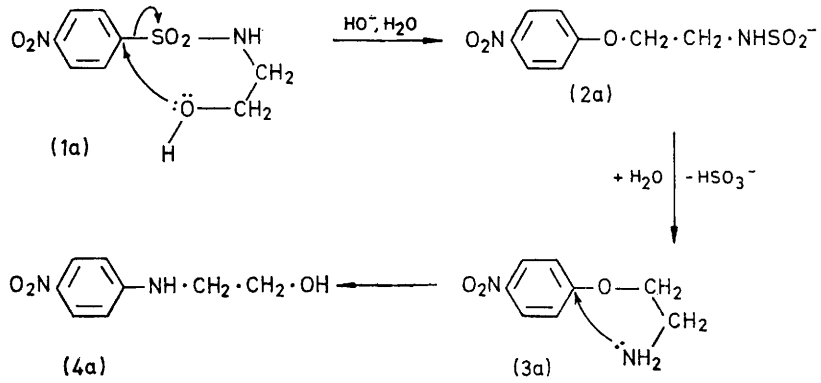
# Kinetics of Desulphonative Double Smiles' Rearrangement of *N*-(2-Hydroxyalkyl)-*p*-nitrobenzenesulphonamides [1]

By **Anthony C. Knipe,*** and **Joseph Lound-Keast,** School of Physical Sciences, The New University of Ulster, Coleraine, N. Ireland

Support for a mechanism of formation of *N*-(2-hydroxyethyl)-*p*-nitroanilines by base-catalysed desulphonation of *N*-(2-hydroxyethyl)-*p*-nitrobenzenesulphonamides has been obtained by kinetic investigation. Derivatives bearing alkyl and aryl substituents on nitrogen, or *C*-alkyl substituents α- or β- to the hydroxy-group have also been studied. Substituent effects on the rate and base dependence of (i) intramolecular aromatic displacement of the sulphonamide group by the neighbouring hydroxy-group and (ii) rearrangement of the intermediate 2-(*p*-nitrophenoxy)alkylamine have been determined for this double Smiles' rearrangement sequence. Intermediate aminoethers have been detected spectroscopically for the first time and have in some cases been isolated.

INTRAMOLECULAR nucleophilic displacement reactions involving skeletal rearrangements of the type: ArXCCYH ⟶ ArYCCXH are generally termed Smiles' rearrangements and have been the subject of two review articles [2,3] and of general texts.[4,5]

In 1968 Kleb [6] reported the conversion of a series of *N*-(2-hydroxyalkyl)-*o*- and -*p*-nitrobenzenesulphonamides into the corresponding *N*-(2-hydroxyalkyl)-*o*- and -*p*-nitroanilines upon reaction in aqueous sodium hydroxide (6%) at 100 °C. Scheme 1 represents his proposed [6] desulphonation mechanism and features two Smiles' rearrangements [(1a) ⟶ (3a) and (3a) ⟶ (4a), respectively]. No direct experimental evidence for the intermediates had, however, been obtained. Two of the proposed intermediate aryloxyaminoethanes [1-(*o*-nitrophenoxy)- and 1-(*p*-nitrophenoxy)-2-aminoethane] were reported previously [7] but this claim has been convincingly disputed by Caldwell and Schweiker.[8]




SCHEME 1

The first step (1) ⟶ (3) of Kleb's unique double

[1] Preliminary communications, A. C. Knipe, *Tetrahedron Letters*, 1973, 3031; 1975, 3563.
[2] J. Bunnett and R. Zahler, *Chem. Rev.*, 1951, **59**, 273.
[3] W. E. Truce, E. M. Kreider, and W. W. Brand, *Org. Reactions*, 1970, **18**, pp. 99—215.
[4] T. S. Stevens and W. E. Watts, 'Selected Molecular Rearrangements,' Van Nostrand Reinhold Co., London, 1973, pp. 120—124.
[5] D. V. Banthorpe in 'The Chemistry of the Amino Group,' ed. S. Patai, Interscience, London, 1968, p. 649.
[6] K. G. Kleb, *Angew. Chem. Internat. Edn.*, 1968, **7**, 291.
[7] A. Weddige, *J. prakt. Chem.*, 1881, **24**, 254.
[8] W. T. Caldwell and G. C. Schweiker, *J. Amer. Chem. Soc.*, 1952, **74**, 5187.

Smiles' rearrangement sequence is itself unique since there has been no previous report of an intramolecular displacement of a sulphonamide group by an alcohol or by alkoxide ion. Displacements of sulphonamide groups by carbanions [9] and by amino-groups [10] have, however, been reported and there are many examples of sulphonyl group displacement by neighbouring alkoxy [11,12] and phenoxy [11–13] groups.

In the second Smiles' rearrangement (3) ⟶ (4) of Kleb's sequence an alkoxy-group is displaced from the activated aromatic nucleus by an amino-group located on the *O*-alkyl side-chain. Only one other example of this variation of the Smiles' rearrangement can be cited [8] although there have been several reports of displacement of phenoxy by arylamino,[14] alkoxy by amido [15] and phenoxy by arylamido [14b,c,16] groups.

In view of the unique nature of this reaction sequence, combined with the absence of direct evidence for the proposed intermediates, we chose to investigate further the desulphonation reactions of a range of *N*-(2-hydroxyalkyl)-*p*-nitrobenzenesulphonamides. We now report a kinetic investigation of (1a—g) the results of which, in principle, support Kleb's proposed mechanism. The effects of substituents on the rates and mechanisms of the consecutive Smiles' rearrangements are discussed. In some cases isolation or detection of intermediate 2-(*p*-nitrophenoxy)aminoalkanes (3) has been effected.

This is one of few investigations of the kinetics of Smiles' rearrangement. There have been recent reports of the kinetic effects of substituents on the Smiles' rearrangement of *O*-*s*-triazinyl-2-aminophenols [17] and of the $N^1 \longrightarrow N^2$ migration of the *s*-triazinyl group of 4-substituted $N^1N^1$-bis-(*s*-triazinyl)*o*-phenylenediamines.[18] However, with the exception of two studies of *o*-hydroxy [19] and *o*-methyl [20] diaryl sulphones, only approximate rate comparisons have previously been made.[11,12,13d,14b,d,16d,21]

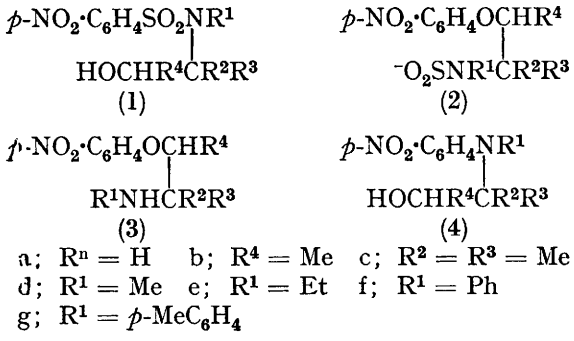



TABLE 1

Preparation and analysis of *N*-(2-hydroxyalkyl)-*p*-nitrobenzene sulphonamides (1a—g)

| Sulphonamide | Reaction Time/h | Reaction Yield/% | M.p. (*t*/°C) | Formula | Required %C | Required %H | Found %C | Found %H |
|---|---|---|---|---|---|---|---|---|
| (1a) | 5 | 60 | 125 | $C_8H_{10}N_2O_5S$ | 39.0 | 4.1 | 39.2 | 3.9 |
| (1b) | 5 | 16 | 101 | $C_9H_{12}N_2O_5S$ | 41.5 | 4.65 | 41.4 | 4.55 |
| (1c) | 5 | 31 | 97 | $C_{10}H_{14}N_2O_5S$ | 43.8 | 5.1 | 44.0 | 5.15 |
| (1d) | 5 | 56 | 93 | $C_9H_{12}N_2O_5S$ | 41.5 | 4.65 | 41.55 | 4.8 |
| (1e) | 5 | 48 | 113 | $C_{10}H_{14}N_2O_5S$ | 43.8 | 5.1 | 44.05 | 4.9 |
| (1f) | 12 | 50—84 | 140 | $C_{14}H_{14}N_2O_5S$ | 52.2 | 4.4 | 52.2 | 4.6 |
| (1g) | 12 | 64 | 135 | $C_{15}H_{16}N_2O_5S$ | 53.6 | 4.8 | 53.4 | 4.9 |

## EXPERIMENTAL

*Materials.*—*N*-2-Hydroxyalkyl *p*-nitrobenzenesulphonamides (1a—g) were prepared by reaction between *p*-nitrobenzenesulphonyl chloride (0.015 mol) and the appropriate 2-hydroxyalkylamine (0.03 mol) in dioxan (15 cm³) under reflux. For each of the sulphonamides (1a—g) reaction conditions, yield, m.p. (from $C_6H_6$), and analysis are recorded in Table 1. Details of the i.r. and n.m.r. spectra are in Table 2. The thin-layer chromatogram of each compound on silica gel with methylene chloride as eluant revealed only one spot.

[9] (*a*) T. Naito, R. Dohmori, and O. Nagase, *J. Pharm. Soc. Japan*, 1954, **74**, 593 (*Chem. Abs.*, 1954, **48**, 10647); (*b*) R. Dohmori, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 595, 601, 591 (*Chem. Abs.*, 1964, **61**, 4305, 4178, 4248); (*c*) T. Naito and R. Dohmori, *Chem. and Pharm. Bull.* (*Japan*), 1955, **3**, 38 (*Chem. Abs.*, 1956, **50**, 1647); (*d*) T. Naito, R. Dohmori, and T. Kotake, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 588 (*Chem. Abs.*, 1964, **61**, 4305).

[10] (*a*) H. J. Backer and H. D. Moed, *Rec. Trav. chim.*, 1947, **66**, 689; (*b*) H. J. Backer and S. K. Wadman, *Rec. Trav. chim.*, 1949, **68**, 595.

[11] F. Galbraith and S. Smiles, *J. Chem. Soc.*, 1935, 1234.

[12] B. A. Kent and S. Smiles, *J. Chem. Soc.*, 1934, 422.

[13] (*a*) O. Hinsberg, *J. prakt. Chem.*, 1914, **90**, 345; 1916, **93**, 277; (*b*) L. A. Warren and S. Smiles, *J. Chem. Soc.*, 1932, 1040; (*c*) C. S. McClement and S. Smiles, *J. Chem. Soc.*, 1937, 1016; (*d*) T. Okamoto and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1956, **78**, 3537; (*e*) A. A. Levy, H. C. Rains, and S. Smiles, *J. Chem. Soc.*, 1931, 3264; (*f*) T. Okamoto and J. F. Bunnett, *J. Org. Chem.*, 1956, **21**, 487; (*g*) A. A. Levi and S. Smiles, *J. Chem. Soc.*, 1932, 1488.

[14] (*a*) G. E. Bonvicino, L. H. Yogodzinski, and R. A. Hardy, *J. Org. Chem.*, 1962, **27**, 4272; (*b*) K. C. Roberts and J. A. Rhys, *J. Chem. Soc.*, 1937, 39; (*c*) K. C. Roberts and C. G. M. de Worms, *J. Chem. Soc.*, 1934, 727; (*d*) K. C. Roberts, C. G. M. de Worms, and H. B. Clark, *J. Chem. Soc.*, 1935, 196.

[15] I. A. Solov'eva and A. G. Guseva, *Zhur. org. Khim.*, 1968, **4**, 1973; *Chem. Abs.*, 1969, **70**, 28585.

[16] (*a*) B. T. Tozer and S. Smiles, *J. Chem. Soc.*, 1938, 2052; (*b*) K. C. Roberts and C. G. M. de Worms, *J. Chem. Soc.*, 1935 1309.

[17] N. Maeno, T. Itagaki, S. Uno, and K. Matsui, *Bull. Chem. Soc. Japan*, 1972, **45**, 3133.

[18] K. Nakamura, N. Nohara, and K. Matsui, *Bull. Chem. Soc. Japan*, 1972, **45**, 3140.

[19] J. F. Bunnett and T. Okamoto, *J. Amer. Chem. Soc.*, 1956, **78**, 5357, 5363.

[20] W. E. Truce and W. J. Ray, *J. Amer. Chem. Soc.*, 1959, **81**, 484.

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*Reaction Kinetics.*—Reactions were initiated by addition of a solution (15 μl; 0.015M) of the sulphonamide (1), in acetonitrile, to aqueous sodium hydroxide (3 cm³; 0.1—1.0M) contained in a cuvette (silica glass; 1-cm path-length) which was thermostatted at 61 ± 0.05 °C in the cell compartment of a Perkin-Elmer 402 spectrophotometer.

A Wayne Kerr Autobalance Universal Bridge B641 was used to monitor the resistance of a glass-sheathed thermistor which was immersed in the reaction mixture.

Where the pseudo-first-order rate constants for the consecutive reactions were of the same order of magnitude (particularly if the wavelength of an isosbestic point for (3) ⟶ (4) could not be confidently assigned or applied to simplify determination of the rate constant for (1) ⟶ (3) they were determined by appropriate analysis of a characteristic sigmoid plot of concentration of (4) (as indicated by absorbance at 410—426 nm) *versus* time, as follows. Absorbance readings (50—200) were recorded at equal time

TABLE 2

N.m.r. (A) † and i.r. (C) ‡ spectra of *N*-(2-hydroxyalkyl)-1-(*p*-nitrobenzenesulphonamides (1a—g), and n.m.r. spectra (B) † of the corresponding trifluoroacetate esters *

| Sulphonamide | Spectrum | |
|---|---|---|
| (1a) | A | ($CF_3CO_2H$), 1.47, 1.8 (4 H, 2 × d, *J* 9 Hz), 5.98 (2 H, t, *J* 5 Hz), 6.6 (2 H, t, *J* 5 Hz) |
| | B | ($CF_3CO_2H$), 1.47, 1.8 (4 H, 2 × d, *J* 9 Hz), 5.4 (2 H, t, *J* 5 Hz), 6.38 (2 H, t, *J* 5 Hz) |
| | C | 3 460, 3 120, 1 350, 1 160, 1 085 |
| (1b) | A | ($CF_3CO_2H$) 1.48, 1.8 (4 H, 2 × d, *J* 9 Hz), 5.5—6.1 (1 H, m), 6.6—6.85 (2 H, m), 8.64 (3 H, d, *J* 7 Hz |
| | C | 3 500, 3 150, 1 340, 1 160, 1 080 |
| (1c) | C | 3 500, 3 150, 1 350, 1 145, 1 055 |
| (1d) | A | ($CF_3CO_2H$), 1.58, 1.95 (4 H, 2 × d, *J* 9 Hz), 5.96 (2 H, t, *J* 5 Hz), 6.56 (2 H, t, *J* 5 Hz), 7.0 (3 H, s), |
| | B | ($CF_3CO_2H$), 1.58, 1.95 (4 H, 2 × d, *J* 9 Hz), 5.39 (2 H, t, *J* 5 Hz), 6.38 (2 H, t, *J* 5 Hz), 7.0 (3 H, s), |
| | C | 3 300—3 540, — , 1 310—1 160 |
| (1e) | A | ($CF_3CO_2H$), 1.53, 1.88 (4 H, 2 × d, *J* 9 Hz), 6.2—6.8 (2 H and 2 H, m), 5.9 (2 H, t, *J* 6 Hz), 8.8 (3 H, t, *J* 7 Hz) |
| | C | 3 500, — , 1 320, 1 150, 1 080 |
| (1f) | A | ($CF_3CO_2H$), 1.56, 2.07 (4 H, 2 × d, *J* 9 Hz), 2.4—3.0 (5 H, m), 6.01 (4 H, s) |
| | B | ($CF_3CO_2H$), 1.56, 2.07 (4 H, 2 × d, *J* 9 Hz), 2.4—3.0 (5 H, m), 5.4, 5.82 (4 H, 2 × t, *J* 5 Hz) |
| | C | 3 580, — ,1 360, 1 165, 1 050 |
| (1g) | A | ($CF_3CO_2H$), 1.6, 2.07 (4 H, 2 × d, *J* 9 Hz), 2.6—3.2 (4 H, m), 6.02 (4 H, s), 7.64 (3 H, s) |
| | B | ($CF_3CO_2H$), 1.6, 2.07 (4 H, 2 × d, *J* 9 Hz), 2.6—3.2 (4 H, m), 5.43, 5.87 (4 H, 2 × t, *J* 5 Hz), 7.64 (3 H, s) |
| | C | 3 580, — , 1 360, 1 165, 1 040 |

* Formed upon reaction of the hydroxyalkyl sulphonamides with $CF_3CO_2H$ at 33 °C ($t_{\frac{1}{2}}$ = *ca.* 120 min). † N.m.r. signals were recorded on a Perkin-Elmer spectrometer, model R10, and are listed as: (solvent), τ (nH, multiplicity, *J*/Hz). Chemical shifts are relative to $SiMe_4$ as internal standard. ‡ The i.r. bands ($cm^{-1}$, KBr disc) are listed in the order: OH str, NH str, $SO_2$ str (anti-symm), $SO_2$ str (symm), CO str.

Corresponding reaction temperatures were read from a calibration graph.

Reactions were followed by repetitive scan of the time-dependent spectra in the wavelength range 200—450 nm. Where the rate of reaction (1) ⟶ (3) was very much faster than that for (3) ⟶ (4) the consecutive pseudo-first-order reactions were followed and analysed independently. The wavelengths corresponding to greatest change in absorbance were *ca.* 265 nm ($\lambda_{max.}^{(1)}$) and *ca.* 410 nm ($\lambda_{max.}^{(4)}$, where R¹ = H or aryl) or 426 nm ($\lambda_{max.}^{(4)}$ where R¹ = alkyl) for the first and second Smiles' rearrangement respectively. Each first-order rate constant was obtained from the slope of a plot of log (O.D.$_\infty$ − O.D.$_t$) *versus* time *t*, up to four half-lives of the reaction. The slope was obtained by least-squares analysis using an ICL 1903A computer at the New University of Ulster and was considered to be acceptable only when the correlation coefficient exceeded 0.998. The consecutive first-order rate constants were alternatively computed from the increase and subsequent decrease in absorbance, at *ca.* 315 nm, which accompanied the formation ($k_A$) of intermediate (3) and its slower rearrangement ($k_B$) to (4).

In those cases where the rate of reaction (1) ⟶ (3) did not greatly exceed that of (3) ⟶ (4) the change in absorbance with time at a wavelength (*ca.* 270 nm) corresponding to an isosbestic point for conversion of (3) into (4) was analysed in order to determine the pseudo-first-order rate constant ($k_A$) for the former reaction.

intervals up to 90% completion of the reaction and their least-squares best-fit to a polynomial expression was computed. The polynominal coefficients were then used to calculate 'smoothed' absorbance values for each time reading. For two consecutive first-order processes

$$(1) \xrightarrow{k_A} (3) \xrightarrow{k_B} (4)$$

we have

$$[1] = [1]_0 e^{-k_A t}$$

$$[3] = [1]_0 k_A(-e^{-k_A t} + e^{-k_B t})/(k_A - k_B)$$

and

$$[4] = [1]_0[1 + (k_B e^{-k_A t} - k_A e^{-k_B t})/(k_A - k_B)]$$

where $[1]_0$ is the concentration of (1) when $t = 0$. Upon substitution of $y_t = (1\text{-}[4]/[1]_0)$ we obtain

$$y_t = [k_B/(k_B - k_A)]e^{-k_A t} - [k_A/(k_B - k_A)]e^{-k_B t}$$

This is an expression of the form

$$f(x) = a_1 e^{\lambda_1 x} + a_2 e^{\lambda_2 x} \ldots a_m e^{\lambda_m x}$$

where $m = 2$, $x = t$. The function $f(x)$ is a measure of the fraction of product as yet unformed at time *t* and is related to the optical density at 410 nm since $y_t = [(\text{O.D.}_\infty - \text{O.D.}_t)/(\text{O.D.}_\infty - \text{O.D.}_0)]$. The expression was solved, to give $a_1$, $a_2$, $\lambda_1$, $\lambda_2$ and hence $k_A$ and $k_B$, by an approximation method which was recently discussed by Fröberg.[22] A

[22] C.-E. Fröberg, 'Introduction to Numerical Analysis,' Addison–Wesley, London, 1966, p. 289.

computer was used to solve, by least-squares analysis, the $n - m + 1$ simultaneous equations derived for $n$ values of $y_t$ at time $t$.

Absorbance readings corresponding to times beyond seven half-lives of the faster reaction fit a first-order expression for the slower reaction alone and were subsequently (4) where appropriate. All kinetic results are given in Table 4.

*Product Isolation.*—For each of the sulphonamides (1a—f) Kleb [6] has reported a yield of the corresponding aniline (4) in excess of 90%, for reaction in aqueous alkali under reflux. With a knowledge of the reaction kinetics

TABLE 3

Changes in u.v.–visible absorption spectra † accompanying the reaction sequence (1) ⟶ (3) ⟶ (4), performed in aqueous alkali

| | $\lambda_{max}$/nm | | | Isosbestic points/nm | | |
|---|---|---|---|---|---|---|
| Index | (1) | (3) | (4) | (1) ⟶ (3) | (3) ⟶ (4) | (1) ⟶ (4) |
| a | 268 | (310) | 235, 410 | (242, 304) | (250), 345 | |
| b | 263 | | 230, 410 | | | 245, 338 |
| c | 265 | 232, 315 | 225, 408 | (305) | 268, 350 | |
| d | 275 | | 240, 420 | | | 254, 335 |
| e | 275 | | <230, 426 | | | 250, 342 |
| f | 266 | 235, 315 | 410 | 250, 288 | 252, 272, 352 | |
| g | 265 | 230, 315 | <230, 415 | (250, 288) | (252, 272, 352) | |

† Figures in parentheses are approximate.

TABLE 4

Kinetics of reaction of sulphonamides (1a—g) in aqueous sodium hydroxide at 61 °C. The constants * $k_cK$, $k_4$, and $(k_5K_3 + k_6)$ were determined by analysis of the base dependence of pseudo-first-order rate constants $k_A$ and $k_B$

| Substrate | [OH⁻]/ l mol⁻¹ | $10^3k_A$/ s⁻¹ | $(10^3k_cK)^* = k$/ dm³ mol⁻¹ s⁻¹ | $10^5k_B$/ s⁻¹ | $10^5k_4$/ s⁻¹ | $10^5(k_5K_3 + k_6)$/ dm³ mol⁻¹ s⁻¹ |
|---|---|---|---|---|---|---|
| (1a) | 0.1 | 0.066 1 | 0.661 | 117 | | |
| | 0.25 | 0.176 | 0.704 | 107 | 113 | <5 |
| | 0.5 | 0.360 | 0.720 | 114 | | |
| | 1.0 | 0.750 | 0.750 | 116 | | |
| | | | Av. (0.709) | | | |
| (1b) | 0.5 | 0.236 | 0.47 | 1—5‡ × 10² | 1—5 × 10² | |
| (1c) | 0.1 | 1.85 | 18.5 | 84.7 | | |
| | 0.25 | 4.23 | 16.9 | 109.5 | | |
| | 0.5 | | | 127.0 | *ca.* 130 § | |
| | 1.0 | 20.4 | 20.4 | | | |
| | | | Av. (18.6) | | | |
| (1d) | 0.1 | 0.359 | 3.59 | | | |
| | 0.25 | 0.880 | 3.52 | >1 800 | >1 800 | |
| | 0.5 | 1.81 | 3.62 | | | |
| | | | Av. (3.58) | | | |
| (1e) | 0.1 | 0.893 | 8.93 | | | |
| | 0.25 | 2.09 | 8.36 | >3 600 | >3 600 | |
| | 0.5 | 3.61 | 7.22 | | | |
| | | | Av. (8.17) | | | |
| (1f) | 0.1 | 0.444 | 4.44 | 0.555 | | 5.55 |
| | 0.25 | 1.03 | 4.12 | 1.41 | | 5.64 |
| | 0.5 | 1.91 | 3.82 | 2.82 | <0.05 | 5.62 |
| | 1.0 | 4.05 | 4.05 | 5.92 | | 5.92 |
| | | | Av. (4.11) | | | Av. (5.68) |
| (1g) † | 0.25 | 1.16 | 4.64 | 10.1 | | 40.4 |
| | 0.5 | 2.47 | 4.94 | 23.4 | <0.05 | 46.8 |
| | 1.0 | | Av. (4.79) | 50.2 | | 50.2 |

* Where R¹ = H (1a—c) $K$ and $k_c$ correspond to $K_1'$ and $k_2'$ respectively, whereas where R¹ = R or Ar (1d—g) the correspondence is with $K_1$ and $k_2$. † The reaction mixture contained acetone (10% v/v). ‡ $k_B$ was just sufficiently faster than $k_A$ to prevent its accurate estimation. § Further preliminary results suggest that at high base concentration $k_B$ is independent of base strength and corresponds to the rate of formation of a spiro-Meisenheimer intermediate. The base dependence of $k_B$ at this low base concentration may reflect onset of a rate dependence on base-catalysed decomposition of such an intermediate.

analysed in order to obtain a further estimate of the lower rate constant. In every case the results obtained by each of the two procedures were in close agreement.

Wavelengths of maximum absorption for (1), (3), and (4) are recorded in Table 3 along with isosbestic points for the transformations (1) ⟶ (4) or (1) ⟶ (3), and (3) ⟶ we have now been able to isolate the intermediates (3f) and (3g) as follows. A solution of the sulphonamide (1f, g) in aqueous sodium hydroxide (0.5M; 200 cm³) containing acetone (30%; v/v) was heated under reflux for a period of 3 h. The amino-ether (3f, g) separated, on the surface of the reaction mixture, as an orange oil which crystallized

on cooling. Recrystallization from benzene gave N-2-(p-*nitrophenoxy)ethylaniline* (3f): 37% yield; m.p. 107 °C; τ ($CDCl_3$) 1.86 (2 H, d, *J* 9 Hz), 3.07 (2 H, d, *J* 9 Hz), 2.6—3.5 (5 H, m), 5.78 (2 H, t, *J* 6 Hz), 6.42 (2 H, t, *J* 6 Hz), 6.6 (1 H, s, exchanged by $D_2O$); i.r. absorption maxima (KBr disc) at 3 400, 1 600, 1 500, 1 450, 1 330, 1 250, 1 100, 1 040, 930, 850, 750, 690, 660, and 500 $cm^{-1}$ (Found: C, 65.0; H, 5.5; N, 10.8. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.5; N, 10.9%); and N-2-(p-*nitrophenoxy)ethyl*-p-*toluidine* (3g), 62% yield; m.p. 129 °C; τ ($CDCl_3$) 1.84 (2 H, d, *J* 9 Hz), 3.06 (2 H, d, *J* 9 Hz), 2.99 (2 H, d, *J* 9 Hz), 3.41 (2 H, d, *J* 9 Hz), 5.77 (2 H, t, *J* 6 Hz), 6.42 (2 H, t, *J* 6 Hz), 7.74 (3 H, s), and 7.0 (1 H, s, exchanged by $D_2O$); i.r. absorption maxima (KBr disc) at 3 400, 1 600, 1 320, 1 250, 1 715, 1 100, 1 050, 930, 850, 810, 750, 660, and 510 $cm^{-1}$ (Found: C, 65.7; H, 5.8; N, 10.1. $C_{15}H_{16}N_2O_3$ requires C, 66.2; H, 5.9; N, 10.3%).

## RESULTS AND DISCUSSION

*Detection of the Intermediate* (3a).—In an attempt to detect intermediate (3a) during the desulphonation of (1a) ($5 \times 10^{-5}$M), in aqueous sodium hydroxide at 61 °C, the time dependence of the absorption spectrum of the reaction mixture was studied in the wavelength range 200—450 nm. For all base concentrations (0.1—1.0M) an absorption maximum at 265 nm decreases in intensity there being a concomitant sigmoid development of a maximum, at 410 nm, which can be attributed to formation of (4a). The overall rate of formation of (4a) increases with concentration of base. The presence of a reactive intermediate is indicated by an increase and subsequent decrease in absorbance at 310—330 nm and is most apparent at high base concentrations.

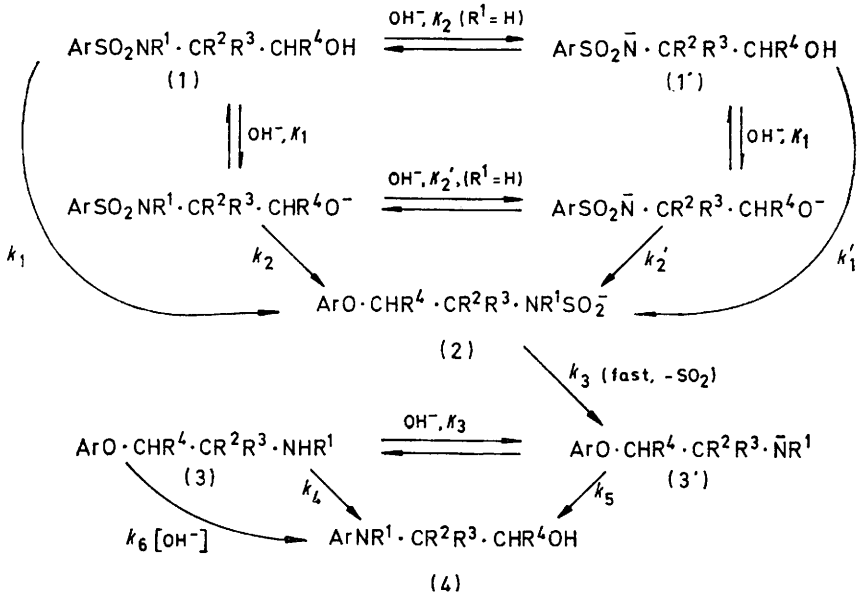
The wavelength (310—320 nm) of maximum absorbance of the intermediate corresponds to that expected [23] of the alkyl *p*-nitrophenyl ether (3a). Since the maximum attainable concentration of (3a) and the rate of formation of (4a) both increase with [$OH^-$] it is clear that the base dependence is greater for formation of (3a) than for its subsequent rearrangement to (4a); the rates of the consecutive reactions are, however, comparable.

*Kinetics of Double Smiles' Rearrangement of* (1a—g).—The behaviour of (1a) [and of (1b—g)] can be accounted for by Scheme 2, where $k_{1-5}$ are first-order rate constants, $K_{1-3}$ represent deprotonation equilibrium constants (for reactions $AH + OH^- \rightleftharpoons A^- + H_2O$) and $k_6$ is a second-order rate constant for a general base (in this case $OH^-$) catalysed reaction.

For a constant hydroxide concentration the overall desulphonative rearrangement can be considered to comprise two consecutive pseudo-first-order reactions, governed by rate constants $k_A$ and $k_B$

$$(1) \xrightarrow{k_A} (3) \xrightarrow{k_B} (4)$$

For (1a) it was necessary to analyse sigmoid absorbance–time curves in order to estimate the rate constants




SCHEME 2

reaction mixture was studied in the wavelength range 200—450 nm. For all base concentrations (0.1—1.0M) an absorption maximum at 265 nm decreases in intensity there being a concomitant sigmoid development of a maximum, at 410 nm, which can be attributed to formation of (4a). The overall rate of formation of (4a) increases with concentration of base. The presence of a reactive intermediate is indicated by an increase and subsequent decrease in absorbance at 310—330 nm and is most apparent at high base concentrations.

The wavelength (310—320 nm) of maximum absorbance of the intermediate corresponds to that expected [23] of the alkyl *p*-nitrophenyl ether (3a). Since the maximum attainable concentration of (3a) and the rate of formation of (4a) both increase with [$OH^-$] it is clear that the base dependence is greater for formation of (3a) than for its subsequent rearrangement to (4a); the rates of the consecutive reactions are, however, comparable.

*Kinetics of Double Smiles' Rearrangement of* (1a—g).—The behaviour of (1a) [and of (1b—g)] can be accounted for by Scheme 2, where $k_{1-5}$ are first-order rate constants, $K_{1-3}$ represent deprotonation equilibrium constants (for reactions $AH + OH^- \rightleftharpoons A^- + H_2O$) and $k_6$ is a second-order rate constant for a general base (in this case $OH^-$) catalysed reaction.

For a constant hydroxide concentration the overall desulphonative rearrangement can be considered to comprise two consecutive pseudo-first-order reactions, governed by rate constants $k_A$ and $k_B$

$$(1) \xrightarrow{k_A} (3) \xrightarrow{k_B} (4)$$

For (1a) it was necessary to analyse sigmoid absorbance–time curves in order to estimate the rate constants $k_A$ and $k_B$. This procedure was, however, unnecessary where the rate constants were sufficiently different in magnitude. Thus, for (1f, g) the reaction occurred in two distinct steps which could be studied independently. In contrast, however, $k_A$ alone determined the rate of formation of (4d, e) from (1d, e) and the larger constant $k_B$ could not, therefore, be determined. Results are given in Table 4.

*Kinetics of the first Smiles' rearrangement* (1) ⟶ (2). According to Scheme 2, wherein the conversion of intermediate (2) into the amino-ether (3) is believed to

[23] C. N. R. Rao, 'Ultraviolet and Visible Spectroscopy,' 2nd edn., Butterworths, London, 1967, p. 66.

occur rapidly, the rate of formation of (3) (for $[OH^-] > 0.1M$) is given by the following:

$$(d[3]/dt)_{formation} = k_2[ArSO_2NR^1{\cdot}CR^2R^3{\cdot}CHR^4O^-] + k_2'[ArSO_2\tilde{N}{\cdot}CR^2R^3{\cdot}CHR^4O^-] + k_1[ArSO_2NR^1{\cdot}CR^2R^3{\cdot}CHR^4OH] + k_1'[ArSO_2\tilde{N}{\cdot}CR^2R^3{\cdot}CHR^4OH] \quad (i)$$

However, for (1a—c) we have

$$[ArSO_2\tilde{N}{\cdot}CR^2R^3{\cdot}CHR^4O^-] = K_1'[OH^-][ArSO_2\tilde{N}{\cdot}CR^2R^3{\cdot}CHR^4OH]$$

$$[ArSO_2NR^1{\cdot}CR^2R^3{\cdot}CHR^4O^-] = K_1[OH^-][ArSO_2NR^1{\cdot}CR^2R^3{\cdot}CHR^4OH]$$

and

$$[ArSO_2NR^1{\cdot}CR^2R^3{\cdot}CHR^4OH] = [ArSO_2\tilde{N}{\cdot}CR^2R^3{\cdot}CHR^4OH]/(K_2[OH^-])$$

thus, the rate expression becomes:

$$(d[3]/dt)_{formation} = k_A[ArSO_2\tilde{N}{\cdot}CR^2R^3{\cdot}CHR^4OH]) \quad (ii)$$

where

$$k_A = (k_1' + k_2K_1/K_2 + k_1/K_2[OH^-] + k_2'K_1'[OH^-]) \quad (iii)$$

For each sulphonamide * (1a—c) the direct proportionality (Table 4) between $k_A$ and $[OH^-]$ requires that

$$k_2'K'_1[OH^-] \gg (k_1' + k_2K_1/K_2 + k_1/K_2[OH^-])$$

although there appears to be a slight salt effect in each case. Likewise, for (1d—g) it is apparent that the term $k_2K_1[OH^-]$ must dominate the rate expression

$$(d[3]/dt)_{formation} = (k_1 + k_2K_1[OH^-])[ArSO_2NR^1{\cdot}CR^2R^3{\cdot}CHR^4OH]$$

such that $k_A = k_2K_1$.

Second-order rate constants $k = k_A/[OH^-]$ have, therefore, been evaluated and averaged for each substrate (1a—g) and are given in Table 4. By definition (Scheme 2) they correspond † to either $k_2K_1$ ($R^1 \neq H$) or $k_2'K_1'$ ($R^1 = H$).

Estimates ($pK_a^{est}$) of the $pK_a$ values for O–H ionisation of substrates (1) or (1′) have been made, as appropriate, and are included in Table 5. From each value the corresponding pre-equilibrium constant $K_1$ (or $K_1'$) was calculated so that the rate constant $k_2$ (or $k_2'$) could be determined. The Taft $\sigma^*$ value for $ArSO_2NHCH_2^-$ should be only slightly greater than that for $CH_3CONHCH_2^-$ for which $\sigma^* = 0.43$. Thus, for ionisation of the hydroxy-group of (1a—g) it can be estimated that $pK_a = ca.\ 15$ since for alcohols $RCH_2OH$ the relationship, $pK_a = 15.9—1.42\sigma^*$, generally holds.[24] In practice, however, where $R^1 = H$ each sulphonamide exists predominantly as (1′) under the conditions employed; by analogy with the differences between $pK_a$ values for the first and second acid dissociations of oxalic acid ($\Delta pK_a = 3.0$) and of *o*-dihydroxybenzene ($\Delta pK_a = 2.96$), the neighbouring negative charge may increase to 18 the $pK_a$ for subsequent ionisation of the O–H group. The dissociation constant $K_1'$ for (1a′) will correspondingly be smaller than $K_1$ for (1d—g) by one thousand-fold.

Absolute values of $K_a^{est}$ for (1b′, c′) have been calculated relative to the estimate for (1a′) and are, therefore, subject to any error in the assumptions described above. The *relative values* of $K_a^{est}$ for (1a—c) have, however, been estimated ‡ by direct analogy with the known effects of alkyl substituents on acid dissociations of simple aliphatic alcohols.

Our results reveal that *N*-arylation (1f, g) or *N*-alkylation (1d, e) of the parent sulphonamide (1a) produces a modest increase ($k^{rel} = 5—12$) in the second-order rate constant $k$. Our estimates of $K_a$ require, however, that for (1d—g) the rate constant $k_2$ of the specific base-catalysed reaction sequence be 100—200 times *less* than $k_2'$ for reaction of (1a′) (see values of $k_c^{rel}$, Table 5).

Intermolecular nucleophilic aromatic displacement of a good leaving group ($pK_a < 3$) by a nucleophile such as alkoxide, $RNH_2$ or $R_2NH$ is believed to proceed by rate-determining formation of a Meisenheimer intermediate which rapidly forms product upon subsequent ejection of the leaving group.[29,30] Thus, there is generally no direct correlation between reaction rate and leaving group ability although the potential leaving group may influence the reactivity at the site of displacement. However, for reaction with aqueous hydroxide, *p*-chloronitrobenzene reacts only three times faster than *p*-nitrophenyl phosphate and the retarding electrostatic effect of the neighbouring dianion is, therefore, believed to be modest.[30]

Likewise, it is to be expected that for (1a′) the constant $k_2'$ is a measure of the rate of intramolecular attack by the oxyanion on the aromatic ring. Any electrostatic effect of $N^-$ should therefore be to slightly *decrease*, *rather than increase* this rate constant relative to $k_2$ for *N*-alkyl or *N*-aryl derivatives.

* It should be noted that, at the hydroxide concentrations employed, each of the sulphonamides (1a—c) (where $R^1 = H$) will exist mainly as the corresponding conjugate base (1′a—c). For N–H ionisation[24—26] of the series $Y{\cdot}C_6H_4{\cdot}SO_2NH_2$ it has been found that $pK_a = 10.00—1.06\sigma$ while for $Y{\cdot}C_6H_4SO_2NH{\cdot}CH_2{\cdot}CH_2Br$ $pK_a = 10.59—0.94\sigma$. Thus, the $pK_a$ values for *p*-nitro-substituted sulphonamides (1a—c) should approximate to $10.59—0.77 = 9.82$ and hence $K_2 = K_a/K_w \simeq 10^{4.2}$.

† It is unlikely that the observed base dependence can be attributed to general base catalysis of intramolecular attack by the unionised hydroxyl group, since its conjugate anion should form at a diffusion controlled rate upon approach of hydroxide ion. We have therefore interpreted our results with reference to the specific base catalysed reaction (1) ⟶ (3) of Scheme 2.

‡ Relative acidities of alcohols in PrⁱOH solution,[27] which generally correspond to those in aqueous solution,[28] suggest that the effect of α-methyl substitution may be to decrease $K'_1$ by up to forty-fold while a decrease of *ca.* two-fold should be the result of ββ-dimethyl substitution.


[24] G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, 75.
[25] Von A. V. Willi, *Helv. Chim. Acta*, 1956, 46.
[26] J. H. Coy, A. F. Hegarty, E. J. Flynn, and F. L. Scott, *J.C.S. Perkin II*, 1974, 53.
[27] J. Hine and M. Hine, *J. Amer. Chem. Soc.*, 1952, **74**, 5266.
[28] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1960, **82**, 795.
[29] J. F. Bunnett, E. W. Garbish, jun., and K. M. Pruitt, *J. Amer. Chem. Soc.*, 1971, **79**, 385.
[30] A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, 1965, **87**, 3217.

The rate constant ($k_2'$) for rearrangement of (1a') is, however, much larger than constants $k_2$ for (1d—g). That this is not attributable to a differential steric effect, of the *N*-substituent ($R^1$), is suggested by the almost identical values of $k_2$ obtained for (1d) and (1f) where $R^1$ = methyl and phenyl respectively.

The effect of the neighbouring nitrogen anion on the nucleophilicity of the oxyanion must be considered. Thus, although the effect of $N^-$ is to reduce the pre-equilibrium constant $K_1'$ for ionisation of (1a—c) [relative to $K_1$ for (1d—g)] this may be partially compensated by an enhancement of nucleophilicity of the oxyanion so formed. This implies that the reaction is governed by a relationship of the form $\log k_c = -\alpha \log K + \text{const}$, where $k_c = k_2$ or $k_2'$, and $K = K_1$ or $K_1'$ as indicated in Table 5. It is also to be expected [26,31] that $\alpha \leqslant 1$, by analogy with the Brönsted relationship for proton-transfer reactions. The value $\alpha = 0.77$ would alone be sufficient to account for the relative rates of reaction of (1a') and (1d—g) as evidenced by the appropriate ratio ($k_2'/k_2$). It is quite probable, however, that $\alpha$ is much less than 0.77 and that cyclisation of the ionised sulphonamides is facilitated by a preferred alignment * of the nitrogen anion with respect to the sulphonyl group. Molecular models make it clear that the preferred conformation is likely to be particularly conducive to $S_NAr$ reaction of the neighbouring oxyanion.

The order of reactivity $k_c^{(1a)} < k_c^{(1b)} < k_c^{(1c)}$ is that expected for an intramolecular cyclisation subject to the accelerative ' Ingold Effect ' of alkyl substituents.[33]

*Kinetics of the Second Smiles' Rearrangement.*—According to Scheme 2 the rate of rearrangement of (3) to (4) can be written

$$(-\mathrm{d}[\mathbf{3}]/\mathrm{d}t)_{\text{rearrangement}} = k_B[\mathrm{ArO{\cdot}CHR^4{\cdot}CR^3R^2{\cdot}NHR^1}]$$

where

$$k_B = \{k_4 + (k_5K_3 + k_6)[OH^-]\}$$

Both specific ($k_5K_3$) and general ($k_6$) base ($OH^-$) catalysis is accommodated by this expression.

The base dependence of $k_B$ was studied in each case so that $k_4$ and ($k_5K_3 + k_6$) could be evaluated.

The extent of dependence of $k_B$ on [$OH^-$] is markedly affected by substituents $R^{1-4}$. Thus, for formation of: (4a), $k_4 \gg (k_5K_3 + k_6)$; (4f, g), $k_4 \ll (k_5K_3 + k_6)$, while the second Smiles' rearrangement to form (4d, e) is too fast, relative to the first, to permit determination of $k_B$. It is probable, however, that *N*-alkyl substituents ($R^1$) enhance the rate of reaction (3d, e) ⟶ (4d, e) [relative to (3a) ⟶ (4a)] by increasing the nitrogen nucleophilicity [30,34] and hence increasing $k_4$. Thus, it is to be expected that for reactions of (3d, e), $k_4 \gg (k_5K_3 + k_6)$.

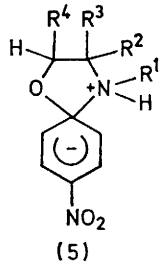
The apparent tendency of $k_B^{(3c)}$ to approach a limiting value at high base concentration may (by analogy with intermolecular $S_NAr$ reactions of amines [35]) be a consequence of base-catalysed decomposition of a spiro-Meisenheimer intermediate (5); at high base concentration the rate of formation ($k_4$) of the intermediate should alone be rate determining.

TABLE 5 *

Estimation of relative values of rate and equilibrium constants for reactions of sulphonamides (1a—g) according to Scheme 2

| Sulphonamide | Estimated† $10^{18}K_a$/mol $l^{-1}$ | $K = (K_a/K_w)$/ 1 $mol^{-1}$ | $k = k_cK/10^{-3}$ 1 $mol^{-1}$ $s^{-1}$ | $k_c = (k/K)$/ $s^{-1}$ | $k^{rel}$ | $K^{rel}$ | $k_c^{rel}$ |
|---|---|---|---|---|---|---|---|
| (1a) | 1.0 | $10^{-4}$ | 0.71 | 7.1 | 1 | 1 | 1 |
| (1b) | 0.025 | $>2.5 \times 10^{-6}$ | 0.47 | <200 | 0.67 | >0.025 | <30 |
| (1c) | 0.5 | $0.5 \times 10^{-4}$ | 18.6 | 372 | 26.2 | 0.5 | 53 |
| (1d) | 1 000 | 0.1 | 3.6 | 0.036 | 5.1 | 1 000 | 0.005 |
| (1e) | 1 000 | 0.1 | 8.2 | 0.082 | 11.5 | 1 000 | 0.012 |
| (1f) | 1 000 | 0.1 | 4.1 | 0.041 | 5.8 | 1 000 | 0.006 |
| (1g) | 1 000 | 0.1 | 4.8 | 0.048 | 6.8 | 1 000 | 0.007 |

* Where $R^1$ = H (1a—c) *K* and $k_c$ correspond to $K_1'$ and $k_2'$ respectively, whereas where $R^1$ = R or Ar (1d—g) the correspondence is with $K_1$ and $k_2$. † $K_a$ for ionisation of the alcohol function of the hydroxyalkyl sulphonamide [or, in the case of (1a—c), the conjugate base formed upon N–H deprotonation] estimated as described in the main text, without temperature correction to 61 °C.




(5)

The effect of *N*-arylation is to considerably reduce $k_4$ and we find that for both (1f) and (1g) the dominant reaction is of first order in [$OH^-$] throughout the range

* It has been established [32] that the energetically more stable configuration of a sulphonamide is generally such that the nitrogen is almost planar with the lone pair occupying a *p*-orbital directed between the oxygen atoms of the O–S–O bond. This configuration is stabilised further by electron-donating substituents on nitrogen. Moreover it has been shown that upon ionization sulphonamides do not adopt *sp*-hybridisation on nitrogen but that the S–N bond length is decreased by an increase of interaction between the N(*p*) and S(*d*) orbitals.

[31] A. C. Knipe, *J.C.S. Perkin II*, 1973, 589.
[32] See F. A. Cotton and P. F. Stokely, *J. Amer. Chem. Soc.*, 1970, **92**, 294 and references listed therein.
[33] See B. Capon, *Quart. Rev.*, 1964, **18**, 109.
[34] H. K. Hall, *J. Org. Chem.*, 1964, **29**, 3539; G. Yagil and M. Anbar, *J. Amer. Chem. Soc.*, 1962, **84**, 1797.
[35] (*a*) C. F. Bernasconi, *M.T.P. Internat. Rev. Sci.: Org. Chem. Ser. One*, 1973, **3**, 33; (*b*) S. D. Ross in ' Comprehensive Chemical Kinetics,' eds. C. H. Bamford and C. F. H. Tipper, Elsevier, London, 1972, vol. **13**, p. 407.

0.1—1.0M. We are, however, unable to cite an intermolecular analogue [36] for which such rectilinear base dependence persists beyond 0.1M. It is unlikely that the rate of deprotonation of the corresponding spiro-Meisenheimer intermediate is rate determining at such high base concentration. We therefore believe that base-catalysed cyclisation constitutes the rate-determining step for Smiles' rearrangement of the *N*-aryl amino-ethers. If it is assumed that $pK_a = ca.$ 29 for N–H ionization of (3f, g) (*cf.* aniline; $pK_a = 27$) it can be calculated that interpretation in terms of a specific base-catalysed mechanism ($k_B = k_5K_3$) requires that the corresponding cyclization rate constants ($k_5$) approach $10^{10}$ s$^{-1}$. This is close to the expected diffusion-controlled rate limit and yet the effect of aryl substitution must be greater on $k_5$ than on $K_3$ [since $k_B^{(3g)} > k_B^{(3f)}$ and $K_a^{(3g)} > K_a^{(3f)}$]. This is unlikely and we therefore favour a mechanism of general base catalysis wherein $k_B = k_6$. We hope to conduct a detailed study of a wider range of *N*-aryl ethers and to determine the Hammett and Brönsted dependences of their base-catalysed rearrangement.

[36] See Table 2.1 in ref. 35*a*.

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