JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2002; **15:** 165–173
DOI:10.1002/poc.468

Kinetics and mechanism of formation and decomposition of substituted 1-phenylpyrrolidin-2-ones in basic medium†

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Received 10 July 2001; revised 5 October 2001; accepted 16 October 2001

ABSTRACT: A study of chemical behaviour of substituted 4-chloro-*N*-phenylbutanamides in aqueous solutions of sodium hydroxide showed that the substrate first undergoes ring closure to give substituted 1-phenylpyrrolidin-2-ones, which are subsequently hydrolysed to substitution derivatives of sodium 4-amino-*N*-phenylbutanoates. Kinetic measurements provided the values of dissociation constants pK_a and cyclization rate constants k_c in water at 25 °C for 2-bromo-4-chloro-*N*-(4-nitrophenyl)butanamide [p$K_a = 11.64 \pm 0.01$; $k_c = (1.94 \pm 0.03) \times 10^{-2}$ s^{-1}], 4-chloro-*N*-(4-nitrophenyl)butanamide [p$K_a = 13.35 \pm 0.02$; $k_c = (1.60 \pm 0.02) \times 10^{-2}$ s^{-1}] and 4-chloro-2-methyl-*N*-(4-nitrophenyl)butanamide [p$K_a = 13.55 \pm 0.03$; $k_c = (7.61 \pm 0.11) \times 10^{-2}$ s^{-1}]. The pK_a and k_c values of individual derivatives differ depending on the substitution at the α-position of the butanamide skeleton. In methanolic sodium methoxide solutions, the course of ring closure of 2-bromo-4-chloro-*N*-(4-nitrophenyl)butanamide is of similar nature but slower [$K = 60.10 \pm 0.08$ and $k_c = (6.52 \pm 0.05) \times 10^{-3}$ s^{-1}]. The subsequent hydrolyses of substituted 1-phenylpyrrolidin-2-ones to substituted 4-aminobutanoic acids also have different courses with different derivatives and depend on the substituents in the aromatic and/or heterocyclic moiety. The rate-limiting step of hydrolysis of 1-(4-nitrophenyl)pyrrolidin-2-one consists of the non-catalysed decomposition of the tetrahedral intermediate. In the case of 3-bromo-1-(4-nitrophenyl)pyrrolidin-2-one at sodium hydroxide concentrations below 0.1 mol l^{-1}, the rate-limiting step is the second reaction pathway, i.e. the hydroxide ion-catalysed decomposition of the tetrahedral intermediate. At sodium hydroxide concentrations above 0.1 mol l^{-1}, the rate-limiting step shifts to formation of the tetrahedral intermediate. This formation of the intermediate is 140 times slower than its hydroxide ion-catalysed decomposition [$k_3/k_{-1} = (1.40 \pm 0.04) \times 10^2$ l mol^{-1}]. Introduction of a 3-bromo substituent into 1-(4-nitrophenyl)pyrrolidin-2-one results in acceleration of all the reaction steps of hydrolysis and increases the acidity of the intermediate. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: reaction kinetics; cyclization; solvolysis; 1-phenylpyrrolidin-2-ones; dissociation constants

INTRODUCTION

Substituted 1-phenylpyrrolidin-2-ones represent important building blocks in syntheses of a number of pharmacologically active substances, such as lactamyl-vinylcefalosporines[1] and some other drugs used for the prevention of arterial thrombosis.[2] One of the possible ways to synthesize the 1-phenylpyrrolidinone cycle consists in intramolecular nucleophilic substitution of chlorine in 4-chloro-*N*-phenylbutanamide derivatives by the amide anion (S_Ni), which must be catalysed by bases. However, solvolysis of the primary γ-lactam cycle[3] can take place subsequently, which is undesirable in the synthesis of the cyclic system (Scheme 1).

The aim of this study was to carry out a kinetic investigation of base-catalysed ring closure of 2-bromo-4-chloro-*N*-(4-nitrophenyl)butanamide (**1a**), 4-chloro-*N*-(4-nitrophenyl)butanamide (**1b**) and 2-methyl-4-chloro-*N*-(4-nitrophenyl)butanamide (**1c**) in water and/or methanol and to examine the subsequent solvolysis of the cyclizates formed, namely 3-bromo-1-(4-nitrophenyl)-pyrrolidin-2-one (**2a**), 1-(4-nitrophenyl)pyrrolidin-2-one (**2b**), 3-methyl-1-(4-nitrophenyl)pyrrolidin-2-one (**2c**) and 3-bromo-1-(4-cynophenyl)pyrrolidin-2-one (**2d**).

EXPERIMENTAL

2-Bromo-4-chloro-N-*(4-nitrophenyl)butanamide (**1a**).*

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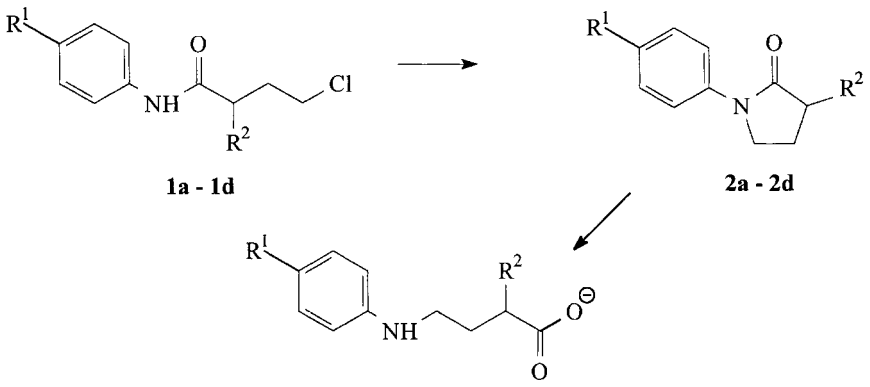
†**Dedicated to Professor Vojeslav Štěrba on the occasion of his 80th birthday**.
Contract/grant sponsor: Max-Planck Society.
Contract/grant sponsor: Grant Agency of the Czech Republic; *Contract/grant number:* 203/01/0227.



1, 2, 3	a	b	c	d
R^1	NO_2	NO_2	NO_2	CN
R^2	Br	H	CH_3	Br

Scheme 1

4-Nitroaniline (2.76 g; 25 mmol) was dissolved in a mixture of dry acetone (25 ml) and triethylamine (3.65 ml; 25 mmol). After cooling to 10 °C, a solution of 2-bromo-4-chlorobutanoyl bromide[4] (6.6 g; 25 mmol) in dry acetone (25 ml) was added drop by drop. The reaction mixture was stirred at room temperature for 2 h. The separated triethylammonium bromide was filtered off and the filtrate was concentrated on a water-bath in vacuum. The crystalline solid obtained was recrystallized (52%, m.p. 178–180 °C). ^{1}H NMR (δ): 2.47 (m, 2H, CH_2); 3.78 (m, 1H, 1/2CH_2); 3.88 (m, 1H, 1/2CH_2); 4.83 (m, 1H, CHBr); 7.90 (d, J = 9.1 Hz, 2H-arom); 8.29 (d, J = 9.1 Hz, 2H-arom); 11.11 (bs, 1H, NH). ^{13}C NMR (δ): 35.9 (CH_2); 42.8 (CH_2Cl); 46.7 (CHBr); 119.3 (CH-arom); 125.1 (CH-arom); 142.9 (C-arom); 144.7 (C-arom); 167.4 (C=O).

Derivatives ***1b–d***. These were synthesized in the same way from 4-nitroaniline, 4-aminobenzonitrile, 4-chlorobutanoyl chloride and 2-methyl-4-chlorobutanoyl chloride,[5] respectively.

*4-Chloro-*N*-(4-nitrophenyl)butanamide (**1b**).* 64%, m.p. 101–102 °C. ^{1}H NMR (δ): 2.10 (m, 2H, CH_2); 2.60 (t, J = 7.3 Hz, 2H, CH_2); 3.76 (t, J = 6.5 Hz, 2H, CH_2Cl); 7.88 (d, J = 8.8 Hz, 2H-arom); 8.25 (d, J = 8.8 Hz, 2H-arom); 10.64 (bs, 1H, NH). ^{13}C NMR (δ): 27.7 (CH_2); 39.8 (CH_2); 45.2 (CH_2Cl); 118.8 (CH-arom); 125.1(CH-arom); 142.1 (C-arom); 145.4 (C-arom); 171.4 (C=O).

*4-Chloro-2-methyl-*N*-(4-nitrophenyl)butanamide (**1c**).* 58%, m.p. 121–123 °C. ^{1}H NMR (δ): 1.21 (d, J = 6.9 Hz, 3H, CH_3); 1.88 (m, 1H, 1/2CH_2); 2.15 (m, 1H, 1/2CH_2); 2.80 (m, 1H, CH); 3.69 (m, 2H, CH_2Cl); 7.90 (d, J = 9.3 Hz, 2H-arom); 8.25 (d, J = 9.3 Hz, 2H-arom); 10.64 (bs, 1H, NH). ^{13}C NMR (δ): 17.6 (CH_3); 35.7 (CH_2); 38.4 (CH); 43.3 (CH_2Cl); 119.0 (CH-arom); 125.0 (CH-arom); 142.2 (C-arom); 145.5 (C-arom); 174.9 (C=O).

*2-Bromo-4-chloro-*N*-(4-cyanophenyl)butanamide (**1d**).* 74%, m.p. 114–116 °C. ^{1}H NMR (δ): 2.45 (m, 2H, CH_2); 3.82 (m, 2H, CH_2Cl); 4.80 (t, J = 7.6 Hz, 1H, CHBr); 7.83 (s, 4H-arom); 10.92 (bs, 1H, NH). ^{13}C NMR (δ): 36.0 (CH_2); 42.7 (CH_2Cl); 46.4 (CHBr); 105.9 (C-arom); 118.9 (CN); 119.6 (CH-arom); 133.4 (CH-arom); 142.7 (C-arom); 167.1 (C=O).

*3-Bromo-1-(4-nitrophenyl)pyrrolidin-2-one (**2a**).* 2-Bromo-4-chloro-*N*-(4-nitrophenyl)butanamide (**1a**) (1.6 g; 5 mmol) was dissolved in 50 ml of dichloromethane. The solution was treated with a mixture of benzyltriethylammonium chloride (0.01 g) and sodium hydroxide solution (50%; 0.4 g; 5 mmol) added at room temperature. The reaction mixture was stirred vigorously for 2 h. The organic phase was separated, dried with anhydrous sodium sulphate and filtered with charcoal (0.1 g). The filtrate was concentrated in a vacuum evaporator to one-third of its original volume and then added to hexane (400 ml) with vigorous stirring. The precipitated crystalline solid was collected by suction and dried in a vacuum desiccator (70%, m.p. 98–100 °C). ^{1}H NMR (δ): 2.42 (m, 1H, 1/2CH_2); 2.84 (m, 1H, 1/2CH_2); 4.04 (m, 2H, CH_2N); 5.00 (m, 1H, CHBr); 8.02 (d, J = 9.2 Hz, 2H-arom); 8.32 (d, J = 9.2 Hz, 2H-arom). ^{13}C NMR (δ): 29.90(CH_2); 46.4 (CHBr); 46.6 (CH_2N); 119.4 (CH-arom); 124.7 (CH-arom); 143.2 (C-arom); 144.6 (C-arom); 170.5 (C=O).

Substituted 1-phenylpyrrolidin-2-ones ***2b–d***. These were synthesized by the same method from the corresponding amides **1b–d**.

*1-(4-Nitrophenyl)pyrrolidin-2-one (**2b**).* 65%, m.p. 127–129 °C. ^{1}H NMR (δ): 2.13 (m, 2H, CH_2); 2.61 (t, J = 8.0 Hz, 2H, CH_2); 3.93 (t, J = 7.0 Hz, 2H, CH_2 N); 7.95 (d, J = 8.3 Hz, 2H-arom); 8.26 (d, J = 8.3 Hz, 2H-arom). ^{13}C NMR (δ): 17.3 (CH_2); 32.5 (CH_2); 48.1 (CH_2N); 118.7 (CH-arom); 124.7 (CH-arom); 142.4 (C-arom); 145.3 (C-arom); 175.2 (C═O).

*3-Methyl-1-(4-nitrophenyl)pyrrolidin-2-one (**2c**).* 73%, m.p. 179–180 °C. ^{1}H NMR (δ): 1.22 (d, J = 7.1 Hz, 3H, CH_3); 1.77 (m, 1H, 1/2CH_2); 2.38 (m, 1H, 1/2CH_2); 2.76 (m, 1H, CH); 3.90 (m, 2H, CH_2N); 8.00 (d, J = 9.2 Hz, 2H-arom); 8.30 (d, J = 9.2 Hz, 2H-arom). ^{13}C NMR (δ): 15.8 (CH_3); 26.2 (CH_2); 37.9 (CH); 46.1 (CH_2N); 118.7 (CH-arom); 124.7 (CH-arom); 142.4 (C-arom); 145.5 (C-arom); 177.5 (C═O).

*3-Bromo-1-(4-cyanophenyl)pyrrolidin-2-one (**2d**).* 64%, m.p. 112–114 °C. ^{1}H NMR (δ): 2.41 (m, 1H, 1/2CH_2); 2.81 (m, 1H, 1/2CH_2); 3.99 (m, 2H, CH_2N); 4.98 (m, 1H, CHBr); 7.95 (m, 4H-arom). ^{13}C NMR (δ): 29.0 (CH_2); 46.2 (CH_2N); 46.7 (CHBr); 106.6 (C-arom); 118.9 (CN); 119.6 (CH-arom); 133.2 (CH-arom); 142.8 (C-arom); 170.2 (C═O).

*4-Amino-2-bromo-*N*-(4-nitrophenyl)butanoic acid (**3a**).* 2-Bromo-4-chloro-*N*-(4-nitrophenyl)butanamide (**1a**) (1.2 g; 3.7 mmol) was mixed with water (10 ml) and aqueous sodium hydroxide solution (50%; 4 g; 5 mmol). After stirring for 4 h at room temperature, the mixture was acidified with dilute hydrochloric acid (pH 7). The crystalline solid that precipitated on cooling was collected by suction on a sintered-glass filter, washed with a small amount of water and recrystallized from water (92%, m.p. 126–128 °C). ^{1}H NMR (δ): 2.15 (m, 1H, 1/2CH_2); 2.35 (m, 1H, 1/2CH_2); 3.33 (m, 2H, CH_2N); 4.58 (m, 1H, CHBr); 6.69 (d, J = 9.0 Hz, 2H-arom); 7.39 (bs, 1H, NH); 8.04 (d, J = 9.0 Hz, 2H-arom). ^{13}C NMR (δ): 33.5 (CH_2); 39.8 (CH_2N); 45.1 (CHBr); 110.9 (CH-arom); 126.3 (CH-arom); 136.1 (C-arom); 154.3 (C-arom); 170.5 (C═O).

Acids ***3b–d***. These were synthesized in the same way from the corresponding amides **1b–d**.

*4-Amino-*N*-(4-nitrophenyl)butanoic acid (**3b**).* 88%, m.p. 181–183 °C. ^{1}H NMR (δ): 1.83 (m, 2H, CH_2); 2.38 (t, J = 7.2 Hz, 2H, CH_2); 3.22 (m, 2H, CH_2N); 6.67 (d, J = 9.9 Hz, 2H-arom); 7.37 (bs, 1H, NH); 8.03 (d, J = 9.9 Hz, 2H-arom). ^{13}C NMR (δ): 23.8 (CH_2); 31.1 (CH_2N); 41.6 (CH_2); 110.8 (CH-arom); 126.3 (CH-arom); 135.7 (C-arom); 154.6 (C-arom); 174.5 (C═O).

*4-Amino-2-methyl-*N*-(4-nitrophenyl)butanoic acid (**3c**).* 83%, m.p. 121–123 °C. ^{1}H NMR (δ): 1.16 (d, J = 7.0 Hz, 3H, CH_3); 1.64 (m, 1H, 1/2CH_2); 1.93 (m, 1H, 1/2CH_2); 2.51 (m, 1H, CH); 3.20 (m, 2H, CH_2); 6.67 (d, J = 8.0 Hz, 2H-arom); 7.37 (bt, J = 5.0 Hz, 1H, NH); 8.02 (d, J = 8.0 Hz, 2H-arom). ^{13}C NMR (δ): 17.1 (CH_3); 32.1 (CH_2); 36.5 (CH); 40.5 (CH_2N); 110.9 (CH-arom); 126.4 (CH-arom); 135.7 (C-arom); 154.6 (C-arom); 177.3 (C═O).

*4-Amino-2-bromo-*N*-(4-cyanofenyl)butanoic acid (**3d**).* 72%, m.p. 130–132 °C. ^{1}H NMR (δ): 2.11 (m, 1H, 1/2CH_2); 2.28 (m, 1H, 1/2CH_2); 3.23 (m, 2H, CH_2N); 4.55 (m, 1H, CHBr); 6.66 (d, J = 7.2 Hz, 2H-arom); 6.77 (bs, 1H, NH); 7.47 (d, J = 7.2 Hz, 2H-arom). ^{13}C NMR (δ): 33.5 (CH_2); 39.8 (CH_2N); 45.1 (CHBr); 96.0 (C-arom); 111.8 (CH-arom); 120.5 (CN); 133.4 (CH-arom); 151.9 (C-arom); 170.4 (C═O).

*Methyl 4-amino-2-bromo-*N*-(4-nitrophenyl)butanoate (**4a**).* A suspension of 4-amino-2-bromo-*N*-(4-nitrophenyl)butanoic acid (**3a**) (1g; 3.3 mmol) in diethyl ether (30 ml) was treated with a freshly prepared solution of diazomethane (0.21 g; 5 mmol) in diethyl ether (30 ml). The suspension was stirred overnight whereby it gradually changed into solution. The solution was evaporated on a water-bath and the evaporation residue was recrystallized from methanol (81%, m.p. 95–97 °C). ^{1}H NMR (δ): 2.18 (m, 1H, 1/2CH_2); 2.38 (m, 1H, 1/2CH_2); 3.33 (m, 2H, CH_2N); 3.75 (s, 3H, CH_3); 4.71 (m, 1H, CHBr); 6.68 (d, J = 9.3 Hz, 2H-arom); 7.39 (bs, 1H, NH); 8.03 (d, J = 9.3 Hz, 2H-arom). MS (*m/z*,%): $[M + H]^+$ 317.1, 97; $[M + H]^+$ with ^{81}Br 319.1, 100; $[M + H - HBr]^+$ 237.1, 28; $[M + H - HBr - NO]^+$ 207.1, 19.

*Methyl 4-amino-*N*-(4-nitrophenyl)butanoate (**4b**).* This was prepared similarly from acid **3b** (83%, m.p. 150–152 °C). ^{1}H NMR (δ): 1.95 (m, 2H, CH_2); 2.44 (m, 2H, CH_2); 3.24 (m, 2H, CH_2N); 3.66 (s, 3H, CH_3); 6.24 (bs, 1H, NH); 6.57 (m, 2H-arom); 8.00 (m, 2H-arom). ^{13}C NMR (δ): 23.3 (CH_2); 30.5 (CH_2); 41.6 (CH_2N); 50.6 (CH_3); 110.1 (CH-arom); 125.4 (CH-arom); 136.0 (C-arom); 153.5 (C-arom); 172.5 (C═O).

The results of elemental analyses of the individual compounds agreed with the calculated values.

Measurement of NMR spectra. The ^{1}H and ^{13}C NMR spectra were measured at 360.14 and 90.57 MHz, respectively, on a Bruker AMX 360 apparatus. For the measurements, the substances were dissolved in hexadeuteriodimethyl sulphoxide (DMSO-d_6). The chemical shifts δ_H and δ_C were referenced to the middle signal of multiplet of the solvent (δ_H = 2.55 ppm; δ_C = 39.6 ppm). The CH, CH_2, CH_3 and C groups in the ^{13}C NMR spectra were differentiated by the APT method. In the case of **4a**, only the ^{1}H NMR spectrum is given, because the

substance decomposed during the ^{13}C NMR measurement. Therefore, we present here also the mass spectrum.

The mass spectrum was measured with a VG Platform II mass spectrometer (Micromass, Manchester, UK) using atmospheric pressure chemical ionization (APCI) and a quadrupole analyser (0–3000 Da). Before the mass spectrometer there was inserted a separation apparatus consisting of a Model 616 high-pressure pump, Model 717 autosampler and Model 966 UV detector (all from Waters, Milford, MA, USA), and a Separon SGX C_{18} octadecylsilica glass cartridge column (150 × 3 mm i.d., 7 μm particle size) (Tessek, Prague, Czech Republic). A mixture of 70% acetonitrile and 30% redistilled water was used as the mobile phase. The effluent from the liquid chromatography was introduced directly into a quadrupole mass spectrometer equipped with APCI probe operated in the positive ion mode. The data were acquired in the *m/z* range 15–600 at 1.9 s per scan. In the APCI mode, the temperatures of the ion source and of the probe were 100 and 500 °C, respectively. The cone voltage was set at 10 V for positive-ion APCl.

Kinetic measurements. The spectrophotometric measurements were carried out on an HP UV/VIS 8453 diode-array apparatus in a 1 cm quartz cell with a lid at the temperatures specified in Table 1. Before the measurements proper, the time dependence of the spectral change was measured for hydrolysis and methanolysis of substituted 1-phenylpyrrolidin-2-ones **2a–d** in the interval 200–1000 nm. These preliminary experiments revealed isosbestic points and showed suitable wavelengths for kinetic measurements. The cyclization reactions of substituted butanamides **1a–c** (Table 1) were followed at the wavelengths of the isosbestic points of solvolyses. The cell was charged with 2 ml of sodium hydroxide or sodium methoxide solution. After attaining the chosen temperature, 20 μl of methanolic solution of substrate was injected into the cell, so the resulting concentration of substrate in the cell was about 1×10^{-4} mol l^{-1}. The measured time dependence of absorbance was treated by an optimization program to obtain the pseudo-first-order rate constants k_{obs}.

RESULTS AND DISCUSSION

The acylation of substituted anilines with 4-chlorobutyryl chloride, 2-bromo-4-chlorobutyryl chloride or 4-chloro-2-methybutyryl chloride gave the respective substituted 4-chloro-*N*-phenylbutanamides **1a–d**. In accordance with what had been suggested, the amides **1a–d** underwent consecutive reactions in sodium hydroxide solution, the first step being ring closure (i.e. formation of **2a–d**) and the next step the hydrolysis of primary substituted 1-phenylpyrrolidin-2-ones to substituted sodium 4-aminobutanoates **3a–d** (Scheme 1). The substituted 1-phenylpyrrolidin-2-ones **2a–d** and substituted 4-aminobutanoic acids **3a–d** were isolated on a preparative scale. Under both the preparative and the kinetic (pseudo-first order reaction) reaction conditions, the α-bromo derivatives **1a** and **1d** unambiguously gave the γ-lactam cycle, the α-lactams not being formed.[6] Also, we never observed the alternative ring closure reaction involving the oxygen anion as internal nucleophile and giving imino lactones.[7] This finding agrees with earlier papers[7,8] reporting the formation of imino lactones from 4-halo-*N*-substituted butyramides in aqueous media at pH values below 10.

The observed rate constants of ring closure were measured at the isosbestic points of hydrolysis (Table 1). From the dependence of observed rate constant k_{obs} on sodium hydroxide concentration (Fig. 1) it can be seen that with derivative **1a** at lower sodium hydroxide concentrations the first reaction (ring closure, formation of **2a**) is faster. At higher concentrations of sodium hydroxide (>0.025 mol l^{-1}), however, the second reaction (hydrolysis, formation of **3a**) is accelerated and becomes faster than the ring closure.

First, we studied in more detail the cyclization reactions of amides **1a–c** to **2a–c**, which differ from each other by substitution at the α-position of the butanamide skeleton. The course of ring closure of *N*-phenylbutanamides can be expressed by Scheme 2.

The formation of amide anion is a fast pre-equilibrium with a subsequent rate-limiting step, namely the intramolecular nucleophilic substitution of a chlorine atom with concomitant formation of a five-membered ring. The rate of the cyclization reaction followed under the conditions of a pseudo-first order reaction can be

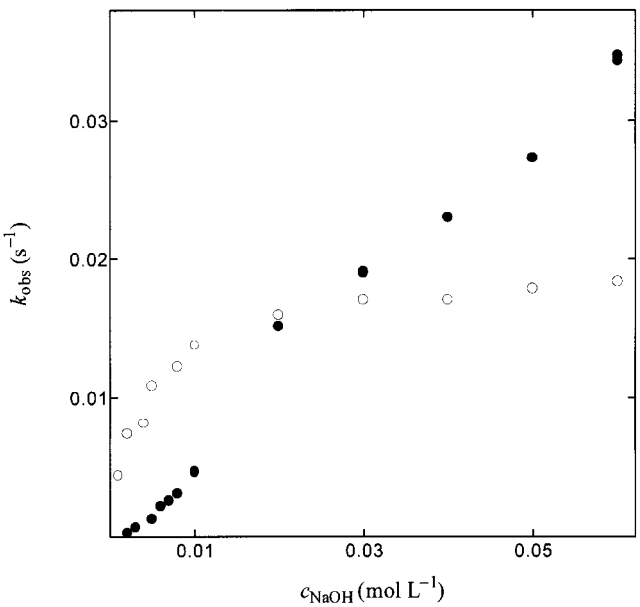
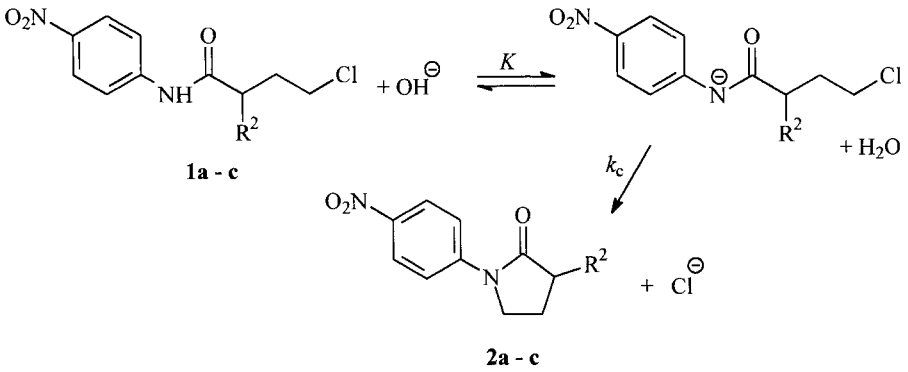


Figure 1. Dependence of observed rate constant (k_{obs}) on concentration of sodium hydroxide (c_{NaOH}) for cyclization reaction **1a** → **2a** (○) and hydrolysis reaction **2a** → **3a** (●) at 25 °C



Scheme 2

expressed by Eqn. (1), derived from Scheme 2:

$$v = k_{obs}c_S = k_c[N^-] \quad (1)$$

where c_S is the total concentration of substrate, $[N^-]$ the actual concentration of the anion and k_c the rate constant of ring closure. From the experimentally found dependences of the observed rate constant (k_{obs}, s^{-1}) on sodium hydroxide concentration (c_{NaOH}, mol l^{-1}) (Fig. 2), it follows that increasing concentration of hydroxide ion causes a non-linear increase in the observed rate constant to the same extent as the concentration $[N^-]$ of anion is increased. In the limiting case, when all the substrate has been converted into the respective anion, the rate becomes independent of the concentration of hydroxide ion (the slope of the mentioned dependence approaches zero).

The dependence depicted in Fig. 2 is expressed by

$$k_{obs} = \frac{k_c K[OH^-]}{1 + K[OH^-]} \quad (2)$$

The experimental values and Eqn. (2) were treated by the optimization program to give the values of the constants K and k_c (Scheme 2). The experimental points were fitted by a curve corresponding to Eqn. (2) into which the calculated values of both K and k_c (Fig. 2) had been introduced. The values of the constants for the hydroxide ion-catalysed ring closure of amides **1a–c** to corresponding lactams **2a–c** are summarized in Table 1, where $pK_a = pK_w - \log K$, pK_w being the ionic product of water.

From the values presented in Table 1, it follows that substrate **1a** (having a bromine substituent at the α-position) is two orders of magnitude more acidic than the unsubstituted derivative (**1b**). This difference corresponds to the difference between the pK_a values of acetic and bromoacetic acids.[9] Derivatives **1b** and **1c** differ in their pK_a values only slightly, the same being true for propanoic and 2-methylpropanoic acids.[10] From Fig. 2, it can be seen that with derivative **1a** the maximum value (k_{obs}) is already reached at a sodium hydroxide concentration of 0.1 mol l^{-1}. At this sodium hydroxide concentration, the observed rate constant k_{obs} is approximately comparable to the observed rate constant of methyl derivative **1c**, and about 5.5 times higher than that of the unsubstituted derivative (**1b**). The initial considerable increase in the observed rate constant (k_{obs}) for **1a** is caused by increased acidity of the amide nitrogen atom due to the bromine substituent. The cyclization rate constants k_c (25 °C) of derivatives **1a** and **1b** (Table 1) are very similar, but k_c for **1c** is more than three times higher. In the derivatives carrying a bromine substituent (**1a**) or methyl group (**1c**) at the α-position of the respective butanamide, the cyclization rate constants k_c can be affected in the following ways:

1. favourable entropy effects: bulky substituents present in the chain undergoing the ring closure can increase

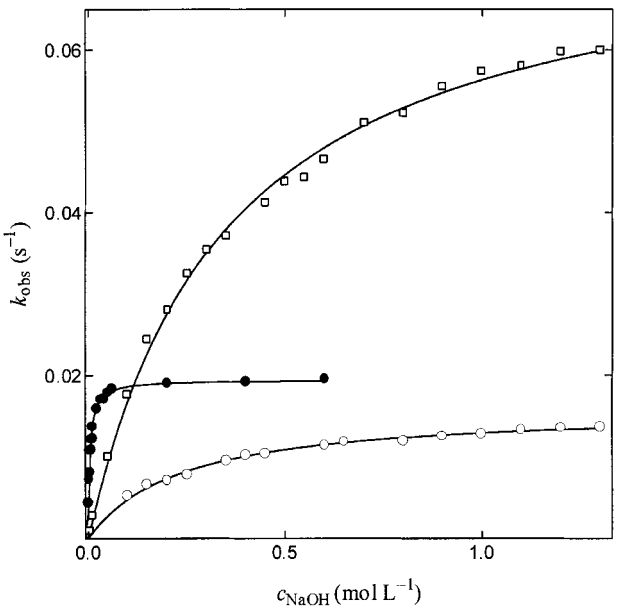


Figure 2. Dependence of observed rate constant (k_{obs}) on concentration of sodium hydroxide (c_{NaOH}) for cyclization reactions **1a** → **2a** (●), **1b** → **2b** (○) and **1c** → **2c** (□) at 25 °C. The experimental points are interlaced by curves corresponding to Eqn. (2)

Table 1. Constants of cyclisation (k_c, K), pK_a and values of activation parameters for cyclization reaction of butanamides **1a–c** in solution of sodium hydroxide

Compound	Temperature (°C)	$10^2\ k_c$ (s^{-1})	K	pK_a	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J mol^{-1} K^{-1})
1a	25	1.94 ± 0.03	229 ± 0.3	11.64 ± 0.01		
1b	15	0.53 ± 0.01	6.71 ± 0.10			
	20	0.99 ± 0.01	5.10 ± 0.12			
	25	1.60 ± 0.02	4.43 ± 0.10	13.35 ± 0.02	74 ± 3	36 ± 6
	32	3.70 ± 0.03	3.27 ± 0.15			
	40	7.01 ± 0.02	3.16 ± 0.13			
1c	15	2.24 ± 0.01	2.65 ± 0.41			
	20	4.44 ± 0.05	2.95 ± 0.36			
	25	7.61 ± 0.11	2.83 ± 0.12	13.55 ± 0.03	72 ± 3	21 ± 6
	32	13.3 ± 0.2	4.07 ± 0.36			
	40	28.9 ± 0.1	4.05 ± 0.45			

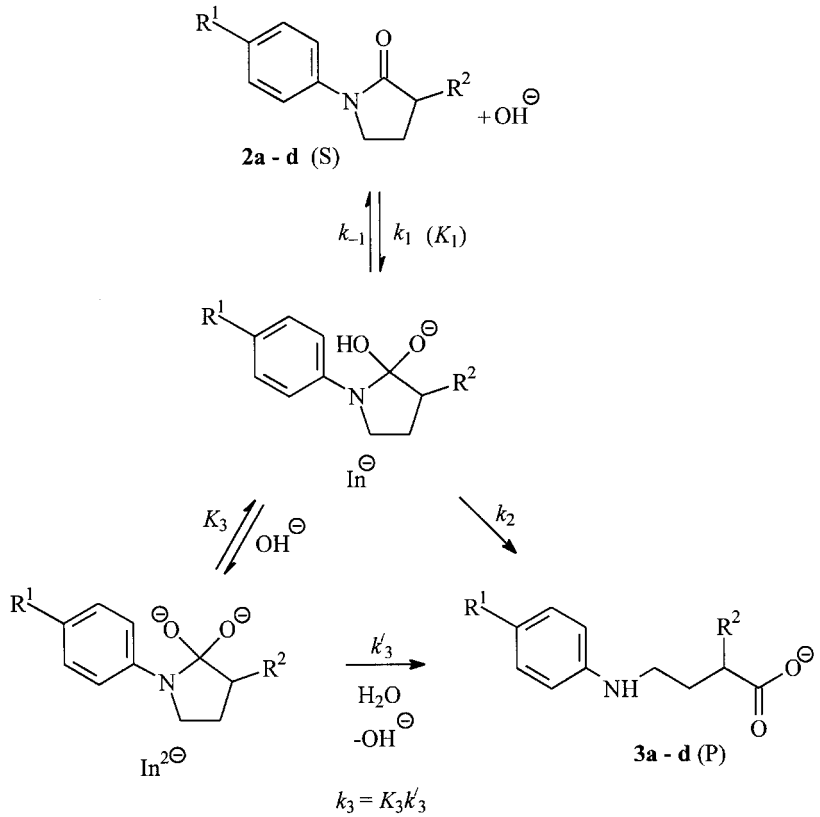
the k_c values by as much as several orders of magnitude;[11]

2. the negative inductive field effect ($-I$) of the bromine substituent lowers the nucleophilicity of reagent and hence also the k_c value;
3. the positive inductive field effect ($+I$) of the methyl group increases the nucleophilicity of the reagent and hence also the k_c value.

On comparing the k_c values of **1a** and **1b**, one can see that they are almost the same, i.e. the above effects 1 and 2 on the cyclization rate must be similar. The k_c value of methyl derivative **1c** is increased (compared with **1a** and **1b**) for the reasons 1 and 3 above. In order to be able to compare quantitatively the entropy advantage for cyclization due to the substitution in the side-chain, the activation parameters of the cyclization reaction (k_c) of derivatives **1b** and **1c** were experimentally determined (Table 1). The values found for the activation enthalpies $\Delta H‡$ are almost identical. The difference between the found activation entropy values $\Delta S‡$ of **1b** and **1c** is indistinct and close to the experimental error. The magnitude of difference between the two $\Delta S‡$ values is similar to that of acid-catalysed cyclizations of substituted *N*-phenylbutanoic acids to substituted 1-phenylpyrrolidin-2-ones.[12]

Furthermore, we studied the ring closure reaction **1a** → **2a** in methanolic solutions of sodium methoxide, and found that the dependence of the observed rate constant on sodium methoxide concentration has a similar character to that for the ring closure in aqueous solutions of sodium hydroxide. The values found from the measured dependence are $k_c = (6.52 \pm 0.05) \times 10^{-3}$ s^{-1} and $K = 60.10 \pm 0.08$ at 25 °C. The decrease in the cyclization rate **1a** → **2a** (k_c) and also the decrease in the equilibrium constant of formation of the reactive anion can be explained, first of all, by changes in the solvation ability on going from water to methanol.[13] The rate of cyclization **1b** → **2b** in methanolic solutions of sodium methoxide is comparable to the rate of methanolysis of **2b** to methyl 4-amino-*N*-(4-nitrophenyl)butanoate (**4b**), and the values of the cyclization rate constant cannot be separately determined by the method adopted by us.

We also studied the second reaction step, i.e. hydrolysis (opening of the pyrrolidine cycle), with derivatives **2a–d** (Scheme 3) (the corresponding amides **1a–d** were also used as the substrates). The hydrolysis under both preparative conditions and conditions of pseudo-first-order kinetics at 25 °C gave sodium salts of substituted 4-amino-*N*-phenylbutanoic acids **3a–d** as the only products. The alkaline hydrolysis of amides and lactams has been studied extensively.[14,15] Tertiary amides and secondary lactams show simpler behaviour than others as concomitant ionization of the weakly acidic amide or lactam NH cannot occur. Evidence exists for both first- and second-order reactions in analogous hydroxide anion reactions.[14] A simplified and generalized mechanistic pathway for the alkaline hydrolysis of secondary lactams, where ionization of the substrates is not possible, is shown in Scheme 3. Moreau *et al.*[16] have reviewed their studies on various series of amides, including some *N*-methylformanilides and *N*-methylacetanilides in which the latter amides conform to the pattern shown in Scheme 3. The alkaline hydrolysis of a series of substituted *N*-methylformanilides,[17] *N*-aryl-β-, -γ- and -δ-lactams[3] in water and aqueous DMSO have been investigated. An important study of the alkaline hydrolysis of *N*-aryl-β-lactams and *N*-methylacetanilides in water was made by Blackburn and Plackett.[18] The results were in contrast with those for the corresponding γ- and δ-lactams and *N*-methylacetanilides. The Hammett ρ value for substitution in the *N*-aryl-β-lactams clearly indicated rate-determinig attack of hydroxide ion on the β-lactam ring, followed by rapid ring fission. The other lactams and acetanilides appear to have as the rate-limiting step the hydroxide ion-catalysed decomposition of a tetrahedral intermediate. All systems showed a first-order dependence on hydroxide ion concentration. From our experimental dependences of the logarithms of the observed rate constants of hydrolysis on the logarithms of sodium hydroxide concentration, it was possible to determine the reaction order in OH^- ion. The slopes of



Scheme 3

these dependences have different values for the individual derivatives **2a–d** differing in substitution of the aromatic and/or heterocyclic moiety. The hydroxide ion-catalysed hydrolysis of the substituted *N*-phenyl-2-pyrrolidinone ring can be interpreted by Scheme 3.

With **2b** and **2c** the slopes of dependences of $\log k_{obs}$ vs $\log c_{NaOH}$ are unity, which means that the main reaction path is the non-catalysed decomposition of intermediate In^- (Scheme 3). This can be simplified by the kinetic Scheme 4.

In this case the observed rate constant can be expressed by

$$k_{obs} = \frac{k_1 k_2}{k_{-1}}[OH^-]; \quad K_1 = \frac{k_1}{k_{-1}} \qquad (3)$$

The values of product $K_1 k_1$ calculated from the experimental results for derivatives **2b** and **2c** are $K_1 k_1 = (6.30 \pm 0.04) \times 10^{-3}$ l mol^{-1} s^{-1} and $(3.18 \pm 0.03) \times 10^{-3}$ l mol^{-1} s^{-1}, respectively. The decrease in the hydrolysis rate of **2c** compared with compound **2b** can then be explained by both steric and inductive field effects of the α-methyl group, which increase the electron density at the carbonyl carbon of the amide group. The methanolysis **2b** → **4b** in methanolic sodium methoxide has the same character as the hydrolysis but is about

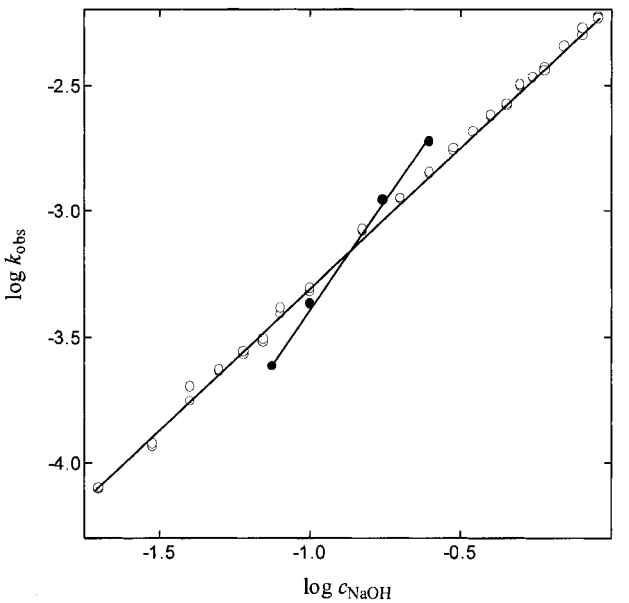
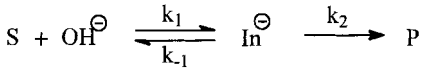


Figure 3. Dependence of logarithm of observed rate constant on logarithm of sodium hydroxide concentration for hydrolysis reaction **2b** → **3b** in aqueous medium (○) and in 10% (v/v) DMSO (●)



Scheme 4

$$S + OH^{\ominus} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} In^{\ominus} \xrightarrow{k_3[OH^-]} P$$

Scheme 5

twice as fast [$K_1k_1 = (1.11 \pm 0.06) \times 10^{-2}$ l mol^{-1} s^{-1}]. If the basicity of the medium is increased by using a solution of sodium hydroxide in 10% (v/v) aqueous DMSO, then the reaction order in OH^- ion is increased, and hence also the slope of dependence of logk_{obs} vs logc_{NaOH} for the hydrolysis of derivative **2b** is increased to 2 (see Fig. 3). This enhancement of the basicity of the medium caused a relative increase in the acidity of intermediate[17] In^-, which means that the second reaction path became significant, i.e. the hydroxide ion-catalysed decomposition of intermediate In^- (the reaction pathway via intermediate In^{2-}) (see Schemes 3 and 5).

From the experimental values and with help of multiple linear regression, it was possible to find that the observed rate constant of hydrolysis of derivative **2b** in 10% (v/v) aqueous DMSO obeys the following rate equation:

$$k_{obs} = a[OH^-] + b[OH^-]^2 \quad (4)$$

From Schemes 3 and/or 5 it follows that the regression parameters a and b correspond to the products K_1k_2 and K_1k_3, respectively (the last constant being $k_3 = K_3k'_3$). The calculated values of the products K_1k_2 and K_1k_3 are $(2.19 \pm 0.05) \times 10^{-3}$ l mol^{-1} s^1 and $(2.17 \pm 0.02) \times 10^{-2}$ l^2 mol^{-2} s^1, respectively.

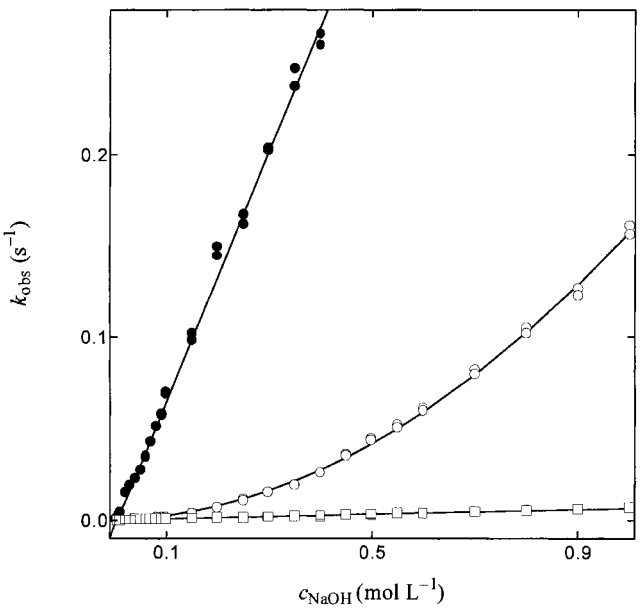


Figure 4. Dependence of observed rate constant (k_{obs}) on sodium hydroxide concentration (c_{NaOH}) for hydrolyses in aqueous medium: **2a** → **3a** (●), **2b** → **3b** (□) and **2d** → **3d** (○)

The same character of the dependence of observed rate constant on concentration of OH^- ion was also observed in the hydrolysis of **2d** in aqueous sodium hydroxide, where only the reaction path via dianion In^{2-} is significant and the values of the products are $K_1k_2 = (8.98 \pm 0.08) \times 10^{-3}$ l mol^{-1} s^1 and $K_1k_3 = (1.49 \pm 0.02) \times 10^{-1}$ l^2 mol^{-2} s^1. Hence it can be stated that the substitution by bromine at the α-position of the γ-lactam ring of derivative **2d** also caused an increase in acidity of intermediate In^-. A further increase in acidity of intermediate In^- was due to replacement of the nitrile group by nitro in the aromatic moiety, as can be seen from the dependence of logk_{obs} vs logc_{NaOH} for **2a**. It was found that the slope of this dependence decreased from 2 to 1. This change in the reaction order in reagent can be interpreted by a change in the rate-limiting step: the OH^- ion-catalysed *decomposition* of tetrahedral intermediate In^- was so much accelerated with increasing concentration of OH^- ion (c_{NaOH} >0.1 mol l^{-1}) that the rate-limiting step shifted to the *formation* of this intermediate. Consequently, the observed rate constant can be expressed as follows:

$$k_{obs} = \frac{b[OH^-]^2}{1 + c[OH^-]} \quad (5)$$

Applying multiple non-linear regression to the experimental k_{obs} values, we calculated the values of regression coefficients b and c, which from their meaning correspond to the values of $K_1k_3 = (9.63 \pm 0.05) \times 10^2$ l mol^{-2} s^{-1} and $k_3/k_{-1} = (1.40 \pm 0.04) \times 10^2$ l mol^{-1}, respectively (Scheme 3). From the ratio of k_3/k_{-1} it follows that the OH^- ion-catalysed decomposition of tetrahedral intermediate In^- is 140 times faster than its formation. The introduction of bromine at the α-position results in acceleration of all reaction steps of hydrolysis and in an increase in acidity of intermediate In^- (Scheme 3). This in turn results in overall acceleration of hydrolysis of bromo derivative **2a** (by two orders of magnitude in 0.05 mol l^{-1} NaOH) compared with that of **2b**.

Figure 4 presents the experimental points of the dependence of the observed rate constant on concentration of sodium hydroxide for hydrolyses of **2a, 2b**, and **2d** interlaced by curves corresponding to Eqns (3), (4) and (5), respectively, the equations containing the calculated regression parameters *a, b* and *c*.

Our suggested mechanism for the alkaline hydrolysis of 1-phenylpyrrolidin-2-ones **2a–d** agrees with the former mechanism[14,15] suggested for solvolyses of tertiary amides and secondary lactams. The differences in the kinetic courses of hydrolysis are determined by differences in the structures of the individual transition states of the rate-limiting step. Owing predominantly to polar and steric effects, the transition state of hydrolysis of bromo derivative **2a** resembles the transition state of hydrolysis of acetanilides.[3] On the other hand, the

transition state of hydrolysis of methyl derivative **2c** resembles more the transition state of hydrolysis of *N*-phenyl-β-lactams.[3]

CONCLUSION

The ring closure of substituted 4-chloro-*N*-phenylbutanamides to 1-phenylpyrrolidin-2-ones is accelerated by substituents at the α-position of the butanamide skeleton. A methyl group at this position accelerates the cyclization more than bromine does, since the latter substituent negatively affects the nucleophilicity of the intramolecular reagent. The ring closure reactions of α-bromo derivatives **1a** and **1d** unambiguously prefer formation of a γ-lactam ring to formation of an α-lactam. With all the derivatives, it is possible to separate the kinetics of ring closure from those of consecutive hydrolysis in aqueous medium. The greatest difference between the rates of ring closure and consecutive hydrolysis was found with methyl derivatives **1c** and **2c**. The solvolysis of substituted 1-phenylpyrrolidin-2-ones follows the same mechanism as the solvolysis of *N*-alkylamides. The hydrolysis of bromo derivatives **2a** and **2d** is not accompanied by splitting off of bromide anion: only the pyrrolidine ring is opened to give the respective substituted 4-aminobutanoic acid as in the other cases, the bromo substituent at the α-position of the γ-lactam ring accelerating all reaction steps of hydrolysis.

Acknowledgements

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

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