um hydride was carefully added with stirring and cooling. Excess benzyl chloride (20 g) was added, and the solution was refluxed for 3 hr and then left at room temperature overnight. Excess hydride was destroyed by careful addition of methanol; then water was added and the product was recovered by ether extraction. The crude product (6 g) was purified by chromatography on grade II neutral alumina using petroleum ether (bp 60–70°) and then 10% ethyl ether in petroleum ether to give 3.5 g of pure liquid product: NMR (CCl_4) δ 3.15 (s, 3), 3.35 (s, 3), 4.24 (s, 2), 4.35 (AB, 2), 7.20 (s, 5), 7.25 (s, 5).

2-Benzoxy-2-phenyl-*N,N*-dimethylethenylamine (5). The acetal ether (0.1 g) was dissolved in 9 ml of acetonitrile and 3 ml of 4 *N* HCl, heated to 60–65° for 20 min, then added to 10 ml of cold water and rapidly extracted with chloroform. The colorless oil recovered was about 25% acetal ether **10** and 75% aldehyde ether **11**: NMR (CCl_4) δ 4.55 (s, 2), 4.63 (d, J = 2 Hz, 1), 7.20 (s, 5), 7.25 (s, 5), 9.45 (d, J = 2 Hz, 1). Attempts to more effectively hydrolyze the ketal gave undesirable side products. The crude aldehyde ether was dissolved in 20 ml of benzene and 5 ml of dimethylamine was added. After 15 min at room temperature, the solvent was evaporated under vacuum without heating to give a light yellow oil: NMR (CCl_4) δ 2.7 (s, 6), 4.6 (s, 2), 5.6 (s, 1), 6.9–7.4 (m, 10); methiodide mp 159–160° (chloroform).

Anal. Calcd for $C_{18}H_{22}NOI$: C, 54.69; H, 5.61; N, 3.54. Found: C, 54.87; H, 5.60; N, 3.33.

Conversion of Enol Ether 5 to Rearrangement Product 4. Freshly prepared enol ether (0.1 g, 4×10^{-4} mol) was dissolved in 0.5 ml of 1 *N* $NaOCH_3$–CH_3OH. The nmr spectrum taken at room temperature showed no change. The NMR probe temperature was raised to 70° and the change followed. After 2 hr essentially all of the enol ether was converted to rearrangement product. The product could be recovered as a light yellow solid: NMR (CCl_4) δ 2.38 (s, 6), 2.8–3.5 (m, 2), 4.2–4.5 (m, 1), 7.1–7.4 (m, 8), 7.8–8.0 (m, 2).

Registry No.—**4**, 30669-80-8; **5a**, 53907-31-6; **5a** methiodide, 53907-32-7; **6**, 2243-35-8; **7**, 53907-33-8; **8**, 6956-56-5; **9**, 21504-23-4; **10**, 53907-36-1; **11**, 38968-65-9.

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Electronic and Steric Effects in Nucleophilic Aromatic Substitution. Reaction by Phenoxides as Nucleophiles in Dimethyl Sulfoxide

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Kinetics of reactions of X-substituted sodium phenolates with *p*-nitrohalogenobenzenes at 25° and 2,6-dimethyl-4-nitrohalogenobenzenes at 50° in DMSO are reported. The electronic effects in the nucleophile, as revealed by ρ values, are large and may depend on the leaving halogen. For these reasons the ratios k_F/k_{Cl} are not a direct measure of the dependence of steric effects on the leaving halogen. Ortho substitution in phenolate shows steric effects which depend on the size of the leaving halogen, the following order of steric effect being observed: F < Cl < Br < I.

Steric effects in nucleophilic aromatic substitutions appear to be an open question mainly as far as steric interaction between the entering and the leaving groups is concerned.

In reactions with 2,4-dinitrohalogenobenzenes, it was established long ago[1,2] that primary and secondary amines reveal differences in rate correlated with interference by alkyl groups branching from the nitrogen atom or adjacent carbons. This behavior is displayed also by anionic nucleophiles such as mercaptides,[3] alkoxides,[4] and phenolates.[5] In all cases the observed steric retardation is also dependent on the size of the leaving halogen.

Moreover, Pietra, studying substitutions on halogenonitrobenzenes by α-alkyl piperidines,[6,7] primary, secondary, or tertiary aliphatic amines in aprotic solvents,[8] and alkoxides,[9] attributed steric retardation to interactions between the nucleophile and the benzene ring carbons and hydrogens in the transition state, rejecting previous ideas[3,5] of steric interactions between entering and leaving groups.

These contrasting interpretations probably result because the data available do not provide good correlation of expected effects with rates of reaction. Also they do not take into account the electronic changes which are operative when the substituents of the nucleophile or the leaving group of the substrate must be changed.

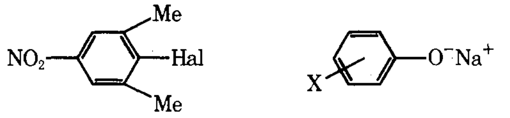
We have investigated the reactions of substituted phenoxides with *p*-nitrohalogenobenzenes and with 2,6-dimethyl-4-nitrohalogenobenzenes in order to evaluate both steric and electronic effects in a more meaningful way.

Results

The reaction rates were measured in dimethyl sulfoxide.

In order to minimize association phenomena low concentrations of phenolates ($<10^{-2}$ *M*) were employed. Under

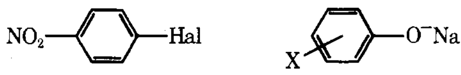
Table I
Experimental Rate Constants[a] for Reactions of 2,6-Dimethyl-4-nitrohalogenobenzenes with X-Substituted Sodium Phenoxides in DMSO at 50°



	X[c]				
Hal[b]	H	*o*-CH$_3$	*p*-CH$_3$	*p*-Cl	*m*-CH$_3$
F	0.49	0.20	1.45	0.12	0.63
Cl	0.0021	0.00087	0.0082	0.00044	
Br	0.0040	0.0011	0.012	0.00067	

[a] k, mol^{-1} l. sec^{-1}. [b] Registry no. are, respectively, 1736-85-2, 38560-96-2, 53906-84-6. [c] Registry no. are, respectively, 139-02-6, 4549-72-8, 1121-70-6, 1193-00-6, 3109-89-4.

Table II
Experimental Rate Constants[a] for Reaction of *p*-Nitrophalogenobenzenes with X-Substituted Sodium Phenoxides in DMSO at 25°



	X			
Hal[b]	H	*o*-CH$_3$	*p*-CH$_3$	2,6-(CH$_3$)$_2$[c]
F	0.52	0.18	1.9	0.13
Cl	0.0020	0.00051	0.0060	0.00022
Br	0.0034		0.0091	0.00028
I	0.00095		0.0036	0.00015

[a] k, mol^{-1} l. sec^{-1}. [b] Registry no. are, respectively, 350-46-9, 100-00-5, 586-78-7, 636-98-6. [c] Registry no., 16081-16-6.

these conditions the rate coefficients (Tables I and II), calculated by second-order plots, remained constant over a range of nucleophile concentration.

The expected substitution products were obtained in almost quantitative yields, except in the cases of 2,6-dimethyl-4-nitroiodobenzene, which showed a very consistent side process of reductive dehalogenation which is analogous to that reported by us some years ago for some heteroaromatic[10] and aromatic[11] halogeno derivatives. For this reason no kinetic data for the 2,6-dimethyl-4-nitroiodobenzene are reported here.

Discussion

Pietra has argued that the bulk of the leaving group does not affect the reactivity of reactants of increasing steric hindrance, on the grounds that for the 1-halogeno-2,4-dinitrobenzenes the ratio $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}}$ varies in a random way with increase in steric requirement of reacting amine.

Some published data and some ratios $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}}$ related to the change of the bulk of the nucleophile are reported in Table III. These data show a clear increase of the ratio $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}}$ on changing steric requirement of the nucleophile, except with 2,4-dinitrohalogenobenzenes reactions with piperidines in benzene.

On the other hand, the use of $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}}$ ratios to evaluate steric effects may be criticized on the basis of an important factor recently pointed out by Fava and coworkers.[12] This is the change of effective electronegativity of the reaction center due to the variation in leaving halogen, which can bring about differences in the sensitivity to polar effects of the substituent on the nucleophile.

For this reason the $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}}$ ratio is not sufficient for the evaluation of steric interactions between entering and leaving groups.

For the reactions between 2,6-dimethyl-4-nitrohalogenobenzenes and phenolates, indeed differences in the $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}}$ values going from the unsubstituted phenolate to the *o*-methyl phenolate might lead one to the conclusion that the size of the leaving halogen is not important in determining steric retardation (for phenolate $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}} = 233$, for *o*-methyl phenolate $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}} = 230$).

Moreover, substituent variations on the nucleophile allow one to calculate ρ values which (though rough because of the limited number of substituents used) display a remarkable sensitivity of the system being intestigated to polar effects of the substituent on the nucleophile. This sensitivity differs from the fluoro to he chloro derivative ($\rho_{\mathrm{F}} = -2.66$, $\rho_{\mathrm{Cl}} = -3.19$); therefore the $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}}$ might be ambiguous in our case.

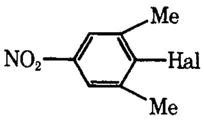
However, a steric retardation free from polar effects can be obtained by kinetic data reported in Table I. If the polar effect of a methyl group is the same in the ortho or para position, as suggested by Taft,[13] then the $k_{p\text{-cresolate}}/k_{o\text{-cresolate}}$

Table III
Values of the Ratios $k_{\mathrm{F}}/k_{\mathrm{Cl}}$ in Nucleophilic Substitution Reaction between Aromatic Substrates and Nucleophiles

	Nucleophile			
Substrates and solvent	Piperidine	2-Methylpiperidine	2,6-Dimethylpiperidine	Ref
Fluorodinitrobenzene and chlorodinitrobenzene in benzene	6.86	35.3	25.0	6
Fluorodinitrobenzene in DMSO; chloronitrobenzene in benzene	7240	10,100	27,000	7
Fluorodinitrobenzene and chlorodinitrobenzene in benzene	*n*-Butylamine 410	*sec*-Butylamine 568[a]	*tert*-Butylamine 1050	8
2-Halogenobenzothiazoles in methanol	Methyl mercaptide 107	Ethyl mercaptide 137	Isopropyl mercaptide 180 *tert*-Butyl mercaptide 384	3
2-Halogenobenzothiazoles in the respective alcohols	Methoxide 1036	Ethoxide 1161	Isopropoxide 2941 *tert*-Butoxide 5333	4

[a] Pietra calculated erroneously a value of 1800, but reported $k_{\mathrm{F}} = 0.023$, $k_{\mathrm{Cl}} = 4.05 \times 10^{-5}$; hence $k_{\mathrm{F}}/k_{\mathrm{Cl}} = 568$.

Table IV



Hal	$\rho(r)$	$k_{p\text{-Me}}/k_{o\text{-Me}}$
F	−2.66 (0.996)	7.2
Cl	−3.19 (0.999)	9.3
Br	−3.17 (0.998)	11

ratio, calculated for each halogeno derivative, will be independent of polar effects.

A comparison of $k_{p\text{-cresolate}}/k_{o\text{-cresolate}}$ values for each halogeno derivative shows now (Table IV) a clear correlation with the size of the leaving halogen; $k_{p\text{-cresolate}}/k_{o\text{-cresolate}}$ increases in the order F < Cl < Br.

The differences seen in the above sequence are significant in that they reflect the differences in size of the leaving halogen mainly as far as chloro and fluoro are concerned; therefore they strengthen the hypothesis of a steric interaction between entering and leaving group (possibly along with steric interactions between other nonbonded atoms in the transition state).

Similar conclusions can be drawn in the case of reactions of *p*-nitrohalogenobenzenes with 2,6-dimethyl phenolate. The following steric retardations (53:82:87:91 for fluoro, chloro, bromo, and iodo derivative, respectively) are obtained if we regard the contribution from the polar accelerating effect of the two methyls in ortho positions as twice the effect of methyl in the para position. The above sequence is clearly correlated with expected increase of steric requirement in the order F ≪ Cl < Br < I.

Experimental Section

Materials. 2,6-Dimethyl-4-nitrohalogenobenzenes were prepared from 2,6-dimethyl-4-nitroaniline (I) via diazonium salt as described by Wepster[14] for the bromo derivative.

2,6-Dimethyl-4-nitrochlorobenzene, mp 102–104° (Anal. Calcd for $C_8H_8ClNO_2$: C, 51.8; H, 4.3; N, 7.5; Cl, 19.1. Found: C, 51.6; H, 4.4; N, 7.6; Cl, 18.9.) was obtained in the same way as the bromo derivative.

2,6-Dimethyl-4-nitroiodobenzene was prepared by adding the diazonium salt of I to a vigorously stirred solution of KI (1 mol of KI for each mole of I used) in H_2O. The precipitated product was filtered and crystallized from ethanol, mp 132–133°. Anal. Calcd for $C_8H_8INO_2$: C, 34.7; H, 2.9; N, 5.1; I, 45.8. Found: C, 34.5; H, 2.9; N, 4.9; I, 45.5.

2,6-Dimethyl-4-nitrofluorobenzene was prepared by adding the diazonium salt of I directly to a HBF_4 solution. The diazonium fluoroborate was filtered and, after washing with cold methanol, was mixed with NaF and thermally decomposed. The pure material was separated by silica gel column chromatography and crystallized from methanol, mp 55.5–56.5°. Anal. Calcd for $C_8H_8FNO_2$: C, 56.8; H, 4.8; N, 8.3; F, 11.2. Found: C, 56.9; H, 5.1; N, 8.2; F, 11.3.

All the 2,6-dimethyl-4-nitroalogenobenzenes prepared, and *p*-nitrohalogenobenzenes (commercial products), were recrystallized several times from methanol or ethanol.

Sodium phenolates were synthesized by the method reported by Kornblum.[15]

The substitution products (aryl ether) were obtained in almost quantitative yields by reactions performed under the same conditions as kinetic runs and were characterized by usual analytical methods.

DMSO was refluxed over calcium hydride and fractionally distilled under a N_2 atmosphere.

Kinetics. All the kinetic reactions were performed in DMSO under a N_2 atmosphere.

In the case of fluoro derivatives the kinetics were determined by following the disappearance of the base. For this, a known excess of HCl added to each portion of the reaction mixture was titrimetrically determined.

In the other cases the appearance of the halide ion was followed via potentiometric titration by $AgNO_3$. The organic substrate was extracted with carbon tetrachloride or chloroform before titration.

The kinetic coefficients were calculated from second-order plots which exhibited a good linear correlation as far as 30%. At higher percent, conversion rate constants were found to decrease into agreement with those found by Berge and Ugelstad.[16]

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Registry No.—2,6-Dimethyl-4-nitroiodobenzene, 53906-85-7.

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