

## A Single Transition State in Nucleophilic Aromatic Substitution: Reaction of Phenolate Ions with 2-(4-Nitrophenoxy)-4,6-dimethoxy-1,3,5-triazine in Aqueous Solution

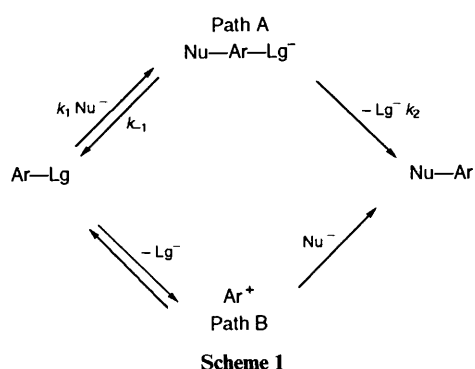
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The absence of curvature in the Brønsted dependence for displacement of 4-nitrophenolate ion from the title ether by phenolate ion nucleophiles with  $pK_s$  well below and above that of the leaving group is consistent with a single step mechanism.

The nucleophilic aromatic substitution reaction constitutes one of the major subjects of mechanistic organic chemistry.<sup>1-8</sup> Both heterolytic and homolytic pathways have been demonstrated for these reactions which embrace benzenoid<sup>1</sup> and hetero-aromatic substitution processes.<sup>4</sup> Nucleophilic aromatic substitution reactions are known to exist which possess heterolytic mechanisms with the two extremes of timing sequence for bond formation and fission as shown in Scheme 1;<sup>1-8</sup> this prompts



the suggestion that conditions might be changed (by suitable manipulation of the structures of solvent, nucleophile, leaving group and aromatic nucleus) to favour a mechanism where the bonding changes are concerted † with each other.

Phenolate ions react in aqueous solution with 2-(4-nitro-phenoxy)-4,6-dimethoxy-1,3,5-triazine ‡ displacing 4-nitrophenolate ion to give product. The second order rate constants for the displacement obey a good linear Brønsted relationship [eqn. (1)] over a range of  $pK_{A,OH}$  values well above and below

$$\log k_{A,RO} = 0.904 \pm 0.039pK_{A,ROH} - 10.65 \pm 0.31 \quad (r = 0.9895) \quad (1)$$

that of the conjugate acid of the leaving 4-nitrophenolate ion (see Fig. 1 for conditions).§ The absence of curvature in the free energy relationship (with no 'break' at the value of  $pK_{A,ROH}$  for the nucleophile equal to that of the leaving group) is good

evidence that there is no change in rate limiting step. The stepwise process (path A) is predicted to involve a change in rate limiting step at  $\Delta pK = 0$  (see later) where forward ( $k_2$ ) and reverse ( $k_{-1}$ ) rate constants would be identical. The linearity of the plot indicates the existence of a single transition state for the substitution reaction which is consistent with a concerted process or at least with a mechanism in the borderline between stepwise and concerted.

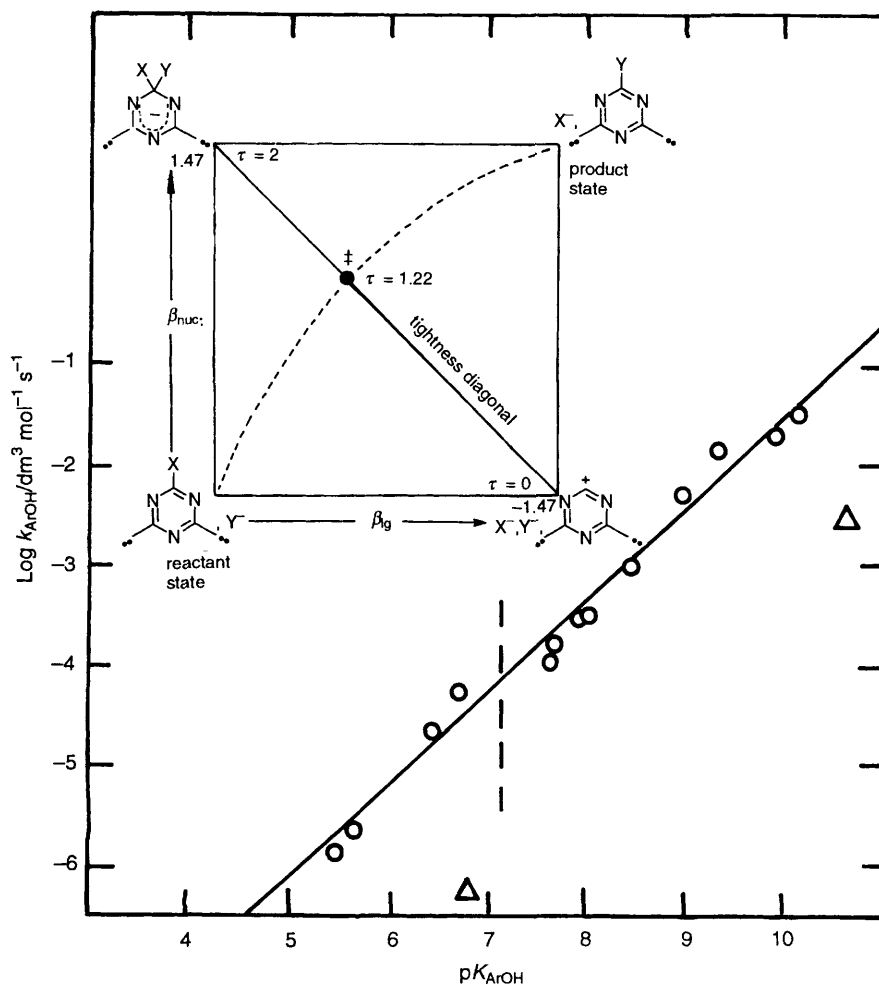
Kinetics were also measured under the same conditions for the reaction of phenolate ions with phenoxytriazines bearing substituents on the phenoxy anion leaving group. Values of  $\beta_{lg}$  were obtained for attack of phenolate ( $\beta_{lg} = -0.36 \pm 0.02$ ), 3-chlorophenolate ( $\beta_{lg} = -0.46 \pm 0.05$ ) and 4-formylphenolate ion ( $\beta_{lg} = -0.53 \pm 0.10$ ). The variation in  $\beta_{lg}$  with  $pK_{nuc}$  ( $p_{xy} = 0.068 \pm 0.017$ ) is good evidence for coupling between bond forming and bond fission consistent with a single transition state.<sup>12</sup> The dependence of  $\beta_{lg}$  on  $pK_{nuc}$  can be utilised to estimate the value of  $\beta_{lg}$  for the displacement reaction when the nucleophile is 4-nitrophenolate ion (for which kinetics are difficult to measure). The  $pK$  of the 4-formylphenol is sufficiently close to that of the 4-nitrophenol for us to be confident in the extrapolated value of  $\beta_{lg}$  ( $-0.57$ ) for the latter nucleophile. A value for  $\beta_{eq}$ <sup>13-15</sup> for the equilibrium constant for transfer of the triazine from 4-nitrophenolate ion to substituted phenolate ions is calculated to be  $\beta_{eq} = \beta_{nuc} - \beta_{lg} = 1.47$ .

Path A predicts a rate constant dependent on the  $pK$  of the attacking phenol obeying the following equation:<sup>16</sup>  $k_{A,RO} = k_o \times 10^{\beta_1 \times \Delta pK} / (1 + 10^{-\Delta \beta \times \Delta pK})$  where  $\Delta pK = pK_{nuc} - pK_{lg}$ ;  $\Delta \beta = \beta_2 - \beta_1$ ;  $\beta_s$  refer to the exponents for Brønsted-type equations for the individual rate constants in pathway A. The absence of detectable curvature in the plot (Fig. 1) indicates that  $\Delta \beta$  is close to zero (when the equation simplifies to a regular

† A concerted mechanism is defined as a reaction pathway with only a single transition state between reactants and products. A synchronous mechanism is a special case of a concerted mechanism where bond fission and formation have progressed to the same extent in the transition state.<sup>9,10</sup>

‡ Prepared from 4-chloro-2,4-dimethoxy-1,3,5-triazine and 4-nitrophenol by the method of Harayama;<sup>11</sup> this material and the ethers obtained from the reaction of other phenols with the chlorotriazine had excellent analytical and spectroscopic data confirming purity and identity.

§ Kinetics of the reactions were measured spectroscopically by use of the 4-nitrophenolate ion chromophore at 400 nm. Product analysis by UV-VIS spectroscopic and HPLC techniques indicate that the reactions go cleanly to the transfer products and that they do not involve any by-products; the ANRORC<sup>1-8</sup> mechanism does not occur in the series under investigation. The enhanced rate constants for nucleophilic substitution induced by the heteroatoms do not suffer from problems (incursion of intramolecular reactions or loss of nitrite ion) inherent with aromatic species activated by nitro groups.<sup>1</sup> Dealkylation of the methyl groups by phenoxide ions instead of displacement of the aryloxyanion is not significant in the reaction in hand although some dealkylation is involved in the reaction with hydroxide ion. The data points have negligible contribution from general base catalysed hydrolysis by phenolate ions as confirmed by the depressed values of  $k_{A,ROH}$  for 2,6-dimethyl- and 2,6-dichloro-phenolate ions (see Fig. 1) and by product analysis. Moreover, the hydroxide ion catalysed hydrolysis rate constant ( $2.75 \times 10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ , corrected for the dealkylation reaction) is over three orders of magnitude below that calculated from the Brønsted eqn. (1).



**Fig. 1** Brønsted dependence for the attack of substituted phenolate ions on 2-(4-nitrophenoxy)-4,6-dimethoxy-1,3,5-triazine at 25 °C (10% v/v dioxane–water). The line is calculated from eqn. (1); identity of the phenolate ions (O) in increasing order of  $pK_{ArOH}$ : pentafluoro; 2,3,4,5-Cl<sub>4</sub>; 2,3,5-Cl<sub>3</sub>; 2,4,5-Cl<sub>3</sub>; 4-CHO; 2,3-Cl<sub>2</sub>; 4-CN; 4-Ac; 2-Cl; 3-Cl; 4-Cl; parent; 4-Me. (Δ), values for the 2,6-dichloro- and 2,6-dimethyl-phenolate ions (increasing order of  $pK_{ArOH}$ ). The dashed vertical line is at  $\Delta pK = 0$ . Inset is the reaction map of the reaction involving displacement of phenolate ion ( $X^-$ ) by nucleophilic phenolate ion ( $Y^-$ ). The transition state is displayed for the identity reaction where 4-nitrophenolate ion displaces 4-nitrophenolate ion. The value  $\tau$  measures coupling between bond formation and bond fission and in this case indicates an almost synchronous process.<sup>22,23</sup>

linear Brønsted law) and we conservatively estimate  $\Delta\beta < 0.1$  on the present data. The value of  $\Delta\beta$  measures the effective charge difference between the transition states in the putative two step process which in the present case would be 0.1 in a total change of 1.47 units (some 6.8% of the total change). It is difficult to account for the stability of an intermediate where the change in effective charge on attacking oxygen from intermediate to one of the transition states (forward or reverse from the intermediate) must be less than 6.8/2% (3.4%) of the total change in effective charge in the substitution reaction.<sup>17–21</sup>

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