Kinetics and Mechanism of the Base-Catalysed Cyclisation of 2-(Substituted benzoylamino)benzamides Giving Quinazolin-4-one and Quinazolin-4-thione Derivatives

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Dedicated to Professor JaromírKaválek on the occasion of his 65th birthday

Keywords: Kinetics / Cyclisations / Sulfur / Nitrogen heterocycles

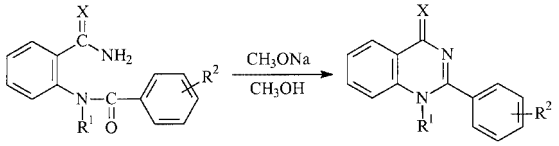
Acylation of 2-aminobenzamide and 2-(methylamino)benzamide with substituted benzoyl chlorides in acetone has been used to prepare the respective 2-(substituted benzoylamino)-benzamides **1a–i**, which were then subjected to sodium methoxide catalysed ring closure to give the respective 2-(substituted phenyl)quinazolin-4-ones **2a–i**. The kinetics of the cyclisation reactions were monitored by UV/Vis spectroscopy at 25 °C in methanolic solutions of sodium methoxide. In the case of 2-(substituted benzoylamino)benzamides **1a–i** and 2-(substituted benzoylamino)thiobenzamides **3a–j**, non-linear dependences of observed rate constants k_{obs} on the sodium methoxide concentrations were obtained, the shape of them being typical of a reaction with rapid pre-equilibrium. All the cyclisation reactions satisfactorily obeyed the Hammett correlation. In the case of 2-[(benzoyl)(methyl)amino]benzamides **1e–i**, increasing sodium methoxide concentration resulted in a progressive increase in k_{obs} values which is probably due to formation of dianion. In the case of 2-(substituted benzoylamino)thiobenzamides **3b** and **3h**, which differ in the presence of a methyl group on the nitrogen atom the values of the activation Gibbs energy $\Delta G^{\ddagger}_{25\,°C}$, activation enthalpy $\Delta H^{\ddagger}_{25\,°C}$, and activation entropy $\Delta S^{\ddagger}_{25\,°C}$ for their respective cyclisations to 2-(substituted phenyl)quinazoline-4-thiones **4b** and **4h** were determined. Whereas the $\Delta G^{\ddagger}_{25\,°C}$ values were very close for the two substances, the $\Delta H^{\ddagger}_{25\,°C}$ and $\Delta S^{\ddagger}_{25\,°C}$ distinctly differed. This was interpreted by the enthalpy and entropy factors operating against each other in the cyclisation.

Introduction

The derivatives of quinazolin-4-one and -4-thione are potential medical drugs.[1] They started to attract attention after the discovery of the antimalarial activity of the natural alkaloid Febrifugin. Along with the development of new antimalarials it was found that quinazolin-4-one derivatives show a general calming effect on the CNS and possess hypnotic,[2] sedative, analgesic, antipyretic,[3] and diuretic[4] properties. At present, about 25 preparations based on quinazolin-4-one are registered.[5]

In our previous paper[6] we dealt with the synthesis and structure of 2-(benzoylamino)thiobenzamides and products of their cyclisation in basic medium, i.e. 2-phenylquinazoline-4-thiones.

The aim of the present paper is to study the kinetics and mechanism of base-catalysed ring closure of substituted 2-(benzoylamino)thiobenzamides (Scheme 1) and to compare their reactivity with that of their oxygen analogues.



1: X = O
3: X = S

2: X = O
4: X = S

1, 2	a	b	c	d	e	f	g	h	i
R^1	H	H	H	H	CH_3	CH_3	CH_3	CH_3	CH_3
R^2	H	4-CH_3	4-Cl	4-NO_2	H	4-CH_3	4-OCH_3	4-Cl	4-NO_2

3, 4	a	b	c	d	e	f	g	h	i	j
R^1	H	H	H	H	H	H	CH_3	CH_3	CH_3	CH_3
R^2	H	4-$N(CH_3)_2$	4-CH_3	4-OCH_3	4-Cl	3-NO_2	H	4-$N(CH_3)_2$	4-CH_3	4-CH_3

Scheme 1

Results and Discussion

The cyclisation reaction was studied in detail using methanolic solutions of sodium methoxide in the concentration range of 0.01−1.6 mol·L^{-1}. The cyclisation rate has been found to depend nonlinearly on the concentration of the base used, i.e. sodium methoxide, which applies to various

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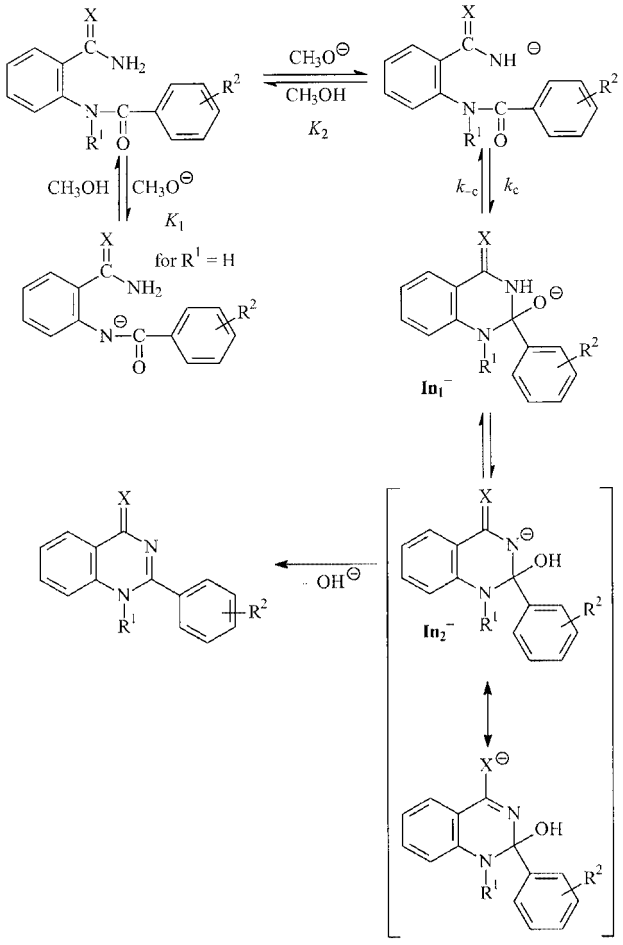
substituents both at the nitrogen atom (R^1 = H, CH_3) and at the benzene ring of the starting 2-(benzoylamino)benzamide or 2-(benzoylamino)thiobenzamide. Scheme 2 can be suggested for the said ring closure



Scheme 2

In the sodium methoxide solutions used, a fast pre-equilibrium deprotonation takes place first: a proton is split off from both the nitrogen atom adjacent to benzene ring (if R^1 = H; the so-called blind alley) and the terminal nitrogen atom ($CXNH_2$ group). The nucleophilic terminal anion formed in the latter case attacks the carbonyl group of the benzoyl moiety to give a tetrahedral intermediate, which undergoes a proton transfer from nitrogen to oxygen atom ($\mathbf{In_1}^- \rightarrow \mathbf{In_2}^-$) and then splits off a hydroxide anion to produce 2-phenylquinazolin-4-one or 2-phenylquinazoline-4-thione, respectively.

1. Cyclisation of 2-[(Benzoyl)(methyl)amino]benzamides 1e−i and -thiobenzamides 3g−j

In the case of the oxygen derivatives **1e−i** (Figure 1), a gradual increase in slope of the dependence of k_{obs} vs. [CH_3ONa] is observed. This can be due to a catalytic effect of the sodium cation.[7a−7c] Therefore, we studied the effect of Na^+ on the cyclisation rate and/or the trend of the k_{obs} vs. [CH_3ONa] dependence. In the presence of an equimolar amount of 18-crown-6 ether, which is an efficient complex former for the Na^+ cation, the cyclisation reaction was slowed down (Figure 1) but the trend of k_{obs} vs. [CH_3ONa] dependence remained unchanged. In addition to that, further additions of 18-crown-6 ether caused further deceleration of the reaction, which can be due to the change of the medium. When the Na^+ concentration was increased by addition of sodium perchlorate at a constant concentration of sodium methoxide, the observed rate constant increased but slightly (Table 1). These findings support the idea that the catalytic effect of Na^+ is small, which is connected with the impossibility of effective stabilisation of the transition state of the rate-limiting step. The catalysis by the sodium ion in methanol is only significant if Na^+ is strongly bound by chelate formation in the transition state.[8a−8c]

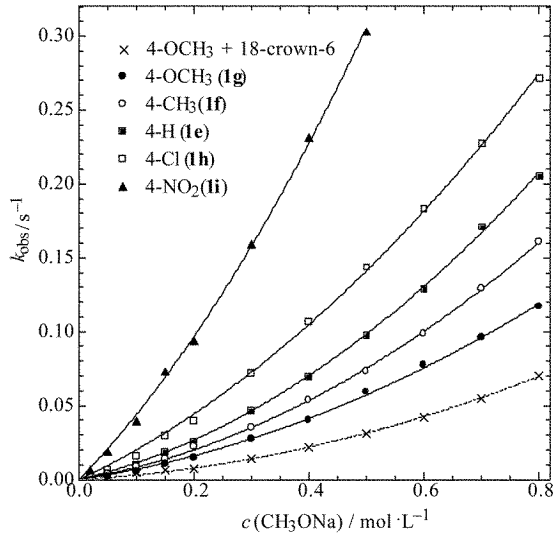


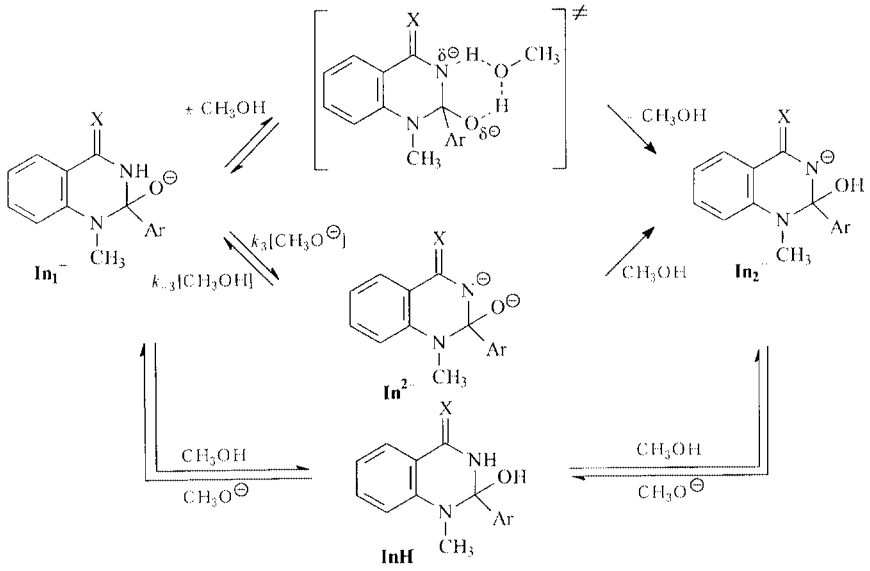
Figure 1. Observed rate constant of the cyclisation (k_{obs}/s^{-1}) of the 2-[(benzoyl)(methyl)amino]benzamides **1e−i** vs. the concentration of sodium methoxide (c/mol·L^{-1}) at 25 °C

Another possibility lies in the participation of two CH_3ONa molecules in the formation of the transition state of the rate-limiting step. That means that the formation of $\mathbf{In_1}^-$ is preceded by a pre-equilibrium, and the rate-limiting step consists of a reaction of this $\mathbf{In_1}^-$ with one CH_3ONa molecule giving the dianion $\mathbf{In^{2-}}$. In principle, the intermediate $\mathbf{In_2}^-$ can be formed by three reaction pathways (Scheme 3).

The first possibility is a solvent-mediated proton transfer[9] from the nitrogen to the oxygen atom mediated by one or two methanol molecules either through a synchronous mechanism or through a cyclic transition state or via intermediate **InH**. The second possibility consists of the formation of the dianion[10,11] of the tetrahedral intermediate $\mathbf{In^{2-}}$, which on further reaction with methanol will give $\mathbf{In_2}^-$. On the basis of Schemes 2 and 3 and using the Bodenstein approximation, we derived Equation (1) for the observed rate constant, where k_3 is the rate constant of the formation of $\mathbf{In^{2-}}$ by the reaction with CH_3ONa, and k_S is the rate constant of the solvent-mediated proton transfer

Table 1. Cyclisation of 2-[(4-methoxybenzoyl)(methyl)amino]benzamide (**1g**) in 0.20 mol·L^{-1} sodium methoxide at 25 °C at varying concentrations of sodium perchlorate

c(NaClO$_4$) [mol·L^{-1}]	$10^2 \cdot k_{poz}$ [s^{-1}] **1g**	c(NaClO$_4$) [mol·L^{-1}]	$10^2 \cdot k_{poz}$ [s^{-1}] **1g**
0.10	1.55	0.40	1.73
0.20	1.55	0.50	1.79
0.30	1.59	0.60	1.90



Scheme 3

from the nitrogen to the oxygen atom through the cyclic mechanism and/or via the **InH** intermediate.

$$k_{obs} = \{k_c \cdot K_2 \cdot [CH_3O^-] \cdot (k_3 \cdot [CH_3O^-] + k_S)\} / (k_{-c} + k_3 \cdot [CH_3O^-] + k_S) \quad (1)$$

When $\mathbf{In_1}^-$ is formed in a fast pre-equilibrium ($k_{-c} >> k_3 \cdot [CH_3ONa] + k_S$), Equation (1) will be simplified after dividing it through [CH_3ONa] to give Equation (2).

$$k_{obs}/[CH_3O^-] = K_c \cdot K_2 \cdot (k_3 \cdot [CH_3O^-] + k_S) \quad (2)$$

The dependence of k_{obs}/[CH_3ONa] vs. [CH_3ONa] is presented in Figure 2. The intercepts at the y axis correspond to the solvent-mediated proton transfer, and the slope of the linear dependence (for R^2 = OCH_3, CH_3, and H) corresponds to the reaction of $\mathbf{In_1}^-$ with CH_3ONa. With derivative **1h** (R^2 = Cl) and still more with **1i** (R^2 = NO_2), increasing sodium methoxide concentration causes the slope to drop because the value of k_3[CH_3ONa] + k_S approaches to k_{-c}. On further increasing the CH_3ONa concentration, the formation of $\mathbf{In_1}^-$ would become rate-limiting, and the dependence again should be linear with a zero slope.

Figure 3 presents the dependence of the observed rate constant k_{obs} on the methoxide concentration for the individual sulfur derivatives **3g**–**j**. From the course of experimentally found dependences it follows that in this case the reaction order in methoxide is equal to one at low [CH_3ONa] values and gradually drops to zero at higher [CH_3ONa] values, which is characteristic of reactions with a fast pre-equilibrium followed by the rate-limiting step. In the compounds of the type −(C=S)−NH−R the proton at the nitrogen atom is much more acidic than that in the type −(C=O)−NH−R. For instance, the pK_a value of 4-nitrophenylthiourea is four orders of magnitude lower than that of 4-nitrophenylurea.[12] In thermodynamically unfavourable proton-transfers between oxygen and nitrogen atoms, the change in log$k$ becomes comparable[13] with that in logK_a, which means that the reaction of $\mathbf{In_1}^-$ with CH_3ONa is much faster for the sulfur derivatives than for the oxygen derivatives, and the formation of $\mathbf{In_1}^-$ becomes rate-limiting. For k_{obs} we can suggest Equation (3), which describes the reacting system very well, and the optimisation leads to values of parameters k_c (the cyclisation rate constant) and K_2 (equilibrium constant of the pre-equilibrium).

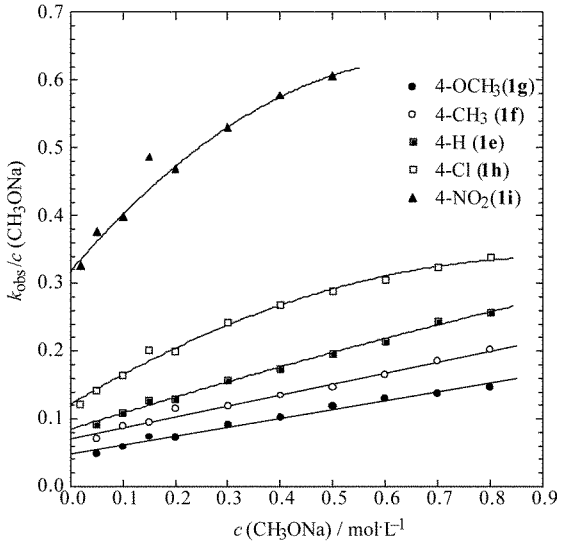


Figure 2. Observed rate constant of the cyclisation divided by the sodium methoxide concentration (k_{obs}/c) of 2-[(benzoyl)(methyl)amino]thiobenzamides **3g**−**j** vs. the concentration of sodium methoxide (c/mol·L^{-1}) at 25 °C

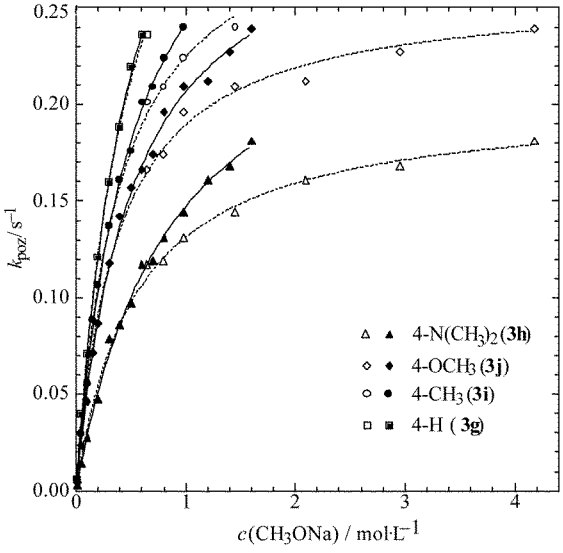


Figure 3. Observed rate constant of the cyclisation (k_{obs}/s^{-1}) of the 2-[(benzoyl)(methyl)amino]thiobenzamides **3g**−**j** vs. the concentration c (solid symbols and solid lines) and vs. the apparent concentration c' (open symbols and dashed lines) of sodium methoxide (c/mol·L^{-1}) calculated by means of the H_M function and Equation (5) at 25 °C

$$k_{obs} = (k_c \cdot K_2 \cdot [CH_3O^-])/(1 + K_2 \cdot [CH_3O^-]) \quad (3)$$

The cyclisation is very fast (the reaction half-life values are about 2 s at the highest sodium methoxide concentrations used) and that is why only the parameters k_c and K_2 (Table 2) could be found for the deactivated substrates **3g**−**j**. Since the pK_a value of thiobenzamide group is very high, the measurements had to be carried out in sodium methoxide solutions with concentrations above 0.6 M, where the basicity of medium is not expressed by [CH_3ONa] and the H_M function[14a,14b] defined by Equation (4) has to be used instead. However, the available literature does not give the H_M function for thiobenzamides and, therefore, we adopted the H_M function for formanilides[14c] and, using it and Equation (5), we calculated the corresponding (apparent − c') concentration of CH_3ONa.

Table 2. The parameters of cyclisation reaction obtained by optimising the data measured for derivatives **3g**−**j** using the sodium methoxide concentration (c/mol·L^{-1}) and the apparent concentration (c'/mol·L^{-1}) calculated from Equation (5)

Compound	R^2	k_c [s^{-1}]	K_2 [L·mol^{-1}]	k_c' [s^{-1}]	K_2' [L·mol^{-1}]
3g	H	0.448	1.86	0.419	2.06
3h	4-N(CH_3)$_2$	0.277	1.14	0.202	1.86
3i	4-CH_3	0.362	2.00	0.312	2.58
3j	4-OCH_3	0.312	1.96	0.259	2.71

$$H_M = pK_S(CH_3OH) + \log c_{CH_3ONa} - \log a_{CH_3OH} - \log(\gamma_B^-/\gamma_{BH}\gamma_{CH_3O^-}) \quad (4)$$

$$H_M = pK_S(CH_3OH) + \log c'_{CH_3ONa} \quad (5)$$

With the sulfur derivatives the rate-limiting step consists of the ring closure of the substrate anion. As the tetrahedral intermediate $\mathbf{In_1}^-$ formed is very unstable, the structure of the transition state will be close to that of this intermediate (the Hammond postulate), so the $\mathbf{In_1}^-$ structure can be used for a qualitative evaluation of the effect of the medium on the transition state, and the effect of the medium on the dissociation of formanilides can be compared with the formation of $\mathbf{In_1}^-$ in methanol. In the case of formanilides, the very strongly solvated CH_3O^- anion and relatively weakly solvated amide are transformed into a strongly solvated amide anion with delocalised charge. In the other case, the weakly solvated amide and thioamide group and strongly solvated CH_3O^- anion will produce the strongly solvated $\mathbf{In_1}^-$, whose charge is concentrated at the oxygen atom, hence the net change in solvation will be much smaller in this case. An analogous situation can be expected with the transition state, which is similar to the intermediate. Therefrom it can be concluded that the basicity of medium for this reaction will lie between the limit cases expressed by the CH_3ONa concentration and the H_M function (or apparent concentration c') for the amides.

The values presented in Table 2 show that the cyclisation constant decreases with increasing ability of the given substituent to donate electrons to the reaction centre. The value of constant K_2 depends only little on the substitution, and amounts to about 2 L·mol^{-1}. From the K_2 values and Equation (6) it is possible to calculate also pK_a of 2-[(benzoyl)(methyl)amino]thiobenzamides **3g**−**j**, which varies from 16.6 to 16.9. The autoprotolysis constant value[15] of methanol at 25 °C used is p$K_S(CH_3OH)$ = 16.916.

$$pK_a = pK_S(CH_3OH) + pK_2 \quad (6)$$

2. Cyclisation of 2-(Benzoylamino)benzamides 1a−d and -thiobenzamides 3a−f

For both groups of derivatives Equation (7) was derived for the observed rate constant in the way analogous to that in the previous case.

$$k_{obs} = (k_c \cdot K_2 \cdot [CH_3O^-])/\{1 + (K_1 + K_2) \cdot [CH_3O^-]\} \quad (7)$$

In contrast to the *N*-methyl derivatives ($R^1 = CH_3$), two protons can be split off in the starting compounds **1a−d** and **3a−f**. The proton easier to split off is at the nitrogen atom adjacent to the benzene ring (the equilibrium constant K_1), but the anion thus formed [N^-] cannot enter cyclisation, so this is the so-called blind alley. The concentration of the reactive anion [NH^-] formed by deprotonation of the terminal $CXNH_2$ group is expressed by the equilibrium constant K_2.

The cyclisation of the oxygen derivatives **1a−g** has already been described,[16] but it was performed in water, not in methanol. The cyclisation rate in methanol is markedly lower than that in water, which is connected with differences in the solvating ability of the starting compound and activated complex. Both the oxygen derivatives **1a−d** and the sulfur analogues **3a−f** obey the given Equation (7) very well. The value of K_2 of the sulfur NH derivatives **3a−f** is probably close to those found for the *N*-methyl derivatives **3g−j**, $K_2 \approx 2$. Under this presumption, K_2 can be introduced in Equation (7), which is valid for 2-(benzoylamino)-thiobenzamides **3g−j**. In this way, Equation (7) is reduced to a two-parameter equation.

However, the above said presumption is an approximation because in some cases an even small variation of the basic skeleton can cause a distinct change in pK_a, as was observed, e.g., with 2,2-dioxo-2,3-dihydro-1*H*-2λ^6-benzo[1,-2,6]thiadiazin-4(3*H*)-ones[17a] and acylthioureas.[17b]

The simplified Equation (7) allows to optimise the values (Table 3) of the remaining parameters (k_c and K_1). However, this procedure cannot be applied to oxygen derivatives **1a−d**, because the K_2 value of the *N*-methyl derivatives **1e−i** is inaccessible from kinetic data. However, the $CONH_2$ group is substantially less acidic than the NH group adjacent to the benzene ring (the anion formed is stabilised by resonance with both carbonyl group and benzene ring). This can be expressed by $K_1 >> K_2$, and Equation (7) can be modified to Equation (8).

$$k_{obs} = (k_c \cdot K_2 \cdot [CH_3O^-])/(1 + K_1 \cdot [CH_3O^-]) \quad (8)$$

Optimisation of measured data provided values of products $k_c \cdot K_2$ and values of K_1. Application of Equation (6) (in which the value of pK_2 is replaced by pK_1) gave the values of pK_{a1} (Table 4).

Table 3. Parameters of the cyclisation reaction obtained by optimisation of data measured for derivatives **3a−f**

Compound	(X = S) R^2	K_1 [L·mol^{-1}]	k_c [s^{-1}]	pK_{a1}
3a	4-H	16.2	0.145	15.7
3b	4-$N(CH_3)_2$	7.6	0.014	16.0
3c	4-CH_3	11.6	0.087	15.8
3d	4-OCH_3	9.6	0.060	15.9
3e	4-Cl	24.9	0.351	15.5
3f	3-NO_2	55.5	1.663	15.2

Table 4. Parameters of cyclisation reaction obtained by optimisation of data measured for derivatives **1a−d**

Compound	(X = O) R^2	$10^3 \cdot k_c K_2$ [L·mol^{-1}·s^{-1}]	K_1 [L·mol^{-1}]	pK_{a1}
1a	4-H	1.55	0.7	17.1
1b	4-CH_3	0.97	0.45	17.3
1c	4-Cl	4.11	3.0	16.4
1d	4-NO_2	22.9	15.4	15.7

The measured data and the curves obtained by means of the optimised parameters for the sulfur derivatives **3a−f** are presented in Figure 4. The values of the optimised parameters k_c and K_1 fulfil the Hammett correlation very well (Figures 5 and 6). The only deviating point in the Hammett correlation of K_1 (Figure 6) is that of the 4-$N(CH_3)_2$ derivative, which exhibits a rather small extent of direct conjugation with the reaction centre, and that is why the application of σ_p^0 constant is more appropriate. The reaction constant $\rho = 1.54 \pm 0.04$, which is not an unusual value for a nucleophilic attack at a benzoyl group.[18,19] The Hammett correlation for the product $k_c \cdot K_2$ (the K_2 parameter refers to the dissociation at a distant reaction centre that is not affected by the substituent) for the four said derivatives leads to $\rho = 1.44 \pm 0.08$. The same reaction in water[16] had a value of $\rho = 0.67$. The given increase in ρ value can be ascribed to the change in solvent polarity,[20,21] as the substituent effects are expected to become more pronounced in a solvent of lower polarity.

3. Activation Enthalpy and Entropy of the Cyclisation Reactions

In order to quantify the effect of the methyl group (R^1 = H, CH_3) in the basic skeleton of cyclising thiobenzamides we tried to find the respective thermodynamic activation parameters. In the case of 2-(benzoylamino)thiobenzamides and/or 2-[(benzoyl)(methyl)amino]thiobenzamides we selected the derivatives with R^2 = 4-$N(CH_3)_2$ [R^1 = H (**3b**), CH_3 (**3h**)] whose ring closures are measurable within the whole range of temperatures and concentrations, and we have determined their thermodynamic activation parameters. With both derivatives we carried out the kinetic measurements at the temperatures of 10, 15, 19, 25, and 30 °C. With the help of Equations (3) and (7) and using the respective dependences of the observed rate constant on the sodium methoxide concentration we determined the values k_c and the values K_1, K_2 for the given temperatures. Then

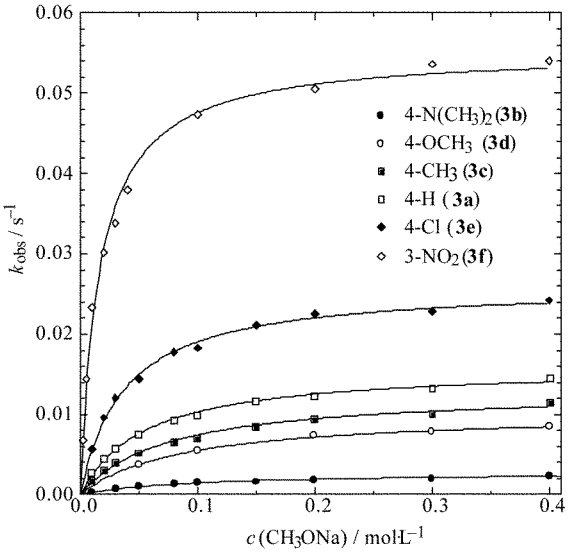


Figure 4. Observed rate constant of the cyclisation (k_{obs}/s^{-1}) of the 2-(benzoylamino)thiobenzamides **3a**−**f** vs. the sodium methoxide concentration (c/mol·L^{-1}) at 25 °C

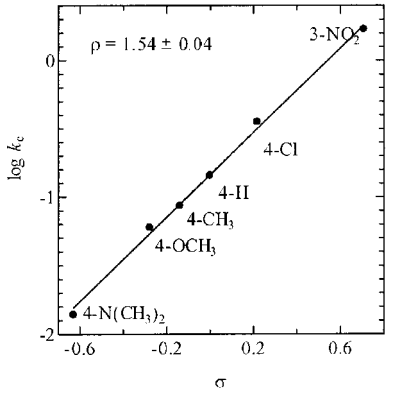


Figure 5. Hammett correlation of the cyclisation rate constant (k_c) of the 2-(benzoylamino)thiobenzamides **3a**−**f**

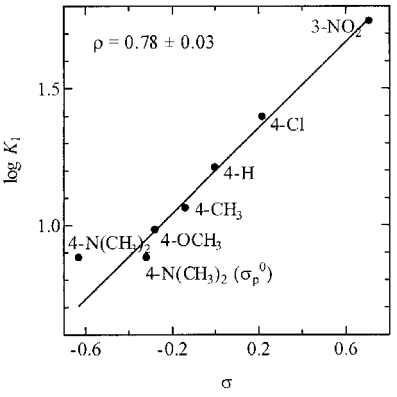


Figure 6. Hammett correlation of the equilibrium constant of the deprotonation (K_1) of the 2-(benzoylamino)thiobenzamides **3a**−**f**

the log k_c values were plotted against the reciprocal value of the thermodynamic temperature (Figure 7). The slope and intercept of the dependence obtained gave the values of activation energy E_a, activation enthalpy $\Delta H^{\ddagger}_{25\,°C}$, Gibbs energy $\Delta G^{\ddagger}_{25\,°C}$, and activation entropy $\Delta S^{\ddagger}_{25\,°C}$, which are summarised in Table 5.

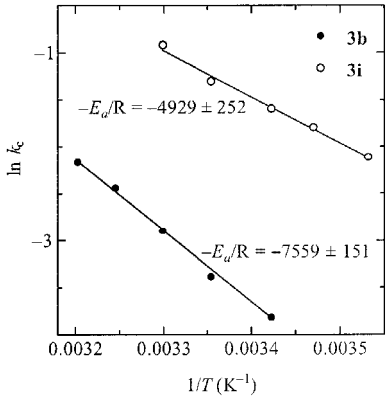


Figure 7. ln k_c vs. $1/T$ for the 2-(benzoylamino)thiobenzamides **3b** and **3h**

Table 5. Thermodynamic activation parameters of the cyclisation reactions **3b** → **4b** and **3h** → **4h**

Compound	E_a [kJ·mol^{-1}]	$\Delta H^{\ddagger}_{25\,°C}$ [kJ·mol^{-1}]	$\Delta S^{\ddagger}_{25\,°C}$ [J·mol^{-1}·K^{-1}]	$\Delta G^{\ddagger}_{25\,°C}$ [kJ·mol^{-1}]
3b	63±1	60±1	−70±4	81±2
3h	41±2	39±2	−126±7	76±3

Table 5 shows that the $\Delta G^{\ddagger}_{25\,°C}$ values are similar for the two compounds, but the $\Delta H^{\ddagger}_{25\,°C}$ and $\Delta S^{\ddagger}_{25\,°C}$ values differ considerably. Apparently, the enthalpy and entropy factors operate against each other, and their effects are partially cancelled. From the values of the activation entropy of the two substances it can be concluded that the difference in the degree of ordering between the starting anion and the activated complex is much higher for compound **3h** than for compound **3b**.

The cyclisation of the non-methylated derivatives can be negatively affected also by intramolecular hydrogen bond formation, which stabilises the starting species (Figure 8). The proton in the hydrogen bond is bound in a relatively rigid six-membered ring, which is transformed into intermediate **In$_1$**$^-$ with a relatively low entropy loss. On the other hand, in the case of the methyl derivative, where the hydrogen bond cannot be formed and the system thus has a higher number of degrees of freedom, the ring closure giving intermediate **In$_1$**$^-$ is connected with a substantially larger entropy drop.

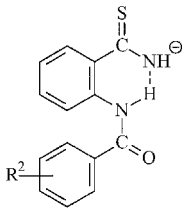
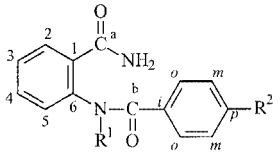


Figure 8. Intramolecular hydrogen bond

Table 6. Survey of the synthesised 2-(benzoylamino)benzamides **1f−i**

Compound	R^1	R^2	M.p. [°C] Yield: g (%)	Empirical formula Formula mass	calcd./found C	H	Cl	N
1f	CH_3	4-CH_3	155−158 1.45 (54)	$C_{16}H_{16}N_2O_2$ 268.31	71.62/ 71.68	6.01/ 6.09		10.44/ 10.54
1g	CH_3	4-OCH_3	127−129 1.1 (45)	$C_{16}H_{16}N_2O_3$ 284.31	67.59/ 67.62	5.67/ 5.75		9.85/ 9.76
1h	CH_3	4-Cl	147−148 1.2 (43)	$C_{15}H_{13}ClN_2O_2$ 288.73	62.40/ 62.50	4.54/ 4.60	12.28/ 12.35	9.70/ 9.59
1i	CH_3	4-NO_2	163−166 1.8 (60)	$C_{15}H_{13}N_3O_4$ 299.28	60.20/ 60.28	4.38/ 4.32		14.04/ 14.01

Table 7. ^{1}H NMR shifts (δ in ppm) of 2-benzoylaminobenzamides **1a−i**



	2-H	3-H	4-H	5-H	*o*-H	*m*-H	NH_2	R^1	R^2
1a	8.77 m, 1 H	7.23 m, 1 H	7.64 m, 4 H	7.96 m, 1 H	7.64 m, 4 H	8.01 m, 2 H	7.91 + 8.49 2 br. s, 2 H	13.02 br. s, 1 H	7.64 m, 4 H
1b	8.76 m, 1 H	7.23 m, 1 H	7.61 m, 1 H	7.95 m, 1 H	7.42 m, 1 H	7.89 m, 2 H	7.94 + 8.49 2 br. s, 2 H	12.98 br. s,1 H	2.43 s, 3 H
1c	8.73 m, 1 H	7.23 m, 1 H	7.62 m, 1 H	7.97 m, 1 H	7.99 m, 2 H	7.69 m, 2 H	7.92 + 8.50 2 br. s, 2 H	13.08 br. s,1H	
1d	8.71 m, 1 H	7.28 m, 1 H	7.65 m, 1 H	7.98 m, 2 H	8.47 m, 2 H	8.21 m, 2 H	7.98 + 8.54 2 br. s, 2 H	13.26 br. s, 1 H	
1e	7.53 m, 1 H	← 7.24−7.32 → m, 2 H		7.08 m, 1 H	7.46 m, 2 H	7.19 m, 2 H	7.59 + 7.89 2 br. s, 2 H	3.33 s, 3 H	7.24- 7.32
1f	7.51 m, 1 H	← 7.25−7.32 → m, 2 H		7.05 m, 1 H	6.99 m, 2 H	7.33 m, 2 H	7.56 + 7.85 2 br. s, 2 H	3.30 s, 3 H	2.29 s, 3 H
1g	7.52 m, 1 H	← 7.27−7.43 → m, 2 H		7.07 m, 1 H	7.41 m, 2 H	6.74 m, 2 H	7.54 + 7.84 2 br. s, 2 H	3.30 s, 3 H	3.72 s, 3 H
1h	7.51 m, 1 H	← 7.30−7.40 → m, 2 H		7.14 m, 1 H	7.45 m, 2 H	7.27 m, 2 H	7.57 + 7.87 2 br. s, 2 H	3.32 s, 3 H	
1i	7.49 m, 1 H	← 7.32−7.35 → m, 2 H		7.27 m, 1 H	8.06 m, 2 H	7.68 m, 2 H	7.58 + 7.87 2 br. s, 2 H	3.34 s, 3 H	

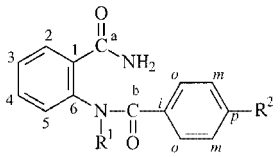
Conclusion

In the ring closure reactions of the oxygen derivatives **1e−i** (X = O), the replacement of a hydrogen atom by a methyl group at the nitrogen atom adjacent to benzene nucleus (R^1 = CH_3) leads to a gradual change in the rate-limiting step. At the beginning the reaction is second order in methoxide and the formation of the intermediate $\mathbf{In^{2-}}$ is rate-limiting. However, an increase of the sodium methoxide concentration changes the rate-limiting step to the formation of intermediate $\mathbf{In_1^-}$, and the reaction order gradually decreases. This decrease occurs earlier with derivatives **1h−i** containing electron-withdrawing substituents (4-Cl and 4-NO_2). Replacement of the oxygen by a sulfur atom in the benzamide group (X = S) causes a distinct acidification of the proton at the terminal nitrogen atom in both sets of derivatives **3a−j** (R^1 = H, CH_3) and that is why, irrespective of ring substitution, the formation of $\mathbf{In_1^-}$ is rate-limiting within the entire sodium methoxide concentration range investigated, and the reaction order gradually decreases from one to zero.

Experimental Section

General Remarks: 2-(Benzoylamino)thiobenzamides **3a−j** and the corresponding 2-phenylquinazoline-4-thiones **4a−j** were prepared by the procedure given in ref.[6] 2-(Benzoylamino)benzamides **1a−i** were prepared by acylating 2-aminobenzamide or 2-(methylamino)-benzamide with substituted benzoyl chlorides, in contrast to the method[16] where compounds **1a−e** were obtained by hydrolysis of 2-(benzoylamino)benzonitriles. The yields of acylation reactions ranged from 40 to 80%, and the melting points agreed with those in ref.[16] Tables 7, 8, 10, 11 summarise the NMR spectra of compounds **1f−i** yet unpublished. The characterisation of compounds **1f−i** so far not described is summed up in Tables 6, 7, and 8. Quinazolin-4-ones **2a−i** were also prepared by known procedure,[16] and the characterisation of newly prepared quinazolin-4-ones **2f−i** is presented in Tables 9, 10, and 11.

Table 8. ^{13}C NMR shifts (δ in ppm) of the 2-(benzoylamino)benzamides **1a**−**i** [the ^{13}C NMR shifts of carbon atoms with similar values of chemical shifts (C-2 and C-4) can be interchanged]

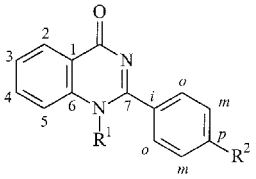


	C-1	C-2	C-3	C-4	C-5	C-6	C=O (a)	C=O (b)	C-*i*	C-*o*	C-*m*	C-*p*	R^1	R^2
1a	119.3	132.2	122.8	132.7	120.2	140.2	171.4	164.6	134.8	127.1	129.1	128.9		
1b	119.1	131.9	122.6	132.7	120.1	140.3	171.3	164.4	128.8	127.1	129.5	142.2		21.1
1c	119.3	132.7	122.9	133.5	120.2	140.1	171.3	163.4	128.8	128.9	129.1	137.0		
1d	119.4	128.9	123.3	132.7	120.3	140.2	171.2	162.6	139.8	128.5	124.1	149.4		
1e	134.0	130.2	128.9	130.8	128.5	142.6	169.8	169.3	136.7	127.4	127.8	129.5	37.9	
1f	133.6	129.9	128.4	130.6	128.4	142.6	169.5	169.0	133.8	127.1	128.6	138.9	37.8	21.0
1g	133.9	130.4	128.7	130.6	128.7	142.8	169.1	169.1	128.5	127.0	112.9	160.0	38.0	55.1
1h	133.8	129.9	128.7	130.8	127.4	142.1	169.0	168.4	134.0	127.7	130.1	135.4	37.7	
1i	134.0	130.0	128.7	130.9	127.2	141.4	168.9	167.6	142.8	129.4	122.8	147.4	37.6	

Table 9. Survey of the synthesised 2-phenylquinazolin-4-ones **2f**−**i**

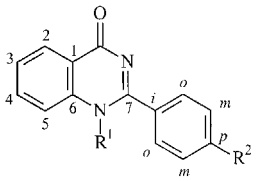
Compound	R^1	R^2	M.p. [°C] Yield: g (%)	Empirical formula Formula mass	calcd./found C	H	Cl	N
2f	CH_3	4-CH_3	170−172 1.1 (45)	$C_{16}H_{14}N_2O$ 250.29	76.78/ 76.82	5.64/ 5.70		11.19/ 11.25
2g	CH_3	4-OCH_3	167−170 1.3 (48)	$C_{16}H_{14}N_2O_2$ 266.29	72.17/ 72.20	5.30/ 5.34		10.52/ 10.58
2h	CH_3	4-Cl	219−220 1.6 (69)	$C_{15}H_{11}ClN_2O$ 270.71	66.55/ 66.60	4.10/ 4.12	13.10/ 13.16	10.35/ 10.40
2i	CH_3	4-NO_2	276−278 1.7 (61)	$C_{15}H_{11}N_3O_3$ 281.27	64.05/ 64.12	3.94/ 4.01		14.94/ 14.88

Table 10. ^1H NMR shifts (δ in ppm) of the 2-phenylquinazolin-4-ones **2a**−**i**



	2-H	3-H	4-H	5-H	*o*-H	*m*-H	R^1	R^2
2a	8.20 m, 1 H	7.52−7.64 m, 4 H	7.85 m, 1 H	7.77 m, 1 H	8.25 m, 2 H	7.52−7.64 m, 4 H		7.52−7.64 m, 4 H
2b	8.19 m, 1 H	7.55 m, 1 H	7.87 m, 1 H	7.77 m, 1 H	8.14 m, 2 H	7.39 m, 2 H	12.49 bs. 1 H	2.43 s, 3 H
2c	8.20 m, 1 H	7.59 m, 1 H	7.90 m, 1 H	7.79 m, 1 H	8.25 m, 2 H	7.68 m, 2 H	12.58 s, 1 H	
2d	8.23 m, 1 H	7.61 m, 1 H	7.90 m, 1 H	7.83 m, 1 H	8.48 m, 2 H	8.43 m, 2 H		
2e	8.17 m, 1 H	7.57−7.63 m, 4 H	7.91 m, 1 H	7.78 m, 1 H	7.57−7.63 m, 4 H	7.73 m, 2 H	3.68 s, 3 H	7.57−7.63 m, 4 H
2f	8.17 m, 1 H	7.60 m, 1 H	7.92 m, 1 H	7.79 m, 1 H	7.41 m, 2 H	7.63 m, 2 H	3.69 s, 3 H	2.45 s, 3 H
2g	8.15 m, 1 H	7.58 m, 1 H	7.91 m, 1 H	7.77 m, 1 H	7.72 m, 2 H	7.14 m, 2 H	3.72 s, 3 H	3.89 s, 3 H
2h	8.17 m, 1 H	7.61 m, 1 H	7.93 m, 1 H	7.80 m, 1 H	7.78 m, 2 H	7.68 m, 2 H	3.68 s, 3 H	
2i	8.20 m, 1 H	7.64 m, 1 H	7.96 m, 1 H	7.84 m, 1 H	8.45 m, 2 H	8.03 m, 2 H	3.66 s, 3 H	

Table 11. ^{13}C NMR shifts (δ in ppm) of the 2-phenylquinazolin-4-ones **2a**−**i** [the ^{13}C NMR shifts of carbon with similar values of chemical shifts (C-2 and C-3) can be interchanged]



	C-1	C-2	C-3	C-4	C-5	C-6	C=O	C-7	C-*i*	C-*o*	C-*m*	C-*p*	R^1	R^2
2a	121.1	127.5	126.5	134.5	125.9	148.9	162.7	152.8	133.1	128.6	127.9	131.4		
2b	121.0	127.4	126.4	134.6	125.9	148.8	162.4	152.4	130.0	127.8	129.3	141.5		21.1
2c	121.1	127.5	126.8	134.8	125.9	148.6	162.3	151.5	131.7	128.8	129.7	136.4		
2d	121.3	127.8	127.3	134.8	126.0	150.8	162.3	151.0	138.8	129.4	123.7	149.0		
2e	119.8	127.1	126.0	133.9	116.8	141.8	167.7	162.1	135.3	128.8	128.5	130.3	37.9	
2f	119.8	127.1	125.9	133.9	116.9	141.9	167.7	162.1	140.2	128.9	129.0	132.4	38.0	21.1
2g	119.8	127.0	125.8	133.8	116.9	142.0	167.8	160.9	127.3	131.0	113.8	161.9	38.3	55.5
2h	119.9	127.2	126.2	134.1	117.0	141.8	167.7	161.2	134.3	130.8	128.6	135.2	38.0	
2i	119.9	127.2	126.4	134.2	116.9	141.7	167.5	160.4	141.3	130.3	123.7	148.3	37.8	

Measurements: ^1H and ^{13}C NMR spectra were measured at 360.14 and 90.57 MHz, respectively, with a Bruker AMX 360 spectrometer at 25 °C. Compounds **1a**−**e** and **2a**−**e** were measured as saturated solutions in hexadeuteriodimethyl sulfoxide, and the chemical shifts are referenced to tetramethylsilane [$\delta(^1H) = 0$ ppm] and the solvent signal [$\delta(^{13}C) = 39.6$ ppm]. The CH, CH_3, and C_{quart} groups in the ^{13}C NMR spectra were distinguished by the APT method.

Kinetic Measurements: These were carried out with an HP UV/Vis 8453 Diode Array apparatus. A 1-cm quartz cell was charged with 2 mL of methanolic sodium methoxide. At 25 °C 50 μL of a methanolic solution of a substrate was injected and the absorbance was measured at a selected wavelength. In the experiment with 18-crown-6 ether, the concentration of the latter was always $2 \cdot 10^{-3}$ mol·L^{-1} higher than that of sodium methoxide. The stability constant[22] for complexation of 18-crown-6 ether with Na^+ at 25 °C is $\log K = 4.36$.

General Method for the Preparation of the 2-(Benzoylamino)benzamides 1a−i: A 100-ml three-necked flask, equipped with magnetic stirrer and dropping funnel, was charged with 10 mmol of benzamide derivative, 40 mL of dry acetone and 10 mmol of triethylamine. 10 mmol of benzoyl chloride derivative, dissolved in 10 mL of acetone, was added dropwise during ca. 5 min. The reaction mixture was stirred for 2 h at room temperature. The separated triethylammonium chloride (TEA·HCl) together with a part of the product was separated by filtration through a sintered glass filter, and TEA·HCl was removed by washing with water to obtain the first portion of product. The mother liquor was concentrated at room temperature, and the residue was recrystallised from toluene or benzene to provide the second portion of product.

Acknowledgments

The authors acknowledge the financial support provided by the Grant Agency of the Czech Republic (Grant No. 203/01/0227).

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Received September 12, 2001
[O01438]