The α-Effect in S_NAr Substitutions − Reaction between Oximate Nucleophiles and 2,4-Dinitrofluorobenzene in Aqueous Solution

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The second-order rate constants (k_1^{ArO}, k_1^{Ox}) for S_NAr substitutions of 2,4-dinitrofluorobenzene (DNFB) by a series of phenoxide and oximate nucleophiles have been measured in aqueous solution at 25 °C, using both a potentiometric procedure involving the use of a fluoride ion selective electrode (FISE) and a classical spectrophotometric procedure. While the rate data for the phenoxide ions conform to a linear Brönsted plot with a slope (β_{Nu} = 0.71) fitting the 0.5–0.7 range commonly found for S_NAr reactions, those for the various oximates studied do not define a meaningful linear plot. Interestingly, the observed variations in k_1^{Ox} reveal a tendency of the reactivity of oximates of $pK_a > 7.5–8$ to level off rapidly, a situation reminiscent of that encountered in other nucleophilic reactions of these species at carbonyl and phosphonyl centres. Our current finding reinforces the idea of a general oximate behaviour pattern originating from an especially strong need for partial desolvation before nucleophilic attack, i.e., asynchronicity or TS imbalance. A major consequence of the observed levelling off is that the extra reactivity reflecting the α character of oximate nucleophiles decreases significantly in magnitude on going from weakly basic oximates ($k_1^{Ox}/k_1^{ArO} \approx 100$) to strongly basic ones ($k_1^{Ox}/k_1^{ArO} \approx 10$). On the basis of the k_1^{Ox}/k_1^{ArO} ratio measured at low pK_a, the α-effect associated with the S_NAr substitution of DNFB is of the same order as that measured for other reactions of oximates at sp^2-carbon centres.

Since Edwards and Pearson first drew attention to the enhanced reactivity of nucleophiles possessing a heteroatom with an unshared pair of electrons adjacent to the nucleophilic atom, numerous studies of the so-called α-effect phenomenon have been reported.[1−7] In the first review of this phenomenon,[3] it was noted that the rate constant ratio, k_{OOH^-}/k_{OH^-}, for nucleophilic attack on carbon substrates in different states of hybridization increased in the order $sp^3 < sp^2 < sp$, as represented by substrates of types $ArCH_2Br$, ArC(O)OR, and ArCN, respectively. While the $k_{\alpha\text{-Nu}}/k_{\text{normal-Nu}}$ rate ratio subsequently became understood as referring to nucleophiles with the same pK_a − i.e. as a positive deviation exhibited by an α-nucleophile from a Brönsted-type nucleophilicity plot − the importance of the hybridization of the carbon centre became firmly established as a factor determining the magnitude of the α-effect.[5−9] Systematic studies have also revealed the importance of the α-effect in nucleophilic reactions at sulfur and phosphorus centres with consequent biological and decontamination applications.[8−13]

Several factors have been recognized as possible contributors to the α-effect phenomenon: ground-state destabilization of the α-nucleophile, transition-state stabilization, thermodynamic stability of products, and solvation differences of the nucleophiles.[5,8,14−16] Extensive discussions of these factors have favoured the conclusion that more than one factor is generally operative in a given system.[5] Recently, separations of ground-state (GS) and transition-state (TS) contributions have been accomplished for the reactions of *p*-nitrophenyl acetate (PNPA) with two α-nucleophiles (the anions of butane-2,3-dione monoxime and α,α,α-trifluoroacetophenone oxime) and a normal nucleophile (*p*-chlorophenoxide) of similar basicities in $DMSO/H_2O$ mixtures. The results highlighted the important role of TS stabilization in determining the α-effect.[15,17] Another important discovery in this regard was the fact that in many processes the reactivity of α-nucleophiles such as oximates in aqueous solution is subject to a saturation effect.[18−21] This behaviour prompted the suggestion that asynchronicity of nucleophile desolvation and bond formation in the related transition states is also a major factor governing the α-effect.[9,17−22]

As far as reactions involving electrophilic sp^2-carbon centres are concerned, the large majority of studies available relate to nucleophilic attack at C=O centres.[5−8] In particular, very little attention has been paid to the α-effect for substitution at aromatic carbon atoms.[3,5][14c] The only meaningful report in this area was that the rate constant for hydrazine showed significant positive deviation from the Brönsted-type plots of normal nucleophiles for 1-X-2,4-dinitrobenzenes (X = F, Cl, I) and for 1-chloro-2,4,6-trinitrobenzene (PiCl) in aqueous solution at 30 °C.[23] However, no Brönsted-type plots have been established for other α-effect amines reacting in S_NAr processes.

In view of the important role of S_NAr substitutions both in synthesis and in mechanistic studies,[24] it appeared desirable to extend previous work on such processes, and we

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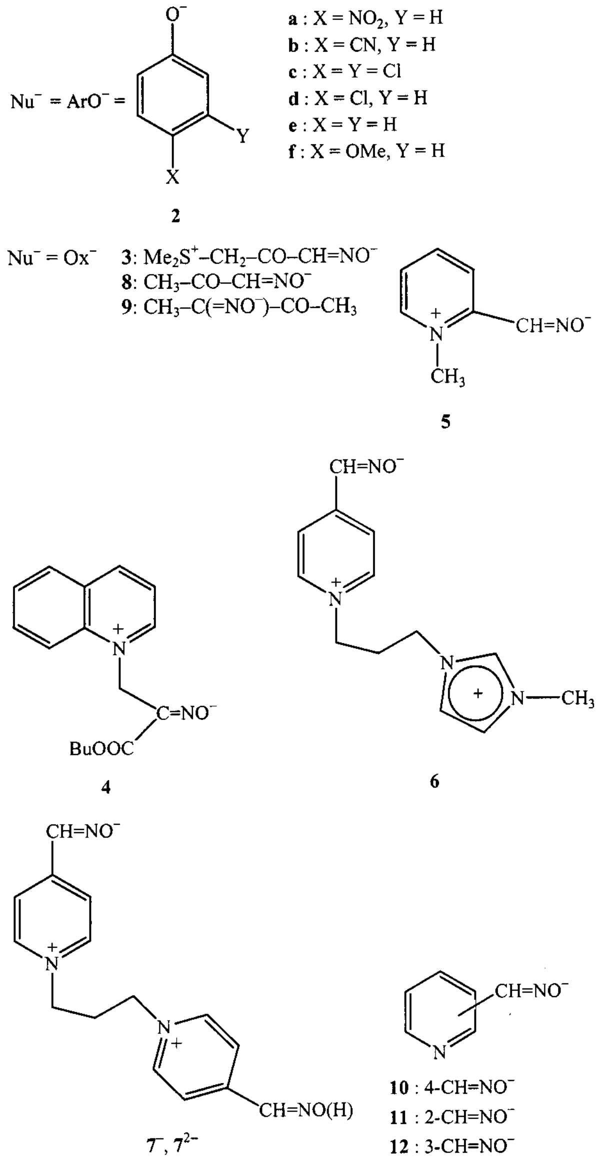
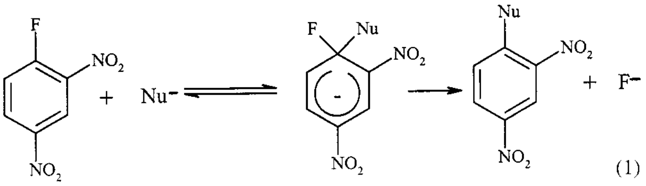
report here a kinetic study of the reactions of two homogeneous series of phenoxide and oximate nucleophiles, **2a−2f** and **3−12** (Scheme 1), with 1-fluoro-2,4-dinitrobenzene (DNFB). Equally important, however, was the pursuit of our strategy for the study of the α-effect, which involves Brönsted-type plots (slope = β_{Nu}) being established concomitantly for series of structurally related α-nucleophiles and normal nucleophiles.[17−19,22,26] Work from our laboratories and by other groups has shown that important information relating to transition-state characteristics can be gleaned from this comparative approach.[17−22,26] Thus, in several instances, oximate nucleophiles in aqueous solution have been found to exhibit abnormally low β_{Nu} values, apparently reflecting specific solvation imbalances in the transition states. This type of situation has also surfaced in this study of the S_NAr reactions shown in Equation (1).



Scheme 1



(1)

Results

Using a fluoride ion selective electrode, according to procedures previously reported in detail,[13,27,28] the rates of reactions according to Equation (1) were first measured by monitoring the appearance of the F^- anion potentiometrically. The reactions were conducted at 25 °C in aqueous solution, at a constant ionic strength I of 0.16 mol L^{-1}. Experiments pertaining to the phenoxide systems could be appropriately carried out in buffers made up from these reagents, varying the concentration of the acid and base components at constant pH while maintaining pseudo-first order conditions with the buffer being in excess throughout (i.e., [DNFB] = 10^{-3} mol·L^{-1}, [ArO−] = $2\cdot10^{-2}$ to 0.1 mol·L^{-1}). Plots of the first-order rate constants, k_{obsd}, versus the ArO^- concentration were linear, with negligible intercepts, for all reaction systems studied (Figure 1). This indicates that k_{obsd} is simply given by Equation (2) and that there is no appreciable contribution of hydroxide ion and/or water to the rate of decomposition of DNFB under the experimental conditions. Second-order rate constants k_1^{ArO} were obtained from the slopes of the various buffer plots and are summarized in Table 1.

$$k_{obsd} = k_1^{Nu}\cdot[Nu] \qquad (2)$$

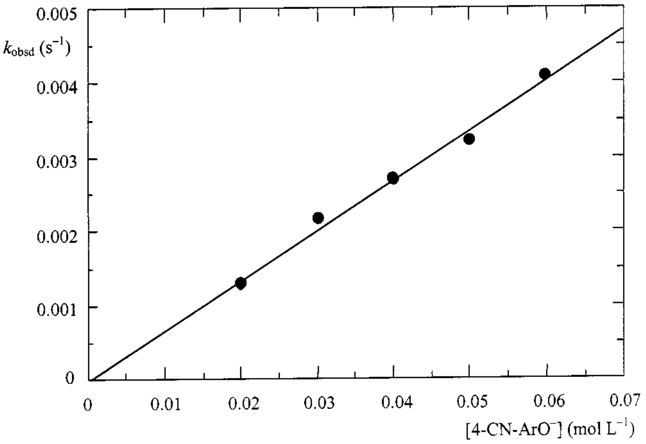


Figure 1. Effect of the *p*-cyanophenoxide concentration on the observed first-order rate constant, k_{obsd}, as measured potentiometrically for S_NAr substitution of DNFB in *p*-cyanophenol buffers in aqueous solution at pH = 7.80 and 25 °C

The rates of the oximate reactions were in general too fast to be investigated by the potentiometric technique

Table 1. Second order rate constants k_1^{ArO} for reactions between DNFB and various phenoxide ions, in aqueous solution at $T = 25$ °C and $I = 0.16$ mol·L^{-1}

Phenoxide ion	pK_a [a]	k_1^{ArO} (L mol^{-1} s^{-1})[b][c]	
2a	7.12	–	0.016
2b	7.80	0.035	0.052
2c	8.51	0.155	0.17[d]
2d	9.30	0.34	0.39 (0.38)[e]
2e	9.88	0.76	0.444[d]
2f	10.27	2.7	–

[a] Data from ref.[29] – [b] Measured by spectrophotometry. – [c] Measured by potentiometry. – [d] Ref.[27b] – [e] In the presence of HEPES as an external buffer.

when the buffer strategy defined for the phenoxide reactions was employed. Potentiometric monitoring of these reactions was thus achieved by a different approach, in which the pH was kept constant with an external buffer 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES, pH = 7.49, $[\text{HEPES}]_{tot} = 0.1$ mol L^{-1}) and 3-{[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino}propane-1-sulfonic acid (TAPS, pH = 8.30, $[\text{TAPS}]_{tot} = 0.1$ mol·L^{-1})]. Again starting with a DNFB concentration of 10^{-3} mol·L^{-1} (C_0), the substitution reaction of this compound by a given oximate was then studied by carrying out experiments in which the total oxime concentration $[\text{Ox}]_0$ introduced into the solutions was variously $4{\cdot}10^{-3}$, $6{\cdot}10^{-3}$, and $8{\cdot}10^{-3}$ mol·L^{-1}. Thus, reaction according to Equation (1) could be carried out in the presence of relatively low concentrations of the reactive oximate species. Neglecting as a first approximation the possible contribution of the OH$^-$ and water pathways to the hydrolysis of DNFB (vide supra), the expected rate law for the above experiments may be written as Equation (3).

$$\frac{d[F^-]}{dt} = k_1^{Ox}[Ox^-][DNFB] \tag{3}$$

The concentration of the reactive oximate species at time *t* is given by Equation (4). In this Equation, *x* is the concentration of fluoride ion generated at time *t*. Integration of Equation (3) then results in Equation (5), which predicts that a plot of the term on the righthand side, denoted *Z* for simplicity, versus time should afford a straight line passing through the origin.

$$[Ox^-] = \frac{[Ox]_0 - x}{1 + 10^{(pKa^{Ox} - pH)}} \tag{4}$$

$$k_1^{Ox} t = \frac{1 + 10^{(pKa^{Ox} - pH)}}{[Ox]_0 - C_0} \, Ln\left[\frac{C_0[Ox]_0 - x}{(C_0 - x)[Ox]_0}\right] = Z \tag{5}$$

An illustration of this approach is given in Figure 2, which refers to the *Z* vs. *t* plot obtained for substitution of DNFB by the butanedione monoxime reagent in an external TAPS buffer of pH = 8.30 ($[\text{Ox}]_{tot} = 4{\cdot}10^{-3}$ mol L^{-1}; pKa^{Ox} = 9.3, $I = 0.16$ mol·L^{-1}). In agreement with Equation (5), this plot is linear with zero intercept, and a k_1^{Ox} value of 4.10 L·mol^{-1}·s^{-1} was calculated from the slope. Similar treatment of the data obtained for the series of oximates under study afforded the k_1^{Ox} values summarized in Table 2.

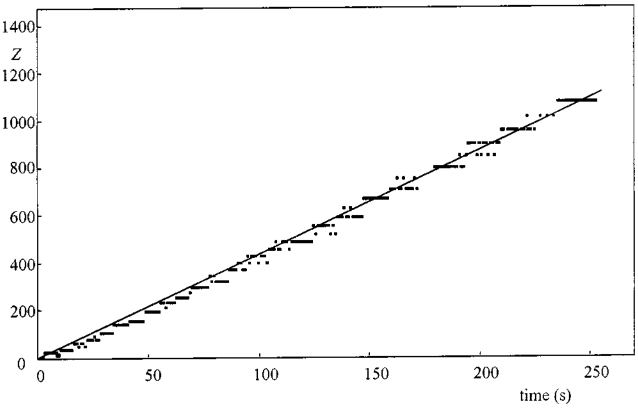


Figure 2. Plot of *Z* vs. *t* [see Equation (5)] for S_NAr substitution of DNFB by the butadione monoximate anion, as derived from potentiometric measurements[13] in an external TAPS buffer containing a total oxime concentration $[\text{Ox}]_0 = 4{\cdot}10^{-3}$ mol·L^{-1} (pH = 8.30) in aqueous solution at 25 °C

Table 2. Second-order rate constants k_1^{Ox} for the substitution of DNFB by various oximate bases in aqueous solution at $T = 25$ °C and $I = 0.16$ mol·L^{-1}

Oximate species	pK_a[a]	k_1^{Ox} (L mol^{-1} s^{-1})[b][c]	
3	6.54	0.38	–
4	6.98	1.4	–
5 (2-PAM)	7.75	1.4	1.47
6 (CEB 1574)	8.05	1.6	
7 (TMB-4)	7.79[d]	1.6[d]	–
	8.55[e]	2.5[e]	–
8 (MINA)	8.3	1.3	0.65
9	9.3	4.1	5.0
10	9.63	4.5	3.03
11	9.85	4.6	2.59[f]
12	9.95	–	2.83[f]

[a] pK_a data from ref.[30] – [b] Measured potentiometrically in the presence of an external buffer: HEPES (**3**, **4**, **5**, **7**) or TAPS (**6–12**); see text. – [c] Measured by spectrophotometry. – [d] pK_a and k_1^{Ox} values refer to the monoximate species derived from TMB4; see Exp. Sect. – [e] pK_a and k_1^{Ox} values refer to the dioximate species derived from TMB4; see Exp. Sect. – [f] In these systems, a notable superposition of the formation and subsequent hydrolysis of the substitution products **1** was observed, allowing only estimates of k_1^{Ox} by spectrophotometry; accordingly, these k_1^{Ox} values were not used to draw the Brönsted plot of Figure 3.

Since we were dealing with relatively fast reactions, it was desirable to check the electrochemical method by repeating some of the results using conventional or stopped-flow spectrophotometry. Using the same buffering methodology as employed for following the phenoxide reactions by potentiometry, it was possible to carry out this spectrophotometric approach successfully both in phenoxide buffers (Table 1) and in four oximate systems (Table 2): namely **5**, **8**, **9**, and **10**, where the strong absorbance of the buffer species did not interfere too much with the absorbance variations associated with a pseudo-first-order conversion of DNFB (ca. $5 \cdot 10^{-5}$ mol·L^{-1}) into the related substitution product **1** [Equation (1)]. Treatment of the collected rate data according to Equation (2) indeed afforded k_1^{ArO} and k_1^{Ox} values in satisfactory agreement with those derived from the potentiometric method, except, however, for the MINA system (**8**), where superposition of absorbances was sufficiently significant to cause greater uncertainty in the derived rate constant. This is evident from the greater deviation of the spectrophotometric point for MINA on the Brönsted-type plot in Figure 3.

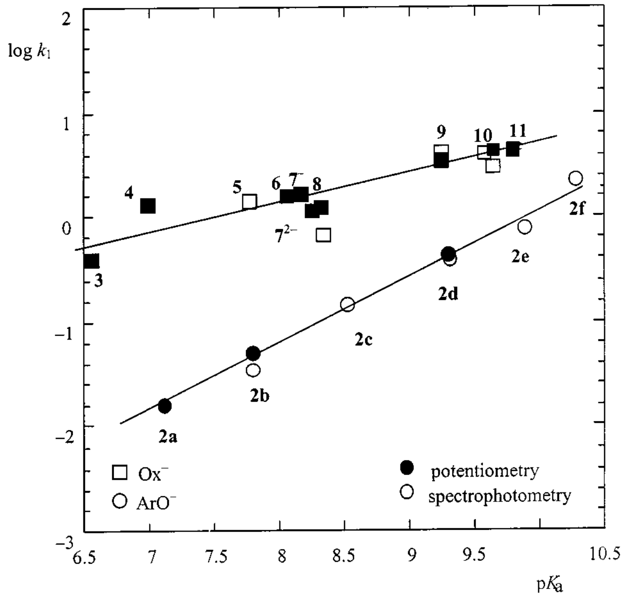


Figure 3. Brönsted plot for S_NAr substitution of DNFB with various phenoxide and oximate bases in aqueous solution; open circles refer to spectrophotometric measurements, filled circles refer to potentiometric measurements of the rate constants (k_1^{ArO}, k_1^{Ox}) at 25 °C

Discussion

This work reports on the reactions between 1-fluoro-2,4-dinitrobenzene (DNFB) and two series of nucleophiles, aryloxides and oximates, shown in Scheme 1. A major feature is the use of an electrochemical method for monitoring the liberation of F^-; this has been shown to be applicable for first-order reaction rates corresponding to half lives of ca. 30 s.[13,27,28] In particular, the method has previously been applied to the substitution of DNFB by various nucleophiles,[27,28] as well as to the study of the decomposition of some organofluorophosphorus compounds: namely sarin, soman, and diisopropylphosphorofluoridate (DFP).[13] That the results obtained by the electrochemical method in this study are found to be consistent with those obtained by conventional or stopped-flow measurements is a significant finding, which gives further credence to the potential applicability of this methodology.

As pointed out in the introduction, only one previous study has so far been reported for the α-effect in nucleophilic substitutions at aromatic carbon centres.[23] In that work, Bruice and co-workers showed that the rate constant for hydrazine exhibited significant positive deviation from the Brönsted-type plot established for the S_NAr reactions of picryl chloride and DNFB with a series of primary aliphatic amines. Importantly, and in contrast with the study of Bruice et al., this study was designed to establish a Brönsted plot for a homogeneous series of α-nucleophiles. For this purpose, we chose a family of oximate α-nucleophiles and compared their reactivities with phenoxide nucleophiles, noting that pK_a values for both series of compounds are known.[29,30] In addition, oximates represent α-nucleophiles of particular interest because of their wide usage in decontamination.[10−13]

Figure 3 displays the kinetic data in the form of Brönsted-type plots for the two sets of reactions depicted in Equation (1). Significantly, the points for the aryloxides define a good straight line, of slope $\beta_{\mathrm{Nu}} = 0.71$ ($R^2 = 0.998$). This value falls in the 0.5−0.7 range defined for the S_NAr reactions of a variety of nitrohalobenzenes reacting with diverse nucleophiles − these include aryloxide anions, thianions, nitranions, and carbanions, as well as neutral amine reagents − in different solvents (H_2O, MeOH, DMSO).[31] As pointed out by Bordwell and others, such β_{Nu} values are indicative of a rather advanced degree of bond formation in the rate-determining transition state of S_NAr reactions, and contrast with S_N2 processes, for which much lower β_{Nu} values (0.2−0.5) are generally the rule.[31]

As can be seen in Figure 3, the points for the various oximates clearly do not define a meaningful straight line. The computer-drawn "best" line has a correlation coefficient of 0.921, contrasting with the 0.998 value for the aryloxides. Should one assume that this line is representative of oximate reactivity, its slope of 0.29 is clearly far below the range expected for an S_NAr substitution (vide supra). Interestingly, this situation is reminiscent of previous observations, in our own laboratory and in others, that the reactivity of oximates of p$K_a \geq 7.5-8$ is subject in nucleophilic reactions at carbonyl and phosphonyl centres to rapid levelling off.[18−21] The demonstration that such a levelling off is also observed in an S_NAr substitution reaction thus reinforces the idea of a general feature of oximate behaviour, not restricted to the electrophilic centres above.

The fact that, within a family of nucleophiles, the reactivity tends to decrease with increasing basicity is a result encountered for various types of oxy anions, notably by Jencks and Hupe in a number of acyl transfer reactions involving strongly basic aryloxide or alkoxide ions.[6b,32,33] This behaviour was accounted for in terms of a need for partial desolvation of these species before nucleophilic attack, this being less important for weakly basic anions than for more basic ones.[6,33,34] While it is reasonable to assume that a similar explanation must apply to oximates, it is remarkable in this family of α-effect nucleophiles that the saturation effect becomes effective at pK_a values much lower than those found for the so-called normal oxy-anionic aryloxide or alkoxide species. This implies that the transition states for oximate reactions are characterized by solvation imbalances much stronger than those for the other oxy-anion reactions.[18,19]

A major consequence of the observed levelling off in oximate reactivity is a narrowing of the gap between the lines defined by the aryloxides and the oximates in Figure 3. Since this gap is the measure of the α-effect, it follows that this effect decreases significantly in magnitude on going from weakly basic oximates ($k^{Ox}/k^{ArO} \approx 100$) to strongly basic ones ($k^{Ox}/k^{ArO} \approx 10$). In other words, the extra reactivity of oximates may be expected to vanish at high pK_a values, as has been noted both by ourselves and by other workers for different systems including acyl transfer reactions.[18−21] As a matter of fact, this conclusion accounts well for the finding that the literature reports abnormally low β_{Nu} values (0.1−0.2) for all reaction systems that have been studied with a series of oximates restricted to relatively high basicities.[7,35]

Conclusion

It follows from the above discussion that *the most meaningful α-effect value pertaining to a given reaction system must relate to the difference in reactivity between weakly basic oximates and ArO^- ions.* On these grounds, the α-effect associated with S_NAr substitution of DNFB [reactions according to Equation (1)] appears to be of two orders of magnitude. This value compares well with the values measured in studies of acyl transfer processes and is therefore consistent with the qualitative trend $sp^3 < sp^2 < sp$ mentioned in the introduction.[3]

Also noteworthy is the fact that our results highlight the dilemma concerning the significance of β_{Nu} as a measure of the extent of bond formation between the electrophile and the nucleophile in the transition state.[6,26] While the linear plot for ArO^- ions in Figure 3 conforms to this analysis, the levelling-type plot precludes this traditional interpretation for Ox^- species. Thus, we posit here that, in the case of α-nucleophiles of the oximate type, the traditional methodology is not valid and no proper information (β_{Nu}) on the transition state structure can be obtained in this way. In turn, the observed levelling off with increasing pK_a is indicative of a lack of synchronization between partial desolvation of the nucleophile and bond formation in the transition state, a situation that Jencks and Bernasconi have referred to as transition-state imbalance.[6b,36]

Experimental Section

Materials: The oxime and phenol precursors of the nucleophiles used in this work were all available from recent studies and were recrystallized from methanol or hexane before use.[29,30] 1-Fluoro-2,4-dinitrofluorobenzene (DNFB) was distilled under vacuum before use. HEPES and TAPS were of the highest quality commercially available and were used without further purification.

Kinetic Measurements: The potentiometric method used to determine the kinetics of the reactions according to Equation (1) by monitoring the appearance of F^- under the various experimental conditions described in the text has been described in detail elsewhere.[13] Spectrophotometric determinations of the rates according to Equation (1) were carried out under pseudo-first-order conditions, with excess buffer base (10^{-3} to 0.065 $mol \cdot L^{-1}$) over the DNFB concentration (ca. $3 \cdot 10^{-5}$ to $5 \cdot 10^{-5}$ $mol \cdot L^{-1}$) and at constant ionic strength ($I = 0.16\ mol \cdot L^{-1}$ using KCl). Measurements were made by monitoring the appearance of the resulting 2,4-dinitrophenyl ether **1** at the wavelengths found to be the most appropriate for minimizing interference between the UV/Vis spectrum of **1** and that of the relevant buffer: $\lambda = 325$ nm in the 4-cyanophenoxide buffers, for example. For a given buffer system, at least six values of the base reagent were employed at constant pH, and each individual experiment was performed in triplicate. In all cases, the reactions were found to be kinetically of first order in **1** up to at least 90% of the overall reaction. In the case of the TMB4 dioxime (OxH_2) system, the reactions of the monoximate and dioximate species (OxH^-/Ox^{2-}) were determined separately, working first at pH = 7.31 with an $[OxH^-]/[OxH_2] = 1{:}3$ ratio and then at pH = 9.30 with an $[Ox^{2-}]/[OxH^-] = 3{:}1$ ratio, and then analysing the rate data as previously described.[19a] The k_{obsd} data are summarized in Tables S_1-S_3 of the Supporting Information

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[34] As pointed out by a referee, it is perhaps useful to recall that nucleophilic saturation effects may reflect a change in the rate-determining step of a two-step process.[6,32,33] For an addition/elimination mechanism of the type shown in Equation (1), such a change will be from rate-limiting leaving group departure with weak nucleophiles (low pK_a) to rate-limiting nucleophilic addition with strong nucleophiles (high pK_a). While such a situation has been found to prevail in many acyl transfer reactions,[6,32,33] it is extremely unlikely here, since F^- is a very good leaving group ($pK_a = 3.45$).

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