Base-Catalyzed Rearrangement of 2-Nitrobenzenesulfenanilides. An Intramolecular Oxygen Transfer Process

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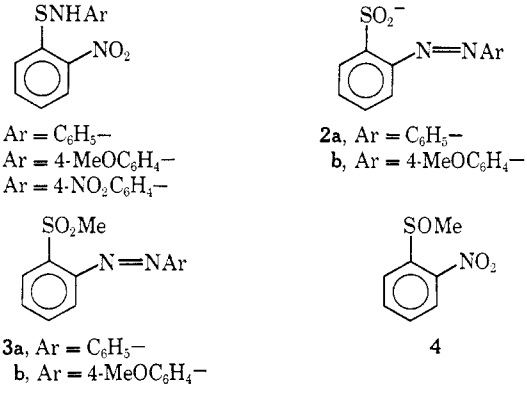
Abstract: The rearrangement of 2-nitrobenzenesulfenanilide (**1a**) and its 4′-methoxy derivative (**1b**) to the azobenzenesulfinates (**2**) in aqueous alcoholic sodium hydroxide has been examined. The reactions are first order in sulfenanilide and in hydroxide ion, and **1b** rearranges at a slightly faster rate than **1a**. ^{18}O-Labeling studies show that transfer of both oxygens from the nitro group to the sulfur atom takes place. These observations, and the failure of the 4′-nitro isomer (**1c**) to rearrange, are rationalized in terms of an intramolecular oxygen transfer mechanism.

In a reexamination of the title rearrangement, Cava and Blake showed[1] that the product from the reaction of **1a** with base was not the sodium salt of an aminothiol, as previously reported,[2] but the azosulfinate, **2a** (Scheme I). This assignment was confirmed

Scheme I



by methylation using methyl iodide, giving the sulfone **3a** whose structure was clearly established. These workers proposed a mechanism for the transformation which involved attack of hydroxide ion on sulfur, ultimately to form S=O bonds, and loss of hydroxide ions from *aci* forms of the nitro group. However, the X-ray structural determination[3] of the related sulfenate ester **4** indicates a strong interaction between one of the oxygen atoms of the nitro group and the sulfur atom, and it seemed that such an interaction might well be involved in the conversion of **1** to **2**. Accordingly, experiments were carried out to check on the origin of the sulfinate oxygens using ^{18}O-labeled material, and these are described below, together with some kinetic and product studies pertinent to the mechanism.

Results and Discussion

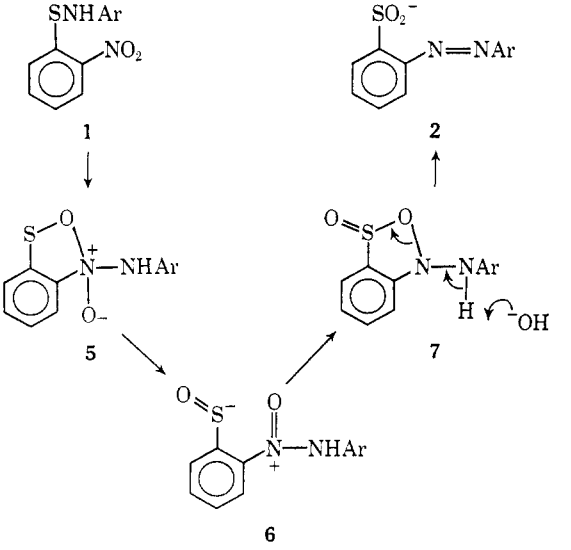
The sulfenanilides **1a** and **1b** were found to rearrange cleanly in aqueous alcoholic media to the azosulfinates **2a** and **2b**, respectively, as expected from previous work.[1,2] When the rearrangement of **1a** was conducted using ^{18}O-labeled sodium hydroxide solution, essentially zero incorporation of label into the sulfinate was observed, as shown in Table I. The sulfinate was converted to the sulfone **2a**, using methyl iodide, for purification before ^{18}O analysis. This would not be expected to lead to any loss of label. These results are unequivocal. They rule out any mechanism involving oxygenation of sulfur by attack of hydroxide ion, and clearly show that *both* oxygens of the nitro group are transferred to sulfur. Hydroxide ions are not therefore required, *per se*, and any comparable strong base should promote rearrangement of **1a** to **2a**. In fact, we found that **1a** was converted to **2a** in good yield by refluxing in dry ethanolic sodium ethoxide. The reported failure[1] of the 4-nitrobenzenesulfenanilide to rearrange, in conjunction with the X-ray data of Hamilton and La Placa,[3] strongly imply that the oxygen transfer is intramo-

Table I. Rearrangement of **1a** in ^{18}O-Labeled Base. ^{18}O Content of **3a**

Expt no.	No. of determinations[a]	Excess ^{18}O (atom %)[b,c]
1	3	0.09 ± 0.04
2	4	0.08 ± 0.04

[a] Each determination involved at least six mass spectral traces. [b] Mean value. The slight excess over the (calculated) experimental error of ±0.04 atom % may be due simply to carry-over from the combustion apparatus, although this was minimized by discarding the CO_2 from the first two combustion procedures from each experiment. [c] Excess ^{18}O content of (OH^- + H_2O) system = 4.60%.

Scheme II

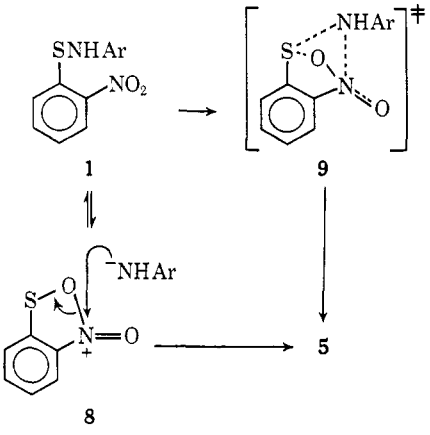


(1) M. P. Cava and C. E. Blake, *J. Amer. Chem. Soc.*, **78**, 5444 (1956).
(2) M. L. Moore and T. B. Johnson, *ibid.*, **57**, 2235 (1935).
(3) W. J. Hamilton and S. J. LaPlaca, *ibid.*, **86**, 2289 (1964).

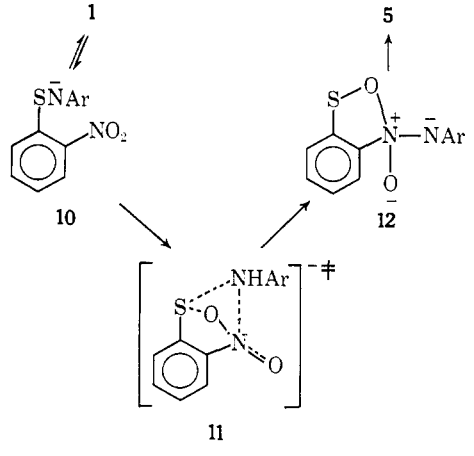
lecular. An alternative mechanistic route may now be outlined, as shown in Scheme II.

In this scheme, the most interesting problem is the formulation of a mechanism for conversion of **1** to **5**. Some possibilities are shown in Schemes III and IV.

Scheme III



Scheme IV



The general route shown in Scheme III considers conversion of sulfenanilide **1** to **5** either *via* the ion pair **8** or concertedly[4] through the [2.1.1]bicyclic transition state complex **9**. The route *via* **8** is of interest in view of the implied possibility of anchimeric assistance to ionization of **1** by the 2-nitro group. Strong kinetic evidence[5] for such participation has recently been presented, and the ion pair **8** is probably an intermediate in the rearrangement of **1a** to 2-nitro-4′-aminodiphenyl sulfide in neutral media.[6] In view of the (probably) high activation energy[7] for formation of **8**, the over-all rate expression for conversion of **1** to **2** should be first order in sulfenamide. An alternative possibility would be to bypass **8** *via* the [2.1.1] bicyclic activated complex **9**. Such a scheme should lead to similar kinetics.

Finally, consideration can be given to mechanisms involving proton abstraction[7] from **1** to give the anion **10**. This could then cyclize as shown in Scheme IV.

In an attempt to clarify this position the kinetics of the rearrangement were studied. The rates were measured in 76% aqueous ethanol at 65°, at a constant ionic strength of 0.5 (added sodium chloride). The results are given in Table II.

Table II. Rates of Rearrangement of **1a** and **1b**

Compd[a]	OH^-, M	NaCl, M	$10^3 k_{obsd}$, min^{-1}	$10^3 k_r$,[b] M^{-1} min^{-1}
1a	0.50		3.10 ± 0.30	6.2 ± 0.6
1a	0.50		2.80 ± 0.20	5.6 ± 0.4
1a	0.40	0.10	2.40 ± 0.10	6.0 ± 0.2
1a	0.25	0.25	1.40 ± 0.15	5.6 ± 0.6
1a	0.10	0.40	0.55 ± 0.05	5.5 ± 0.5
1b	0.50		7.10 ± 0.60	14.2 ± 1.2
1b	0.25	0.25	3.90 ± 0.40	15.6 ± 1.6

[a] [Sulfenanilide] = 5×10^{-3} M. [b] Mean values of k_r for **1a** and **1b** are $(5.80 \pm 0.30) \times 10^{-3}$ and $(14.9 \pm 0.7) \times 10^{-3}$ M^{-1} min^{-1}, respectively.

The process is clearly seen to be second order (a plot of k_{obsd} against OH^- for **1a** is linear and passes through the origin, indicating that the uncatalyzed reaction is negligibly slow). These results can only be reconciled with the ionization or concerted mechanism (Scheme III) if we assume that the rate-determining step is removal of a proton from **7** formed from **1** by a series of relatively fast steps. This unlikely situation is made the more so when we consider the effect of the methoxyl group on the rate. This would be expected to markedly *hinder* conversion of **7** to **2**. The small rate enhancement actually observed was at first sight difficult to rationalize, and as a start to a more careful examination of substituent effects, attempts were made to rearrange the 4′-nitro derivative **1c**. Under conditions which led to complete rearrangement of **1a** and **1b**, **1c** failed to rearrange, and instead gave a 71% yield of 4-nitroaniline.

This significant observation can be rationalized in terms of the mechanism shown in Schemes II and IV. That is, the sulfenanilide **1** and hydroxide are in equilibrium with the anion **10**. This cyclizes (in the case of **1a** and **1b**) to **12** in a slow step (k_5); proton abstraction from the solvent gives **5** and ultimately, in a series of fast steps, **2** is formed. In the case of **1c**, however, cyclization is suppressed by the nitro group, and at the same time the leaving-group potential of the anilide anion is increased. Direct attack of hydroxide on sulfenyl sulfur in the unionized sulfenanilide can therefore occur more readily, giving 4-nitroaniline and 2-nitrobenzenesulfenic acid. In keeping with this suggestion, the blue color associated with anion of this acid[8] was detected in the following way. The sulfenanilide **1c** was added to dry ethanolic sodium ethoxide and briefly heated to produce 4-nitroaniline and ethyl 2-nitrobenzenesulfenate; addition of water precipitated the amine and caused the mother liquor to turn green-blue in color.

This scheme will lead to a rate expression of the form

$$\text{rate} = k_5 K[OH^-][\text{sulfenanilide}]$$

The effect of the nitro group indicates that the numerical value[9] of ρ for the cyclization step is larger than that for the equilibrium between **1** and **10**. This explains the small increase in over-all rate produced by the 4′-

(4) See M. S. Newman and C. Courduvelis *J. Am. Chem. Soc.*, **86**, 2942 (1964)] for [2.2.1] analogs.

(5) A. D. Mease, M. J. Strauss, I. Horman, L. J. Andrews, and R. M. Keefer, *ibid.*, **90**, 1797 (1968).

(6) M. L. Moore and T. B. Johnson, *ibid.*, **57**, 1517 (1935).

(7) The helpful comments of a referee on these points are gratefully acknowledged.

(8) C. Brown and D. R. Hogg, *Chem. Commun.*, 38 (1967).

(9) Hammet ρ value.

methoxyl substituent arising from a decrease in K but a larger increase in k_5.

Experimental Section[10]

2-Nitrobenzenesulfenanilide (1a). This material was prepared as previously described[11] from aniline and 2-nitrobenzenesulfenyl chloride in 80% yield. Recrystallization from ether–hexane gave orange crystals: mp 94–95° (lit.[11] mp 94°); ν_{max} ($CHCl_3$) 3400 cm^{-1}; λ_{max} (EtOH) 241 and 371 mμ.

4′-Methoxy-2-nitrobenzenesulfenanilide (1b). Reaction of *p*-anisidine similarly gave **1b** in 86% yield as orange needles from benzene: mp 141.5–142.5°; ν_{max} ($CHCl_3$) 3400 cm^{-1}; λ_{max} (EtOH) 243, 272, and 371 mμ; nmr ($CDCl_3$) complex absorption from δ 6.8 to 8.4 (8 H), broad singlet at 5.05 (1 H), and sharp singlet at 3.71 (3 H).

Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.6; H, 4.35; N, 10.1; S, 11.6. Found: C, 56.3; H, 4.3; N, 10.1; S, 11.7.

4′-Nitro-2-nitrobenzenesulfenanilide (1c). Attempts to prepare this compound were complicated by solubility problems, so the following procedure was devised. To a solution of 1.9 g of 2-nitrobenzenesulfenyl chloride in 70 ml of benzene were added 10 drops of pyridine and 2.8 g of *p*-nitroaniline. The mixture was heated to boiling when the amine dissolved and a flocculent yellow precipitate formed. Heating (with shaking) was continued for 15 min and the solid material was filtered off. This solid (4.2 g) was washed repeatedly with water and twice with 50 ml of ethanol. Centrifugation gave 1.9 g of a yellow solid, shown to be homogeneous by tlc. The infrared spectrum of this material (Nujol) had a sharp singlet at 3350 cm^{-1} (–NH–) and characteristic absorption for 1,2 and 1,4 disubstitution in the 700–900-cm^{-1} region. The nmr (DMSO) had a singlet at δ 9.08 (1 H), an A_2B_2 pattern at 8.10 and 7.15 (J_{AB} = 9 cps, 4 H), and complex absorption between 8.4 and 7.15 (4 H). Recrystallization from acetone gave yellow crystals, which decomposed without melting at *ca.* 160°.

Anal. Calcd for $C_{12}H_9N_3O_4S$: C, 49.4; H, 3.1; N, 14.4; S, 11.0. Found: C, 49.2; H, 3.3; N, 13.9; S, 11.05.

Base-Catalyzed Rearrangement of 1a to Sodium 2-Azobenzenesulfinate (2a). This was carried out as previously[1] described. From 2.1 g of **1a** was obtained 1.4 g of **2a** as orange plates. The infrared spectrum of the product lacked the nitro group absorptions at 1575 and 1345 cm^{-1} present in **1a**. The uv-visible spectrum of this material had a shoulder at 228 mμ and λ_{max} 320 mμ.

The above experiment was repeated twice, using a solution of aqueous alcoholic sodium hydroxide of the same concentration, but with an ^{18}O enrichment of 4.6% excess ^{18}O ($H_2O + OH^-$). In each case *ca.* 1.4 g of salt was isolated (tlc examination showed a trace of starting material as the only nonionic compound present in the reaction mixture). The infrared spectra of the isolated salts were identical with that of product from the "unlabeled" experiment.

Sodium 4′-Methoxy-2-azobenzenesulfinate (2b). This compound was obtained in 90% yield as fine orange needles, mp 125–130° dec. Again the nitro group absorptions (1575 and 1347 cm^{-1}) of the starting material **1b** were absent from the infrared spectrum of **2b**.

2-Methylsulfonylazobenzene (3a). The sodium salt (**2a**) was methylated as previously described to give red crystals, mp 94.5–95.5°, in 80% yield. The sulfones obtained by methylation of the salts from the "labeled" experiments had infrared spectra identical with that of material from "unlabeled" experiments (strong absorption at 1150 and 1320 cm^{-1}, $-SO_2-$). The nmr spectra (CCl_4) exhibited a singlet at δ 3.30 (3 H) and complex absorption between 7.3 and 8.2 (9 H).

4′-Methoxy-2-methylsulfonylazobenzene (3b). This sulfone was similarly obtained in 60–70% yield. The product crystallized from ethanol as fine orange needles, mp 105.5–106.5°. The infrared spectrum of this material had strong bands at 1120 and 1300 cm^{-1} (Nujol) and the nmr ($CDCl_3$) showed complex absorption at δ 6.9–8.4 (8 H) and singlets at 3.88 (3 H) and 3.40 (3 H).

Anal. Calcd for $C_{14}H_{14}N_2O_3S$: C, 58.1; H, 4.8; N, 9.65; S, 11.1. Found: C, 58.0; H, 5.0; N, 9.9; S, 10.95.

Reaction of 1a with Dry Sodium Ethoxide in Ethanol. A solution of sodium ethoxide was prepared by dissolving 0.1 g of sodium in 5 ml of dry ethanol. To this solution was added 2.1 g of **1a** and the mixture was refluxed for 6 hr. Dilution with water and refrigeration gave **2a** in good yield (infrared spectrum identical with authentic material).

Attempted Rearrangement of 4′-Nitro-2-nitrobenzenesulfenanilide. The sulfenanilide (**1c**), 1.3 g, was suspended in 7 ml of ethanol and treated with 4 ml of 20% sodium hydroxide solution. A wine-red solution formed immediately, and this was heated under reflux for 5 hr. Dilution with water gave 0.43 g (71%) of 4-nitroaniline, mp 148–150° (from water), identity confirmed by ir comparison with authentic material.

Determination of Rates of Rearrangement of 1a and 1b. A spectrophotometric method was employed. Preliminary experiments showed that the compounds obeyed Beer's law over the required concentration range. In a typical run a solution of the sulfenanilide (*ca.* 1 mg ml^{-1}) in aqueous alcohol containing the appropriate amounts of sodium hydroxide and sodium chloride was prepared and 3-ml aliquots were pipeted into N_2-flushed ampoules. The ampoules were sealed and immersed in an oil-filled thermostat bath maintained at 65 ± 0.1°. Ampoules were withdrawn and quenched in ice–water at suitable intervals. A 1-ml aliquot of their contents was pipeted into 10 ml of nearly saturated sodium chloride contained in a small separating funnel. The unreacted sulfenanilide was then exhaustively extracted from the mixture with a 2:1 pentane–methylene chloride mixture. The total extracts were collected in a 25-ml volumetric flask containing a constant amount of anhydrous sodium sulfate, made up to the mark with pentane–methylene chloride mixture, and the concentration of the solution was determined by measuring the optical density at 371 mμ. Control experiments with sulfenanilide solutions of known concentration in the presence and absence of azosulfinate showed that concentrations could be determined to within ±5% of the calculated value using this method.

When using lower concentrations of hydroxide, and consequently longer reaction times, downward drift in rate was observed, presumably due to attack of hydroxide on the glass ampoules, as evidenced by the formation of a sticky, water-soluble colorless material in ampoules left in the bath for more than 2 days. Rates measured within 1 or 2 days were not so affected. Rate constants were calculated from the integrated form of the rate expression for a first-order process, and are quoted as the mean and mean deviation from the mean.

Determination of ^{18}O Content of 2a. Determinations were carried out using the modified Unterzauker apparatus and method[12] described by Goering and Pombo.

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(10) Melting points are uncorrected; nmr spectra were obtained with a Varian 60A spectrometer and uv and visible spectra with a Cary Model 11 spectrophotometer. Analyses were performed by Weiler and Strauss, Oxford, England.

(11) T. Zincke and F. Farr, *Ann.*, **391**, 79 (1912).

(12) H. L. Goering and M. M. Pombo, *J. Amer. Chem. Soc.*, **82**, 2515 (1960).