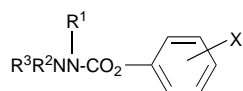


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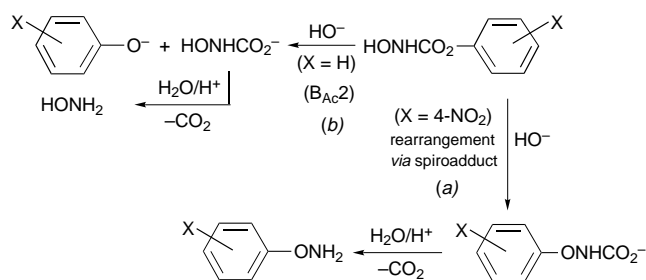
Hydrolysis of aryl carbazates ($\text{H}_2\text{NNHCO}_2\text{Ar}$ with Ar = phenyl, 3- or 4-chlorophenyl, 3- or 4-nitrophenyl, 4-methylphenyl and 4-methoxyphenyl) and/or their 2- or 3-methyl derivatives in aqueous buffers or sodium hydroxide solutions gives phenolate and sodium carbazate. The kinetics and acidity constants and thermodynamic parameters are given. By analysing the pH profiles, the activation entropy, and effects of the substituent on the aromatic ring it was found that aryl carbazates containing a methyl group in the 2 position are hydrolysed by a $\text{B}_{\text{Ac}2}$ mechanism and the others by an E1cB mechanism. The pH profiles of nitrophenyl carbazates show a maximum. The rate of decarboxylation of carbazic acid decreases with increasing pH value.

Aryl carbazates (**1a–5a**) exhibit fungicidal,¹ antihypertensive² and anthelmintic³ activities. The structure of these compounds



- 1: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$; 2: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{R}^3 = \text{Me}$; 3: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{H}$;
 4: $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$; 5: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$.
 a: X = H; b: X = 3-Cl; c: X = 4-Cl; d: X = 3-NO₂; e: X = 4-NO₂;
 f: X = 4-Me; g: X = 4-OMe

is a specific example of aryl carbamates which can exhibit similar hydrolytic stability in living organisms. The alkaline hydrolysis of similar alkyl carbazates⁴ or structurally close phenyl *N*-hydroxycarbamate, which we studied earlier,⁵ follows the same mechanism as that proposed for the hydrolysis of carbamates [Scheme 1 (a)] but for 4-nitrophenyl *N*-hydroxycarbamate another pathway is conceivable⁶ [Scheme 1 (b)].



Scheme 1

The aryl carbazates and some of their 2-methyl derivatives (**1a–2g**, **3b–3e**) are crystalline substances; the other methyl derivatives (**3a**, **3f–5a**) are liquids soluble in common organic solvents. They are decomposed in water or by action of moisture in air, whereas the corresponding hydrochlorides are relatively stable. The aryl carbazates (**1a–5a**) are hydrolysed by aqueous sodium hydroxide to give the respective sodium phenoxide and sodium carbazate. As in the case of carbamates, two mechanisms, E1cB and $\text{B}_{\text{Ac}2}$, can be considered for hydrolytic reaction of aryl carbazates (Scheme 2).

The profiles of the plot in Fig. 1 of model carbazates **1a**, **2a** and **3a** are in agreement with the two general eqns. (1) and (2),

$$\text{for } \text{B}_{\text{Ac}2}: k_{\text{obs}} = k_2 K_w / (K_a + a_{\text{H}}) \quad (1)$$

$$\text{for } \text{E1cB}: k_{\text{obs}} = k_1 K_a / (K_a + a_{\text{H}}) \quad (2)$$

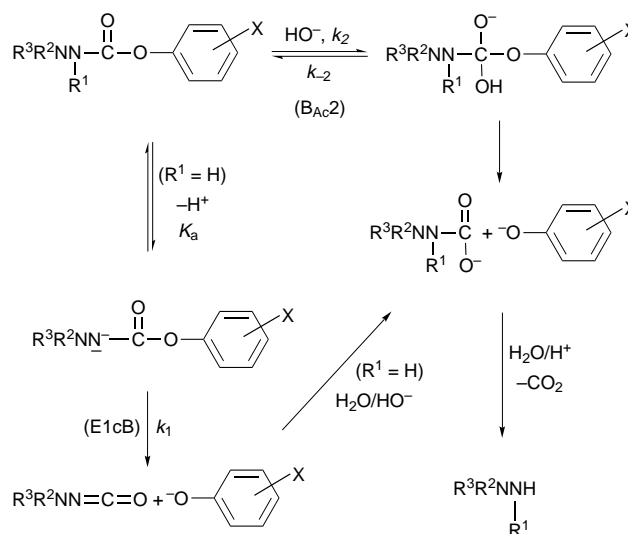
as shown by the linear section with the slope equal to 1 followed by a plateau. In the cases where $K_a \ll a_{\text{H}}$, the two equations can be modified to the form (3).

$$k_{\text{obs}} = \text{pH} + \log k_2 K_w = \text{pH} + \log k_1 K_a = k_{\text{OH}} [\text{HO}^-] \quad (3)$$

The two mechanisms mentioned cannot be differentiated kinetically. They differ from each other only by formation of aminyl isocyanate in the E1cB reaction. Because of its very high reactivity, the presence of this intermediate could not be verified. Therefore, other means were needed for elucidating the reaction mechanism. Two criteria are used for verification of reaction mechanisms:

(a) The reaction constant $\rho > 1$ in the Hammett equation $\log k_{\text{OH}} = \rho\sigma$ indicates the E1cB mechanism. The high ρ value (ca. 3) together with σ^- dependence is consistent with considerable C–O cleavage in the transition state of the rate-determining step.

(b) The formation of tetrahedral intermediates in reactions going by $\text{B}_{\text{Ac}2}$ mechanism is characterized by large negative



Scheme 2

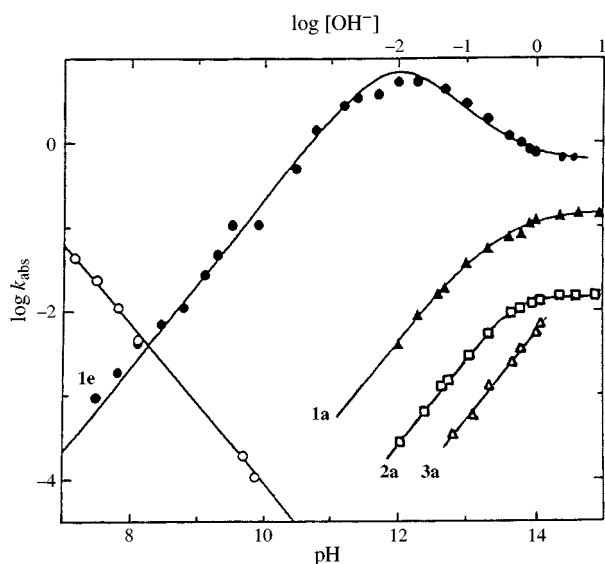


Fig. 1 Comparison of pH dependences of $\log k_{\text{obs}}$ of hydrolysis of aryl carbazates **1a**, **1e**, **2a**, **3a** and decarboxylation of carbazic acid (O)

values of the activation entropy, ΔS^\ddagger . The first three most reactive carbazates were chosen for the following discussion. Each model was extended to obtain a series of compounds differing in the substituents in the benzene ring, and the individual series will be treated separately below. Upon acidification with hydrochloric acid, the carbazic acid formed is decomposed to the corresponding hydrazine (hydrochloride) and carbon dioxide. The observed rate constants of decarboxylation of carbazic acid together with $\log k_{\text{obs}}$ of hydrolysis of aryl carbazates **1a**, **2a**, **3a** and **1e** are given in Fig. 1. The rate of decarboxylation of these substances shows a linear decrease with increasing pH according to eqn. (4). In most cases the

$$\log k_{\text{obs}} = -(0.96 \pm 0.05)\text{pH} + 5.48 \quad (4)$$

decarboxylation is several orders of magnitude slower than the hydrolysis of carbazates, but it is *ca.* two orders faster than the decarboxylation of 3-phenylcarbazic acid.⁴

Hydrolysis of aryl 2-methylcarbazates

Fig. 1 depicts the dependences of $\log k_{\text{obs}}$ of carbazate **3a** on $\log [\text{HO}^-]$. The values of bimolecular rate constants k_{OH} of a series of similar models **3a–3f** are presented in Table 1. The evaluation of the Hammett equation using the σ constants led to relation (5).

$$\log k_{\text{OH}} = -(0.80 \pm 0.09)\sigma - 2.28 \quad (r = 0.975) \quad (5)$$

The application of σ^- constants led to a worse correlation ($r = 0.965$) but the low ρ value obtained also indicates the $B_{\text{Ac}2}$ mechanisms. The activation entropy for phenyl 2-methylcarbazate **1a**, ΔS^\ddagger , is $-151 \text{ J mol}^{-1} \text{ K}^{-1}$. Calmon *et al.*⁴ studied the hydrolysis of related alkyl 3-phenylcarbazates and found the following values: $\rho = -0.89$; $\Delta S^\ddagger = -167 \text{ J mol}^{-1} \text{ K}^{-1}$ (for 2,2,2-trichloroethyl 3-phenylcarbazate) therefrom they postulated the $B_{\text{Ac}2}$ mechanism. In the case of the model of aryl 2-methylcarbazates the hydrolysis undoubtedly must follow the same mechanism since these compounds have no ionisable hydrogen at the nitrogen atom adjacent to the carboxylic group (Scheme 2).

Hydrolysis of aryl 3,3-dimethylcarbazates

Fig. 1 presents the pH dependence of k_{obs} values of hydrolysis of compound **2a**. The line fitted to the individual sets of points expresses the average statistical dependence obtained by non-linear regression according to eqn. (2). In this way we calculated

the magnitude of ionization constant pK_a of carbazate, and the k_1 constants for the splitting off of the aryloxy group were also calculated from relation (2). These constants are given in Table 1 together with the thermodynamic parameters for the hydrolysis. The pH profile of **2a** differs markedly from that of **3a** in Fig. 1. The observed rate constants are independent of hydroxide concentration at higher concentrations of hydroxide ion. The value of ρ in eqn. (6) together with the entropy value

$$\log k_{\text{OH}} = (4.04 \pm 0.14)\sigma - 1.68 \quad (r = 0.991) \quad (6)$$

$\Delta S^\ddagger = 8.4 \text{ J mol}^{-1} \text{ K}^{-1}$ (for **2a**) indicate the E1cB mechanism given in Scheme 2.

The k_{OH} values have been calculated from eqn. (3) and the pK_a and k_1 values from eqn. (2).

They also show good Hammett correlations: pK_a ($\rho = 1.04$) and for k_1 ($\rho = 2.65$), and their sum agrees with the values given in eqn. (6).

Hydrolysis of aryl carbazates

Fig. 1 presents the dependence of the observed rate constants on pH and on hydroxide ion concentration for compounds **1a** and **1e**. The experimental points of the dependence were not fitted with a curve given by eqn. (2) since the character of the 'pH profiles' for **1e** (and **1d**) of the series differs considerably from such a dependence. The ascending section of curves have similar shapes as those in the 3,3-dimethylcarbazate series. At $\text{pH} > 12$, the observed rate of hydrolysis of 3- and 4-nitrophenyl derivatives decreases. In the case of other derivatives this decrease could not be followed because it was impossible to determine the constants at sufficiently high concentrations of hydroxide ion. The bimolecular rate constants k_{OH} for carbazates **1a–1c**, **1f** were calculated from $\log k_{\text{obs}}$ values within all 'pH profiles' by eqn. (2), and for carbazates **1d**, **1e** from analogous values only of ascending regions of 'pH profiles'. All the k_{OH} constants were used to derive the Hammett relation (7).

$$\log k_{\text{OH}} = (3.44 \pm 0.15)\sigma - 0.43 \quad (r = 0.987) \quad (7)$$

The equation along with the value ΔS^\ddagger ($-8.61 \text{ J mol}^{-1} \text{ K}^{-1}$ for **1a**) support the hydrolysis by E1cB mechanism (Scheme 2). For this series, too, we correlated the pK_a and k_1 values from Table 1 using the Hammett equations: for pK_a ($\rho = 1.18$) and for k_1 ($\rho = 2.27$).

In the case of 3- and 4-nitro derivatives for which ionization is easiest we can see a maximum and subsequent decrease nearly linearly proportional to pH values with a slope of -1 . The different behaviour of carbazates **1d** and **1e** could be interpreted by subsequent ionization and formation of the less reactive dianion $\text{NHN}=\text{C}(\text{OAr})\text{O}^-$ from the more reactive monoanion $\text{H}_2\text{NN}^-\text{CO}_2\text{Ar}$. This possibility was not confirmed by the analysis of products. If the dianion had been formed from 4-nitrophenyl carbazate **1e**, the hydrolysis products would have involved 4-nitrophenylhydrazine in the same way as *O*-(4-nitrophenyl)hydroxylamine is formed from 4-nitrophenyl *N*-hydroxycarbamate [Scheme 1(b)]. This analogous transformation can go *via* the structurally similar dianion $\text{O}^-\text{N}=\text{C}(\text{OAr})\text{O}^-$ (ref. 6). On the other hand it might be expected that the reactivity of the dianion will be higher than that of the monoanion, which we have confirmed kinetically in the hydrolysis of the analogous phenyl *N*-hydroxycarbamate⁵ [Scheme 1(a)]. We have no satisfactory interpretation for the change in reaction mechanism of hydrolysis of carbazates **1d** and **1e** at $\text{pH} > 12$.

Experimental

Synthesis of aryl carbazates

Carbazates **1a–5a** were prepared by addition of an aryl chloroformate or diaryl carbonate to the corresponding hydrazine.

Table 1 Physicochemical data of carbazates **1a–5a**. The rate and dissociation constants were measured at 25 °C.

No.	pH range	$-\log k_{\text{obs}}$	$(\text{p}K_{\text{a}})^a$	$k_{\text{HO}^-}/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	k_1/s^{-1}	Mp/°C
1a	<11.9, 14.9>	<2.42, 0.82>	13.6 ^b	0.331 ± 0.012	0.145	—
1b	<9.7, 12.9>	<3.34, 0.27>	13.1	11.1 ± 0.42	0.856	110–111
1c	<10.7, 14.9>	<2.75, 0.65>	13.2	2.74 ± 0.20	0.326	139–141
1d	<9.4, 14.9>	<2.63, 1.02>	12.6 ^a	76.7 ± 3.3	6.55	121–123 ^c
1e	<7.5, 13.9>	<3.02, 0.18>	11.9 ^a	1680 ± 72	17.3	111–113 ^c
1f	<12.0, 14.9>	<2.91, 1.14>	13.7	0.105 ± 0.023	6.00 × 10 ⁻²	115–117
2a	<12.0, 14.9>	<3.62, 1.97>	13.6 ^b	(2.8 ± 0.2) × 10 ⁻²	1.38 × 10 ⁻²	—
2b	<11.1, 14.9>	<2.78, 0.74>	13.1	0.781 ± 0.011	0.151	88–90 ^c
2c	<11.7, 14.9>	<2.91, 1.31>	13.3	0.264 ± 0.015	4.84 × 10 ⁻²	129–131
2d	<9.9, 13.9>	<3.15, 0.32>	12.8	11.45 ± 0.30	0.648	110–112 ^c
2e	<9.4, 13.9>	<1.88, -0.80>	12.1	406 ± 22	6.91	118–120
2f	<11.7, 14.9>	<2.95, 2.28>	13.8	(4.56 ± 0.19) × 10 ⁻³	5.62 × 10 ⁻³	124–126
2g	<11.7, 14.9>	<2.95, 2.51>	14.0	(5.05 ± 0.43) × 10 ⁻³	3.38 × 10 ⁻³	102–103
3a	<12.7, 13.9>	<3.45, 2.13>	<i>b</i>	(6.80 ± 0.20) × 10 ⁻³	—	<i>cde</i>
3b	<12.7, 13.9>	<3.45, 2.03>	—	(8.94 ± 0.11) × 10 ⁻³	—	31–34 ^d
3c	<12.7, 13.9>	<3.59, 2.21>	—	(7.33 ± 0.34) × 10 ⁻²	—	161–163
3d	<12.7, 13.9>	<3.12, 1.62>	—	(2.13 ± 0.02) × 10 ⁻³	—	83–88 (decomp.)
3e	<12.7, 13.9>	<2.91, 1.42>	—	(2.96 ± 0.41) × 10 ⁻²	—	93–97 (decomp.)
3f	<12.7, 13.9>	<3.80, 2.45>	—	(3.69 ± 0.21) × 10 ⁻³	—	<i>dc</i>
4a	<13.0, 13.9>	<4.42, 3.39>	<i>b</i>	(4.65 ± 0.07) × 10 ⁻⁴	—	<i>de</i>
5a	<13.6, 14.1>	<4.97, 4.53>	<i>b</i>	(2.55 ± 0.07) × 10 ⁻⁵	—	<i>de</i>

^a Kinetically determined. ^b $E^\ddagger/\text{kJ mol}^{-1}$, $\Delta H^\ddagger/\text{kJ mol}^{-1}$, $\Delta S^\ddagger/\text{J K}^{-1} \text{ mol}^{-1}$: for **1a** 75.7 ± 7.4, 73.2 ± 7.7, -8.6 ± 0.3; for **2a** 86.9 ± 6.7, 84.4 ± 6.1, 8.42 ± 0.9; for **3a** 42.8 ± 6.8, 40.3 ± 5.9, -151.2 ± 10.5; for **4a** 69.3 ± 7.3, 66.9 ± 5.6, -169.3 ± 7.2; for **5a** 62.7 ± 5.9, 39.6 ± 4.3, -166.4 ± 9.7. All thermodynamic parameters were calculated from k_{obs} at four different temperatures in the range 25–60 °C. ^c Mp of hydrochloride: **1d** 147–149 °C; **1e** 149–151 °C; **2b** 135–139 °C; **2d** 151–152 °C. ^d Bp for **3a** 155–157 °C at 1.3 kPa; for **3b** 123–125 °C at 0.2 kPa; **3f** 110–115 °C at 0.1 kPa; **4a** 102–103 °C at 0.4 kPa; **5a** 94–97 °C at 0.4 kPa. ^e n_D^{20} for **3a** 1.5298; for **4a** 1.5250; for **5a** 1.5148.

For details of their preparation and spectroscopic data see ref. 7.

Identification of hydrolysis products

A mixture of phenyl carbazate (0.05 g) in dioxane (1 ml) and sodium hydroxide (0.1 mol dm⁻³; 15 ml) was boiled for 1 h. One half of the reaction mixture was saturated with carbon dioxide to pH 8–9. The solution was extracted with diethyl ether and analysed by means of HPLC. The second part of the reaction mixture was acidified with hydrochloric acid, the gaseous product was introduced into barium hydroxide by a stream of nitrogen. After evaporation of the acidic residue *in vacuo*, the evaporation residue was mixed with excess 50% sodium hydroxide and diethyl ether. The organic phase was analysed chromatographically.

Kinetic experiments

Solutions of aryl carbazates or their methyl substituted analogues or carbazic acid in methanol were injected into phosphate (prepared by mixing the aqueous solutions 0.05 mol dm⁻³ Na₂HPO₄ and 0.1 mol dm⁻³ NaOH), borax (from 0.025 Na₂B₄O₇·10 H₂O and 0.1 mol dm⁻³ NaOH), or tris buffer [from 0.1 mol dm⁻³ 2-amino-2-(hydroxymethyl)propane-1,3-diol and 0.1 mol dm⁻³ NaOH], or solutions of sodium hydroxide under nitrogen. The ionic strength was adjusted at 1.0 by addition of KCl. The ionic strength of sodium hydroxide solutions with acidity function higher than 14 was not modified and the values of acidity function were taken from the literature.⁸ The final concentration of the substrate was 10⁻⁴ mol dm⁻³. Methanolic solutions of nitrocarbazate hydrochlorides were used instead of their free bases. The pH values of the individual buffers were determined with a Radiometer pHM62 apparatus at 25 °C. The hydrolysis rates were measured spectrophotometrically on the basis of increment of the substituted phenol formed (Specord Carl-Zeiss Jena M40, Hewlett-Packard-HP8452A-Diode Array-Spectrophotometer, and Durrum-Gibson D-110 Spectrophotometer) at 25 °C or at higher temperatures. The rate of

carbazic acid decarboxylation was measured from its decrease in a similar way.

Dissociation constant

Values for the carbazates **1a–1f** and **2a–2g** were evaluated statistically from the observed velocity constants and corresponding proton activities by the method of nonlinear regression under eqn. (2).

Chromatographic checking

This was carried out on an HPLC apparatus Varian Model 5000 using Separon SGX C18 in 80% aqueous methanol and GC Chrom-5 apparatus (Laboratorní přístroje Praha) on Chromosorb A-SE52.

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