

Diarylbis(acylamino)spiro- λ^4 -sulfanes and cyclic acylaminosulfonium salts. A kinetic study of equilibrium and hydrolysis reactions

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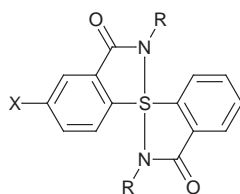
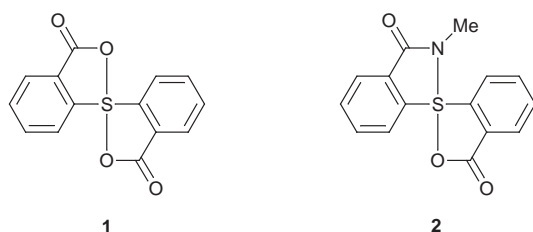
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Kinetics for the hydrolysis of diarylbis(acylamino)spiro- λ^4 -sulfanes **3a–e** and **9** and precursor acylaminosulfonium salts **5a–e** and **8** both leading to sulfoxides **6a–e** and **10**, respectively, have been studied under pseudo-first-order conditions in dioxane–water mixtures. Medium, substituent ($\rho^+ -0.44$) and solvent isotope effects ($k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} \approx 2$) indicate that the cleavage of one of the S–N bonds and a simultaneous proton-transfer from H_2O to the leaving carbamoyl group take place in the rate-determining step of the hydrolysis of spiro- λ^4 -sulfanes **3a–e**. The acylaminosulfonium and OH^- ion intermediates formed together are converted to sulfoxides **6a–e** in fast steps. The hydrolysis of acylaminosulfonium salts shows deviation from first-order kinetics at the starting period of the reaction, which may be ascribed to an equilibrium formation of spiro- λ^4 -sulfanes. The equilibrium between **3a** and **5a** has been studied by spectroscopic methods, and $K_{35} 5 \times 10^{-7} \text{ mol dm}^{-3}$ was obtained in 70:30 (v/v) dioxane–water, at 25 °C. The equilibrium is shifted towards the acylaminosulfonium salts as the acidity of the solvent increases with the progress of the hydrolysis, or when acid is added to the mixture. In the case of hydrolysis of **5a–e** and **8** the medium, substituent and deuterium solvent isotope effects ($k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} \approx 4.3$) as well as the general base catalytic effect of acetate ions suggest that a nucleophilic attack of water on the sulfonium centre occurs in the rate-determining step with the cleavage of one of the OH bonds in water and with the formation of a hydroxy(acylamino)- λ^4 -sulfane. Acylaminosulfonium salt **12**, having a sterically hindered reaction centre, undergoes hydrolysis only with more nucleophilic OH^- ions. Relative reactivities and different ring-size effects observed for bis(acyloxy)-, (acyloxy)(acylamino)- and bis(acylamino)-spiro- λ^4 -sulfanes and cyclic acylaminosulfonium salts are compared and interpreted.

Introduction

Diarylspiro- λ^4 -sulfanes (earlier spirosulfuranes), e.g. **1**, **2** and **3a–f**, are excellent models for studying both the hypervalent



X	R
a	H
b	OMe
c	Me
d	Cl
e	NO ₂
f	H

bonding systems about the four-coordinated sulfur(IV) atom and the reactions occurring at a sulfur atom with a trigonal bipyramidal configuration.^{1–6} If the axial hetero atoms are identical, e.g. as in **1** and **3a**, the two axial bonds (S–O or S–N) are equivalent (see Table 1). In ‘non-symmetric’ spiro- λ^4 -sulfane **2** the short S–N and long S–O distances (Table 1) point to a

Table 1 IR carbonyl frequencies ($\nu_{\text{C=O}}$) and axial bond lengths in spiro- λ^4 -sulfanes **1**, **2**, **3a** and **9**, and in acylaminosulfonium salts **5a**, **8** and **12**

Compound	$\nu_{\text{C=O}}^a/\text{cm}^{-1}$		Axial bond lengths/Å		Ref.
	Acyloxy	Acylamino	S–N	S–O	
1	1740			1.842	1
2	1649	1693	1.734	2.132	4
3a		1645	1.898 ^b		10
5a	1623	1723	1.685	2.373	4
8		1630, 1660	1.671	2.448	4
9		1622, 1662			4
12		1629, 1689	1.664	2.795	4

^a In KBr disc. ^b Bond length data obtained for the *N,N*-diisopropyl derivative **3f**.²

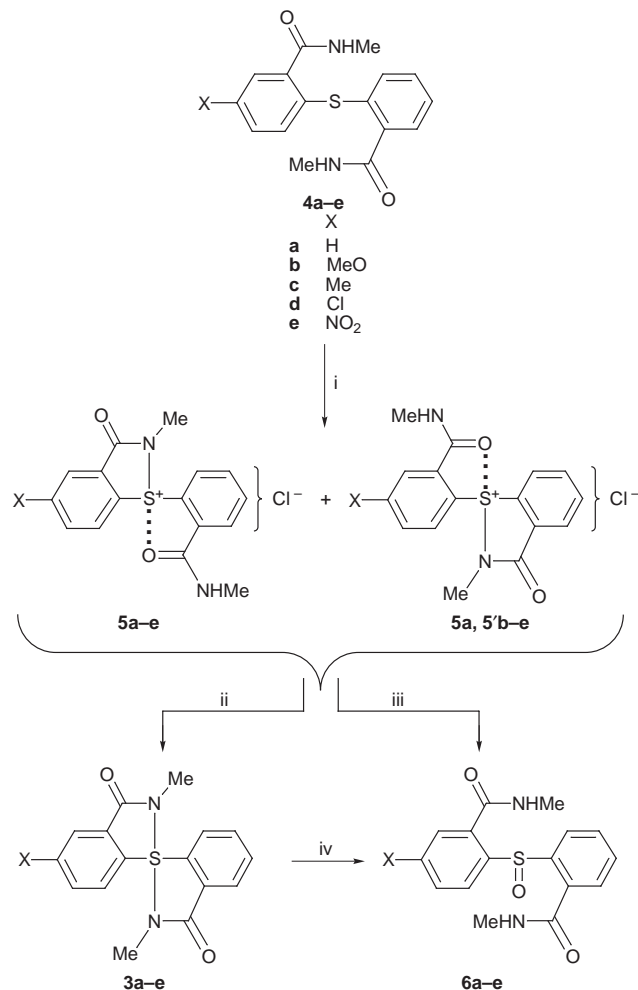
nearly covalent single S–N bond and an extremely polarized hypervalent $\text{S}^{\delta+} \text{---} \text{O}^{\delta-}$ bond, i.e. this structure is nearly zwitterionic. Cyclic acylaminosulfonium salts **5a–e**, **8** and **12** also have a spiro- λ^4 -sulfane-like configuration stabilized by a $\text{S} \cdots \text{O}$ close contact in which the distance of sulfur and oxygen atoms is not too much longer than that in S–O hypervalent bonds (cf. refs. 4 and 7).

In previous papers the hydrolysis of diarylbis(acyloxy)spiro- λ^4 -sulfane **1**⁵ and diaryl(acylamino)(acyloxy)spiro- λ^4 -sulfane **2**⁶ leading to the corresponding sulfoxides were studied by kinetic methods. In the case of the ‘symmetric’ spiro- λ^4 -sulfane **1** we could explain the reaction by a rate-determining spiro-ring-opening. In contrast, the nucleophilic attack of water on the positive sulfonium centre proved to be rate-controlling for ‘non-symmetric’ spiro- λ^4 -sulfane **2**.

In this paper we report on the kinetics and mechanism of the hydrolysis of both the diarylbis(acylamino)spiro- λ^4 -sulfanes (earlier diazasulfuranes) **3a–e** and **9**, and the precursor carbamoyl-substituted cyclic acylaminosulfonium salts **5a–e**

(together with the isomeric 5'b-e), 8 and 12, which yield the corresponding sulfoxides 6a-e, 10 and 14. In discussions we also make use of earlier conclusions about λ^4 -sulfanes^{2,5-8} and aminosulfonium salts.⁹

The model compounds were prepared by known methods.¹⁰ Sulfides (4a-e and 7) were oxidized to cyclic acylaminosulfonium salts (5a-e, 5'b-e and 8), and subsequently deprotonated to spiro- λ^4 -sulfanes (3a-e and 9). Both types of compounds hydrolyse easily to sulfoxides (6a-e and 10) (Schemes 1 and 2).



Scheme 1 Synthesis and hydrolysis of acylaminosulfonium salts 5a-e–5'a-e and spiro- λ^4 -sulfanes 3a-e. Reagents and conditions: (i) Bu'OCl, CH₂Cl₂, 20 °C; (ii) KH, dioxane, 20 °C; (iii) KHCO₃ aq, 20 °C; (iv) H₂O-CH₂Cl₂, 20 °C.

The acylaminosulfonium salt 12 obtained from the substituted dinaphthyl sulfide 11 could not be cyclized to spiro- λ^4 -sulfane 13, and its hydrolysis to give sulfoxide 14 needed neutral or basic (pH > 5) experimental conditions (Scheme 3).

Results and discussion

Hydrolysis of spiro- λ^4 -sulfanes 3a-e and 9

The rate of hydrolysis of spiro- λ^4 -sulfanes 3a-e and 9, was measured by a UV spectrophotometric method in various dioxane-water mixtures. The reactions followed first-order kinetics, the calculated k_3 rate constants for reaction of 3a are given in Table 2. The activation parameters for 3a in 70:30 (v/v) dioxane-water are ΔH^\ddagger 78.7 kJ mol⁻¹ and ΔS^\ddagger -25.1 J mol⁻¹ K⁻¹.

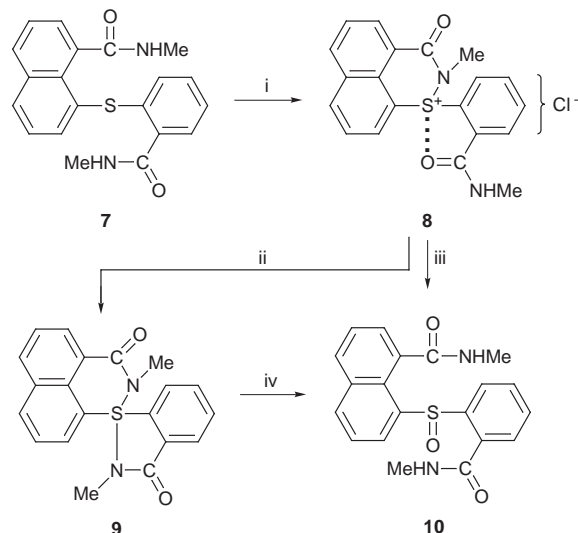
The rate of hydrolysis of compound 3a increased faster than the water content of the solvent (Table 2). Eqn. (1) shows that a

$$\log k_3 = (0.164 \pm 0.003)E_T - (12.0 \pm 0.2) \quad (r 0.998) \quad (1)$$

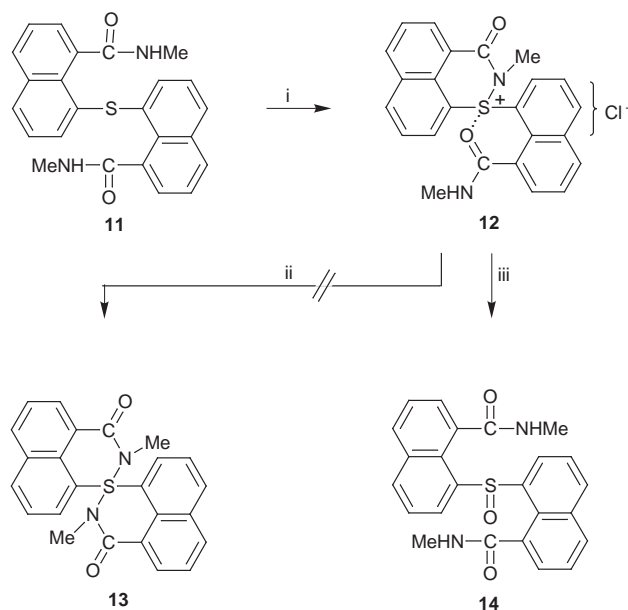
Table 2 Rate constants (k_3) for the hydrolysis of spiro- λ^4 -sulfane 3a in various dioxane-H₂O mixtures at 25 °C and the corresponding E_T solvent polarity parameters

H ₂ O (% v/v)	$k_3/10^{-3} \text{ s}^{-1}$	$E_T^b/\text{kcal mol}^{-1}$
2	0.103	49.1
2.5	0.151	49.7
5	0.440	52.5
10	1.06	55.4
15	1.97	56.6
20	3.06	57.6
25	4.07	58.5
30	5.46 ^a	59.3

^a Rate constants are 1.76×10^{-3} , 2.14×10^{-3} , 3.05×10^{-3} and $8.77 \times 10^{-3} \text{ s}^{-1}$ at 15.0, 17.5, 20.0 and 30.0 °C, respectively. ^b See Experimental section.



Scheme 2 Synthesis and hydrolysis of acylaminosulfonium salt 8 and spiro- λ^4 -sulfane 9. Reagents and conditions: see Scheme 1.



Scheme 3 Synthesis and hydrolysis of acylaminosulfonium salt 12. Reagents and conditions: see Scheme 1.

good linear correlation can be obtained between $\log k_3$ and the solvent polarity parameter E_T ¹¹ (cf. ref. 5).

The deuterium solvent isotope effect ($k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$) for spiro- λ^4 -sulfanes 3a, b and e was found to be between 1.7–2.0, pointing to a primary kinetic isotope effect (Table 3).

The substituent effect controlling the hydrolysis reaction of

Table 3 Substituent and kinetic solvent isotope effects for the hydrolysis of spiro- λ^4 -sulfanes **3a–e** in 80:20 (v/v) dioxane–H₂O and dioxane–D₂O mixtures at 25 °C

Spiro- λ^4 -sulfane	$k_3/10^{-3} \text{ s}^{-1}$	$k_3^a/10^{-3} \text{ s}^{-1}$	$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$
3a	3.06	1.66	1.8
3b	6.42	3.21	2.0
3c	3.95		
3d	2.42		
3e	1.34	0.807	1.76

^a In dioxane–D₂O.

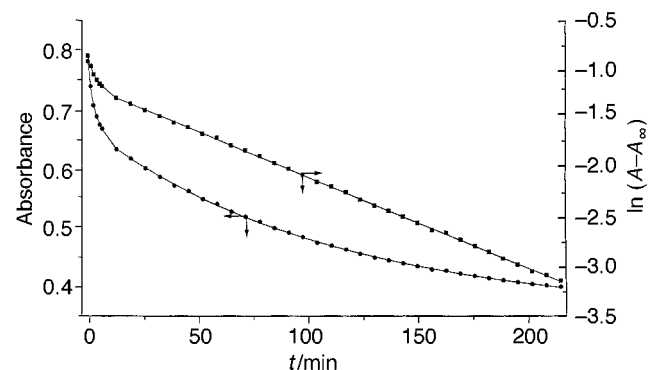


Fig. 1 Absorbance (A) versus time and $\ln(A - A_\infty)$ versus time plots for the hydrolysis of **5a**, $\{[\mathbf{5a}]_0, 2.0 \times 10^{-4} \text{ mol dm}^{-3}; 75:25 \text{ (v/v) dioxane-H}_2\text{O at } 25^\circ\text{C}; \lambda, 290.5 \text{ nm}\}$

spiro- λ^4 -sulfanes **3a–e** was studied in 80:20 (v/v) dioxane–water mixtures (Table 3). The reaction was promoted by electron-releasing groups in the phenyl ring. The Hammett plot [eqn. (2)]

$$\log k = \rho\sigma + \text{constant} \quad (2)$$

using the σ_p constants was not found to be linear ($\rho = -0.58, r = 0.962$). Better correlation was obtained by using the σ_p^+ substituent constants ($\rho^+ = -0.44, r = 0.997$). Substituent constants were taken from ref. 12. The positive polarization of the sulfur atom in the transition state is supported by the good correlation obtained with the σ_p^+ constants.

Spiro- λ^4 -sulfane **9**, which contains a five- and a six-membered ring, hydrolyses one hundred times faster than compound **3a** with two five-membered rings. The rate constant for **9** could be measured only at a low water concentration; k_9 was $1.05 \times 10^{-2} \text{ s}^{-1}$ in 98:2 (v/v) dioxane–water at 25 °C.

Hydrolysis of acylaminosulfonium salts **5a–e**

Rate of hydrolysis of 5a. The hydrolysis of **5a**, investigated in dioxane–water mixtures by a UV spectrophotometric method, showed deviations from simple first-order kinetics, although water was in great excess in the solvent. As shown in Fig. 1, the absorbance versus time plots can be divided into two parts. The absorbance values change very quickly in the first short period of the reaction and, at the same time, the $\ln(A - A_\infty)$ versus time plot is curved. After the initial period the hydrolysis follows first-order kinetics.

The fast period of the reaction is longer and can be observed especially well if the measurements are carried out in a dilute solution of the substrate ($5 \times 10^{-5} \text{ mol dm}^{-3}$). On the other hand, the fast period is shortened with an increase in the initial concentration of the acylaminosulfonium salt, and it cannot be observed at all in acidic solutions where the hydrolysis does not deviate from first-order kinetics.

The first-order k_5 rate constants were calculated from the linear part of the $\ln(A - A_\infty)$ versus time plots of the hydrolysis of compound **5a**. The calculated values agree well, within the experimental errors, with those obtained from the first-order reaction of **5a** carried out in the presence of $2 \times 10^{-3} \text{ mol dm}^{-3}$

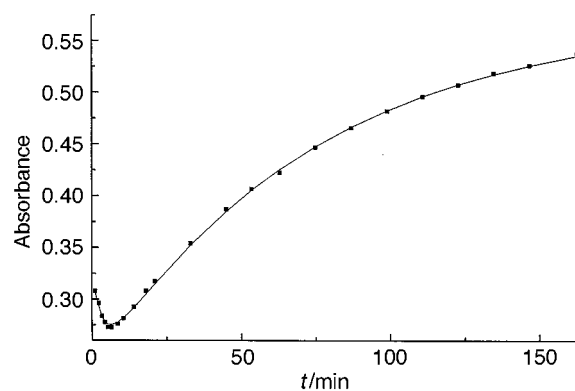


Fig. 2 Absorbance (A) versus time plot for the hydrolysis of **5a**, at 302.0 nm $\{[\mathbf{5a}]_0, 2.01 \times 10^{-4} \text{ mol dm}^{-3}; 70:30 \text{ (v/v) dioxane-H}_2\text{O, at } 25^\circ\text{C}\}$. The curve was calculated using the method described in ref. 13.

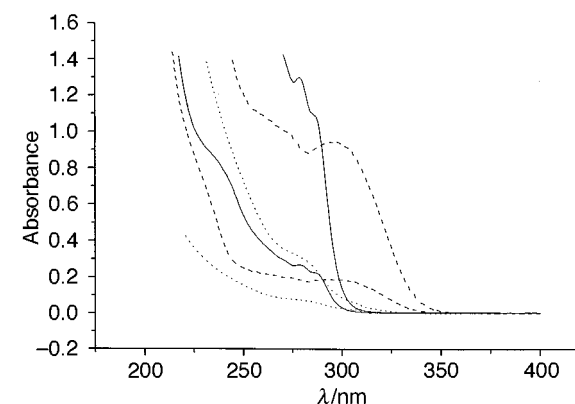
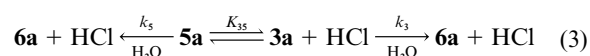


Fig. 3 UV spectra of **5a** $\{(\text{—}); [\mathbf{5a}], 2.01 \times 10^{-4} \text{ mol dm}^{-3}; d, 0.2 \text{ and } 1 \text{ cm}; \text{ solvent: } 0.3 \text{ mol dm}^{-3} \text{ HCl in } 97:3 \text{ (v/v) dioxane-H}_2\text{O}\}$, **3a** $\{(\text{---}); [\mathbf{3a}], 2.02 \times 10^{-4} \text{ mol dm}^{-3}; d, 0.2 \text{ and } 1 \text{ cm in dioxane}\}$, and **6a** $\{(\cdots); [\mathbf{6a}], 2.01 \times 10^{-4} \text{ mol dm}^{-3}; d, 0.2 \text{ and } 1 \text{ cm in dioxane}\}$

HCl or TsOH (Table 4). The activation parameters for **5a** calculated from the k_5 rate constant are $\Delta H^\ddagger, 55.7 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger, -128.9 \text{ J mol}^{-1} \text{ K}^{-1}$ in 70:30 (v/v) dioxane–water (Table 4). The rate of hydrolysis of the acylaminosulfonium salt **5a** is about 25 times lower than that of spiro- λ^4 -sulfane **3a**.

Equilibrium between acylaminosulfonium salt 5a and spiro- λ^4 -sulfane 3a. If the rate of hydrolysis for **5a** is measured at a wavelength longer than 300 nm the absorbance versus time plot has a minimum (Fig. 2), indicating the formation of an intermediate during the hydrolysis. A comparison of the UV absorption spectra obtained for compounds **3a**, **5a** and **6a** (Fig. 3) suggests that the intermediate is presumably identical with spiro- λ^4 -sulfane **3a**. The absorption of **3a** is smaller at a wavelength lower than 290 nm, but much larger above 300 nm than that of **5a**.

Accepting this view, we may explain the change of absorptivity for the hydrolysis of **5a** (see Fig. 2) in the following way. When dissolved in a dioxane–water mixture, acylaminosulfonium salt **5a** is partly converted into spiro- λ^4 -sulfane **3a** in a very fast equilibrium reaction. Although **3a** undergoes hydrolysis more rapidly than **5a** to give sulfoxide **6a** (cf. Tables 2 and 4), the equilibrium is shifted towards **5a** when the concentration of acid (HCl) increases with the progress of the hydrolysis, or when acid is added to the reaction mixture [eqn. (3)]. The conversion of **5a** into **3a** is obviously very fast because



it involves only deprotonation and a subsequent ring-closure reaction between near-lying sulfur and nitrogen atoms. Spiro- λ^4 -sulfane **3a** is also instantly transformed into acylaminosulfonium salt **5a** when acid is added to its solution.

Table 4 Rate constants (k_5 and k_8) for the hydrolysis of acylaminosulfonium salts **5a** and **8** in various dioxane–H₂O and dioxane–D₂O mixtures at 25 °C, the corresponding E_T solvent polarity parameters, and the kinetic isotope effect for the hydrolysis of **5a**

H ₂ O (% v/v)	$k_5/10^{-4} \text{ s}^{-1}$	$k_5^a/10^{-4} \text{ s}^{-1}$	$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$	$k_8/10^{-4} \text{ s}^{-1}$	$E_T/\text{kcal mol}^{-1}$
20	1.00 ^b			0.351	57.6
25	1.50	0.360	4.2		58.5
30	2.22 ^{c,d}			0.448	59.3
35	2.72				59.6
40	3.68	0.800	4.6		60.6
45	4.60	1.08	4.3		61.2
50	5.55	1.24	4.5		62.1
55	6.87				62.9
60	8.57			1.02	63.5
100				4.18	70.0

^a In dioxane–D₂O. ^b Rate constants 1.06×10^{-4} , 1.04×10^{-4} and $1.14 \times 10^{-4} \text{ s}^{-1}$ were measured when the solution contained 2.0×10^{-4} , 2.0×10^{-3} and $2.0 \times 10^{-2} \text{ mol dm}^{-3}$ TsOH, respectively. ^c Rate constants 1.33×10^{-4} , 3.02×10^{-4} , 4.34×10^{-4} and $6.11 \times 10^{-4} \text{ s}^{-1}$ were measured at 20, 30, 35 and 40 °C, respectively. ^d Rate constants 2.04×10^{-4} , 2.03×10^{-4} and $2.37 \times 10^{-4} \text{ s}^{-1}$ were measured when the solution contained 2.7×10^{-4} , 2.7×10^{-3} and $3.4 \times 10^{-2} \text{ mol dm}^{-3}$ HCl, respectively. ^e See Experimental section.

Table 5 Effect of the concentration of salts on the rate constants (k) of hydrolysis of acylaminosulfonium salts **5a**, **8** and **12** in aqueous acetate buffers at 25 °C

Compound	pH	[NaOAc]/ $10^{-3} \text{ mol dm}^{-3}$	$k^a/10^{-3} \text{ s}^{-1}$	[NaCl]/ $10^{-3} \text{ mol dm}^{-3}$	$k^b/10^{-3} \text{ s}^{-1}$
5a	3.55	4.70	8.61	2.35	8.32
5a	3.55	2.35	5.59	4.70	5.28
8	3.55	2.54	3.25	5.10	3.09
8	3.55	5.08	4.73	2.55	4.80
12	5.61	85.0	0.0653		
12	5.61	56.0	0.067	28.8	0.0636
12	5.61	28.0	0.0738	57.7	0.0633

^a Measured in acetate buffer without added NaCl. ^b Measured in acetate buffer in the presence of NaCl.

Using the known k_3 and k_5 rate constants and the absorptivities of **3a** ($\epsilon_{302 \text{ nm}} 4800 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$) and **5a** ($\epsilon_{302 \text{ nm}} 259 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$), we calculated the K_{35} equilibrium constant from the UV absorption *versus* time profiles of the hydrolysis of compound **5a** (e.g. from Fig. 2) by kinetic model simulation and parameter optimization,¹³ and $K_{35} (5 \pm 1) \times 10^{-7} \text{ mol dm}^{-3}$ was obtained as a mean value in 70:30 (v/v) dioxane–water at 25 °C. The method used for the calculation of K_{35} proved to be suitable as the measured and calculated absorption *versus* time profiles for the hydrolysis of acylaminosulfonium salt **5a** fitted well (e.g. see Fig 2). The low value of K_{35} indicates that the equilibrium in eqn. (3) is strongly shifted towards the acylaminosulfonium salt **5a** in the given solvent, and spiro- λ^4 -sulfane **3a** can form in detectable amounts only in dilute solutions. Thus, we could not detect the bands of spiro- λ^4 -sulfane **3a** in the IR and NMR spectra of acylaminosulfonium salt **5a** obtained in a 70:30 (v/v) [²H₈]dioxane–D₂O solution at $10^{-2} \text{ mol dm}^{-3}$ concentration [**5a**: $\nu_{\text{max}}/\text{cm}^{-1}$ 1724s, 1631s (CO); δ_{H} 3.45 (s, 3H, MeN), 3.18 [s, 3H (NH)Me]; **3a**: $\nu_{\text{max}}/\text{cm}^{-1}$ 1652s CO; δ_{H} 3.18 (s, 6H, MeN)]¹⁰ because only 0.7% of **5a** should transform into **3a** under these circumstances. On the other hand, in UV measurements carried out at the lower concentration of $2 \times 10^{-4} \text{ mol dm}^{-3}$, the equilibrium between **5a** and **3a** may already have a distinct influence on the rate of hydrolysis because 4.9% of the acylaminosulfonium salt **5a** is converted into spiro- λ^4 -sulfane **3a** in the given dilute solution.

Medium effect. The rate of hydrolysis of acylaminosulfonium salt **5a** increases more steeply than the water content of the solvent used (see Table 4). In dioxane–water mixtures from 20 to 60% (v/v), the rate of hydrolysis increased about eight-fold. A good linear correlation was found between $\log k_5$ and the solvent polarity parameter E_T ¹¹ (cf. refs. 5 and 6) [eqn. (4)].

$$\log k_5 = (0.147 \pm 0.009)E_T - (12.4 \pm 0.5) \quad (r 0.988) \quad (4)$$

When NaCl was added up to 0.17 mol dm^{-3} concentration to a 80:20 (v/v) dioxane–water mixture, the rate of hydrolysis of

Table 6 Catalytic constants (k_0 and k_{cat}) for the hydrolysis of acylaminosulfonium salts **5a** and **8** measured in aqueous acetate buffers at 25 °C

Compound	Concentration range [AcO ⁻]/ $10^{-3} \text{ mol dm}^{-3}$	pH	$k_0/10^{-3} \text{ s}^{-1}$	$k_{\text{cat}}/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
5a	1–4	4.65	10.3	1.10
5a	1–5	4.45	7.01	1.25
5a	1.41–1.69	4.05	3.85	1.21
5a	0.587–7.05	3.55	2.57	1.25
8	1–4	4.65	7.30	0.712
8	1–5	4.45	4.97	0.723
8	1–7.6	4.05	2.52	0.713
8	2.35–7.05	3.55	1.67	0.601

5a did not change [$k_5 (1.07 \pm 0.07) \times 10^{-4} \text{ s}^{-1}$] despite the increase in ionic strength.

Catalysis. The rate of hydrolysis of acylaminosulfonium salt **5a** was not accelerated by strong acids. In the concentration range 2.0×10^{-4} – $3.4 \times 10^{-2} \text{ mol dm}^{-3}$ of acids the rate constant k_5 showed a flat minimum (Table 4).

The hydrolysis of **5a** was catalysed by acetate buffer. In aqueous solutions, at constant pH, the rate constant was a linear function of the concentration of acetate ions [eqn. (5)]

$$k = k_0 + k_{\text{cat}}[\text{OAc}^-] \quad (5)$$

and proved to be independent of the ionic strength of the medium (Table 5, cf. ref. 14). The rate constants k_0 and k_{cat} calculated from eqn. (5) are listed in Table 6. The values of k_{cat} for **5a** are independent of pH within the experimental errors. The rate constant k_0^5 that characterizes the rate of hydrolysis of **5a** in aqueous solutions of different pH in the absence of AcO⁻ ions is a linear function of [OH⁻] [eqn. (6)]. The linear dependence

$$k_0^5 = (1.87 \pm 0.10) \times 10^{-3} + (1.87 \pm 0.04) \times 10^7 [\text{OH}^-] \quad (r 0.9998) \quad (6)$$

of k_0^5 on $[\text{OH}^-]$ may be explained in two ways. We may assume that acylaminosulfonium salt **5a** can be hydrolysed with both H_2O and OH^- , as shown by eqn. (7) in which $k_{\text{H}_2\text{O}}^5$ and $k_{\text{OH}^-}^5$

$$k_0^5 = k_{\text{H}_2\text{O}}^5 + k_{\text{OH}^-}^5 [\text{OH}^-] \quad (7)$$

represent the rate constants for the hydrolysis of **5a** with H_2O and OH^- , respectively. On the other hand, we may also suppose that the equilibrium between **5a** and **3a** [eqn. (3)] is shifted towards **3a** with the increase of pH, and the rate of hydrolysis increases because of the greater reactivity of **3a**, see eqn. (8)

$$k_0^5[\text{S}] = k_5[\text{5a}] + k_3[\text{3a}] \quad (8)$$

where $[\text{S}] = [\text{5a}] + [\text{3a}]$ is the stoichiometric concentration of **5a**. On the basis of eqn. (3) one can derive eqns. (9) and (10).

$$[\text{5a}] = \frac{[\text{H}^+]}{[\text{H}^+] + K_{35}} [\text{S}] \quad (9)$$

$$[\text{3a}] = \frac{K_{35}}{K_{35} + [\text{H}^+]} [\text{S}] \quad (10)$$

Substituting eqns. (9) and (10) into eqn. (8) we obtain eqn. (11) if $K_{35}[\text{OH}^-] \ll K_w$, (K_w represents the ionic product of water).

$$k_0^5 = k_5 + \frac{K_{35}k_3}{K_w} [\text{OH}^-] \quad (11)$$

Both eqns. (7) and (11) indicate that the rate constant k_0^5 is a linear function of $[\text{OH}^-]$. Because the rate of hydrolysis of **5a** was found to be independent of the concentration of added salts, *i.e.* of the ionic strength (Table 5), the reaction between oppositely charged sulfonium and hydroxide ions, which is suggested by the first mechanism, is not verified. The increase of rate constant k_0^5 with the pH may be explained by the shift of the equilibrium of **5a** and **3a** towards **3a**.

Substituent effect. Acylaminosulfonium salts having a substituent on one of the aromatic rings are formed as mixtures of two isomers (**5b–e** and **5'b–e** in Scheme 1). In samples prepared the ratio of isomers was determined by ^1H NMR spectroscopy, by measuring the intensities of the signals of NH–Me and Ar–H groups at 10.65–10.21 and 9.30–7.60 ppm.¹⁰ In every case the **5'**-type isomer was formed in a larger amount: the isomeric ratios 30:70, 5:95, 6:94 and 19:81 were measured for the **5b–5'b**, **5c–5'c**, **5d–5'd**, **5e–5'e** pairs of isomers, respectively, in dry $[\text{H}_6]\text{DMSO}$. In the case of the **5e–5'e** mixture the same product distribution was measured in $[\text{H}_8]\text{dioxane–D}_2\text{O}$ to be 90:10 (v/v) as in $[\text{H}_6]\text{DMSO}$, but in the former solvent the ratio of isomers changed from 19:81 to 7:93 during 90 min, and 85% of the isomeric mixture hydrolysed to sulfoxide **6e**.

The k_5 rate constants of hydrolysis for isomeric mixtures of substituted acylaminosulfonium salts (**5b–e** and **5'b–e**) in 70:30 (v/v) dioxane–water (Table 7) show that the hydrolysis is promoted by electron-withdrawing X groups in the phenyl ring. Because the measured rate constants (k_5) are the weighted average of the rate constants of the two isomers (**5b–e** and **5'b–e**), the Hammett equation cannot be applied to k_5 data, and so we cannot evaluate the substituent effect quantitatively.

Deuterium solvent isotope effect. The solvent isotope effect for **5a** was measured in different dioxane– D_2O mixtures ($k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ 4.4 ± 0.2) and proved to be independent of the composition of the solvent used (Table 4).

Hydrolysis of acylaminosulfonium salt **8**

The kinetics of hydrolysis of acylaminosulfonium salt **8** to yield sulfoxide **10** in dioxane–water mixtures show a strong similarity to those of **5a**. In the fast starting period of the reaction spiro- λ^4 -sulfane **9** formed by equilibrium deprotonation hydrolyses

Table 7 Rate constants (k_5) for the hydrolysis of acylaminosulfonium salts **5a** and isomeric mixtures of **5b–e** and **5'b–e** in 70:30 (v/v) dioxane– H_2O mixture at 25 °C

Compound	$k_5/10^{-4} \text{ s}^{-1}$
5a	2.22
5b + 5'b	1.15
5c + 5'c	1.25
5d + 5'd	11.0
5e + 5'e	57.8

Table 8 Rate constants (k_8) for the hydrolysis of acylaminosulfonium salt **8** at different acid concentration in 40:60 (v/v) dioxane– H_2O and dioxane– D_2O at 25 °C

$[\text{TsOH}]/\text{mol dm}^{-3}$	$k_8^a/10^{-4} \text{ s}^{-1}$	$k_8^b/10^{-5} \text{ s}^{-1}$	$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$
6×10^{-4}	1.33	2.75	4.8
6×10^{-3}	0.963	2.38	4.0
6×10^{-2}	1.43	3.36	4.2

^a 40:60 (v/v) dioxane– H_2O . ^b 40:60 (v/v) dioxane– D_2O .

with water much faster than acylaminosulfonium salt **8** [eqn. (12)]. Table 4 shows that the reactivity of compound **8** is lower



than that of **5a**. The hydrolysis of **8** is a first-order reaction in the presence of acids, and k_8 rate constants show a flat minimum in the function of acid concentration (Table 8). The log k versus E_T plots indicate that the rate of hydrolysis of **5a** increases with increasing polarity of the solvent about twice as fast as that of **8** [Table 4; eqns. (4) and (13)].

log $k_8 =$

$$(0.0878 \pm 0.0033)E_T - (9.54 \pm 0.21) \quad (r 0.9993) \quad (13)$$

In dioxane– D_2O mixtures a primary kinetic isotope effect was observed: $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ was about 4.3 (Table 8). As in the case of **5a**, the reaction is catalysed by acetate ions; the rate constant is a linear function of $[\text{AcO}^-]$, but independent of the added NaCl, *i.e.* of the ionic strength (Table 5). The rate constants calculated from eqn. (5) are listed in Table 6; the catalytic constant (k_{cat}) is independent of pH, whereas the k_0 rate constants depend linearly on $[\text{OH}^-]$ concentration [eqn. (14)].

$$k_0^8 = (1.13 \pm 0.07) \times 10^{-3} + (1.38 \pm 0.03) \times 10^7 [\text{OH}^-] \quad (r 0.9996) \quad (14)$$

Hydrolysis of acylaminosulfonium salt **12**

The reactivity of compound **12**, having two naphthalene rings, is markedly decreased as compared to that of **5a** and **8**, so it hydrolyses to sulfoxide **14** at a measurable rate only if $\text{pH} > 5$. The reaction follows first-order kinetics in buffered solutions and the formation of a spiro- λ^4 -sulfane intermediate (**13**) was not observed. At constant ionic strength the rate constant k_{12} was independent of the concentration of the acetate buffer, but increased with the decrease of the ionic strength (Table 5). In acetate (pH 5.00–5.61) and PIPES buffers (pH 6.23–7.29; ionic strength 0.1 mol dm^{-3}), the rate constant k_{12} was a linear function of $[\text{OH}^-]$ [eqn. (15)]. These observations can be explained

$$k_{12} = (2.08 \pm 0.80) \times 10^{-5} + (1.07 \pm 0.01) \times 10^4 [\text{OH}^-] \quad (r 0.9997) \quad (15)$$

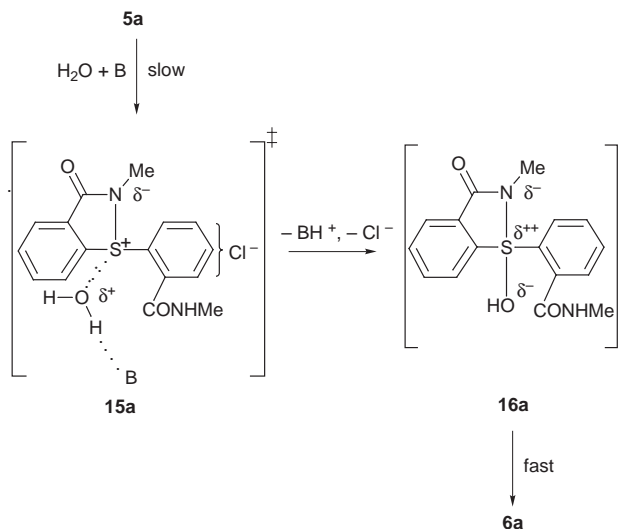
by a reaction of two oppositely charged ions, *i.e.* by that between the sulfonium centre and an OH^- ion.

These findings indicate that acylaminosulfonium salt **12** undergoes hydrolysis only with hydroxide ions, whereas acetate ions and water do not take part in the reaction.

Mechanism

Acylaminosulfonium salts. (i) At the starting period of the hydrolysis reactions, a small portion of acylaminosulfonium salts **5a–e** and **8** is converted into spiro- λ^4 -sulfanes **3a–e** and **9**, respectively [eqns. (3) and (12)]. Owing to the increasing acidity of the medium equilibria are shifted towards the acylaminosulfonium salts with the progress of hydrolysis. Thus, the hydrolysis of acylaminosulfonium salts may also proceed without any intervention of a spiro- λ^4 -sulfane intermediate.

(ii) On the basis of the observed medium, substituent, catalytic and kinetic isotope effects, we may suppose that water attacks the sulfonium centre of acylaminosulfonium salts **5a–e** and **8** in the rate-determining step of the hydrolysis. Simultaneously one of the bonds in water is broken, which is promoted by the general base catalysis of acetate ions (Scheme 4).



Scheme 4 Reaction pathway for the hydrolysis of acylaminosulfonium salt **5a** to sulfoxide **6a**

(iii) The lack of acid catalysis, however, demonstrates that the 'leaving' lactam moiety is not protonated in the rate-determining step of the hydrolysis. Therefore we may assume that a monocyclic (acylamino)(hydroxy)- λ^4 -sulfane with a somewhat elongated S–N bond (e.g. **16a**) is formed, and this intermediate is transformed into sulfoxide (e.g. **6a**) in a fast proton-transfer. A similar mechanism was proposed previously⁶ for the hydrolysis of compound **2**. The smaller reactivity of compound **8** compared to **5a** may be ascribed to a ring-size effect as cyclic sulfonium salts with a five-membered ring are known to undergo nucleophilic displacements faster than their six-membered analogues.¹⁵

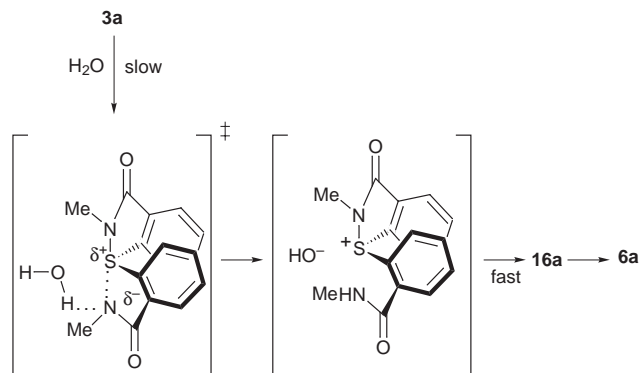
(iv) In contrast with compounds **5a** and **8**, the acylaminosulfonium salt **12** with two naphthalene rings reacts only with OH^- ions that are stronger nucleophiles than H_2O molecules, and so the hydrolysis reaction is not catalysed by AcO^- ions. The poor reactivity of compound **12** may be attributed to the bulky substituents on sulfur rather than to the lack of spiro- λ^4 -sulfane formation.

(v) The $\text{S}\cdots\text{O}$ interaction, which stabilizes the most favourable conformation of carbamoyl-substituted acylaminosulfonium salts, decreases in the order **5a** > **8** > **12** as is reflected by the increase of $\text{S}\cdots\text{O}$ distances (see Table 1). Because the decrease of reactivity towards hydrolysis follows the same order, we may conclude that it is not the $\text{S}\cdots\text{O}$ close contact, which controls the order of reactivity of sulfonium salts.

(vi) The sulfonium centre in acylaminosulfonium salt **5a** is less shielded by $\text{S}\cdots\text{O}$ close contact than that in the analogous, sulfoniumcarboxylate-like diaryl(acylamino)(acyloxy)spiro- λ^4 -sulfane **2** by the polarized hypervalent S–O bond. Consequently, the former compound hydrolyses in dioxane–water

mixtures containing 20–60% water about 20–50 times faster than the latter (see Table 4 and Table 2 in ref. 6).

Spiro- λ^4 -sulfanes. (i) We presume that the hydrolysis of diarylbis(acylamino)spiro- λ^4 -sulfanes proceeds as shown in Scheme 5 for the conversion of **3a** into **6a**. In the rate-



Scheme 5 Reaction pathway for the hydrolysis of spiro- λ^4 -sulfane **3a** to sulfoxide **6a**

determining step one of the S–N hypervalent bonds in the spiro-rings is split with a simultaneous proton-transfer to the nitrogen atom. A hydroxide ion is formed, which attacks the positive sulfur atom of the acylaminosulfonium ion intermediate in a subsequent fast step to form a diaryl(acylamino)-(hydroxy)- λ^4 -sulfane (**16a**) intermediate, which is converted into sulfoxide **6a** (cf. the last step in Scheme 4).

(ii) The substituent effect observed for **3a–e** derivatives ($\rho^+ -0.44$) reveals that the positive charge on sulfur should increase in the transition state. This is consistent with the rate-determining cleavage of one of the S–N bonds involving the formation of a sulfonium centre (like the case of **1**⁵). On the other hand, the negatively charged amidate moiety is a poor leaving group, so its leaving ability is obviously promoted by the protonation of nitrogen. The solvent isotope effect ($k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ 1.8–2.0) indicates that the splitting of one of the S–N hypervalent bonds somewhat precedes the proton-transfer.

(iii) The enthalpy of activation is higher for the hydrolysis of spiro- λ^4 -sulfane **3a** than that for acylaminosulfonium salt **5a** (ΔH^\ddagger 78.7 and 55.7 kJ mol⁻¹, respectively). In the former case the cleavage of the S–N bond takes place in the rate-determining step, whereas in the latter case the formation of a hypervalent S–O bond is accompanied only by a loosening (elongation) of the S–N bond. On the other hand, the entropy of activation has a less negative value in the hydrolysis of **3a** than in that of **5a** (ΔS^\ddagger –25.1 and –128.9 J mol⁻¹ K, respectively). This may be explained by the fact that the rate-determining step of the conversion of **3a** is a unimolecular reaction, whereas that of **5a** is bimolecular.

(iv) The medium effect on the hydrolysis of spiro- λ^4 -sulfanes and acylaminosulfonium salts follows the order **1** > **3a** > **5a** [see eqn. (4) in ref. 6, and eqns. (1) and (13)] indicating that the polarity of transition states may also change in the same order. In the reaction of spiro- λ^4 -sulfane **1** a zwitterion,⁵ in the case of **3a** a sulfonium ion and a separated hydroxide ion, is formed in the rate-determining step, whereas the hydrolysis of **5a** is a simple $\text{S}_{\text{N}}2$ -type displacement on a sulfonium centre with the formation of a neutral λ^4 -sulfane intermediate.

(v) Spiro- λ^4 -sulfanes **3a–e** and **9** proved to be much more reactive toward hydrolysis than the precursor acylaminosulfonium salts **5a–e** and **8** [k_3/k_5 30, in 80:20 (v/v) dioxane–water, cf. Tables 2 and 4; k_9/k_8 1780 in 98:2 (v/v) dioxane–water, k_8 5.9×10^{-6} s⁻¹ was calculated from eqn. (13)]. This observation does not contradict the proposed mechanism in Scheme 5, because the hydrolysis of diarylbis(acylamino)spiro- λ^4 -sulfanes involves the reaction of acylaminosulfonium intermediates with highly nucleophilic hydroxide ions, whereas

acylamino-sulfonium chlorides react only with water in acidic medium.

(vi) Spiro- λ^4 -sulfane **9** hydrolyses in a 98:2 (v/v) dioxane–water mixture about one hundred times faster than **3a**. Thus the ring-size effect on the hydrolysis of diarylbis(acylamino)spiro- λ^4 -sulfanes corresponds to that of diarylbis(acyloxy)spiro- λ^4 -sulfanes (*cf.* ref. 5), but it is opposite to that observed for acylaminosulfonium salts. It seems very likely that the enhanced reactivity of compound **9** pertains to the six-membered spiro-ring, which is more polarized than the five-membered one (*cf.* ref. 16 and $\nu_{C=O}$ data in Table 1). The weaker S–N bond in the six-membered spiro-ring results in a higher reactivity of compound **9**.

Experimental

Materials

The following model compounds were prepared by known methods¹⁰ (see the Introduction and Schemes 1–3); (i) *diaryl-bis(acylamino)spiro- λ^4 -sulfanes*: 5-X-substituted 2,2'-dimethyl-3,3'-dioxo-1,1'-spirobi[2,3-dihydro-1,2-benzothiazole] (**3a–e** with X = H, OMe, Me, Cl and NO₂, respectively), 2,2'-dimethylspiro[2,3-dihydro-1,2-benzothiazol-3'-one-1',1-2,3-dihydronaphtho[1,8-*de*][1,2]thiazin-3-one] (**9**); (ii) *diaryl-(acylamino)sulfonium salts*: 2-methyl-1-[2-(*N*-methylcarbamoyl)phenyl]-3-oxo-2,3-dihydro-1,2-benzothiazol-1-ium chloride (**5a**), isomeric mixtures of 5-X- and 4'-X-substituted derivatives of **5a** (**5b–e** and **5' b–e** with X = H, OMe, Me, Cl and NO₂, respectively), 2-methyl-1-[2-(*N*-methylcarbamoyl)phenyl]-3-oxo-2,3-dihydronaphtho[1,8-*de*][1,2]thiazin-1-ium chloride (**8**) and 2-methyl-1-[8-(*N*-methylcarbamoyl)-1-naphthyl]-3-oxo-2,3-dihydronaphtho[1,8-*de*][1,2]thiazin-1-ium chloride (**12**); (iii) *bis(N-methylcarbamoyl)-substituted diaryl sulfoxides*: bis[2-(*N*-methylcarbamoyl)phenyl] sulfoxide (**6a**), 2-(*N*-methylcarbamoyl)phenyl 2-(*N*-methylcarbamoyl)-4-X-phenyl sulfoxides (**6b–e** with X = OMe, Me, Cl and NO₂, respectively), 8-(*N*-methylcarbamoyl)-1-naphthyl 2-(*N*-methylcarbamoyl)phenyl sulfoxide (**10**) and bis[8-(*N*-methylcarbamoyl)-1-naphthyl] sulfoxide (**14**).

Mps were determined by a Boëtius micro melting point apparatus. Toluene-*p*-sulfonic acid was recrystallized from concentrated HCl solution. Spectroscopic grade abs. dioxane used in kinetic measurements was obtained from analytical grade solvent (Reanal, Budapest) by distillation from Na.¹⁷ Acetate (Reanal, Budapest) and PIPES buffers (Merck) were used in the concentration ranges 2.0×10^{-3} – 9.4×10^{-2} mol dm⁻³ and 9.3×10^{-2} – 9.8×10^{-2} mol dm⁻³, respectively. pH values were measured using a Radelkis (Budapest) OP-208/1 pH meter.

Kinetics

Kinetic measurements were carried out in dioxane–water mixtures [2–100% (v/v) of H₂O] in tempered quartz cells (1–4 cm) of a UV–VIS spectrophotometer (Specord M40, Zeiss, Jena; Cary 3E, Varian), in the wavelength range 278–362 nm, where the absorption of reactants and products differed significantly. The initial concentrations of the acylaminosulfonium salts and spiro- λ^4 -sulfanes were varied between 1.3×10^{-5} – 4.9×10^{-3} . The reaction was started by dissolving the reactants quickly in different dioxane–water mixtures containing salts, buffer and/or acids as required. Acetate and PIPES buffers were used in the pH ranges 3.6–5.6 and 6.2–7.3, respectively. The solvent isotope effect was measured in dioxane–D₂O mixtures. Standard deviations of the rate constants are $\pm 5\%$.

E_T values for dioxane–water mixtures

E_T values were determined for dioxane–water mixtures by 2,4,6-triphenyl-1-(4-hydroxyphenyl)pyridinium betaine.⁵ E_T^N and $E_T(30)$ values of the same solvent mixtures were calculated by linear interpolation of the literature data, and by the method

of Langhals,¹¹ respectively. We found good linear correlations between E_T , E_T^N and $E_T(30)$ as shown by eqns. (16) and (17).

$$E_T = (39.7 \pm 0.6) + (31.7 \pm 0.9)E_T^N \quad (s \ 0.17; r \ 0.997) \quad (16)$$

$$E_T = (14.9 \pm 1.0) + (0.873 \pm 0.020)E_T(30) \quad (s \ 0.02; r \ 0.998) \quad (17)$$

Spectra

Spectra were recorded on the following instruments: UV–VIS, Zeiss (Jena) Specord M 40, Varian Cary 3E; IR, Zeiss (Jena) IR 75, Bruker IFS 55; NMR, Bruker DRX-500 (500 MHz for ¹H), Varian VXR-400 (400 MHz for ¹H), Bruker WM 250 (250 MHz for ¹H), Bruker WP 80 SY (80 MHz for ¹H), internal reference: SiMe₄ (δ_H 0.00 for ¹H).

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References

- I. Kapovits and A. Kálmán, *J. Chem. Soc., Chem. Commun.*, 1971, 649; A. Kálmán, K. Sasvári and I. Kapovits, *Acta Crystallogr., Sect. B*, 1973, **29**, 355; I. Kapovits, J. Rábai, D. Szabó, K. Czákó, Á. Kucsman, Gy. Argay, V. Fülöp, A. Kálmán, T. Koritsánszky and L. Párkányi, *J. Chem. Soc., Perkin Trans. 2*, 1993, 847.
- L. J. Adzima, Chian C. Chiang, I. C. Paul and J. C. Martin, *J. Am. Chem. Soc.*, 1978, **100**, 953.
- D. Szabó, M. Kuti, I. Kapovits, J. Rábai, Á. Kucsman, Gy. Argay, M. Czugler, A. Kálmán and L. Párkányi, *J. Mol. Struct.*, 1997, **415**, 1.
- D. Szabó, I. Kapovits, Á. Kucsman, P. Huszthy, Gy. Argay, M. Czugler, V. Fülöp, A. Kálmán, T. Koritsánszky and L. Párkányi, *J. Mol. Struct.*, 1993, **300**, 23.
- E. Vass, F. Ruff, I. Kapovits, J. Rábai and D. Szabó, *J. Chem. Soc., Perkin Trans. 2*, 1993, 855.
- E. Vass, F. Ruff, I. Kapovits, D. Szabó and Á. Kucsman, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2061.
- Á. Kucsman and I. Kapovits in *Organic Sulfur Chemistry: Theoretical and Experimental Advances*, ed. F. Bernardi, I. G. Csizmadia and A. Mangini, Elsevier, Amsterdam, 1985, pp. 185–245.
- J. C. Martin and T. M. Balthazor, *J. Am. Chem. Soc.*, 1977, **99**, 152.
- E. Vilsmaier and W. Sprügel, *Tetrahedron Lett.*, 1972, 625; J. A. Franz and J. C. Martin, *J. Am. Chem. Soc.*, 1975, **97**, 583; G. F. Koser, P. B. Kokil and M. Shah, *Tetrahedron Lett.*, 1987, **28**, 5431.
- D. Szabó, T. Ádám and I. Kapovits, *Sulfur Lett.*, 1997, **21**, 21, and refs. therein.
- T. M. Krygowski, P. K. Wrona, U. Zielkowska and C. Reichardt, *Tetrahedron*, 1985, **41**, 4519; C. Reichardt, *Chem. Rev.*, 1994, **94**, 2319; H. Langhals, *Angew. Chem., Int. Ed. Engl.*, 1982, **28**, 724.
- C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.
- A. Demeter, B. László and T. Bérces, *Ber. Bunsenges., Phys. Chem.*, 1988, **92**, 1478; A. Demeter and T. Bérces, *J. Phys. Chem.*, 1991, **95**, 1228.
- T. Higuchi and K.-H. Gensch, *J. Am. Chem. Soc.*, 1966, **88**, 3874, 5486; K.-H. Gensch, I. H. Pitman and T. Higuchi, *J. Am. Chem. Soc.*, 1968, **90**, 2096.
- S. Tamagaki, M. Mizuno, H. Yoshida, H. Hirota and S. Oae, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 2456; R. Curci, F. DiFuria, A. Levi and G. Scorrano, *J. Chem. Soc., Perkin Trans. 2*, 1975, 408.
- R. A. Hayes and J. C. Martin, in *Organic Sulfur Chemistry: Theoretical and Experimental Advances*, ed. F. Bernardi, I. G. Csizmadia and A. Mangini, Elsevier, Amsterdam, 1985, pp. 408–483.
- D. D. Perrin, L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 2nd edn., 1980.

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