

Electronic and Steric Effects in Nucleophilic Aromatic Substitution. Kinetic Studies on the Reactions between Ethers and Thioethers of 2,4-Dinitrophenol and Nucleophiles

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Steric retardation, observed in nucleophilic aromatic substitution, has been attributed in part to interaction between hindered nucleophile and leaving group during the transition state;¹ however, this has been the subject of dispute, since there are circumstances² reported in which no predictable fall in reactivity occurs with increasing size of displaced groups. Moreover, our recent studies³ on halogen displacement by action of ortho-hindered phenoxides on 2,6-dimethyl-4-nitrohalogenobenzenes showed that the expected effect of leaving group size can be obscured by the influence of its electronic effect. In fact, recalculation of experimental data, corrected for contribution of electronic effects, established the expected correlation between size of leaving groups and retardation in reactivity. In the present studies we attempt to evaluate the influence of hindered leaving groups in nucleophilic aromatic substitution. For this purpose we performed kinetic studies on the reactions between 2,4-dinitrodiphenyl ethers with methoxide and thiomethoxide ions and thioethers with methoxide ion at 25°C in methanol. The electronic contribution of displaced groups to reactivity was also investigated.

Results

The second-order rate constants of all reaction series are listed in Table I. When possible, the data were calculated by means of two independent kinetic procedures (see Experimental Section). All reactions of diphenyl ethers with thiomethoxide ion were performed in the presence of high concentrations of free methyl mercaptan. These experimental conditions were necessary, because the acid-base interaction of MeS⁻ with MeOH yields free methoxide which could compete for phenoxy displacement. In spite of higher reactivity of MeS⁻, a considerable amount (~10%) of methoxy substitution was detected in reaction products in the absence of free CH₃SH. Concentrations above 1 × 10⁻¹ M were required to minimize this competitive reaction. No influence on rate by CH₃SH was observed when its free concentration ranged between 1 × 10⁻¹ and 1 M. Very likely, owing to the small difference in pK_a values between ethanethiol and methanol, the addition of relatively small amounts of the former species does not influence proticity of the medium.

Discussion

As expected the reactivity increases when the displaced group becomes more electron withdrawing. There is an excellent correlation between experimental data of meta- and para-substituted leaving groups from each series and σ^0

Table I
Nucleophilic Displacement of Z-C₆H₅-X Groups:
Experimental Rate Constants of Reactions between
Ethers and Thioethers of 2,4-Dinitrophenol
and Nucleophiles (N)

Z	$k_2, \text{sec}^{-1} \text{mol}^{-1} \text{l.}$		
	X = O N = CH ₃ O ⁻	X = S N = CH ₃ S ⁻	X = O N = CH ₃ S ⁻
<i>o</i> -OCH ₃	1.3 × 10 ⁻³	4.6 × 10 ⁻⁵	4 × 10 ⁻¹
<i>p</i> -OCH ₃	3.3 × 10 ⁻³	6.8 × 10 ⁻⁵	6.9 × 10 ⁻¹
<i>p</i> -CH ₃	4.5 × 10 ⁻³	8.7 × 10 ⁻⁵	8.5 × 10 ⁻¹
H	5.0 × 10 ⁻³	1.1 × 10 ⁻⁴	1.1
<i>m</i> -Cl	1.5 × 10 ⁻²	4.0 × 10 ⁻⁴	2.8
<i>m</i> -NO ₂	4.8 × 10 ⁻²	1.5 × 10 ⁻³	7.9
<i>p</i> -NO ₂	7.7 × 10 ⁻²	2.6 × 10 ⁻³	1.1 × 10 ⁻¹
<i>o</i> -NO ₂	1.2 × 10 ⁻²	3.5 × 10 ⁻³	2.9
ρ	1.3	1.6	1.2
<i>s</i>	0.07	0.05	0.04
<i>r</i>	0.999	0.999	0.999

values;⁴ ρ values, standard errors (*s*),⁵ and correlation coefficients (*r*) are listed at the bottom of Table I. The use of σ^0 scale appears to be appropriate, since in this system no direct conjugative transmission from Z substituent to reaction center can be operative, owing to an insulating effect of oxygen or sulfur bridges. This conclusion is strengthened by comparing the present results with those reported by Bunnett⁶ on nucleophilic displacement on the same compounds by action of piperidine or OH⁻; in that case, the "primary" σ values⁷ are used; thus the 4-methoxyphenyl ether does not quite fit the $\rho\sigma$ relationship in contrast with the other compounds. This is a consequence of the fact that the "primary" σ scale was calculated from systems in which conjugative effects are involved for strong electron-releasing groups.⁸ The ρ value for reaction of thioethers with methoxide ion is somewhat higher than that for ethers with the same nucleophile. This difference can be attributed to a more efficient transmission of polar effects by sulfur atom. Our results are in good agreement with those reported by Kajimoto⁹ et al. for very similar systems on ionization equilibrium constants of ring-substituted *cis*- β -phenoxy and thiophenoxy acrylic acids.

In sharp contrast with ideas that the leaving group size cannot be involved in steric effects, the ortho-substituted diphenyl ethers show a high steric retardation. In fact, if compared to the para derivative, the *o*-nitro compound with methoxide ion is sevenfold less reactive, while the *o*-methoxydiphenyl ether shows a smaller effect according to the E_s ¹⁰ value scale.

These steric effects cannot be observed in the corresponding reactions of thioethers, where reactivity is actually larger for ortho as compared to para derivative. These findings can be interpreted on the basis of length differences¹¹ between C-O (1.28 Å) and C-S (1.75 Å) linkages in diphenyl ethers and thioethers, respectively, such that in the latter circumstance the site of hindered group is further away from the reaction center. The higher flexibility of sulfur bridge can also help, minimizing steric compression. Similar conclusions were reached previously when we examined the steric effect of hindered nucleophiles. In those

Table II
 $k_{o\text{-obs}}/k_{o\text{-exd}}^a$ and $k_{o\text{-obs}}/k_{p\text{-exd}}$ Values for Reactions of
 2,4-Dinitrophenyl Ethers with MeO^- and MeS^-

Substituent	MeO^-		MeS^-	
	A	B	A	B
NO_2	0.12	0.16	0.18	0.26
OCH_3	0.58	0.39	0.77	0.58

^a $k_{o\text{-exd}}$ was calculated from ρ and σ^o ortho values.

studies,¹² based upon reactions between halogenbenzothiazoles and thioalkoxy ions, high steric retardation occurred only with α -branched nucleophiles; in contrast, when the bulky group was moved further away in β position, there was an increase of reactivity owing to increasing basicity. In addition, substituting¹³ oxygen for sulfur in these hindered nucleophiles caused a higher steric effect.

Since geometry at the reaction center closely approximates tetrahedral structure and free rotation exists around the linkage between the reaction carbon center and leaving group in the transition state, the distance between the displaced group on one side and both the entering group and the benzenoid substrate ring on the other side must be approximately the same. This mitigates against assigning the observed effects exclusively to steric compression during the transition state either between leaving group and entering group or between leaving group and hydrogen and carbon atoms of the substrate.

Nevertheless, the observed lessening of steric phenomena, when the nucleophile is thiomethoxide ion, strongly suggests that in this case the interaction with benzenoid substrate ring is less important.

Finally, assuming complete lack of steric effects for thioethers, σ^o ortho values of *o*-nitro (+0.93) and *o*-methoxy groups (-0.26) can be calculated.¹⁴

Thus we can estimate the actual steric retardation as expressed by $k_{o\text{-obs}}/k_{o\text{-exd}}$ ratio, where $k_{o\text{-exd}}$ represents the expected rate constant in the absence of steric phenomena and $k_{o\text{-obs}}$ is the experimental one. In Table II these ratio values are compared with $k_{o\text{-obs}}/k_{p\text{-obs}}$ values, which would represent a more immediate, but an approximate valuation of steric effects. $k_{o\text{-obs}}/k_{o\text{-exd}}$ ratios are somewhat higher for the nitro group and somewhat less for the methoxy group. This can be taken as additional evidence that contribution of electronic effect should be accounted for in order to evaluate steric effects with a high degree of accuracy.

Experimental Section

Materials. Methanol (reagent grade) was purified by distillation over magnesium. 2,4-Dinitrophenyl ethers were prepared by refluxing a mixture, prepared from 0.2 mol of the appropriate phenol and 0.1 mol of NaOH in 50 ml of methanol, with 0.1 mol of 2,4-dinitrochlorobenzene in 50 ml of methanol. The mixture was diluted with a large amount of alkaline water and then quickly filtered. The precipitated product was washed and crystallized from ethanol. Thioethers were prepared by the same procedure from 0.1 mol of the appropriate thiophenol and 0.1 mol of 2,4-dinitrochlorobenzene by performing the reaction at room temperature.

Rate Measurements. Reactions of Diphenyl Ethers with MeO^- . For all derivatives kinetic experiments were performed by following the appearance of phenoxide ions. The same titrimetric procedure as described by Ogata¹⁷ was used. When possible, a spectrophotometric procedure was also applied. This was for example the case of *Z'*-nitro substituted compounds. These reactions (performed under pseudo-first-order conditions) were run in the thermostatic cells of a Gilford automatic spectrophotometric apparatus, by following the appearance of the developed nitrophenoxide ion at the appropriate wavelength.

Reactions of Diphenyl Thioethers with MeO^- . Kinetic experiments were performed by following the appearance of thiophenoxide ions by the iodimetric method.¹⁸

In the case of nitro-substituted compounds an additional spectrophotometric procedure, as above described, was also applied.

Reactions of Diphenyl Thioethers with MeS^- . A spectrophotometric procedure was used for all kinetic experiments, by following the appearance of reaction products (2,4-dinitrophenyl methyl thioether) except in the case of nitro derivatives, in which the appearance of nitrophenoxide ions was again followed. For this very fast system the Durrum-Gibson stopped-flow apparatus was used.

In all cases, in which two different kinetic procedures were applied, a good agreement of calculated second-order rate constants was obtained.

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Registry No.—1-(2-Methoxyphenoxy)-2,4-dinitrobenzene, 2363-29-3; 1-(4-methoxyphenoxy)-2,4-dinitrobenzene, 2363-27-1; 2,4-dinitrophenyl *p*-tolyl ether, 2363-25-9; 2,4-dinitrophenyl phenyl ether, 2486-07-9; *m*-chlorophenyl 2,4-dinitrophenyl ether, 2363-38-4; 2,4-dinitrophenyl *m*-nitrophenyl ether, 2548-97-2; 2,4-dinitrophenyl *p*-nitrophenyl ether, 2363-36-2; 2,4-dinitrophenyl *o*-nitrophenyl ether, 2363-39-5; 1-[(2-methoxyphenyl)thio]-2,4-dinitrobenzene, 42178-88-1; 1-[(4-methoxyphenyl)thio]-2,4-dinitrobenzene, 1871-44-9; 2,4-dinitrophenyl *p*-tolyl sulfide, 20114-05-0; 2,4-dinitrophenyl phenyl sulfide, 2486-09-1; *m*-chlorophenyl 2,4-dinitrophenyl sulfide, 56679-05-1; 2,4-dinitrophenyl *m*-nitrophenyl sulfide, 1657-86-9; 2,4-dinitrophenyl *p*-nitrophenyl sulfide, 20834-66-6; 2,4-dinitrophenyl *o*-nitrophenyl sulfide, 20834-65-5; CH_3O^- , 3315-60-4; CH_3S^- , 17302-63-5.

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Nucleophilic Displacements on Halogen Atoms. VI.¹ Determination of σ^- Values for the Carboxyl, Carboethoxy, and Methylsulfonyl Groups.

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Recently, we² have shown that the reaction of triphenylphosphine (TPP) with α -halobenzyl phenyl sulfones in