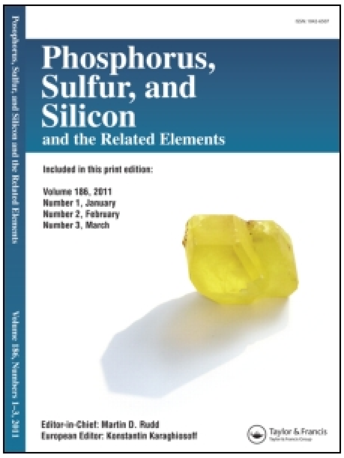

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REACTION OF *p*-NITROPHENYL *p*-TOLUENESULFONATE WITH NUCLEOPHILIC REAGENTS IN AQUEOUS ETHANOL[1]

by

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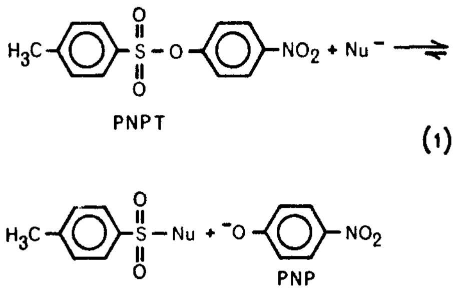
ABSTRACT

The rate of nucleophilic reaction of anions and amines with *p*-nitrophenyltosylate has been determined in a 41% w/w ethanol–water mixture at 25°. For weakly basic amines, the reaction is general base and general acid catalyzed. Aldoximates and thiophenolate show an enhanced nucleophilicity compared to phenolates of same basicity. The results are interpreted in terms of charge and frontier controlled reactions.

For a few years, we have been interested in the study of electrophilic reactivity of sulfonyl sulfur, particularly owing to its biochemical interest as a blocking agent of nucleophiles in aqueous medium.[2] In addition, this reactivity towards a given set of nucleophiles can help to a better understanding of the factors which influence the reactivity of tetracoordinated sulfur VI.

The reactivity of sulfonyl sulfur has been well investigated in the case of aryl α disulfones[3] and sulfonyl halides[4] but only a few kinetic data are available concerning the reactivity of sulfonic esters: Alkaline hydrolysis,[5] action of substituted pyridines,[6] nucleophilic catalysis of the solvolysis by tertiary amines,[7] competition between attack on sulfur and aromatic nucleophilic substitution,[8] data which can hardly be compared due to the very different experimental conditions. In this paper, we report a study on the relative reactivity of phenolates, thiophenolate, aldoximates and amines towards *p*-nitrophenyl *p*-toluene sulfonate (PNPT) under the same conditions of solvent (ethanol-water mixture 41% w/w), temperature (25°C) and ionic strength (0.16).

Nucleophilic attack on sulfur has only been observed according to eq. (1).



(1)

We have followed the course of the reaction by monitoring the increase in the absorbance of the solution, due to the release of *p*-nitrophenolate anion (PNP) at 410 nm, under the conditions of pseudo-first-order kinetics, the nucleophile being in large excess. The expression of the rate is:

$$v = d\,\frac{[\mathrm{PNP}]}{dt} = -\frac{d[\mathrm{PNPT}]}{dt} = k_{\mathrm{obs}}[\mathrm{PNPT}]$$

The very small occurrence or complete absence of aromatic nucleophilic substitution has been checked by the fact that the final concentration of PNP which can be released only by nucleophilic attack on sulfur§ is equal to the initial concentration of PNPT.

Phenolates and Thiophenolate Reactivity

The observed rate constants measured at various pH's are proportional to the concentration of the anion of the nucleophile, so the rate constant for nucleophilic attack on sulfur is:

[†] *This paper is part of "Thèse de Doctorat-ès-Sciences" to be submitted by P. Monjoint (CNRS number A0 9978).*

[‡] *Equipe de recherche associé au CNRS, n° 318.*

§ *The possiblity of PNP anion arising by S_NAr reaction of PNPT with water or OH^- anion is ruled out by the fact that in most of our experiments hydrolysis is very small compared to attack by Nu^-.*

$$k_n = \frac{k_{obs}}{[ArX^-]} \quad (X = O, S)$$

Results are summarized in Table I and Figure I.

TABLE I

Reaction of Nucleophiles with PNPT at 25° in 41% w/w Ethanol-Water. $\mu = 0.16$

Nucleophiles	pK_a*	$10^4 k_n$ (M^{-1} s^{-1})
$C_6H_5S^-$	7.94	3.9
p-Cl–$C_6H_4O^-$	9.54	2.0
p-Br–$C_6H_4O^-$	10.46	3.2
$C_6H_5O^-$	11.13	4.0
p-CH_3–$C_6H_4O^-$	11.36	5.1
p-Cl–C_6H_4–$CH{=}NO^-$ (E)	11.70	55
p-CH_3O–C_6H_4–$CH{=}NO^-$ (E)	12.09	62
p-NO_2–C_6H_4–$CH{=}NO^-$ (Z)	11.35	150
p-Cl–C_6H_4–$CH{=}NO^-$ (Z)	12.48	270

* pK_a determined under the conditions described in Experimental Section.

We observe a Brønsted-like correlation for phenolates.

$$\log k_n = 0.2pK_a - 5.7$$

This shows a weak sensitivity of the reactivity to the basicity.

Aldoximates Reactivity

The reaction is also first order in nucleophile. But, aldoximes being weaker acids than phenols, we had to work at higher pH where the solvolysis rate cannot be neglected.

$$k_n = \frac{k_{obs} - k_{solv}}{[Ar{-}CH{=}NO^-]}$$

Results given in Table I and Figure I show that aldoximates are more reactive than phenolates of the same pK_a: this enhancement is due to the lone pair of electrons on the adjacent atom to the reactive center (α-effect).[9] This has already been observed for some oximes[10] and especially for aldoximes reacting with *p*-nitrophenylacetate (PNPA).[11] We also observe, as the latter authors do, a different reactivity for the E and Z isomers. But, if the reaction of E isomer shows the same rate enhancement for PNPT and PNPA, the ratio $k_n(Z)/k_n(E)$ is smaller for PNPT than for PNPA. This fact can possibly be attributed to some steric reasons: the oxygen anion is *cis* to the aryl group in Z isomer and the approach of the substrate could be more difficult in the case of tosyl group than acyl group.

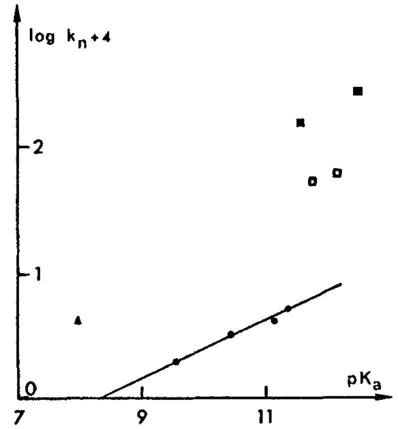


FIGURE I

Plot of the logarithm of second order rate constant in M^{-1} s^{-1} versus pK_a of nucleophile at 25°; $\mu = 0.16$ M; 41% w/w ethanol-water: ●, phenolate; ▲, thiophenolate; □, benzaldoximate E; ■, benzaldoximate Z.

Amines Reactivity

We have followed the course of reaction of PNPT with amines of various structures and in a pK range between 8.48 and 11.06.

In all cases studied, the only products formed are the sulfonamide and PNP. Our results are summarized in Table II.

For the more basic amines (cyclohexylamine, diethylamine, diisopropylamine, piperidine, pyrrolidine), we observe a good second order rate constant (k_n). For less basic amines, there is no proportionality between k_{obs} and amine concentration. The apparent second order rate constant k_{obs}/amine shows a good linearity with amine concentration at each pH studied. This pH dependence represents both general acid and general base catalysis. Thus, the expression of the observed pseudo-first-order rate constant is:

$$k_{obs} = k_n[B] + k_B[B]^2 + k_{BH^+}[B][BH^+]$$

where [B] and [BH$^+$] represent concentrations in free amine and its conjugate acid respectively: k_n, k_B, k_{BH^+} rate constants for nucleophilic attack, general base, and general acid catalyzed nucleophilic attacks.

The treatment of data is given for *n*-butylamine on Figures II, III and IV. Figure III gives k_n as an intercept and as slope $k' = k_{BH^+}[BH^+]/[B] + k_B$; k_{BH^+} and k_B are determined by plotting k' versus $[BH^+]/[B]$ (Figure IV).

The general acid catalysis cannot be attributed to a specific salt effect because we do not observe any significant effect on the rate when the ionic strength was maintained at 0.16 by either potassium chloride or benzyltriethylammonium chloride (Table III).

TABLE II

Rate Constants for the Aminolysis of PNPT. μ = 0.16; T = 25°; 41% w/w Ethanol-Water

Amines	pK_a*	pH*	[B]^a M	$10^6.k_{obs}$ s^{-1}	$10^6.k_n$ $M^{-1}.s^{-1}$	$10^6.k_B$ $M^{-2}.s^{-1}$	$10^6.k_{BH^+}$ $M^{-2}.s^{-1}$	$10^6.k_{calc.}$ s^{-1c}
1 Morpholine	8.48	8.45	0.10	0.63	3.6 ± 0.25	$\leqslant 2^b$	27 ± 1	0.63
			0.16	1.3				1.27
		9.31	0.245	1.1				1.12
		9.40	0.285	1.3				1.3
			0.32	1.5				1.5
2 Ethanolamine	9.58	9.45	0.106	0.37	1.4	$\leqslant 1^b$	13	0.35
			0.136	0.53				0.53
		10.05	0.18	0.39				0.41
			0.24	0.58				0.62
			0.30	0.81				0.88
		10.35	0.24	0.55				0.50
			0.274	0.64				0.60
			0.31	0.78				0.71
3 *n*-Butylamine	10.25	9.76	0.025	0.28	7.7	25 ± 2	35 ± 2	0.27
			0.05	0.67				0.71
		10.26	0.08	1.1				1.0
			0.10	1.5				1.37
			0.16	2.9				2.77
		10.72	0.21	3.3				3.23
			0.24	3.9				3.96
			0.27	4.8				4.75
			0.30	5.7				5.6
4 Cyclohexylamine	10.49	10.50	0.12	0.51	4.7			0.56
			0.16	0.72				0.75
		10.97	0.225	1.1				1.05
			0.30	1.5				1.41
5 Diethylamine	10.67	10.67	0.16	1.8	11			1.72
		11.15	0.24	2.55				2.6
6 Diisopropylamine	10.86	10.86	0.12	2.2	20			2.4
		11.28	0.30	6.3				6.0
		11.36	0.24	4.85				4.8
7 Piperidine	10.92	10.44	0.025	2.9	125			3.12
			0.05	6.1				6.25
		10.92	0.08	11				10
			0.12	13.5				15
			0.16	22				20
		11.30	0.15	19				18.7
			0.225	32.5				28
			0.3	36				37.5
8 Pyrrolidine	11.06	11.09	0.16	8.3	52			8.32
		11.51	0.30	15.5				15.6

* pH and pK_a determined under the conditions described in Experimental Section.

[a] [B] = concentration in free amine.

[b] Less than 5%.

[c] k calculated from k_n, k_B, k_{BH^+}.

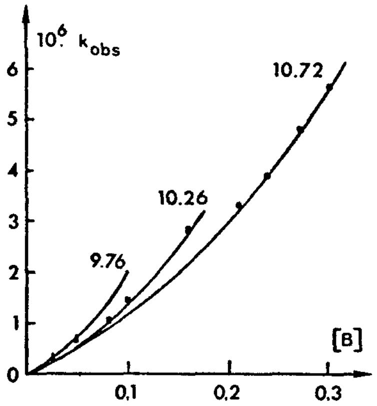


FIGURE II

Plot of the pseudo-first-order rate constant (s^{-1}) versus the concentration of neutral *n*-butylamine [B] in M, 25°, μ = 0.16, at different pH's. The solid lines were calculated from k_n, k_B and k_{BH^+} (Table II).

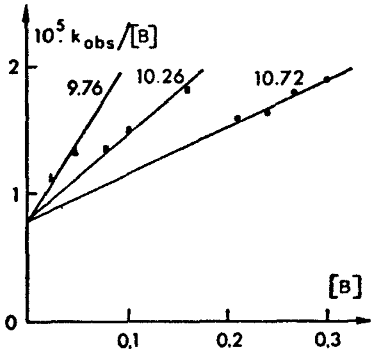


FIGURE III

Linear dependence of the apparent second-order rate constant $k_{obs}/[B]$ on [B] for the reaction of *n*-butylamine at three pH's.

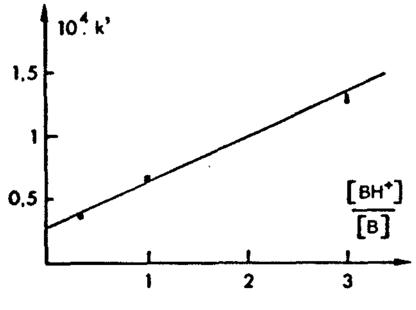


FIGURE IV

Plot of the slopes of Figure III versus $10^{pK_a-pH} = [BH^+]/[B]$ providing k_B as intercept and k_{BH^+} as slope.

Salt effects are often observed in aminolysis[12], especially for general acid catalysis[13] but the salt concentrations generally used are higher than those we used here.

TABLE III

Variation of the Observed Rate Constant with the Nature of the Salt in the Reaction of Butylamine ($[BH^+]$ = 0.05 M, [B] = 0.05 M) with PNPT at 25° and 41% w/w Ethanol-Water. Ionic Strength μ = 0.16

[KCl]	0.11 M	0.055 M	0.03 M	0
$[(\Phi\text{-}CH_2\text{-}\overset{+}{N}Et_3)Cl^-]$	0	0.055 M	0.08 M	0.11 M
$10^6\ k_{obs}\ (s^{-1})$	5.35	5.2	5.6	5.4

The percentage of tosylamide arising through the mechanisms of aminolysis associated with the various rate constants is dependent on the pH as shown in Table IV.

TABLE IV

Ratio of Tosylamide Formed by the Various Reaction Paths of the *n*-Butylamine with PNPT: [B] + $[BH^+]$ = 0.05 M at μ = 0.16 and *T* = 25° in 41% w/w Ethanol-Water

	$k_n[B]$ %	$k_B[B]^2$%	$k_{BH^+}[B]\ [BH^+]$ %
pH = 9.76	54	9	37
pH = 10.72*	81	13	6

* Percentages are calculated from k_n, k_B, k_{BH^+} tabulated in II.

In the case of reaction of amines with phenyl acetate, Bruice[14] notes that any primary and secondary amine can react via all paths according to:

$$k_{obs} = k_n[B] + k_B[B]^2 + k_{BH^+}[B][BH^+] \\ + k_{HO^-}[B][HO^-] + k_{H^+}[B][H^+]$$

In our experimental conditions, the last two terms are not detected. When observed, the ratio k_{BH^+}/k_B is greater for PNPT than the one observed for acyl derivatives.[15] The term k_{BH^+} does not decrease with increasing pK_a of amines; this was already found with δ thiolvalerolactone as a substrate.[16] The nucleophilic rate constants show a greater sensitivity to basicity than phenolates do (Figure V). Morpholine and piperidine are more reactive and cyclohexylamine less reactive than other primary and secondary amines. Aside from dependence on basicity, this appears to show that amine reactivity is dependent on steric interference between the approaching amine nitrogen and the sulfur atom.

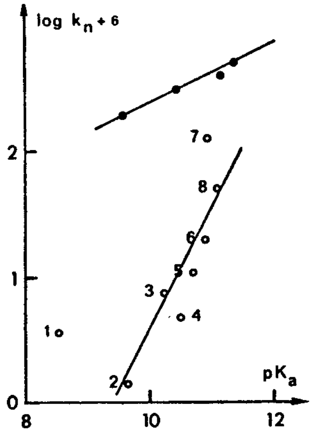


FIGURE V

Plot of the logarithm of second rate constant in M^{-1} s^{-1} versus pK_a of nucleophile at 25°; $\mu = 0.16$; 41% w/w ethanol-water; ● phenolates; ○ amines: 1, morpholine; 2, ethanolamine; 3 *n*-butylamine; 4, cyclohexylamine; 5 diethylamine; 6, diisopropylamine; 7, piperidine; 8, pyrrolidine.

Discussion

Among the theories which try to give an interpretation of chemical reactivity the Klopman-Hudson theory[17] is generally accepted as a good approximation. The simplified equation giving an expression of perturbation energy is:

$$\Delta E_p = -q_r q_s \Gamma_{rs} + \frac{2(C_r{}^m C_s{}^n \beta_{rs})^2}{E_m - E_n} + \Delta E_s$$

The first term represents the coulombian interaction (Γ_{rs}) between charges of nucleophile (q_r) and substrate (q_s) (charge-controlled effect); the second one determines the frontier controlled effect in which $E_m - E_n$ is the energy difference between the HOMO of nucleophile and LUMO of substrate, and β_{rs} is the overlap integral, ΔE_s being a term of solvation.

In the case of sulfonyl sulfur, the presence of both *d* orbitals and an important positive charge on sulfur atom allows frontier and charge effects to occur together, their relative importance depending on the nature of the nucleophile. The sensitivity of the nucleophilicity to basicity, given by Brønsted-like correlations, has been often interpreted as a contribution of charge-controlled effects to the reactivity. This would mean, in the present case, that this contribution is more important for amines than for phenolates. This interpretation seems to be too straightforward: a linear correlation between pK_a's and ionization potentials has been found for a number of substituted pyridines[18] and could indicate that, more generally, pK_a's are not independent on polarizability terms, so a Brønsted-like correlation would not permit charge and frontier controlled effects to be separated.

Two facts in our study appear to show that there is a significant contribution of the frontier term:

a) The enhanced reactivity of thiophenolate, due to the presence of polarizable *d* orbitals both on nucleophile and substrate, allow sulfur-sulfur long-range interactions and a favorable overlap in the transition state which implies a high value of overlap integral.

b) The α-effect with aldoximates, which is usually explained as a repulsive interaction between unshared electron pairs on oxygen and adjacent nitrogen atom, leads to a destabilization of fundamental state so that the term $E_m - E_n$ tends to decrease hence the frontier term to increase.[10d]

Amines are less reactive than phenolates towards the sulfonyl group by contrast with their greater reactivity on carbonyl group[12] and similar reactivity on phosphate triesters.[19] Solvation plays an important role in this type of reaction and could explain the differences between charged and uncharged nucleophiles, but we need more information on it and now we attempt to study thoroughly the role of the solvent in nucleophilic substitution on sulfonyl sulfur.

Experimental Section

Materials

p-Nitrophenyltosylate was prepared according to Reverdin and Cremieux.[20] Aldoximes were prepared by literature procedures: *p*-chlorobenzaldoxime E (mp = 110°);[21] *p*-chlorobenzaldoxime Z (mp = 154°);[22] *p*-nitrobenzaldoxime Z (mp = 176°);[23] *p*-methoxybenzaldoxime E (mp = 65°).[24] Phenols and amines were fractionally distilled or recrystallized before use. Water was freshly glass-distilled and boiled before use; ethanol was distilled over sodium hydroxide pellets. Inorganic salts were R. P. Prolabo or Merck reagents. HCl and NaOH solutions were prepared from titrisols (Merck).

Kinetic Measurements

The appearance of *p*-nitrophenolate anion was followed spectrophotometrically at 410 nm, using a Cary model 15 or a Unicam SP 1805 spectrophotometers equipped with thermostated cell compartments. The temperature was maintained at 25 ± 0.1°. For slowest reactions, aliquots were removed for spectrophotometric determination of the extent of reaction. The ionic strength was brought to 0.16 by appropriate addition of KCl, unless noted otherwise. The pH was maintained constant either by adding calculated amounts of HCl for amines, or by using external buffered solutions (monopotassic phosphate/sodium hydroxide or sodium acid carbonate/sodium hydroxide according to Clark and Lubs[25]) for oximes. The concentration of nucleophile (10^{-3}–10^{-1} M) was always in large excess relative to the concentration of ester (*ca.* $4 \cdot 10^{-5}$ M) so that pseudo-first order kinetics were obtained.

pH Measurements and pK_a Determinations

pK_a of phenols and amines were determined using a Radiometer TTT 1C autotitrator equipped with a PHA 630T scale expander and a ABU 12 Autoburet unit. Reference calomel electrode K 401 and glass electrode G 202 B, stored in a 41% w/w EtOH-H_2O mixture and calibrated on aqueous standard buffers[25] were used. Owing to their high values, pK_a of oximes were determined by a spectrophotometric method. All pH's and pK_a's were measured in the conditions of kinetic measurements (temperature, solvent and ionic strength).

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