

Relative Nucleophilicities of Aryldisulphide and Thiolate Ions in Dimethylacetamide Estimated from their Reaction Rates with Alkyl Halides

Meriem Benaïchouche, Gérard Bosser, and Jacky Paris*

Groupe de Physico-Chimie Analytique des Solutions, UFR Sciences, Parc de Grandmont 37200 Tours, France
 Vincent Plichon
 Laboratoire de Chimie et Electrochimie des Matériaux Moléculaires, ESPCI, 10, rue Vauquelin, 75231 Paris Cedex 05, France

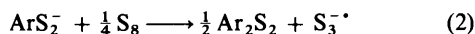
The relative rates of nucleophilic substitution (S_N2) of alkyl halides by aromatic thiolates ArS^- and aryldisulphide ions ArS_2^- have been studied in dimethylacetamide by UV-visible spectrophotometry for $Ar = 4$ -nitrophenyl (1), 2-nitrophenyl (2), and 8-quinolyl (3). Rate constants are relative to the rate constants for benzenethiolate ions (4), studied as reference. With $Ar =$ (1), the reaction rate for disulphide ions is ten times higher than that for monosulphide ions stabilized by the elevated delocalization of their charge. With $Ar =$ (2) and (3), the reactivity of disulphide ions is higher than that of the corresponding thiolates. Our study is consistent with the uncomplicated introduction of a disulphide bond into various substrates from aryldisulphide ions stabilized in aprotic dipolar media.

In aprotic dipolar medium, the nucleophilicity of anions is generally enhanced as a result of their lower solvation.¹ The greatest number of anion substitutions on alkyl halides has been done in dimethylformamide² (DMF). Kinetic studies of bimolecular processes, Parker,³ imply a classification of various nucleophiles at 25 °C, to which we may add the superoxide anion radical $O_2^{\cdot-}$,⁴ in comparison with the same substrate CH_3I : $O_2^{\cdot-} > C_6H_5S^- > CN^- > 4-NO_2C_6H_4S^-$, $AcO^- > N_3^-$, Cl^- , $Br^- > I^- > SCN^-$. The rates of S_N2 reactions studied in dimethylacetamide^{2,3} (DMA) with SCN^- , N_3^- , and Cl^- suggest that the nucleophilicities of the anions are similar in DMF and DMA.

Using spectroelectrochemistry in DMA, we recently showed⁵ that the reaction between sulphur and a series of aromatic thiolates, ArS^- , led to aryldisulphide ions [equation (1)].



ArS_2^- ions are then oxidized to disulphides Ar_2S_2 [equation (2)].



The synthesis of several $ArSCH_3/ArS_2CH_3$ mixtures^{5b} ($Ar = 2$ - or 4- $NO_2C_6H_4$ and C_6H_5) by direct reaction of ArS^-/ArS_2^- solutions with methyl iodide illustrates the possibility of deriving the S-S bond from ArS_2^- nucleophilic agents.

When ArS^- and ArS_2^- ions absorb in the UV or visible at sufficiently different wavelengths, their concentrations can be easily determined spectrophotometrically, allowing the kinetics of their substitution reactions to be followed. The present report compares the respective nucleophilicities of aryldisulphide and thiolate ions in DMA, which in this case are $Ar = 4-NO_2C_6H_4$ (1), 2- $NO_2C_6H_4$ (2) and 8-quinolyl (3), based on the study of their reaction rates with several alkyl halides. Benzenethiolate ions (4) are also tested as reference.

Results

Generation and Characteristics of Solutions of Thiolate and Aryldisulphide Ions in DMA.—Solutions of ArS^- ions (1)–(4)

were generated by electrolysis of symmetrical disulphides Ar_2S_2 . Electrochemical reduction occurred according to the overall reaction,⁶ equation (3).



The addition of sulphur led to a mixture of ArS^- and ArS_2^- in solution according to reaction (1), which is an equilibrium highly shifted toward the formation of disulphide ions when the Ar group is weakly electron attracting (3) and (4). The composition of the solutions could be determined. The spectrophotometric characteristics^{5b} of the ions, λ_{max} and ϵ_{max} , are summarized in Table 1. The constants $K_1 [ArS_2^-][ArS^-]^{-1} [S_8]^{-1/8}$ and $K_2 [Ar_2S_2]^{1/2} [S_3^{\cdot-}][ArS_2^-]^{-1} [S_8]^{-1/4}$, were determined^{5b} for species (1) and (2): K_1 0.53 (1) and 14.0 (2), and K_2 2×10^{-2} (1) and 1.1×10^{-2} (2).

Reactivity of Thiolate Ions Towards Alkyl Halides.—Individual alkyl halides were (Table 2) added initially to ArS^- solutions [(1)–(4)] in order to study the rate of the substitution reactions (4) in the absence of sulphur.



The change in the concentration of thiolate ions with time was deduced from the changes in absorbance at λ_{max} , which did not interfere with that of the product $ArSR$ at this wavelength. The equation of rate v_t is expressed by invoking the usual S_N2 mechanism $v_t = k_1 [ArS^-]_t [RX]_t$. We easily obtain expression (5).

$$X_t = \frac{1}{[ArS^-]_0 - [RX]_0} \ln \frac{[RX]_0 [ArS^-]_t}{[ArS^-]_0 [RX]_t} = k_1 t \quad (5)$$

This relationship was well verified for all reactions which were not too fast to be followed with our method ($k_1 < 250 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, see the Experimental section). A representative example is shown in curve X, Figure. The rate constants thus determined are listed in Table 2.

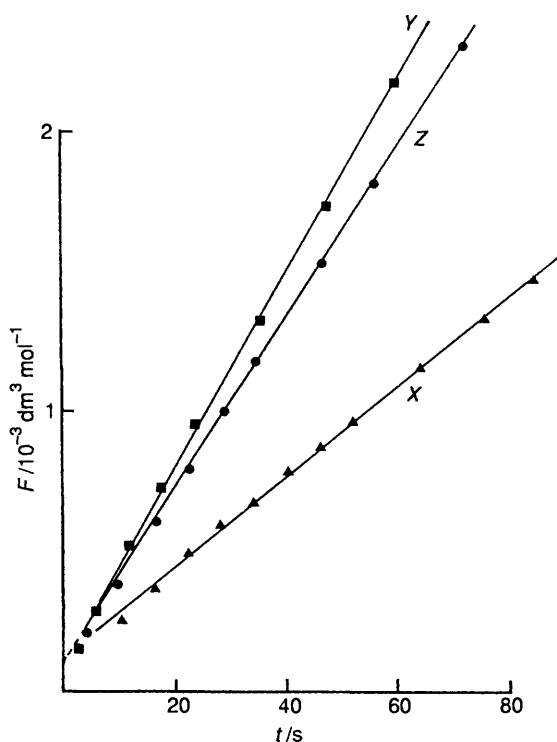
Table 1. Spectrophotometric characteristics of thiolate and disulphide ions (1)–(4) in dimethylacetamide.

Ar	ArS ⁻		ArS ₂ ⁻	
	λ _{max} /nm	ε/dm ³ mol ⁻¹ cm ⁻¹	λ _{max} /nm	ε/dm ³ mol ⁻¹ cm ⁻¹
(1)	502	30 000	600	11 000
(2)	502	2 000	681	5 000
(3)	445	5 300	495	4 000
(4)	310	21 800	310	3 200

Table 2. Rate constants k_1^a (dm³ mol⁻¹ s⁻¹) of the reactions of thiolate ions (1)–(4) with alkyl halides in DMA at 20.0 ± 0.5 °C. Ionic strength = 0.1 mol dm⁻³.

	MeI	EtI	PrI	PrBr	PrI
(1)	200 ^b	5.7(3)	3.3(2)	0.19(1)	0.060(3)
(2)	fast ^c	53(3)	16(1)	0.85(5)	0.34(4)
(3)	fast	fast	220 ^b	14(1)	3.5(3)
(4)	fast	fast	fast	68(4)	14(1)

^a Experimental error in the last digit from deviation of several kinetic runs (parentheses) ^b k_1 values ± 25% close by the limit of the method. ^c Fast with respect to experimental conditions.

**Figure.** Kinetic studies of the reactions of 2-nitrophenyl thiolate and disulphide ions with 1-iodopropane.

X = $f(t)$: $[\text{ArS}^-]_0 = 0.19 \times 10^{-2}$ mol dm⁻³; $[\text{RX}]_0 = 0.70 \times 10^{-3}$ mol dm⁻³.

Y = $f(t)$: $[\text{ArS}^-]_0 = 0.23 \times 10^{-2}$ mol dm⁻³; $[\text{S}_8]_0 = 0.17 \times 10^{-3}$ mol dm⁻³; $[\text{RX}]_0 = 0.36 \times 10^{-3}$ mol dm⁻³.

Z = $f(t)$: $[\text{ArS}^-]_0 = 0.137 \times 10^{-2}$ mol dm⁻³; $[\text{S}_8]_0 = 0.52 \times 10^{-2}$ mol dm⁻³; $[\text{Ar}_2\text{S}_2]_0 = 0.335 \times 10^{-2}$ mol dm⁻³; $[\text{RX}]_0 = 0.30 \times 10^{-3}$ mol dm⁻³.

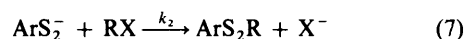
For each of the ArS⁻ anions, the decreased reaction rates with RX derivatives as a function of the nature of the group (Me ≫ Et > Pr > Prⁱ) or that of the halogen (I > Br) was

Table 3. Rate constants k_2 (dm³ mol⁻¹ s⁻¹) of the reactions between aryl disulphide ions (1)–(3) and alkyl halides in DMA at 20 ± 0.5 °C. Ionic strength = 0.1 mol dm⁻³.

	MeI	EtI	PrI	PrBr	PrI
(1)	fast	52(4)	26(2)	1.5(1)	0.70(3)
(2)	fast	47(3)	34(2)	1.5(1)	0.54(4)
(3)	fast	fast	fast	27(2)	12(0)

consistent with an S_N2 process. The classification of the rates for the same RX derivative agrees with the degree of electronic delocalization related to the ArS⁻ structure: $v(4) > v(3) > v(2) > v(1)$. Even with nitrophenylthiolate ions, nucleophilicity remained much higher than that of acetate ions³ (k_1 20 dm³ mol⁻¹ s⁻¹ for the reaction AcO⁻ + MeI in DMF at 25 °C).

Reactivity of ArS₂⁻ Ions.—After the addition of sulphur to ArS⁻ solutions in a ratio of initial concentrations $Y = [\text{S}_8]_0/[\text{ArS}^-]_0 < \frac{1}{8}$, both species are simultaneously in solution as a result of equilibrium (1), and reoxidation (2) does not occur. Kinetics were studied with species (1), (2), and (3) for values of Y lower than $\frac{1}{2}$, with the model of presumed second-order concurrent reactions (6) and (7).



The alkyl halide was added at the concentration $[\text{RX}]_0$ to a solution defined by Y in a ratio $[\text{RX}]_0/[\text{ArS}^-]_0$ less than 1. The absorption measurement at λ_{max} of ions ArS⁻ (1) and (3) or ArS₂⁻ (2) as a function of time led to $[\text{ArS}^-]_t$ and $[\text{ArS}_2^-]_t$. The ratio of rates at time t enables equation (8) to be written.

$$\frac{d[\text{ArS}^-]_t}{d[\text{ArS}_2^-]_t} = \frac{k_1[\text{ArS}^-]_t}{k_2[\text{ArS}_2^-]_t} \quad (8)$$

When RX was practically consumed, $[\text{ArS}^-]_\infty$ and $[\text{ArS}_2^-]_\infty$ were deduced from the corresponding spectrum and an approximate value of k_2/k_1 is accessible using the integrated form of equation (8).

$$\frac{k_2}{k_1} = \ln \frac{[\text{ArS}_2^-]_\infty/[\text{ArS}_2^-]_0}{[\text{ArS}^-]_\infty/[\text{ArS}^-]_0} = \alpha$$

The concentrations $[\text{ArS}^-]_t$ and $[\text{ArS}_2^-]_t$ are themselves related, equation (8b).

$$[\text{ArS}^-]_t = \frac{[\text{ArS}^-]_0}{[\text{ArS}_2^-]_0^{1/\alpha}} [\text{ArS}_2^-]_t^{1/\alpha} = \beta [\text{ArS}_2^-]_t^{1/\alpha} \quad (8b)$$

β is a constant which depends only on initial conditions.

The following relation can thus be established:

$$Y_t = - \int \frac{d[\text{ArS}_2^-]_t}{[\text{ArS}_2^-]_t([\text{ArS}_2^-]_t + \beta[\text{ArS}_2^-]_t^{1/\alpha} - [\text{ArS}^-]_0 + [\text{RX}]_0)} = k_2 t \quad (9)$$

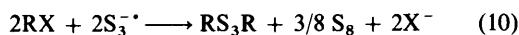
In the case of derivatives (1), (2), and (3) (example curve Y , Figure), its verification led to the values of rate constants k_2 of ArS₂⁻ ions with the halogenated derivatives chosen (Table 3).

Table 4. Calculated composition (molar%) of anionic solutions, obtained from initial conditions: $[S_8]_0 = 5.20 \times 10^{-3} \text{ mol dm}^{-3}$; $[ArS^-]_0 = 1.37 \times 10^{-3} \text{ mol dm}^{-3}$; $[Ar_2S_2]_0 = 3.35 \times 10^{-3} \text{ mol dm}^{-3}$.

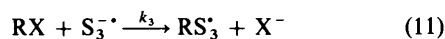
	% ArS^-	% ArS_2^-	% S_3^{2-}
(1)	78	22	0.02
(2)	12	87	ca. 1

When Ar = 4- or 2-nitrophenyl, the results were confirmed by repeating all the studies with a large excess of sulphur in comparison with thiolate ions in order to increase the proportion of ArS_2^- ions in the initial reaction mixtures by shifting equilibrium (1). The concentration of S_3^{2-} ions arising from equilibrium (2) was decreased by working in the presence of Ar_2S_2 . Table 4 furnishes an example of initial anionic compositions estimated from constants K_1 and K_2 .

Even though the concentration of polysulphide ions S_3^{2-} was very low, their reactivity could be much higher than that of ArS^- and ArS_2^- ions and was not *a priori* neglected. We have shown elsewhere⁷ that these ions react with alkyl halides according to the overall reaction (10).



The analogous^{7,8} behaviour of S_3^{2-} and O_2^{2-} towards RX derivatives is consistent with the slow step equation (11).



With initial concentrations of sulphur and disulphides Ar_2S_2 high in comparison with anions, and assuming the shift of equilibria (1) and (2) to be rapid, the following relationships could be verified at any time:

$$[ArS^-]_t = \gamma [ArS_2^-]_t, \text{ with } \gamma = K_1^{-1} [S_8]^{-1/8} = \text{cte}$$

$$[S_3^{2-}]_t = \delta [ArS_2^-]_t, \text{ with } \delta = K_2 [S_8]^{1/4} [Ar_2S_2]^{-1/2} = \text{cte}$$

$\delta \ll 1$.

Rate equations lead to expression (12):

$$Z_t = - \int \frac{d[ArS_2^-]_t}{[ArS_2^-]_t \{ (1 + \gamma + \delta) [ArS_2^-]_t - [ArS^-]_0 + [RX]_0 \}} = k_c t \quad (12)$$

$$\text{with } k_c = \frac{k_1 \gamma + k_2 + k_3 \delta}{1 + \gamma + \delta}$$

Regardless of the alkyl halide reacting with derivatives (1) and (2), the values of k_c determined from the curves $Z = f(t)$ were very close to the values calculated $k_c = (k_1 \gamma + k_2) / (1 + \gamma)$ with k_1 and k_2 (Tables 2 and 3). For example in experimental conditions of Table 4 concerning Ar = 2-nitrophenyl (curve Z, Figure): $\gamma = 0.139$, $\delta = 0.50 \times 10^{-2}$, k_c 31 (2) $\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and k_c 32 (3) $\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. The S_3^{2-} ions are, therefore, not to be taken into account when processing kinetics yielding the constants k_2 .

Discussion

The reactivities of the species ArS^- and ArS_2^- can be compared by using the ratios k_2/k_1 (Table 5).

When Ar = 4- $\text{NO}_2\text{C}_6\text{H}_4$, electron delocalization induced by the NO_2 substituent in *para* position is notable in the

Table 5. Comparison of the nucleophilicities of ArS^- and ArS_2^- ions [$Ar = (1)-(3)$] using the k_2/k_1 ratios as a function of RX.

	EtI	PrI	PrBr	Pr'I
(1)	9	8	8	12
(2)	1	2	2	1.6
(3)	—	—	2	3.4

thiolate ion, whereas the S-S bond does not transmit the conjugation.⁹ The reaction rate of disulphide ions increases in this case by a factor of about ten in comparison with that of ArS^- ions, regardless of the nature of RX. This result has been verified qualitatively from syntheses carried out elsewhere^{5b} with methyl iodide: the proportion of ionic species (molar %) in the initial solution, $[ArS_2^-]_0/[ArS^-]_0 = 19/81$, leading to a mixture of products $ArS_2CH_3/ArSCH_3 = 37/63$ at room temperature.

The nucleophilicities of 2- and 4-nitrophenyldisulphide ions appear to be similar, from the respective values of k_2 , regardless of the nature of RX. Stabilization of 2- $\text{NO}_2\text{C}_6\text{H}_4\text{S}_2^-$ ions by interaction between the anionic charge and the *ortho* nitrogen can explain why constants k_1 and k_2 are relatively similar in this instance.

More generally in the absence of an electron-withdrawing group on rings, charge delocalization on thiolate ions is low and their reactivity is much higher than that of ArO^- ions in aprotic dipolar medium.¹⁰ The phenylthiolate ion is among the most powerful nucleophilic agents: thus, k_1 50 $\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the reaction $\text{BuBr} + \text{C}_6\text{H}_5\text{S}^-$ in DMF at 25 °C and k_1 68 $\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for $\text{PrBr} + \text{C}_6\text{H}_5\text{S}^-$ in DMA (Table 2). The enhanced reactivity of ArS_2^- ions, as noticed also with Ar = 8-quinolyl analogous to Ar = phenyl, could be explained by the ' α -effect'¹¹ produced by the presence of unshared electron pairs on the sulphur atom adjacent to the nucleophilic centre. Aubort and Hudson^{11b} attributed this α -effect to 'a decrease in the overlap integral of orbitals containing lone pairs of electrons in the course of a chemical reaction.' They suggested that anionic α nucleophiles such as ClO^- , RO_2^- , and RS_2^- should, therefore, exhibit enhanced reactivity towards all substrates. Consistent results were found with ClO^- and peroxy anions,^{11c} therefore, the present work confirms the expected increase in nucleophilicity for disulphide ions. Some confirmation of this α -effect can also be sought by the fact that RS_2^- ions are more easily oxidized into R_2S_2 than RS^- species.⁵

Organic disulphides have been the object of considerable work, primarily because of the biological importance of the S-S bond. Stable ArS_2^- ions are easily generated from sulphur and thiolate ions in solvents such as DMA. The present study confirms that these species can be used to introduce the disulphide bridge into various substrates under mild conditions.

Experimental

Materials and Equipment.—All products used were commercially obtained. The alkyl halides were used as received except for 2-iodopropane, which was distilled over potassium iodide. Bis(nitrophenyl) disulphides were recrystallized from benzene. Solvent purification, equipment and electrodes were as previously reported.¹² The thermostatted flow-through cell for the spectroelectrochemical studies is also described elsewhere,¹² and assembled as with the flow apparatus of Billon *et al.*¹³

Kinetic Studies.—Solutions of ArS^- were directly generated in the cell by electro-reduction at controlled potential on a large gold-grid electrode of diaryl disulphides. The cathodic and anodic compartments were separated by a sintered porous glass. The supporting electrolyte was tetraethylammonium per-

chlorate at 0.1 mol dm^{-3} . Electrolysis was performed on Ar_2S_2 solutions (35 cm^3) in order to obtain ArS^- concentrations less than $2.5 \times 10^{-3} \text{ mol dm}^{-3}$. Their progress was followed by conventional voltammetry with a rotating gold disk electrode. The composition of initial anionic solutions was precisely determined by using the known spectrophotometric and electrochemical characteristics^{5b} of Ar_2S_2 , ArS^- , and ArS_2^- when working in the presence of sulphur. $\text{ArS}^-/\text{ArS}_2^-$ solutions were obtained by adding defined quantities of a sulphur solution at $9.0 \times 10^{-3} \text{ mol dm}^{-3}$. A small volume of a concentrated solution of alkyl halide in DMA ($v_{\text{max}} = 1 \text{ cm}^3$) was then added in default in comparison to the anionic reagents. The disappearance of ArS^- or ArS_2^- was followed at $20 \pm 0.5^\circ\text{C}$ at λ_{max} . When equilibrium was reached, RX was added once or twice again. The entire length of complete homogenization of the initial reaction solution when transferred to the spectrophotometric cell (1 mm pathlength) was about 8 s. At the level of the concentrations used, the determination of rate constants was consequently limited to values lower than $250 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.

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