Base Catalysed Addition of Phenols to Aryl Vinyl Sulphones

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The addition of some phenols to aryl vinyl sulphones was studied in 1 : 1 (v/v) aqueous ethanol at 25 °C in the presence of a basic catalyst. The reaction follows second-order kinetics, being first order in the sulphone and first order in the phenolate ion, the only active nucleophile. The Hammett and Brønsted equations were used to correlate the effects of substituents in the aromatic ring of the substrate and of the nucleophile. These both indicate that while there is a large accumulation of negative charge on the carbon α to the sulphonyl group in the transition state, the degree of formation of the C–O bond depends on the substituent in the ring of the sulphone. The reactivity of the phenolates, despite their greater basicity, is lower by a factor of some 4×10^4 than that of the arenethiolates studied previously. The following order of reactivity has been established: PhO⁻ < OH⁻ < EtO⁻ ≪ PhS⁻; this indicates that polarizability and/or solvation are more important than Brønsted basicity in determining the reactivity in the addition of anionic nucleophiles to aryl vinyl sulphones.

THE mechanism of the reaction of acidic nucleophiles with electrophilic olefins is thought [1] to consist of a slow addition of the conjugate base of the nucleophile followed by rapid protonation of the intermediate carbanion. This mechanism was originally proposed [1] primarily on the basis of Jones' work [2] involving the addition of hydrocyanic acid to sodium cyanocinnamate.

More recent kinetic studies have confirmed this proposed mechanism for the addition of amino-thiols,[3] alcohols,[4] and benzenesulphinic acids [5] to acrylonitrile, of alcohols [6] to vinyl sulphones and vinylsulphonamides, and of thiophenols [7] to vinyl sulphones. There is also evidence of a linear correlation between the nucleophilicity (log k) of the various anions and their basicity

(pK_a), which has been found to hold 'within single classes of nucleophiles' for various sulphur anions [5] and for some alkoxides [4] and thiophenoxides.[7] Nevertheless, depending on the substrate, when various classes of nucleophiles are considered, the nucleophilic reactivity [8] is often determined by factors other than basicity, in particular by polarizability and/or solvation.[9]

In the present work we chose phenolate ions as nucleophiles, with the aim of comparing the behaviour of phenols with that of the thiophenols studied previously.[7] The basicity criterion should clearly favour the reactivity of the phenolate ions (which have a pK_a ca. 3 units higher), while the factors of polarizability and solvation should favour the thiophenolates.

[1] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, Ithaca and London, 1969, 2nd. edn., p. 1015.
[2] W. J. Jones, *J. Chem. Soc.*, 1914, 1547.
[3] M. Friedman, J. F. Cavins, and J. S. Wall, *J. Amer. Chem. Soc.*, 1965, **87**, 3672.
[4] B. A. Feit and A. Zilkha, *J. Org. Chem.*, 1963, **28**, 406.
[5] Y. Ogata, Y. Sawaki, and M. Isono, *Tetrahedron*, 1970, **26**, 3045.

[6] W. G. Davies, E. W. Hardisty, T. P. Nevell, and R. H. Peters, *J. Chem. Soc.* (B), 1970, 998.
[7] (a) P. De Maria and A. Fini, *J. Chem. Soc.* (B), 1971, 2335; (b) P. De Maria and M. Falzone, *Chimica e Industria*, 1972, **54**, 791.
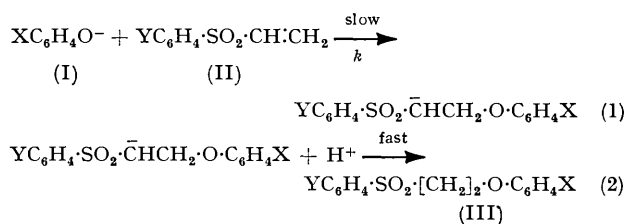[8] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 16.
[9] E. P. Grimsrud and J. W. Taylor, *J. Amer. Chem. Soc.*, 1970, **92**, 739.

RESULTS AND DISCUSSION

It is known [10] that phenol in pyridine adds to phenyl vinyl sulphone to give the corresponding phenyl β-phenylsulphonylethyl ether. We have found that the same reaction takes place between variously substituted aryl vinyl sulphones and phenols, in 1 : 1 (v/v) aqueous ethanol, in the presence of sodium hydroxide as the catalyst. The phenol, catalyst, and substrate concentrations can be adjusted in such a way as to make negligible the addition of ethoxide [6] and hydroxide ions,[11] which could act as competitive nucleophiles (see Experimental section).

In accordance with the generally accepted mechanism,[1] the reaction can be represented by the Scheme. It is known [12] that the reverse reaction, i.e. β-elimination of phenol with the formation of a vinyl sulphone, occurs with ethanolic sodium ethoxide. We have established

$$XC_6H_4O^- + YC_6H_4 \cdot SO_2 \cdot CH{:}CH_2 \xrightarrow[k]{\text{slow}}$$
$$\text{(I)} \qquad\qquad \text{(II)}$$

$$YC_6H_4 \cdot SO_2 \cdot \bar{C}HCH_2 \cdot O \cdot C_6H_4X \quad (1)$$

$$YC_6H_4 \cdot SO_2 \cdot \bar{C}HCH_2 \cdot O \cdot C_6H_4X + H^+ \xrightarrow{\text{fast}}$$
$$YC_6H_4 \cdot SO_2 \cdot [CH_2]_2 \cdot O \cdot C_6H_4X \quad (2)$$
$$\text{(III)}$$

SCHEME

that under our experimental conditions reaction (2) proceeds to completion, since the resulting ether is a

much weaker acid than either the phenol or the solvent. The kinetic experiments were conducted at 25 °C at constant ionic strength $I = 0.26$ (NaClO$_4$). To prevent hydrolysis of the phenolate, a suitable excess of the corresponding phenol was always maintained. In this way, since equilibrium (3) is clearly displaced to the

$$XC_6H_4OH + OH^- \rightleftharpoons XC_6H_4O^- + H_2O \quad (3)$$
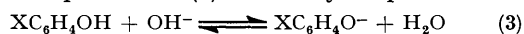
right, the reaction should, in agreement with the Scheme, be first order in the phenolate (or catalyst) and in the vinyl sulphone.

To check this point we conducted kinetic experiments with p-chlorophenyl vinyl sulphone, which is a convenient substrate from the standpoint of its rate of reaction. The molar concentration of the phenolate was varied over a factor of 10, that of the substrate over a factor of 8, and that of phenol over a factor of ca. 4. Some of the experiments were conducted with one

phenolate concentration but with various buffer ratios [PhO⁻] : [PhOH]. The results are given in Table 1. Since the phenolate was always in a large excess over the substrate, the second-order rate constants were calculated by dividing the pseudo-first-order rate constants by the initial phenolate concentration (which did not differ from the final concentration). It was found that (a) the reaction is effectively second order, i.e. first order in the substrate and first order in the phenolate, (b) the phenolate is the only active nucleophile, without any competition from phenol, ethoxide, and/or hydroxide, and (c) the phenolate is ca. 7×10^4 times less reactive than the toluene-p-thiolate anion.[7]

It has been reported [11] that in water at 25 °C and pH >11, phenyl vinyl sulphone reacts with hydroxide ions to give β-hydroxyethyl phenyl sulphone, with a rate constant $k = 6.2 \times 10^{-3}$ l mol⁻¹ s⁻¹. We treated phenyl vinyl sulphone with various concentrations of sodium hydroxide in 1 : 1 (v/v) aqueous ethanol and found, by g.l.c., that the β-hydroxy-derivative is formed in a proportion of <5% to the principal product, β-ethoxyethyl phenyl sulphone. The reaction is second order, i.e. first order in the substrate and first order in the hydroxide, with an experimental rate constant $k_{obs} = 5.30 \times 10^{-2}$ l mol⁻¹ s⁻¹. The results are given in Table 2. Taking in account the relative acidity [13] of water and ethanol, we obtain a rate constant for the ethoxide addition $k_{EtO^-} = 12.0 \times 10^{-2}$ l mol⁻¹ s⁻¹. The higher

value reported [6] ($k_{EtO^-} = 48.9 \times 10^{-2}$ l mol⁻¹ s⁻¹) for this reaction can be explained by the fact that, according to

the simple Laidler–Eyring treatment, reactions between ions and neutral molecules are expected to be faster in a medium having a lower dielectric constant.[14]

TABLE 1

Reaction between p-chlorophenyl vinyl sulphone (II; Y = p-Cl) and phenol in 1 : 1 (v/v) aqueous ethanol at 25 °C

[C$_6$H$_5$OH]/M	[C$_6$H$_5$O⁻]/M	10^3[II; Y = p-Cl]/M	$10^5 k_{obs}$/s⁻¹	$10^4 k$/l mol⁻¹ s⁻¹
0·503	0·026	1·8	2·45	9·40
0·517	0·052	3·6	4·85	9·33
0·519	0·104	3·6	9·50	9·13
0·509	0·260	3·6	24·7	9·50
0·260	0·104	1·8	10·0	9·67
1·034	0·104	1·8	9·87	9·48
0·612	0·208	0·9	19·2	9·23
0·962	0·260	7·2	24·3	9·37

TABLE 2

Apparent rate constants for the addition of ethanol to phenyl vinyl sulphone (II; Y = H) in 1 : 1 (v/v) aqueous ethanol at 25 °C

10^3[NaOH]$_{stoich}$/M	10^3[II; Y = H]/M	$10^5 k$/s⁻¹	$10^2 k$/l mol⁻¹ s⁻¹
0·4	4·37	2·33	5·85
1·0	3·11	5·50	5·50
1·7	2·97	9·25	5·45
3·0	3·11	14·2	4·72
4·0	3·11	20·5	5·12
5·0	3·11	26·0	5·20

[10] T. Nambara, J. Pharm. Soc. Japan, 1954, 74, 17.
[11] I. Sestakova, P. Zuman, and W. Horak, Coll. Czech. Chem. Comm., 1966, 31, 827.
[12] J. Crosby and C. J. M. Stirling, J. Chem. Soc. (B), 1970, 671.
[13] J. Hine and M. Hine, J. Amer. Chem. Soc., 1952, 74, 5266.
[14] (a) A. A. Frost and R. G. Pearson, ' Kinetics and Mechanism,' Wiley, New York, 1963, p. 147; (b) E. S. Amis, ' Solvent Effects on Reaction Rates and Mechanisms', Academic Press, New York, 1966.

To investigate the effect of substituents on the reaction rate we used a series of phenols and aryl vinyl sulphones carrying various substituents in the aromatic ring. Table 3 shows the results for the addition of phenol

TABLE 3

Second order constants for the addition of phenol and p-methoxyphenol to aryl vinyl sulphones (II) at 25 °C

		$10^4 k/l\ mol^{-1}\ s^{-1}$	
Y	σ	(I; X = H)	(I; X = p-MeO)
p-MeO	−0·268	1·53	
p-Me	−0·170	2·72	6·00
H	0·000	3·17	7·33
m-MeO	0·115	3·38	
p-Cl	0·227	9·39	13·6
m-Cl	0·373	19·2	39·3
p-NO₂	0·778	310	602

(I; X = H) and p-methoxyphenol (I; X = p-MeO) to aryl vinyl sulphones. Each value of k is the mean of at least two values obtained in experiments reproducible to better than 7% and conducted with different phenolate concentrations. The buffer ratio $[XC_6H_4O^-]:[XC_6H_4OH]$ was frequently varied. Table 3 also gives the data necessary for the application of the Hammett equation,[15] the normal values of σ being taken.

The correlation is only fair for this particular case and the following values are obtained for the slope by the method of least squares: ρ (I; X = H) = +2·13 (r 0·980) and ρ (I; X = p-MeO) = +2·18 (r 0·966).

Table 4 gives the results for the addition of various para-substituted phenols to phenyl vinyl sulphone (II;

TABLE 4

Second order constants for the addition of phenols (I) to phenyl vinyl sulphone and to p-nitrophenyl vinyl sulphone at 25 °C

	Apparent		$10^4 k/l\ mol^{-1}\ s^{-1}$	
X	$pK_a{}^a$	σ⁻	(II; Y = H)	(II; Y = p-NO₂)
p-MeO	11·50	−0·268	7·33	602
p-Me	11·60	−0·170	4·85	362
H	11·16	0·000	3·17	310
p-Cl	10·60	0·227	0·903	
p-Br	10·57	0·232	0·887	148
p-COMe	9·06	0·874		53·5
p-NO₂	7·89	1·270		26·3

a From ref. 17.

Y = H) and to p-nitrophenyl vinyl sulphone (II; Y = p-NO₂). In this case also each value of k is the mean of results obtained in kinetic experiments conducted at various concentrations and buffer ratios. The substituent constants used are the σ⁻ values proposed by Jaffé[16] for the reactions of phenols and anilines. The values of the apparent pK_a in 1 : 1 (v/v) aqueous ethanol at 25 °C have been taken from the literature.[17]

In this case the Hammett equation is obeyed quite

15 L. P. Hammett, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1940.
16 H. H. Jaffé, Chem. Rev., 1953, 53, 191.
17 (a) L. A. Cohen and W. M. Jones, J. Amer. Chem. Soc., 1963, 85, 3397; (b) G. Schwarzenbach and E. Rudin, Helv. Chim. Acta, 1939, 22, 360.
18 R. P. Bell, 'The Proton in Chemistry,' Methuen, London, 1959, p. 155.

satisfactorily with ρ (II; Y = H) = −1·83 (r 0·991) and ρ (II; Y = p-NO₂) = −0·845 (r 0·992). Table 4 also gives data necessary for the application of the Brønsted equation,[18] and the graphs of log k vs. apparent pK_a have the following slopes: β (II; Y = H) = 0·84 (r 0·974) and β (II; Y = p-NO₂) = 0·34 (r 0·980). It is interesting to note that p-methoxy- and p-methyl-phenol exhibited the same inversion of the nucleophilicity values with respect to the basicities (pK_a) as has been observed in the case of thiophenols.[7]

This demonstrates once more the inadequacy[19] of Brønsted basicity as a thermodynamic parameter to be correlated with nucleophilicity. From our results it is evident that the reaction is favoured when the substituent Y is electron attracting and the substituent X electron repelling, and it is more sensitive to variations in Y than in X. There appears to be a strong accumulation of negative charge on the carbon adjacent to the sulphonyl group in the transition state. The value of ρ is positive, independent of the type of phenol, and very large especially in view of the attenuation of the electronic effects of Y due to the introduction of the sulphonyl group between the aromatic nucleus and the reaction centre.

An analogous conclusion was reached[7] for the addition of toluene-p-thiol (ρ = +2·03), the difference between the three values being of the order of the uncertainty in ρ.[7] As regards the variation of the substituent in the aryl group of the nucleophile, the values of ρ and also of β appear to be a function of the substituent Y. Both ρ[20] and β[21] have been interpreted as a measure of the degree of bond formation in the transition state. In the present case the formation of the C–O bond in the transition state is more pronounced for the less reactive substrate (II; Y = H). In other words, there is a 'selectivity–reactivity' relationship[22] in agreement with which the transition state of the less reactive and more selective vinyl sulphone (II; Y = H) is more product-like than the transition state of the less selective vinyl sulphone (II; Y = p-NO₂). The arenethiolate ions[7] are ca. 10⁴ times

TABLE 5

Reactivities of some anionic nucleophiles with phenyl vinyl sulphone at 25 °C

Nucleophile	Solvent	$k/l\ mol^{-1}\ s^{-1}$	Relative nucleophilicity
PhO⁻	Aqueous ethanol	3·17 × 10⁻⁴	1
OH⁻ *a*	Water	6·20 × 10⁻³	20
EtO⁻	Aqueous ethanol	1·20 × 10⁻¹	378
PhS⁻ *b*	Aqueous ethanol	1·20 × 10	37,800

a From ref. 11.   *b* From ref. 7.

more reactive than the corresponding phenolates. The relative nucleophilic strengths of the anionic nucleophiles considered in this work are listed in Table 5.

19 J. Hine and R. D. Weimar, jun., J. Amer. Chem. Soc., 1965, 87, 3387.
20 C. G. Swain and W. P. Langsdorf, J. Amer. Chem. Soc., 1951, 73, 2813.
21 J. F. Bunnett, Ann. Rev. Phys. Chem., 1963, 14, 271.
22 J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York and London, 1963, p. 162.

While it has been demonstrated [4,5,7a] that basicity is an important factor determining the reactivity of a nucleophile in addition to electrophilic olefins, the present results are in agreement with the general observation [23] that such parallelism is restricted to classes of similar nucleophiles having a common attacking atom. In particular, the well known [24,25] enhanced nucleophilicity of arenethiolates is attributed to the high polarizability and the poor solvation of this ion. Edwards and Pearson [8] have demonstrated that the importance of such factors as basicity and polarizability, when determining the reactivity of a nucleophilic agent, is very dependent on the class of substrate.

Our results indicate that polarizability and/or solvation of the nucleophile are of primary importance in addition reactions, at least in additions to aryl vinyl sulphones. All these observations confirm the formal analogy that has already been indicated [3] between nucleophilic addition and substitution at a saturated carbon atom.

EXPERIMENTAL

Solvents and reagents were pure or purified as described previously.[7] The aryl vinyl sulphones were prepared by known methods.[25-27]

Commercial phenols were carefully purified to constant m.p.s.

phenyl sulphone, phenol, and β-ethoxyethyl phenyl sulphone (comparison of retention times with those of authentic samples). Quantitative analysis was carried out after a linear correspondence had been established between the peak area and the product concentration, giving the product ratio 5 : 41 : 54, respectively. Therefore, under these conditions, 88% of the phenyl vinyl sulphone reacted with the phenoxide, 11% with ethoxide, and 1% with hydroxide.

In the kinetic measurements the conditions were varied so as to suppress the side reactions. The buffer ratio [PhO⁻] : [PhOH] of 1 used above represents an upper limit; in the kinetic measurements it was always <1. Under these conditions the side reactions were suppressed.

Ring-substituted ethers were prepared by the procedure described above. Sufficient NaOH was added to give a suitable phenol–phenolate buffer. The ethers were filtered off, recrystallized, and purified (Table 6). Some of them were identified by comparison with authentic samples.[28]

Kinetic Measurements.—Suitable quantities of phenol, NaOH, and NaClO₄ (when necessary) in 1 : 1 (v/v) aqueous ethanol were placed in a thermostat at 25 °C and the reaction was initiated by the addition of aryl vinyl sulphone (previously thermostatted at the same temperature). Portions (5 ml) of the reaction mixture were taken at intervals and made to react with a suitable excess of n-dodecanethiolate.[29] After 5 min the mixture was acidified with 1M-sulphuric acid and diluted to 50 ml. The excess of the

TABLE 6

Analyses

Ether (III)		C (%)		H (%)		N (%)		
Y	X	Calc.	Found	Calc.	Found	Calc.	Found	M.p. (°C)
H	p-Br	49·3	49·8	3·84	3·90			84—85
p-Me	p-MeO	62·5	62·8	5·90	5·61			83—84
m-MeO	H	61·6	61·3	5·51	5·21			126—127
p-Cl	p-MeO	55·1	55·3	4·62	4·60			77—78
m-Cl	p-MeO	55·1	55·2	4·62	4·60			66—68
m-Cl	H	56·7	56·8	4·41	4·08			59—60
p-NO₂	p-MeO	53·4	53·5	4·48	4·32	4·15	4·26	162—164
p-NO₂	p-Me	56·1	55·9	4·70	4·41	4·35	4·33	170—172
p-NO₂	p-Br	43·5	43·5	3·13	3·02	3·62	3·55	210—211
p-NO₂	p-COMe	55·0	54·8	4·32	4·41	4·00	4·19	136—138
p-NO₂	p-NO₂	47·7	47·7	3·43	3·43	7·95	7·90	198—199

G.l.c. was carried out on a Carlo Erba Fractovap G.V. with a 2·5 m column packed with SE 52 (5%) on Chromosorb W 60—80 at 200 °C; the carrier gas was nitrogen.

Microanalyses were carried out with an F.M. 185 CHN Analyser.

Addition Products.—Phenyl vinyl sulphone (2·5 × 10⁻³ mol) reacted at 25 °C with phenol (5 × 10⁻³ mol) in 1 : 1 (v/v) aqueous ethanol (10 ml) with NaOH (2·5 × 10⁻³ mol) as catalyst. Phenyl β-phenylsulphonylethyl ether (0·570 g) slowly precipitated and was filtered off and characterized both qualitatively and quantitatively.

Extraction of the filtrate with diethyl ether gave an oil (0·130 g), which was subjected to g.l.c. Three peaks were obtained, corresponding respectively to β-hydroxyethyl

thiol was titrated iodometrically with starch as indicator. Kinetic measurements were carried out under nitrogen to avoid oxidation and absorption of carbon dioxide by the reaction mixture. The reactants, products, and solvents do not interfere during the titration. When calculating concentrations, the 4% volume contraction occurring when equal volumes of water and ethanol are mixed [30] was taken into account at all times.

[23] T. C. Bruice and S. J. Benkovic, ' Bioorganic Mechanisms,' Benjamin, New York, 1966, vol. I, p. 30.
[24] A. Streitwieser, *Chem. Rev.*, 1956, **56**, 571.
[25] S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc. (B)*, 1967, 348.
[26] L. I. Smith and H. R. Davis, *J. Org. Chem.*, 1950, **15**, 824.

[27] J. Heyna and W. Reimenschneider, Ger.P. 932,488.
[28] J. Crosby and C. J. M. Stirling, *J. Chem. Soc. (B)*, 1970, 679.
[29] D. W. Beesing, W. P. Tyler, D. M. Kurz, and S. A. Harrison, *Analyt. Chem.*, 1949, **21**, 1073.
[30] ' Handbook of Chemistry and Physics,' 49th edn., 1968—1969, D-151, F-3.