido)benzotrile to 3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline-2-thione in acetonitrile in dependence on the catalyst concentration (water or methanol) and temperature was studied. The cyclization reaction was found to be irreversible following the kinetic equation of the first order with respect to the starting concentration of the substrate and the catalyst. From the temperature dependence of the rate of the cyclization and the Arrhenius equation values of the activation energy and the frequency factor were calculated. From the Eyring equation values of the activation enthalpy and entropy were calculated. On the basis of the experimental results the probable mechanism of reaction is discussed.

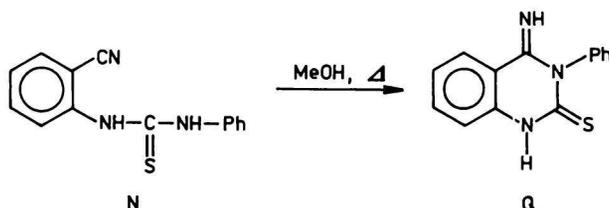
It has been already published [1, 2] that 2-(3-R-thioureido)benzotriles cyclize under heating in methanol to 3-substituted 4-imino-1,2,3,4-tetrahydroquinazoline-2-thiones. The rates of the quinazoline ring formation in the series of ethyl, benzyl, isopropyl, cyclohexyl, and *tert*-butyl derivatives depend on the branching of the alkyl group. 2-(3-*tert*-Butylthioureido)benzotrile does not undergo the mentioned cyclization. The rate of cyclization increases from isopropyl to cyclohexyl and benzyl derivatives. 2-(3-Ethylthioureido)benzotrile cyclizes immediately after its formation in the reaction of 2-isothiocyanatobenzotrile with ethylamine [2].

The cyclization of 2-(3-phenylthioureido)benzotrile (N) to 3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline-2-thione (Q) proceeds already at room temperature during several minutes in aqueous ethanol or in aqueous acetone solution and practically instantaneously in the solution of 2-methoxyethanol [1]. The aim of our work was to investigate the rate of the given cyclization in acetonitrile in dependence on the concentration of the catalyst (methanol, water) and temperature (Scheme 1).

Experimental

UV—VIS spectra were recorded on a spectrophotometer UV 3000 (Shimadzu) in 0.5 cm quartz cells at the temperature of 25, 30, 35, 40, and 50 °C (accuracy 1 °C). The

used solvents were purified by the methods given in literature [3] (acetonitrile) and [4] (methanol). The content of water in acetonitrile determined by the Fischer method was in the interval of 1.3—5.6 mmol dm⁻³. Compounds N and Q were prepared according to [1]. UV—VIS spectra (acetonitrile), $\lambda_{\text{max}}/\text{nm}$ ($\epsilon \cdot 10^{-4}/(\text{m}^2 \text{mol}^{-1})$) for compound N: 231 (1.62), 275 (1.22); compound Q: 235 (1.68), 293 (2.02). The rate of the cyclization of N to Q was determined by spectrophotometry. Absorbance of the reaction mixture was monitored at the longwavelength band of the compound Q ($\lambda = 293 \text{ nm}$). An influence of the added catalyst on this band was not observed. Molar absorption coefficient of the starting compound N at the mentioned wavelength was $1.04 \times 10^4 \text{ m}^2 \text{mol}^{-1}$.

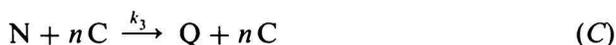
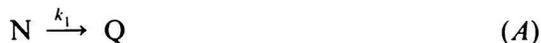


Scheme 1

The starting concentration of the compound N *i.e.* $[\text{N}]_0 = 0.204 \text{ mmol dm}^{-3}$, the concentration of water $[\text{H}_2\text{O}] = 4.1 \times 10^{-3}$ — 4.12 mol dm^{-3} , the concentration of methanol $[\text{MeOH}] = 3.1 \times 10^{-3}$ — 1.84 mol dm^{-3} . The content of water during the investigation of the dependence of the reaction rate on methanol concentration was 2.0 mmol dm^{-3} . The time after addition of 1/2 of the volume of the thermostated mixture of catalyst and acetonitrile into compound N in a 500 cm^3 flask was taken as a start of the reaction. After the compound dissolved a part of the mixture was poured into a thermostated cell and then the dependence of absorbance on time was registered. From this curve 25 values of absorbance in the region of 20—80 % conversion were used for the following calculations.

Derivation of relations for the kinetic evaluation of data

The cyclization reaction of compound N to Q may be described by a set of the following chemical equations



where C is the catalyst (water, methanol), n is the number of molecules of catalyst taking part in the reaction, k_1 , k_2 , k_3 are the rate constants (for $n = 0$ eqns (A) and (C) are identical).

For all the three cases the rate of a decrease in the concentration of the compound N may be expressed by eqns (1–3) or after their integration by eqns (4–6)

$$-d[\text{N}]/dt = k_1[\text{N}] \quad (1)$$

$$-d[\text{N}]/dt = k_2[\text{N}]^2 \quad (2)$$

$$-d[\text{N}]/dt = k_3[\text{N}][\text{C}]^n \quad (3)$$

$$\ln([\text{N}]/[\text{N}]_0) = -k_1 t \quad (4)$$

$$1/[\text{N}]_0 - 1/[\text{N}] = -k_2 t \quad (5)$$

$$\ln([\text{N}]/[\text{N}]_0) = -k_3 t [\text{C}]^n \quad (6)$$

where [N] is the concentration of the starting compound N in time t .

Absorbance A of the reaction mixture at a certain wavelength according to the Lambert—Beer law is given by the equation

$$A = A_N + A_Q = (\varepsilon_N[\text{N}] + \varepsilon_Q[\text{Q}])l \quad (7)$$

where A_i is the absorbance of the i component of the reaction mixture at the wavelength of the measurement, ε_i is their molar absorption coefficient, l is the thickness of the cell (absorbance of the other components of the reaction mixture at the given wavelength is negligible).

In case the material balance is valid

$$[\text{N}]_0 = [\text{N}] + [\text{Q}] \quad (8)$$

one can rearrange eqns (4–6) and express the relations in the form of eqns (9–11) (*cf.* [5])

$$\ln(l[\text{N}]\varepsilon_Q - A) = -k_1 t + \ln([\text{N}]_0(\varepsilon_N - \varepsilon_Q)l) \quad (9)$$

$$(\varepsilon_N - \varepsilon_Q)/(A - \varepsilon_Q[\text{N}]_0 l) = k_2 t + 1/[\text{N}]_0 \quad (10)$$

$$\ln(l[\text{N}]_0 \varepsilon_Q - A) = -k_3 t [\text{C}]^n + \ln([\text{N}]_0(\varepsilon_N - \varepsilon_Q)l) \quad (11)$$

From the dependence of the absorbance of the reaction mixture on time using eqn (9) values of the rate constants of the cyclization of the compound N to Q in the presence of water or methanol were calculated (assuming that the mechanism is monomolecular) (Tables 1 and 2).

The rate constants k_3 (Tables 1 and 2) and the reaction order with respect to the starting concentration of catalysts n were calculated from the dependence of

Table 1

Values of the rate constants k_1/s^{-1} and $k_3/(dm^3 mol^{-1} s^{-1})$ of the cyclization of compound N in the presence of water at the temperature of 25°C and the dependence of the constants k_1 on the concentration of water

$[H_2O]/(mol dm^{-3})$	$-\log [H_2O]$	k_1	$-\log k_1$	r	$-\log k_3$
4.1×10^{-3}	2.387	$(4.17 \pm 0.05) \times 10^{-6}$	5.386	0.990	2.999
6.0×10^{-3}	2.222	$(6.07 \pm 0.08) \times 10^{-6}$	5.217	0.992	2.995
1.00×10^{-2}	2.000	$(9.82 \pm 0.11) \times 10^{-6}$	5.008	0.994	3.008
4.00×10^{-2}	1.298	$(3.00 \pm 0.04) \times 10^{-5}$	4.523	0.994	3.125
8.00×10^{-2}	1.097	$(6.06 \pm 0.05) \times 10^{-5}$	4.218	0.995	3.121
5.00×10^{-1}	0.304	$(4.62 \pm 0.05) \times 10^{-5}$	3.335	0.995	3.031
9.25×10^{-1}	0.034	$(8.67 \pm 0.09) \times 10^{-5}$	3.062	0.992	3.028
1.380	-0.140	$(1.32 \pm 0.02) \times 10^{-4}$	2.880	0.991	3.020
2.900	-0.462	$(2.30 \pm 0.04) \times 10^{-4}$	2.630	0.989	3.100
4.120	-0.615	$(3.28 \pm 0.05) \times 10^{-4}$	2.484	0.988	3.099

$$n = 0.984 \pm 0.03 \quad \log k_3 = -3.061 \pm 0.049 \quad r = 0.998$$

Table 2

Values of the rate constants k_1/s^{-1} and $k_3/(dm^3 mol^{-1} s^{-1})$ of the cyclization of compound N in the presence of methanol and the dependence of the rate constants k_1 on the concentration of methanol

$[MeOH]/(mol dm^{-3})$	$-\log [MeOH]$	k_1	$-\log k_1$	r	$-\log k_3$
3.1×10^{-3}	2.505	$(1.00 \pm 0.02) \times 10^{-5}$	5.000	0.989	2.495
6.0×10^{-3}	2.222	$(1.95 \pm 0.08) \times 10^{-5}$	4.710	0.990	2.491
9.04×10^{-3}	2.044	$(2.95 \pm 0.03) \times 10^{-5}$	4.530	0.992	2.486
1.19×10^{-2}	1.924	$(3.94 \pm 0.04) \times 10^{-5}$	4.405	0.994	2.481
1.50×10^{-2}	1.824	$(4.78 \pm 0.05) \times 10^{-5}$	4.321	0.997	2.497
5.96×10^{-2}	1.225	$(1.96 \pm 0.03) \times 10^{-4}$	3.798	0.995	2.483
9.10×10^{-2}	1.041	$(2.88 \pm 0.04) \times 10^{-4}$	3.541	0.993	2.500
1.10×10^{-1}	0.959	$(3.60 \pm 0.04) \times 10^{-4}$	3.444	0.992	2.485
8.10×10^{-1}	0.092	$(2.54 \pm 0.03) \times 10^{-3}$	2.595	0.990	2.501
1.480	-0.265	$(5.81 \pm 0.06) \times 10^{-3}$	2.236	0.989	2.501

$$n = 0.996 \pm 0.02 \quad \log k_3 = -2.498 \pm 0.092 \quad r = 0.999$$

Table 3

Dependence of the rate constants k_3 of the cyclization of compound N in the presence of water
 ($[\text{H}_2\text{O}] = 4.00 \times 10^{-2} \text{ mol dm}^{-3}$) on the temperature

$\theta/^\circ\text{C}$	k_1/s^{-1}	$-\log k_1$	r	$-\log k_3$	$k_3/(\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1})$
25	$(3.00 \pm 0.04) \times 10^{-5}$	4.523	0.994	3.125	7.50×10^{-4}
30	$(4.86 \pm 0.04) \times 10^{-5}$	4.337	0.994	2.939	1.15×10^{-3}
35	$(7.72 \pm 0.08) \times 10^{-5}$	4.157	0.993	2.759	1.74×10^{-3}
40	$(1.21 \pm 0.02) \times 10^{-4}$	3.984	0.991	2.586	2.59×10^{-3}
50	$(2.82 \pm 0.04) \times 10^{-4}$	3.652	0.990	2.254	5.58×10^{-3}

1. $\log k = -(a/T) + b$ $a = -3323.5 \pm 60.1$ $E_A = 63.6 \text{ kJ mol}^{-1}$
 $b = \log P = 8.015 \pm 1.28$ $r = -0.997$

2. $\log(k/T) = -(a/T) + b$ $a = -3189.8 \pm 58.1$ $\Delta H^\ddagger = 61.1 \text{ kJ mol}^{-1}$
 $b = 5.093 \pm 0.942$ $\Delta S^\ddagger = -100.0 \text{ J mol}^{-1} \text{ K}^{-1}$
 $r = -0.997$

Table 4

Dependence of the rate constants k_3 of the cyclization of compound N in the presence of methanol and water
 ($[\text{H}_2\text{O}] = 2.0 \text{ mmol dm}^{-3}$, $[\text{MeOH}] = 1.50 \times 10^{-2} \text{ mol dm}^{-3}$) on the temperature

$\theta/^\circ\text{C}$	k_1/s^{-1}	$-\log k_1$	r	$-\log k_3$	$k_3/(\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1})$
25	$(4.78 \pm 0.05) \times 10^{-5}$	4.321	0.997	2.497	3.18×10^{-3}
30	$(7.54 \pm 0.08) \times 10^{-5}$	4.122	0.994	2.329	4.69×10^{-3}
35	$(1.17 \pm 0.08) \times 10^{-4}$	3.930	0.993	2.165	6.84×10^{-3}
40	$(2.00 \pm 0.03) \times 10^{-4}$	3.699	0.992	2.006	9.86×10^{-3}
50	$(4.09 \pm 0.05) \times 10^{-4}$	3.388	0.992	1.705	1.97×10^{-2}

1. $\log k = -(a/T) + b$ $a = -3025.0 \pm 57.1$ $E_A = 57.9 \text{ kJ mol}^{-1}$
 $b = \log P = 7.642 \pm 1.14$ $r = -0.998$

2. $\log(k/T) = -(a/T) + b$ $a = -2890.3 \pm 52.1$ $\Delta H^\ddagger = 55.3 \text{ kJ mol}^{-1}$
 $b = 4.717 \pm 0.840$ $\Delta S^\ddagger = -107.3 \text{ J mol}^{-1} \text{ K}^{-1}$
 $r = -0.997$

the values k_1 on the concentration of the catalyst in the reaction mixture according to the equation

$$\ln k_1 = n \ln [C] + \ln k_3 \quad (12)$$

Values of the activation energy E_A and the frequency factor P were calculated according to the Arrhenius equation (13) from the dependence of the rate constants k_3 on absolute temperature T (Tables 3 and 4)

$$\ln k_3 = E_A/(RT) + \ln P \quad (13)$$

The values of activation enthalpy ΔH^\ddagger and activation entropy ΔS^\ddagger were calculated according to the Eyring equation

$$\ln(k_3/T) = -(\Delta H^\ddagger/RT) + (\Delta S^\ddagger/R) + \ln(k_B/h) \quad (14)$$

where R , k_B , h are the gas, the Boltzmann, and the Planck's constant, respectively. The results are presented in Tables 3 and 4. In all the mentioned calculations the method of least squares has been used.

Discussion

The compound N was chosen for our study because it cyclizes at room temperature at a reasonable rate and this compound as well as the product of cyclization well and quickly dissolve in polar solvents in concentrations suitable for the kinetic measurements. Also in the electronic spectra of the compounds N and Q there are regions in which a significant difference in their values of molar absorption coefficient exists having essential influence on the results of the measurements.

As a solvent acetonitrile was chosen due to good solubility of both compounds N and Q and because it can easily be purified and prepared anhydrous to be able to serve for our measurement.

Water and methanol were found to have an accelerating influence on the cyclization [2] and therefore we used them as catalysts. The influence of primary, secondary or tertiary amines as catalysts on the reaction rate of the cyclization could not be quantitatively evaluated because of their interaction with a proton. Both substrate N and compound Q in their presence lose proton like in the presence of inorganic bases (sodium hydroxide, ammonia, sodium carbonate, *etc.*). As a response to it is the bathochromic and hyperchromic shift of the longwavelength band in the UV—VIS spectra. Similar changes were observed after splitting off of a proton from substituted 2-nitrophenylguanidines, -thio-ureas, and -ureas [6].

The cyclization reaction described by the reaction equations (A—C) is in the first approach considered to be irreversible. The solution of N in the mixture of acetonitrile and water ($\varphi_r = 4:1$) after 24 h of the reaction showed that the concentration of Q calculated from the Lambert—Beer law corresponded to the starting concentration $[N]_0$.

The relations between the reaction rate and the concentration of water or methanol show that the reaction rate of the cyclization is well described by eqns (3) and (6), respectively and simultaneously the 1st order of the reaction with respect to the concentration of the catalyst is confirmed. At the same time it is evident that the addition of methanol has a greater influence on the reaction rate than the addition of water of the same quantity.

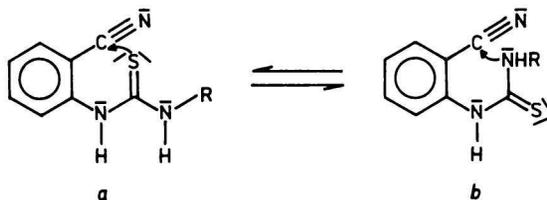
In case the concentration of water in the reaction mixture was 6.0 mmol dm^{-3} the value of the rate constant k_2 ($(6.09 \pm 2.11) \times 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$) was evaluated from eqn (10) from the dependence of the reaction mixture absorbance on time. The low value of the correlation coefficient ($r = 0.904$) in comparison with the correlation coefficient obtained from the experimental results and eqn (9) ($r = 0.989$) does not allow us to draw definite conclusion about the order of the reaction with respect to the concentration of substrate N. However, the starting concentration of substrate $[N]_0$ calculated from experimental data by relation (10) ($[N]_0 = 2.60 \text{ mol dm}^{-3}$) is in comparison with the actual value ($2.04 \times 10^{-4} \text{ mol dm}^{-3}$) by about four orders higher. On the other hand, the value $[N]_0 = 1.89 \times 10^{-4} \text{ mol dm}^{-3}$ calculated from eqn (9) shows that the studied reaction is well described by relations (1) and (4), respectively.

Thus obtained experimental data on the influence of the reaction medium on the reaction rate of the cyclization of N to Q and the influence of the substituent at position 3 of compound N on the course of its cyclization enable us to think about a probable mechanism of this action.

The compound N or generally 2-(3-R-thioureido)benzonitrile can exist due to restrictions of free rotation around the bond N—(C=S) [7, 8] of the thioureido group in several conformations being in thermodynamic equilibrium. As can be seen from the molecular model of the compound N there are two conformations *a* and *b* significant from the viewpoint of cyclization (Scheme 2; under consideration that the most energetically advantageous system is that with the maximum overlap of *p*-orbitals of carbon atoms with the lone electron pairs of nitrogen atoms and with the minimalized repulsion of the bound atoms or groups).

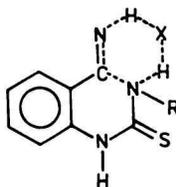
Conformation *a* where one can expect an interaction of the sulfur atom of the thioureido group with the carbon atom of the cyano group might be the conformation taking part in the cyclization reaction of the substrate in concentrated sulfuric acid giving rise to 2-amino-substituted 4*H*-4-iminobenzo-[*d*]-[1,3]-thiazines [9]. Conformation *b* seems to be advantageous for the forma-

tion of the quinazoline ring. It is characterized by the interaction of the donor-acceptor type between the lone electron pair of N-3 atom and the carbon atom of the cyano group. This interaction gets more pronounced during the rotation of the lone electron pair of N-3 atom towards the carbon atom of the cyano group under simultaneous deformation of the bond angle C—C=N from former 180° to the value of about 120° . In this situation the orientation of the hydrogen atom to N-3 atom is disadvantageous for an intramolecular transfer. Its migration in a state very close to a transition state can proceed in two ways.



Scheme 2

In case there is a proton acceptor of the type HX (water, methanol, *etc.*) in the system, a coordination of the hydrogen atom being at N-3 with the lone electron pair of nitrogen atom of the cyano group can take place. Thus formed six-membered transition system after redistribution of the electron density (bonds) and catalyst HX splitting off forms the quinazoline ring. The existence of such a highly organized system could be supported by the calculated values of activation entropy and the frequency factor for the transition state with the presence of molecule of water or methanol (Tables 3 and 4). The values of the activation entropy show [10, 11] that the transition state with the molecule of methanol is more organized. On the other hand, the values of the activation energy or enthalpy show that in this case the reaction overcame a lower energetic barrier.



Formula 1

In the second case when the catalyst is not present the transfer of proton probably takes place also through a cyclic transition state (Formula 1) formed

from two molecules of substrate by the interaction of the nitrogen atom of the deformed cyano group with the hydrogen atom bound at N-3 of the second molecule.

One can assume that due to the high value of the activation entropy and also the high value of the activation enthalpy the reaction needs more energy to be able to overcome such a transition state than it is needed in the presence of a catalyst HX. Therefore without the catalyst the cyclization can proceed at higher temperatures only.

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