

4-Substituted 2-nitrophenylguanidines

III. Kinetic study of the cyclization

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Dedicated to Professor RNDr. J. Hadáček, in honour of his 80th birthday

The rate of cyclization of 4-X-2-nitrophenylguanidines to 3-amino-7-X-1,2,4-benzotriazine-1-oxides was searched in dependence on pH and substituent X by spectrophotometry.

The cyclization was found to be an irreversible reaction. The rate constant was shown to be a linear function of the hydroxide ion concentration. The values of the logarithm of rate constant of cyclization of the individual 4-substituted 2-nitroguanidines are in good correlation with Hammett σ_m constants of substituents X.

The dependence of the reaction rate on the guanidine concentration and on the temperature of reaction was investigated for the derivative with X = OCH₃. It was proved that the reaction is of the first order with respect to substrate. The energy of activation and the frequency factor were calculated from the dependence of the reaction rate on temperature and from Arrhenius equation. The entropy and the enthalpy of activation were calculated from Eyring equation.

Спектрофотометрически изучалась скорость циклизации 4-X-2-нитрофенилгуанидинов в 3-амино-7-X-1,2,4-бензотриазин-1-оксиды в зависимости от pH реакционной среды и заместителя X.

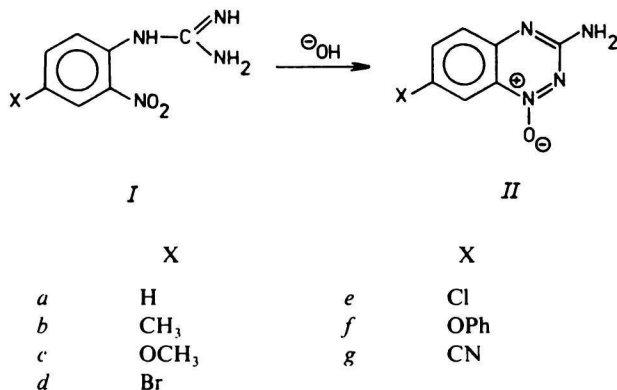
Показано, что циклизация является необратимой реакцией, константа скорости которой линейно зависит от концентрации гидроксид-ионов, и что значения логарифмов констант скоростей циклизации отдельных замещенных в положении 4 2-нитрофенилгуанидинов хорошо коррелируют с величинами Гамметтовых констант σ_m заместителей X.

Для X = OCH₃ изучена зависимость скорости реакции от концентрации исходного гуанидинового производного и от температуры. Обнаружено, что реакция имеет первый порядок по субстрату. Исходя из зависимости скорости реакции от температуры и из уравнения Аррениуса, была вычислена энергия активации реакции и частотный фактор, а, исходя из уравнения Эйринга, величины энтальпии и энтропии активации данной реакции.

4-Substituted 2-nitrophenylguanidines cyclize under treatment of boiling alkaline hydroxide to 3-amino-7-substituted 1,2,4-benzotriazine-1-oxides [1, 2].

In order to learn more about the pathway of this cyclization reaction we carried out kinetic measurement. The reaction rate was searched in dependence on hydroxide ion concentration in the series of compounds *I* (Scheme 1).

The dependence of the reaction rate on substrate concentration and temperature was investigated with compound *Ic*.



Scheme 1

Experimental

Spectrophotometric measurements were carried out on Unicam SP 1800 with the thermostated cell compartment SP 874. pH was measured on pH-meter Radelkis OP-208 with the combined glass electrode OP-8083. The calibration was carried out with the set of standard buffer solutions supplied by the Institute of Sera and Vaccines, Prague and with the saturated calcium hydroxide aqueous solution at 25 °C (pH = 12.454) [3].

Conditions of measurement

The course of the reaction was followed by spectrophotometry. The increase in absorbance of the forming benzotriazine derivative in dependence on time at constant temperature and constant value of pH was investigated. The absorbance was measured at the wavelength of the maximum absorption of compounds *II* (Scheme 1) in the longwave region of the spectrum (Table 1).

The values of pH were set up with Sørensen buffer [4] the pH—temperature dependence of which is known from 20—70 °C. An extrapolation was made to the temperature of 80 °C.

The reaction was carried out in a flask under a cooler with a stopper with potassium hydroxide. The volume of the reaction mixture was 200 cm³. The apparatus was thermo-

Table 1

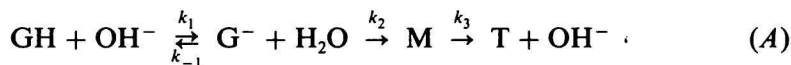
Values of the molar absorption coefficient ϵ and the wavelengths λ_{\max} of the compounds *II* at which the kinetics was measured

Compound	λ_{\max}/nm	$\epsilon \cdot 10^{-3}/(\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1})$
<i>Ila</i>	445	4.97
<i>Ilb</i>	426	3.30
<i>Ilc</i>	414	4.54
<i>Ild</i>	424	4.80
<i>Ile</i>	422	4.96
<i>Ilf</i>	442	4.01
<i>Ilg</i>	432	4.01

stated. About 10—15 samples were taken away in chosen time periods. The sample of the volume of 2 cm³ was immediately cooled down to room temperature and then recorded on the spectrophotometer in a 1 cm cell at 25 °C.

Evaluation of the kinetic data

The following scheme of the reaction was proposed for the compilation of the kinetic equation



where GH is compound *I*, T is compound *II*, and M is intermediate.

The first reaction step which is characterized by the constants k_1 and k_{-1} seems to be reversible in accordance with the behaviour of compound *I* in both alkaline hydroxide and mineral acid. The irreversibility of the whole reaction was proved by spectrophotometry. The concentration of the product formed in the reaction, *i.e.* 3-amino-1,2,4-benzotriazine-1-oxide, corresponds, after a sufficiently long boiling in alkaline medium, to the concentration of the starting stuff.

The rate of concentration decrease of the starting 2-nitrophenylguanidine (compound *Ia—Ih*) in alkaline aqueous solution may be derived from eqn (A) and has the following form

$$-\frac{d[\text{GH}]}{dt} = k_1[\text{GH}][\text{OH}^-] - k_{-1}[\text{G}^-][\text{H}_2\text{O}] \quad (1)$$

where $[\text{GH}]$, $[\text{OH}^-]$, $[\text{G}^-]$ are the compound concentrations, k_i is the rate constant of a partial reaction, and t is time.

When one takes into account the stationary state then relation (2) is valid

$$\frac{d[G^-]}{dt} = k_1[GH][OH^-] - k_{-1}[G^-][H_2O] - k_2[G^-] = 0 \quad (2)$$

and from this for the concentration of G^- it holds

$$[G^-] = \frac{k_1}{k_{-1}[H_2O] + k_2} [GH][OH^-] \quad (3)$$

Using expression (3) in eqn (1) we come to expression (4) for the rate of the concentration decrease of the compound GH

$$-\frac{d[GH]}{dt} = \frac{k_1 k_2}{k_{-1}[H_2O] + k_2} [GH][OH^-] \quad (4)$$

Provided we work in a buffer solution expression (5) is valid

$$-\frac{d[GH]}{dt} = k_1[GH] \quad (5)$$

where

$$k_1 = k_{11}[OH^-] = \frac{k_1 k_2}{k_{-1}[H_2O] + k_2} [OH^-] \quad (6)$$

or

$$-\frac{d[GH]}{dt} = k_{11}[OH^-][GH] \quad (7)$$

The rate constant k_1 characterizes a pseudounimolecular reaction of compound *I* to *II* in a buffered medium, constant k_{11} characterizes a bimolecular course of the reaction.

The integration of eqn (5) led to relation (8) expressing the dependence of the starting compound *I* concentration on the time

$$\ln \frac{[GH]}{[GH]_0} = -k_1 t \quad (8)$$

where $[GH]_0$ is the concentration of the starting compound *I*.

Absorbance *A* of the reaction mixture in a cell ($l_0 = 1$ cm) in accordance with the Lambert—Beer law at a constant wavelength and on the assumption that the molar absorption coefficient ϵ_M of the compound *M* does not differ very much from the molar absorption coefficient of the compound G^- and the other components do not absorb in this region, is given by the following equation

$$A = A_{GH} + A_{G^-} + A_T = (\epsilon_{GH}[GH] + \epsilon_{G^-}[G^-] + \epsilon_T[T]) l_0 \quad (9)$$

The starting concentration of compound *I* in the given time may be expressed by the relation

$$[\text{GH}]_0 = [\text{GH}] + [\text{G}^-] + [\text{T}] \quad (10)$$

and then for the first step of the cyclization reaction, *i.e.* the acid—base equilibrium in eqn (A), in diluted aqueous solutions it is valid

$$K_a = \frac{k_1}{k_{-1}} = \frac{[\text{G}^-][\text{H}_2\text{O}]}{[\text{GH}][\text{OH}^-]} \quad (11)$$

and from this

$$[\text{G}^-] = \frac{K_a [\text{GH}][\text{OH}^-]}{[\text{H}_2\text{O}]} \quad (12)$$

After adding relation (12) into eqns (9) and (10) and after rearrangement we get a relation for [GH] in arbitrary time

$$[\text{GH}] = \frac{A - \varepsilon_T [\text{GH}] l_0}{((\varepsilon_{\text{GH}} - \varepsilon_T) + K_a [\text{OH}^-] (\varepsilon_{\text{G}^-} - \varepsilon_T) [\text{H}_2\text{O}]^{-1}) l_0} \quad (13)$$

The addition of this relation into eqn (8) leads to the relation

$$\begin{aligned} \log(A - \varepsilon_T [\text{GH}]_0 l_0) = & -\frac{k_1 t}{2.303} + \log\{[\text{GH}]_0 [(\varepsilon_{\text{GH}} - \varepsilon_T) l_0 + \\ & + K_a [\text{H}_2\text{O}]^{-1} [\text{OH}^-] (\varepsilon_{\text{G}^-} - \varepsilon_T) l_0]\} \end{aligned} \quad (14)$$

The function of logarithm is defined for the values greater than zero only.

As we found out relation (15) is valid

$$\varepsilon_T > \varepsilon_{\text{G}^-} > \varepsilon_{\text{GH}} \quad (15)$$

and therefore for the argument of the logarithm in eqn (14) on the right side it holds

$$[\text{GH}]_0 [(\varepsilon_{\text{GH}} - \varepsilon_T) l_0 + K_a [\text{H}_2\text{O}]^{-1} [\text{OH}^-] (\varepsilon_{\text{G}^-} - \varepsilon_T) l_0] < 0 \quad (16)$$

and so

$$(\varepsilon_{\text{GH}} - \varepsilon_T) l_0 + K_a [\text{H}_2\text{O}]^{-1} [\text{OH}^-] (\varepsilon_{\text{G}^-} - \varepsilon_T) l_0 < 0 \quad (17)$$

Therefore the argument of the logarithm on the right side of eqn (14) must be in absolute value. The argument on the left side of eqn (14) at a conversion smaller than 100 % in accordance with eqns (10) and (15) must fulfil the relation

$$A - \varepsilon_T [\text{GH}]_0 l_0 > 0 \quad (18)$$

Table 2

Survey of the measured rate constants k_i/s^{-1} and $k_{ii}/dm^3 s^{-1} mol^{-1}$ of the cyclization of compounds *I* to *II* in dependence on pH at 70°C

Compound	$-\log\{k_i\}$	$-\log\{k_{ii}\}$	pH	Compound	$-\log\{k_i\}$	$-\log\{k_{ii}\}$	pH		
<i>Ia</i>	5.912	2.804	9.57	<i>Ic</i>	5.915	2.577	9.34		
	5.657	2.799	9.82		5.642	2.564	9.60		
	5.585	2.797	9.89		5.298	2.570	9.95		
	5.443	2.795	10.03		5.191	2.611	10.10		
	5.221	2.791	10.25		4.983	2.583	10.28		
	4.859	2.759	10.58		4.695	2.555	10.54		
	4.614	2.746	10.81		4.589	2.549	10.64		
	4.573	2.753	10.86		4.320	2.542	10.90		
	4.264	2.738	11.17		4.029	2.531	11.18		
	<i>Ib</i>	6.021	3.033		9.69	<i>Id</i>	5.425	1.587	8.84
		5.744	3.104		10.04		5.047	1.549	9.18
5.626		3.058	10.11	4.856	1.568		9.39		
5.514		3.084	10.25	4.517	1.589		9.75		
5.340		3.070	10.41	4.222	1.592		10.05		
5.125		3.045	10.60	3.869	1.549		10.38		
5.091		3.123	10.71	3.613	1.565		10.63		
4.711		3.053	11.02	3.457	1.557		10.78		
4.546		3.048	11.18	3.061	1.543		11.16		

Table 2 (Continued)

Compound	$-\log\{k_1\}$	$-\log\{k_{11}\}$	pH	Compound	$-\log\{k_1\}$	$-\log\{k_{11}\}$	pH
<i>Ie</i>	5.440	1.642	8.88	<i>If</i>	6.007	2.219	8.88
	5.349	1.661	8.99		5.674	2.236	9.24
	5.105	1.637	9.21		5.366	2.238	9.55
	4.796	1.658	9.54		5.091	2.233	9.82
	4.534	1.656	9.80		4.878	2.220	10.02
	4.210	1.652	10.12		4.326	2.208	10.56
	3.914	1.636	10.40		4.105	2.207	10.78
	3.536	1.608	10.75		3.930	2.212	10.96
	3.264	1.626	11.04		3.659	2.201	11.22
					<i>Ig</i>	5.221	0.963
			4.766	0.948		8.86	
			4.625	0.937		8.99	
			4.520	0.942		9.10	
			4.346	0.938		9.27	
			3.989	0.941		9.63	
			3.711	0.943		9.91	
			3.462	0.924		10.14	
			3.000	0.912		10.59	

Relation (14) is an expression of the straight line equation and was used for calculations of rate constant k_1 from the absorbance dependence on time.

The absorbance dependence on the time gained by spectrophotometry was worked up for individual measurements by the method of the least squares [6] with a Texas Instruments 58 calculator. The logarithmic form of eqn (6) for numerical values of arguments is as follows

$$\log \{k_1\} = \log \{k_{11}\} + \log \{[\text{OH}^-]\} \quad (19)$$

This, after addition of expression (20) for the concentration of hydroxide anion, drawn from the expression for the autoprotolysis constant of water, gives relation (21) for the rate constant of the cyclization in case of the bimolecular course.

$$[\text{OH}^-] = \frac{K_w^T}{[\text{H}^+]} \quad (20)$$

$$\log \{k_{11}\} = \log \{k_1\} - \log \{K_w^T\} - \text{pH} \quad (21)$$

where K_w^T is the autoprotolysis constant of water at the temperature T [5].

Calculated values of $\log \{k_1\}$ and $\log \{k_{11}\}$ in dependence on pH values for the individual derivatives are given in Table 2. A survey of the rate constants of the cyclization of compound *Ic* to *I1c* in dependence on temperature is given in Table 3.

The dependence of $\log k_1$ on substrate concentration for compound *Ic* is summarized in Table 4. The correlation of $\log k_{11}$ with the Hammett σ_m constants is presented in Table 5.

Values of the activation energy and the logarithm of the "pre-exponential factor" A were calculated according to the Arrhenius equation (22) from the dependence of $\log k_{11}$ on temperature for compound *Ic*.

$$\log \{k_{11}\} = \frac{E_A}{RT \ln 10} + \log A \quad (22)$$

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

$$\log \left\{ \frac{k_{11}}{T} \right\} = - \frac{\Delta H^\ddagger}{RT \ln 10} + \frac{\Delta S^\ddagger}{R \ln 10} + \log \left\{ \frac{k_B \kappa}{h} \right\} \quad (23)$$

where k_B is the Boltzman constant, h Planck's constant, R universal gas constant, and κ transmission coefficient (supposed to be equal to 1). Results are presented in Table 5.

Table 3

Survey of the measured rate constants k_1/s^{-1} and $k_{11}/dm^3 s^{-1} mol^{-1}$ of the cyclization of compound *Ic* to *IIc* in dependence on pH at the temperatures of 50, 60, and 80 °C

Compound	$\theta/^\circ C$	$-\log \{k_1\}$	$-\log \{k_{11}\}$	pH
<i>Ic</i>	50	6.579	3.277	9.92
		6.415	3.253	10.09
		6.228	3.266	10.29
		6.071	3.279	10.46
		5.728	3.248	10.80
		5.592	3.260	10.92
		5.406	3.256	11.10
		5.184	3.242	11.31
		5.007	3.235	11.48
<i>Ic</i>	60	6.130	3.010	9.78
		5.801	3.011	10.11
		5.680	2.990	10.21
		5.457	3.027	10.47
		5.250	3.000	10.65
		5.076	2.996	10.82
		4.923	2.993	10.97
		4.553	2.953	11.30
		4.361	2.941	11.48
<i>Ic</i>	80	3.510	2.141	11.10
		3.933	2.183	10.72
		4.203	2.183	10.45
		4.464	2.195	10.20
		4.835	2.166	9.80
		5.175	2.206	9.50
		5.345	2.246	9.37
		5.786	2.187	8.87
		6.108	2.259	8.62

Table 4

Survey of the measured rate constant k_1 of the cyclization of compound *Ic* to *IIc* in dependence on the starting concentration c_0 at the temperature of 70 °C and at pH 10.64

$c_0 \cdot 10^4 / (mol dm^{-3})$	$k_1 \cdot 10^3 / s^{-1}$	$\log \{c_0\}$	$\log \{k_1\}$
1.25	0.478	-3.903	-3.320
3.75	1.546	-3.426	-2.811
7.10	3.064	-3.149	-2.514
9.33	4.056	-3.030	-2.392
12.8	5.644	-2.893	-2.248

$$\log \{k_1\} = a \cdot \log \{c_0\} + b$$

$$a = 1.062 \pm 0.011$$

$$b = 0.828 \pm 0.004$$

$$r = 0.999$$

Table 5

Values of the rate constant k_{II} logarithm ($k_{II}/\text{dm}^3 \text{s}^{-1} \text{mol}^{-1}$) of the cyclization of compound *I* to *II* and their dependence on the Hammett σ_m constants of the substituents X at 70°C and the dependence on the temperature of the cyclization of compound *Ic* to *IIc*

$-\log \{k_{II}\}$	X	$\theta/^\circ\text{C}$	σ_m	Ref.
3.069 ± 0.024	CH ₃	70	-0.07	[7]
1.641 ± 0.014	Cl	70	0.37	[7]
2.776 ± 0.021	H	70	0.00	
1.567 ± 0.015	Br	70	0.39	[7]
2.219 ± 0.014	OPh	70	0.25	[8]
0.939 ± 0.011	CN	70	0.62	[8]
2.565 ± 0.019	OCH ₃	70	0.12	[7]
2.196 ± 0.030	OCH ₃	80	—	
2.991 ± 0.023	OCH ₃	60	—	
3.257 ± 0.012	OCH ₃	50	—	

- $\log \{k_{II}\} = \rho\sigma_m + b$
 $\rho = 3.115 \pm 0.127$
 $b = -2.860 \pm 0.042$
 $r = 0.994$
- $\log \{k_{II}\} = -\frac{a}{\{T\}} + b$
 $a = (-4.109 \pm 0.485) \times 10^3$
 $b = 9.414 \pm 0.894 = \log A$
 $r = -0.994$
 $E_A = 78.753 \text{ kJ mol}^{-1}$
 $A = (1.226 \pm 0.125) \times 10^4 \text{ dm}^3 \text{ s}^{-1} \text{ mol}^{-1}$
- $\log \left\{ \frac{k_{II}}{T} \right\} = \frac{a}{\{T\}} + b$
 $a = -3962.7 \pm 15.9$
 $b = 6.450 \pm 0.267$
 $r = -0.994$
 $H^* = 75.874 \text{ kJ mol}^{-1}$
 $S^* = -74.06 \text{ J mol}^{-1} \text{ K}^{-1}$

where r is the correlation coefficient, E_A activation energy, and A frequency factor.

Results and discussion

A linear dependence of the logarithm of the rate constant k_1 for the pseudo-unimolecular course of the reaction on the concentration of hydroxide ion (the slope very close to 1) was proved by the results of the kinetic measurements of the cyclization reaction. So it was shown that the reaction is of the first order with respect to the concentration of hydroxide ion, which corresponds with the proposed general scheme of the reaction.

The results of the kinetic measurements of compound *Ic* show that the cyclization follows the kinetic equation of the first order with respect to the starting material concentration. The dependence of the numerical value of rate

constant k_1 logarithm on the numerical value of concentration logarithm of compound Ic is linear with the slope equal to 1.062. Due to a structural resemblance we suppose analogously this relation to be valid for the other derivatives of the studied series as well.

At the same time the values of the logarithm of the rate constant k_{11} for the entire second order of the reaction were proved to undergo a good correlation with the Hammett σ_m constant of the substituents X in position 4. The reaction constant ρ has the value +3.115 and the coefficient of correlation $r = 0.994$.

The value of the reaction constant ρ indicates that a substituent in position 4 of the starting compound I has a significant influence upon the electron density at the nitrogen atom of the nitro group. (An electron deficit is necessary for the ring closure of the benzotriazine ring during the nucleophilic attack at the mentioned nitrogen atom with the nitrogen atom of amino, or imino group of the guanidine part of the molecule.) At the same time it is shown that the substituent X has no influence upon the nucleophilicity of the attacking nitrogen atom of the guanidine part of molecule which is probably not in conjugation with the nitrophenyl system (M-effect is not possible) and the inductive effect is negligible for such a distance.

The dependence of the rate constant k_1 logarithm on the temperature for the derivative Ic was investigated at 50, 60, 70, and 80 °C. The high calculated values of the entropy of activation $\Delta S^\ddagger = -74 \text{ J mol}^{-1} \text{ K}^{-1}$ and the logarithm of the "pre-exponential factor" $\log A = 9.114 \text{ dm}^3 \text{ s}^{-1} \text{ mol}^{-1}$ indicate a cyclic transition state in the rate-limiting reaction step [7, 9].

The energy of activation $E_A = 78.7 \text{ kJ mol}^{-1}$ and the enthalpy of activation $\Delta H^\ddagger = 75.8 \text{ kJ mol}^{-1}$ were calculated from the temperature dependence. These values refer to a significant temperature dependence of the cyclization rate and to the fact that the reaction proceeds through a highly energetic transition state.

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