Enolate Structures Contributing to the Transition State for Nucleophilic Substitution on α-Substituted Carbonyl Compounds[1]

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Abstract: The high S_N2 reactivity of α-halocarbonyl compounds is explained by the lowering of the intrinsic barrier by a major contribution of enolate structure to the transition state. This theoretical conclusion is now shown experimentally. The evidence is as follows: (1) Change in structure of a leaving arenesulfonate ion does not change the rates of attack of benzenesulfonate ion by nearly as much as it changes the equilibrium constants. A charge on the transferring phenacyl group of −0.48 is deduced. (2) The ρ value (−3.9) for attack of substituted thiophenoxides on phenacyl bromide is much more negative than that for attack on methyl iodide (−1.8). (3) A related ρ value is found for reaction of 2,4,6-trimethylphenacyl bromide with thiophenoxides (−2.2), showing a lesser, but still large sensitivity to nucleophile structure where addition to the carbonyl is sterically forbidden. The enolate structure leaves the attacking or leaving nucleophiles with a single electron each instead of the unshared pairs. Thus, the enolate structure is emphasized if the leaving group and the nucleophile readily lose an electron.

The high reactivity of α-halocarbonyl systems in S_N2 reactions is well-known.[2,3] It is not always very high; some reactions of phenacyl bromide with first-row nucleophiles, especially amines, are not conspicuously fast. One measure of the high reactivity is the comparison of the rate of phenacyl bromide with that of methyl iodide,[4] where rate ratios of somewhat less than one to many times greater than one have been found. The high reactivity has been explained in many conflicting ways. An electrostatic rate enhancement from the interaction of the negative charge on the nucleophile with the positive end of the carbonyl dipole was an early suggestion.[5] A prior addition of the nucleophile to the carbonyl group[6] or a partial bonding of this nature in the single transition state[7] has also been proposed. A more complex mechanism with an intermediate epoxide[8] was shown to be conceivable, although not strongly supported. A qualitative general explanation has been offered that there is a favorable overlap between the leaving and attacking orbitals and the π orbital of the carbonyl group.[3,9]

Recently, several more quantitative approaches to the effect of the α-carbonyl group have been offered. Kost and Aviram[10] use an ab initio modeling of the transition state for the α-X-acetaldehyde identity reaction with the nucleophile X^-. They show that the conformation with the aldehyde plane normal to the XCX line is usually favored. This preference, which is that required for enolate contribution, is greatest with $X^- = H^-$ and decreases through $X^- = F^-$ and $X^- = NH_3$ to nothing with $X^- = BH_4^-$.

Shaik[11] uses a valence bond approach to estimate the effect of α-substitution on CH_3X, including the α-carbonyl substituent. The accelerating effect of the α-carbonyl is recognized as a resonance effect in the transition state.

McLennon and Pross[12] also conclude by a less quantitative treatment that the enolate contribution (contributing along with product-like and reagent-like structures) is the major source of rate acceleration relative to saturated systems.

Carrion and Dewar[13] have used the MINDO method to calculate the energies and structures of identity S_N2 reactions with the α-carbonyl group. They conclude that "The acceleration of an S_N2 reaction by an adjacent carbonyl group must therefore be due *entirely* to a mesomeric interaction in the transition state, analogous to that in an α-acylcarbanion".

Bach and co-workers[14] use a frontier orbital approach with ab initio orbitals for chloroacetaldehyde to consider the reaction with various nucleophiles and again conclude that the transition state is enolate-like.

The geometry of the transition state and the source of the rate enhancement by carbonyl substitution are thus shown by several theoretical approaches. Theory does not make an experimental demonstration unnecessary; indeed it almost demands it. This paper supplies some of this evidence, provides a description of the charge distribution, and discusses a few cases where the rate enhancement seems to be absent.

The charge on the transferring group is a factor in S_N2 transition states which facilitates a qualitative understanding. For methyl transfers this charge has been measured by the magnitude of substituent effects in the attacking nucleophile or the leaving group on identity reactions[15] or on near-identity reactions[16,17] scaled to the substituent effect on the equilibrium. The charge was positive for transfer between arenesulfonates (+0.2),[15] but was nearly zero for transfers between substituted thiophenoxide anions[17] and negative (−0.24) for transfer between aryl selenide anions.[18] It appeared that a transition state with a negative charge on the transferring group would be especially favorable if the negative charge could be stabilized by conjugation, for instance as in an enolate. In this paper we explore the possibility that this approach to the unusual reactivity of α-halocarbonyl compounds may reveal the extent of the contribution of an enolate structure to this S_N2 transition state.

Transition states for S_N2 reactions have been characterized as "loose", meaning that the bond-breaking is ahead of bond-making, and "tight", with bond-breaking less advanced than bond-making. Loose transition states can be identified with those with a positive charge on the transferring group, for which unbonded structure **1a** contributes more than **1b** or **1c**. The attack on α-halocarbonyl

$$\underset{\mathbf{1a}}{[X^- R^+ Y^-]^-} \qquad \underset{\mathbf{1b}}{[X\text{–}R^-\text{–}Y]^-} \qquad \underset{\mathbf{1c}}{[X\cdot\ R^-\cdot Y]^-}$$

(1) This paper is to be regarded as paper 1 in a series on group transfers; this is a generalized form of the papers on methyl transfers, the last of which is ref 18.
(2) Conant, J. B.; Kirner, W. R. *J. Am. Chem. Soc.* **1924**, *46*, 232.
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Table I. Rate and Equilibrium Constants for the Reaction of Sodium Benzenesulfonate with Substituted Phenacyl Arenesulfonate Esters (Eq 1) in Sulfolane at 50 °C

X	$k^a/(10^{-5}\ M^{-1}\ s^{-1})$	K^b
4-OMe	4.46 ± 0.08	0.098[c]
4-Me	6.37 ± 0.4[f]	0.14[c]
4-F	7.66 ± 0.19	0.95[d]
4-Cl	8.79 ± 0.20	2.2[d]
3-CF_3	22.2 ± 0.5	26[d]
3,4-Cl_2	26.5 ± 0.9	46[e]

[a] Determined under pseudo-first-order conditions with excess (ca. 50:1) ester over benzenesulfonate ion and divided by the excess sulfonate ester concentration. The indicated errors are the errors in slope calculated by the least-squares fit. It is probably a small underestimate as seen in footnote *f*. [b] The error in the equilibrium constants is uncertain; we estimate an error less than 20% but not less than 10%. [c] Determined in the forward direction. [d] Determined against the 3,4-dichlorobenzenesulfonate ion. [e] Determined in the reverse direction. [f] The error is estimated from the agreement between duplicate runs. The error estimate for each run was ±0.3.

Table II. Rate Constants for the Reaction of Phenacyl Bromide and 2,4,6-Trimethylphenacyl Bromide with X-Substituted Sodium Thiophenoxides in Sulfolane/Dimethyl Sulfone Eutectic at 42 °C

	$k^a/(10^3\ M^{-1}\ s^{-1})$	
X	phenacyl bromide	2,4,6-trimethyl-phenacyl bromide
4-Me	202 ± 6[b]	12.9 ± 0.2[b]
H	104 ± 0.5	11.6 ± 0.3
4-F	12.0 ± 0.5	2.97 ± 0.13
4-Cl	2.66 ± 0.08	1.69 ± 0.03
3-Cl	2.32 ± 0.06	0.721 ± 0.001
3,4-Cl_2	0.173 ± 0.003	0.342 ± 0.002

[a] Determined by dividing a pseudo-first-order rate constant by the concentration of phenacyl bromide or 2,4,6-trimethylphenacyl bromide. [b] Error estimates based upon reproducibility of several runs.

compounds is sometimes described as having a tight transition state. It presumably has the excess negative charge on the transferring group and is possibly related to excess contribution of hypervalent structure **1b**,[19] which certainly has bond-making before bond-breaking, but does not have any familiar predictable properties. However, structure **1c** (with the two odd electrons paired) also has the negative charge on transferring R, the charge on the attacking negative nucleophile has disappeared, and that on the leaving group is not yet formed. It is not obvious that structure **1c** would be well described by the term "tight" even though all the negative charge is centrally located. In this paper we study substitution on phenacyl (benzoylmethyl) derivatives in sulfolane solution to explore the adequacy of the enolate contribution description.

Results

The experimental studies reported are phenacyl group transfers, including near-identity reaction 1, for which both rates and equilibria are reported, and reactions 2 and 3, for which only rates are reported. The rates and equilibria for reaction 1 in sulfolane

$$PhSO_3^- + ArSO_3CH_2COPh \rightarrow ArSO_3^- + PhSO_3CH_2COPh \quad (1)$$

at 50 °C were measured by using an HPLC analysis for the neutral sulfonate esters. The results are presented in Table I. In all the tables X means the substituent in a phenyl group represented in the equations by Ar.

Table II shows the rates for reactions 2 and 3 at 42 °C, also in sulfolane (with the melting point depressed with dimethyl sulfone).[20] These rates, much faster than those of reaction 1,

$$ArS^- + PhCOCH_2Br \rightarrow PhCOCH_2SAr + Br^- \quad (2)$$

$$ArS^- + MesCOCH_2Br \rightarrow MesCOCH_2SAr + Br^- \quad (3)$$

Mes = 2,4,6-trimethylphenyl

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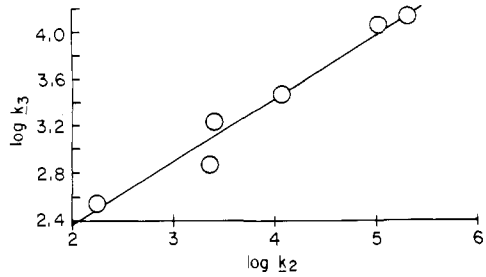

Figure 1. Plot of log k_3 vs log k_2 for several substituents. The slope of the least-squares line is 0.53, showing the lower sensitivity to substituent in ArS^- for the mesityl ketone than the phenyl ketone.

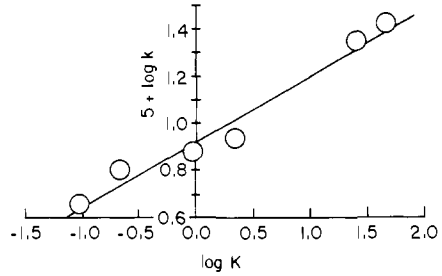

Figure 2. Plot of log k against log K for reaction 1. The least-squares line shown has a slope of 0.26, far lower than 0.5 expected for an uncharged transferring group. The substituents are from left to right 4-OCH_3, 4-CH_3, 4-F, 4-Cl, 3-CF_3, and 3,4-Cl_2.

were followed by stopped-flow methods similar to those established for the methyl iodide–thiophenoxide reactions,[21] using an excess of the bromo ketone to make the reactions follow a pseudo-first-order course.

Experimental errors in both tables are estimated first from the fit to the usual first-order plot, and in one case in Table I and in all of Table II, the reproducibility of two or more runs. The errors in the equilibria are less certain. Each equilibrated solution was subjected to several HPLC analyses, giving some suggestion of the analytical errors, but equilibrium constants far from unity may have errors as large as 20%.

The rates and equilibria were fitted to the Hammett equation. Reaction 1 fitted best when σ^0 was used and gave $\rho_{rate} = +0.84$ and $\rho_{eq} = +3.2$. Reactions 2 and 3 were fitted with σ^- (as before)[21] and gave $\rho = -3.9$ for reaction 2 and $\rho = -2.2$ for reaction 3. The quality of the fits was not very good, attributable in part to experimental error and in part to solvent effects on σ. A plot of log k_3 vs log k_2 is shown in Figure 1; the slope is 0.53, compared to the ρ ratio 0.56. Corresponding plots with the CH_3I data[21] do not have enough points in common to give a meaningful plot. The fact that reaction 2 actually represents the reaction was shown by the isolation and characterization of phenacyl thiophenoxide in high yield.

Discussion

The striking feature of reaction 1 is the fact that ρ_{rate} is much less than half of ρ_{eq}. The value for ρ_{eq} is quite comparable to the value 2.94 ± 0.14 for the analogous methyl transfers.[15] The ratio of these two ρ values, 0.26, is made more convincing by the plot of log k_1 vs log K_1 in Figure 2. The slope of the least-squares line is also 0.26 and is very clearly much less than a slope of $^1/_2$. This slope indicates a charge of −0.26 on the leaving group, assuming only that ρ_{rate} measures the change in the charge of the leaving group and that ρ_{eq} corresponds to the change from zero in the ester to −1 in the isolated anion. The attacking nucleophile must in these symmetrical reactions also have a charge −0.26 in the transition state. This requires the phenacyl group to bear the remaining charge of −0.48. Since we only "measure" by ρ_{rate}/ρ_{eq} the charge on the arenesulfonate groups, the charge on the

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transferring group is determined only by difference. We do not determine in any way the distribution of charge between the various carbon, hydrogen, and oxygen atoms, although it is reasonable to conclude that, as in a stable enolate ion, it is probably mostly on oxygen.

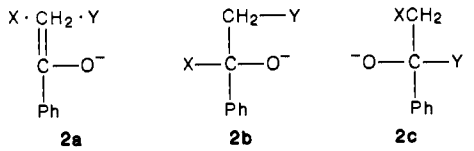
The plot also allows calculation of the identity rate for the unsubstituted benzenesulfonate leaving group of 8×10^{-5} M^{-1} s^{-1}, very close to the value of 1×10^{-4} (interpolated from data at 45 and 55 °C) for the corresponding methyl transfer.[12] If we assume that the Marcus equation holds for phenacyl transfer as it does for methyl transfer, we can deduce a ρ value for the identity rates for phenacyl transfer between arenesulfonates. The relation between Hammett ρ_{rate} for the leaving group variation, ρ_{eq} for the same process, ρ_{id} for the identity reaction, and δ (the charge on the transferring group) has been derived before.[15] Specifically $\rho_{id} = 2\rho_{rate} - \rho_{eq}$, in this case −1.5, a marked contrast to the positive value of +0.6 for the methyl transfer between arenesulfonates.[14] To the question of why there is no rate acceleration when these anionic contributions appear to be especially stabilizing, one can note that the stabilization from **1a** must for electrostatic reasons be less than with methyl transfer and also note that the difference in ρ_{rate} values is enough to make some of the phenacyl rates faster than the methyl rates. This comparison of methyl and phenacyl ignores any steric problems in the latter case.

The low slope of Figure 2 shows that the effect of structural change in the leaving group on the rate is small. Correspondingly, the sensitivity to structural change in the attacking nucleophile must be large; the charge on this group changes from −1 in the reagent to −0.26 in the transition state. Methyl transfers have been shown to have very nearly the same selectivities between nucleophiles independent of the leaving group.[21,22] If we can translate the results on methyl transfer to these phenacyl transfers, we can expect the high sensitivity of phenacyl transfers to nucleophile structure to persist with other leaving groups and nucleophiles. The study of reaction 2 was so motivated, and the large negative ρ for variation in the nucleophile is in accord with expectation. However, without a value[23] for the equilibrium ρ we cannot immediately estimate charge distribution or even, without some other calibration, assert that ρ really is large. Fortunately, we have for comparison reaction 4, and $\rho = -1.8$ under the same conditions has been measured.[21] The phenacyl transfer value is clearly much more negative than that for the methyl transfer, so the high sensitivity to nucleophile structure is quantitatively confirmed.

$$ArS^- + MeI \rightarrow ArSMe + I^- \qquad (4)$$

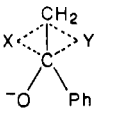
Equivalent to this interpretation of the large negative ρ is the use of ρ for the proton-transfer equilibrium as a measure of ρ for the alkyl-transfer equilibrium or the more general use of β_{nuc} to include non-Hammett changes. Then the charge change in the transition state on the thiophenoxide fragment is the slope of the plot of log k_2 vs pK_a, which is also the ratio of the two ρ values. The parallelism between the carbon-transfer equilibrium and the proton-transfer equilibrium is imperfect,[24] and furthermore, the acid strengths of thiophenoxides have not been measured in sulfolane, only in methanol[25] and in aqueous ethanol,[26] both with $\rho \sim 2.9$. An unreasonable β_{nuc} of >1 is calculated from these values, but the roughness of the assumptions and the fit to the log k vs pK_a plots, as well as the small number of points, renders this only qualitatively useful; the conclusion that β_{nuc} is exceptionally large is solid and in agreement with the conclusion based upon comparison with the CH_3I rates.

The negative charge on the transferring fragment does not distinguish between a pure enolate structure, such as **2a**, and the one often proposed either as an intermediate or a contributor, **2b**.



2a **2b** **2c**

Structure **2b** is, however, incompatible with the symmetry required for the identity or near-identity reactions; to achieve the necessary symmetry, not only must X bond to the carbonyl carbon, but so must Y to give the apparently fanciful structure **3** for the one



3

symmetrical transition state. An alternative, still compatible with the symmetry, is to have **3** as a transition state between structure **2b** and **2c**, each of which might represent a potential minimum along the reaction path. Although these choices appear rather forced and are not suggested by the theoretical treatments,[10-14] they cannot be summarily dismissed. All these structures have the common structural feature of the tetrahedral intermediate characteristic of nucleophilic addition to carbonyls.

A carbonyl group that is highly resistant to nucleophilic attack is that with a mesityl group attached to the carbonyl. Table II includes rates for attack of thiophenoxides on 2,4,6-trimethylphenacyl bromide, and the attack is facile. This experiment is not entirely novel; Pearson[8] and co-workers included this compound and its reaction with thiourea in the early study of α-halo ketones and related substances. When these rates were compared with those with the nucleophile pyridine, 2,4,6-trimethylphenacyl bromide fell in a class with phenacyl bromide and ethyl bromoacetate rather than in that with alkyl, benzyl, or allyl bromides. Nevertheless, Bunton[27] supported contribution of structures such as **2b**: "This model explains the very low reactivity of 2,4,6-trimethylphenacyl bromide to nucleophilic attack, because the carbonyl carbon atom is almost inaccessible to nucleophilic attack". In fact, the reactivity is not "very low". The mesityl bromo ketone reacts slightly more rapidly than ethyl bromide with pyridine and almost 10 times more rapidly than ethyl bromide with thiourea.[8] The fact that it is slower than unsubstituted phenacyl (a factor of 200 with pyridine and 700 with thiourea) is in part attributable to the electronic effect of the substituents in the ring. Thus *p*-bromophenacyl bromide reacts about half again as fast as the unsubstituted one with pyridine or thiourea,[8] and the reaction with benzoates or cinnamates with substituted phenacyl bromides has a ρ of +1.06.[28] Models do suggest a little steric interference of the *o*-methyl groups with the attacking and leaving groups in an ordinary linear S_N2 transition state, possibly accounting for some more of the lower rate.

In Table II the rates of 2,4,6-trimethylphenacyl bromide with thiophenoxides in sulfolane are with one exception lower than those of unsubstituted phenacyl bromide. The ρ value for the latter is more negative than for the former, but the latter ρ value, −2.2, is still more negative than for methyl iodide, $\rho = -1.8$. We conclude that trimethylphenacyl bromide shares some of the reactivity and some of the high sensitivity to the nature of the nucleophile, and thus they both have enolate contributions to the transition state (**2a**) rather than contributions of structures like **2b** or **2c**.

A classic paper by Bartlett and Trachtenburg[29] studies a cyclic structure, which prevents, as they point out, major contribution of structures like **2b** because the attacking group as well as the

(22) Lewis, E. S.; Douglas, T. A.; McLaughlin, M. L. *Adv. Chem. Ser.* **1987**, *No. 215*, 35.
(23) An equilibrium ρ for ArS^- (with PhSMe) has been measured,[17] but at very high temperatures in a different solvent. The values cannot be reliably extrapolated.
(24) Lewis, E. S. In *Investigations in Rates and Mechanisms of Reactions*; Bernasconi, C., Ed.; Wiley-Interscience: New York, 1986; p 889.
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(28) Srinivasan, C.; Shunmugasundaram, A.; Arumugam, N. *J. Chem. Soc., Perkin Trans. 2* **1985**, 17.
(29) Bartlett, P. D.; Trachtenburg, E. N. *J. Am. Chem. Soc.* **1958**, *80*, 5808.

leaving group must lie in the nodal plane of the carbonyl. However, the contribution of structure **2a** with a planar enolate is also not allowed by this structure; thus their experiment does not allow distinction between enolate contribution and carbonyl attack contribution. The study of 2,4,6-trimethylphenacyl bromide allows the distinction to be made, for the enol[30] or enolate of trimethylacetophenone is quite reasonable and the carbonyl addition is not.

The remaining question about phenacyl transfer transition states relates to the nature of the nucleophiles and leaving groups. The conclusion we would draw from the contribution of structure **2a** is that in order for **2a** to contribute heavily, not only must the transferring group be able to bear the negative charge, but the loss of negative charge from the nucleophile or leaving group must also be considered. With methyl transfers the structure analogous to **2a** increases in importance from X = Y = $ArSO_3$[15] (where the net charge on CH_3 is +0.2), to X = Y = Ar^+SeCH_3[16] (the methyl is still slightly positive), to X = Y = ArS[17] (with a zero or slightly negative charge), to X = Y = ArSe,[18] with a charge on the methyl of −0.24. We may expect a similar trend on the phenacyl transfers, but now starting even with the sulfonates at −0.48 charge on the phenacyl group in the transition state and becoming even more negative with the sulfur or selenium nucleophiles.

This trend among nucleophiles, $ArSO_3^- < ArSeMe < ArS^- < ArSe^-$, is plausibly related to the ionization potential of these nucleophiles, which must fall in this order (this does not appear to be the order of basicities, since H_2Se is reported to be a stronger acid than H_2S). The ionization potential measures the ease of conversion of X^- to $X^\bullet$, required for structure **2a**. The nucleophiles and leaving groups that promote **2a** are thus "soft" or "polarizable", and the rate enhancement with phenacyl compounds has long been known to be associated with these nucleophiles. Thus, some of the largest accelerations were found early by Conant for the reactions with iodide ion in acetone.[2] The reaction rates of phenacyl bromide compared to those of methyl iodide[4] show substantial acceleration of more than an order of magnitude for the nucleophiles chloride ion, thiourea, thiocyanate, and selenocyanate. The rates of reaction with first-row nucleophiles are within an order of magnitude the same for phenacyl bromide and methyl iodide. These rates appear to show much less special reactivity than originally claimed, but the difference is mostly in the reference. Conant's work[2] is usually referred to *n*-butyl chloride, which with most nucleophiles reacts a few thousand times more slowly than methyl iodide.

A further effect is that of the difference between neutral nucleophiles and anionic ones. The latter case, with which we have been mostly concerned, gives (at least in methyl transfers) transition states nearly as symmetrical as the identity transfers. These also give the largest rate accelerations with phenacyl systems. The neutral nucleophiles with all neutral alkyl halides give ionic products, the rates and equilibria are very solvent sensitive, and the transition states are often described as "early", in part because the rates are not very sensitive to the nature of the nucleophile. A good collection of arguments on this question has been presented.[31] At present we cannot fit these into the same picture as the cases with neutral alkylating agents and anionic nucleophiles (or presumably cationic alkylating agents with neutral neucleophiles). Some theoretical justification for the smaller rate enhancements in amine attack has been offered.[10,14] Nevertheless, the high reactivity of phenacyl compounds when compared to saturated halides persists as shown for example in Table 10 of Streitwieser's review.[3] When the character of the transition-state structure is measured by β_{nuc} most nucleophiles, including the neutral ones and the first-row ones in most solvents, show a value of β_{nuc} greater than a half with phenacyl bromide: phenoxyacetates (80% acetone–water), $\beta_{nuc} = 0.72$;[32] anilines (90% acetone–water), $\beta_{nuc} = 0.79$,[33] although for anilines in methanol,[34] $\rho_{rate}/\rho_{K_a} \simeq 0.3$; benzoate ions (50% aqueous acetone), $\beta_{nuc} = 0.523$; phenoxide ions (50% acetone), $\beta_{nuc} = 0.700$.[35] Okamoto[35] also collects values of β_{nuc} (called α) for a variety of other substitution reactions, nearly all with smaller β_{nuc} values.

These data generally support, but do not convincingly prove, the idea that substitutions on phenacyl (and other α-halocarbonyl and α-halo nitriles) are unusually sensitive to the structure of the nucleophile. When we look at the other examples of α-halo ketones, esters, and nitriles,[3] it is seen that the rates are highest for halogen derivatives of the most acidic compounds; i.e., $PhCOCH_2X > CH_3COCH_2X > EtOCOCH_2X$. This is predictable; in terms of enolate stabilization, the somewhat higher rate for chloroacetonitrile than for ethyl chloroacetate can be attributed to a smaller steric effect in the former, even though ethyl acetate is said to be a stronger acid than acetonitrile.

If enolate stabilization of the S_N2 transition state accounts for the high rates of α-halocarbonyl (and nitrile) substitutions, why is this not seen for α-halo sulfones and α-halonitro compounds, which also can give anions readily?

The case of α-halo sulfones has been answered by Bordwell.[36] The effect of the sulfone on nucleophilic attack on carbon is primarily steric, and the removal of the steric effect with only an attenuation of the electronic effect by interspersing a double bond between the sulfone and the halomethyl group leads to a compound of slightly enhanced reactivity. This demonstration followed that of Bartlett and Rosen,[37] who demonstrated that the unreactivity of neopentyl halides is primarily steric in nature.

The reported unreactivity of halonitromethane and 1-halo-1-nitroalkanes is in some ways more difficult to nail down. There are virtually no established cases of substitution of halogen on carbon in these systems. Halonitromethanes are sterically similar to isobutyl halides, which react about 10^3 times more slowly than the corresponding methyl halides. Thus, a little of the low substitution reactivity is attributable to steric effects, but clearly not enough to account for no examples at all. The explanation apparently comes from the facile presence of alternative reaction courses. With bases, the significantly acidic halonitromethanes can easily lose a proton. For example, for chloronitromethane, $pK_a = 6.2$.[38] The rate constant for the attack even of water as a base on bromonitromethane is 1×10^{-5} M^{-1} s^{-1} at 25 °C in water,[39] and the methanolysis of phenacyl bromide is much slower than this.[34] Stronger bases must be even faster. The proton-loss reactions are therefore at least comparable in rate with substitution reactions on phenacyl bromide. In studies in protic solvents this would be irrelevant unless the bromonitroalkane were extensively converted to its anion, which would be the case if strong bases were used, or (as may very likely be the case) reversion to the nitro compound from its anion is not the major reaction of this nitronate anion.

The other facile reaction of halonitro compounds is the nucleophilic attack on the halogen:

$$BrCH_2NO_2 + Nu^- \rightleftarrows NuBr + \bar{C}H_2NO_2 \qquad (5)$$

Thus the bromination or iodination of nitro compounds is perceptibly reversible,[40] and on a preparative scale the reaction of bromonitromethane with benzenesulfinate ion, originally said to give the sulfone, has been shown to give an essentially quantitative yield of nitromethane.[41] However, a rare example of substitution on carbon has been found in the reactions of a few weak nu-

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Table III. Melting Points and Accurate Masses for the Phenacyl Arenesulfonates[a]

X	mp[b]/°C	M^+ calcd	M^+ found
3,4-Cl_2	86.0–86.2	343.9677	343.9686
3-CF_3	71.0–71.2	344.0330	343.0331
4-Cl	95.0–95.2	310.0066	310.0071
4-F	94.5–94.7	294.0362	294.0355
H	81.0–81.5	276.0456	276.0460
4-Me	94.5–95.0	290.0613	290.0613
4-OMe	128.0–128.5	306.0562	306.0560

[a] All esters crystallized as white needles from ethanol. Arene = X-substituted benzene. [b] Melting points by Fisher-Johns apparatus, uncorrected.

Table IV. ^1H NMR Chemical Shifts[a] and Assignments for the Arenesulfonate Fragment for the Phenacyl Arenesulfonates of Eq 1

X[b]	H2	H3	H4	H5	H6	CH_2	H(X)
3-CF_3	8.33[c]		7.93	7.96[d]	8.31	5.72	
3,4-Cl_2	8.14[c]			*e*	*e*	5.69	
4-Cl	7.91	7.61		7.61	7.91	5.41	
4-F	*f*	*g*		*g*	*f*	5.58	
H	7.88	7.65[h]	*i*	7.65[h]	7.88	5.42	
4-Me	7.82	7.42		7.42	7.82	5.37	2.39
4-OMe	7.86	7.07		7.07	7.86	5.33	3.85

[a] In ppm, referenced to either CD_2HCN at 1.93 ppm or $(CD_2H)_2C{=}O$ at 2.04 ppm. All peaks are doublets with $^3J_{H-H}$ = 8.0–9.0 Hz, unless otherwise stated. [b] X is the substituent in benzenesulfonate. [c] Singlet. [d] Triplet. [e] Overlapping at 7.90–7.98 ppm. [f] Multiplet: 8.06–8.11 ppm. [g] Multiplet: 7.41–7.54 ppm. [h] Triplet, *J* = 8 Hz, overlapping H4. [i] Triplet, overlapping with H(3,5).

cleophiles with bromonitromethane.[42] The attack on bromine is more common. Halonitro compounds are therefore typical "positive halogen" compounds, and the S_N2 reaction can only compete rarely with both of these faster reactions; the common failure to observe the S_N2 is understandable. There are also examples of this nucleophilic attack on halogens occurring in the α-halo sulfones.[43]

Experimental Section

Materials. All reagents, unless otherwise stated, were obtained from Aldrich. Sulfolane was obtained from Phillips and purified by the literature[44] method. The phenacyl sulfonates were all synthesized by the reaction of 1-phenyl-2-bromoethanone, hereafter called phenacyl bromide, with the appropriately substituted silver sulfonate in acetonitrile solvent.

The silver salts were made by neutralizing the appropriate sulfonyl chloride or sulfonic acid with a small excess of silver oxide. They were isolated at pH 5.5, recrystallized from water, and stored in amber bottles in a desiccator over silica gel and calcium hydride. All the salts are snow-white crystalline solids which quickly turn gray upon exposure to light.

The phenacyl esters all crystallized as white needles from ethanol and were >98.5% pure by HPLC. The major impurity (ca. 1%) was phenacyl alcohol. The remaining impurities, <0.5%, were present also in the starting material, phenacyl bromide. Interestingly, phenacyl alcohol was not observed in either the mass spectra or the ^1H NMR spectra of the pure esters, suggesting either that those methods were not sensitive enough or that hydrolysis occurred near the injection point of the HPLC column. All esters were characterized with satisfactory high-resolution mass spectra (Table III), ^1H NMR (Table IV), and ^{13}C NMR (Table V). The NMR spectra were taken in CD_3CN or $(CD_3)_2C{=}O$. The phenacyl phenyl proton chemical shifts are the same in all the sulfonate esters: *o*, δ 7.83 (d); *m*, δ 7.48 (t); *p*, δ 7.63 (t). All *J* values were 7.5 ± 1 Hz.

Phenacyl 4-Fluorobenzenesulfonate. Silver oxide (25.5 g, 0.11 mol) was added in portions to a rapidly stirred slurry of 4-fluorobenzenesulfonyl chloride (19.5 g, 0.10 mol) in water (300 mL). The resultant gray suspension (pH 5.5) was filtered through a fine-porosity Büchner filter to remove excess silver oxide and silver chloride, and the clear supernatant liquid evaporated to yield silver 4-fluorobenzenesulfonate in almost quantitative yield. The salt was dried on the filter and then in a vacuum desiccator and used in the next step.

Silver 4-fluorobenzenesulfonate (13.4 g, 0.05 mol) was added quickly to a 500-mL boiling flask containing a rapidly stirred solution of phenacyl bromide (purified by recrystallization from ethanol) in rigorously dried acetonitrile (300 mL) and the flask was then tightly stoppered. The initially colorless solution immediately gave a pale green suspension, which was left stirring overnight. The solvent was removed in vacuo and the product was extracted from the resulting green solid with ether (4 × 100 mL). The remaining residue, assumed to be almost pure silver bromide, was kept. The ethereal layers were combined, dried ($MgSO_4$, 50 g) and evaporated to give the phenacyl ester in almost quantitative yield but contaminated with phenacyl alcohol. Three recrystallizations from ethanol afforded pure product but reduced the yield to ca. 80%. The melting points and high-resolution molecular ion masses are given in Table III; the ^1H and ^{13}C NMR spectra are given in Tables IV and V, respectively.

Attempts to prepare the 4-NO_2, 3-NO_2, and 4-CN derivatives by the above method all failed, yielding pure phenacyl alcohol as the only product. Modifications of the above preparation to rigorously exclude water (e.g., by carrying out the extraction with low-boiling petroleum ether rather than diethyl ether and removing all solvents with a mechanical pump, not the aspirator) also failed, again giving the pure alcohol. The alternative route using phenacyl alcohol and the appropriately substituted sulfonyl chloride with pyridine in rigorously dried acetonitrile also gave the same product.

More disappointingly, *all* the above methods failed for the corresponding 2,4,6-trimethylphenacyl sulfonate esters, none of which were made, even under the most mild conditions: the product in each case was 2,4,6-trimethylphenacyl alcohol, as characterized by ^1H and ^{13}C NMR and by its mass spectrum.

Sodium 3,4-Dichlorobenzenesulfonate. A solution of purified silver 3,4-dichlorobenzenesulfonate (1.60 g, 0.005 mol) in water (20 mL) was added to a stirred solution of sodium chloride (AnalR; 0.292 g, 0.005 mol) in water (10 mL) in a 50-mL beaker at room temperature. The white precipitate of silver chloride was filtered off and kept. The remaining solution was evaporated to dryness and the resultant white solid recrystallized from ethanol to yield sodium 3,4-dichlorobenzenesulfonate (87.5%) (dried in vacuo and kept in a desiccator over silica gel and calcium hydride).

2,4,6-Trimethylphenacyl bromide was made by the literature[8] method in 66.8% yield (from the ketone): mp 53.5–54.5 °C (uncorr) (lit. mp 54 °C, 54–55 °C); mass spectrum, 240.0148 (calcd 240.0150).

Phenacyl Thiophenoxide. Thiophenol (11.1 g, 0.11 mol) was added quickly to a solution of sodium hydroxide (4.0 g, 0.10 mol) in methanol (200 mL) in a 500-mL boiling flask. The solvent was removed in vacuo to leave a thick syrup to which was added a solution of phenacyl bromide (19.9 g, 0.1 mol) in sulfolane (250 mL). The resultant slurry was stirred vigorously at room temperature for 15 min and water (200 mL) was then added to the mixture. The products were extracted with diethyl ether (4 × 200 mL), and the ethereal layers were combined, dried ($MgSO_4$; 50 g), and evaporated to yield buff-colored needles of phenacyl thiophenoxide in 98.3% yield: mp 149.5–151 °C; mass spectrum, 228.0604 (calcd 228.0609). HPLC analysis of the reaction mixture on the reversed-phase column with 1/1 (v/v) MeCN/water as mobile phase showed the major peak accounted for 98.5% of all detected peaks at 250 nm. The major impurity (0.8%) was thiophenol.

Kinetics. The reactions of eq 1 were carried out under argon in 18-mm (o.d.) glass tubes (equipped with a septum seal) suspended in a 20-L silicone oil bath. The bath temperature was maintained at 50.0 ± 0.1 °C with a Bayley Instruments Model 253 precision temperature controller and was checked periodically with a thermometer calibrated to 0.1 °C.

Kinetic runs were started by weighing the ester into a 10-mL volumetric flask containing a solution of the nucleophile, sodium benzenesulfonate (previously purified by recrystallization from ethanol), and a large excess (ca. 2 equiv) of 18-crown-6 in purified solfolane and then diluting to the mark. The purpose of the excess is only to increase the rate of solution. Typical initial concentrations were [ester] = 0.5 M and [$NaSO_3Ph$] = 10^{-2} M, i.e., with a ca. 50-fold excess of the ester over the nucleophile, thereby ensuring pseudo-first-order kinetics throughout. Even at these low initial concentrations, and despite the presence of excess crown ether, the sodium benzenesulfonate dissolved only grudgingly, and it was often found necessary to heat the volumetric flask with a hot-air gun and then allow it to cool in a desiccator over silica gel and calcium hydride before weighing in the ester.

Samples (ca. 0.1 mL) were removed from the reaction mixtures by using a 0.25-mL syringe with a 9-in. Luer-lok needle at intervals ranging from ca. 30 min for the fast reactions (e.g., with the 3,4-dichloro-

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Table V. ^{13}C NMR Chemical Shifts[a] and Assignments for the Phenacyl Arenesulfonates of Eq 1[b]

X	C1	C2	C3	C4	C5	C6	CH_2	C=O	C(X)
3-CF_3	*c*	131.6[d]	132.3[e]	125.6[f]	131.8	132.6	72.4	191.1	126.1[g]
3,4-Cl_2	137.4	132.7	*h*	134.1[i]	128.7	130.7	72.6	191.1	
4-Cl	141.3	130.8	130.7	135.5	130.7	130.8	72.4	191.7	
4-F	133.4	132.0[j]	117.5[k]	166.7[l]	117.5[h]	132.0[j]	71.9	191.1	
H	136.7	130.5	128.8	135.3	128.8	130.5	72.0	191.7	
4-Me	133.6	131.0	128.8	146.6	128.8	131.0	71.8	191.7	21.7
4-OMe	127.8	131.1	115.6	165.1	115.6	131.1	71.6	191.9	56.6

[a] In ppm from TMS measured relative to internal acetone-d_6 at 29.81 ppm or CD_3CN at 1.30 ppm. [b] Phenacyl ring carbon chemical shifts are constant (to within 0.1 ppm) and are as follows: ipso, 134.8 ppm; *o*, 129.8 ppm; *m*, 128.8 ppm; *p*, 135.1 ppm. [c] Overlapped. [d] Quartet: $^3J_{C-F}$ = 2.3 Hz. [e] Quartet: $^2J_{C-F}$ = 33.2 Hz. [f] Quartet: $^3J_{C-F}$ = 3.0 Hz. [g] Quartet: $^1J_{C-F}$ = 271.8 Hz. [h] Overlapped. [i] C3 and C4 assignments are interchangeable. [j] Doublet: $^3J_{C-F}$ = 10.1 Hz. [k] Doublet: $^2J_{C-F}$ = 23.3 Hz. [l] Doublet: $^1J_{C-F}$ = 261.2 Hz.

benzenesulfonate ester) to ca. 20 h for the slowest (the *p*-OMe ester); similarly, t_∞ values (>7 half-lives) were taken in triplicate over periods ranging from ca. 1 day to 2 weeks. All samples were analyzed by HPLC using a Kontron 414LC pump with a Valco C6W manual injection valve and a Spectroflow 757 UV detector operating at 250 nm. With the singular exception of X = OMe, all reaction mixtures were followed in reverse phase using a 25-cm Custom LC C18 ODS column and 1/1 (v/v) MeCN/water as mobile phase. The samples were diluted ca. 10:1 (v/v) with acetonitrile prior to injection. Typical operating parameters were as follows: injection volume = 2 μL; flow rate = 1.9 mL min^{-1}; pressure = 1800 psi; retention time = 2.11 min (for $PhCOCH_2OSO_2Ph$). All the substituted esters with the exception of 4-OMe had longer retention times and were therefore readily resolved from the product. For X = OMe, this ester was resolved from the unsubstituted ester with a 15-cm Custom LC silica (3 μm) column with neat chloroform as dilutant and mobile phase. Typical operating parameters were as follows: injection volume = 3 μL; flow rate = 1.5 mL min^{-1}; pressure = 2000 psi; retention times = 3.95 min (for $PhCOCH_2OSO_2Ph$) and 5.58 min (for the 4-OMe substituted ester).

Peak areas were obtained with an HP 3390A integrator. Reactions were followed to ca. 2–3 half-lives by observing the increase in the area of the very small product peak using the starting ester peak as internal standard. Pseudo-first-order rate constants were therefore obtained from the exponential approach to the "infinity" value. Knowing the initial concentration of the standard then affords the second-order rate constant according to

$$k_2 = k_{obsd}/[\text{standard}] \quad (6)$$

In one case, X = Me, the validity of the method was checked by repeating the run with twice the excess (i.e., ca. 1 M) of phenacyl ester. The resultant second-order rate constant, $k_2 = (6.08 \pm 0.25) \times 10^{-5}$ M^{-1} s^{-1}, is the same (within experimental error) as the value given in Table I.

All the reactions of eq 2 and 3 were followed under pseudo-first-order conditions in sulfolane/dimethyl sulfone eutectic as solvent[45] in a Durrum Series D100 stopped-flow spectrophotometer operating in the absorbance mode connected to a Biomation 805 waveform recorder and a nonretentive Tektronix 545A oscilloscope. The Biomation output was interfaced with a Digital PDP 11/70 computer. A linear least-squares treatment of eq 7 afforded the pseudo-first-order rate constants, k_{obsd}.

$$\ln [V_t - V_\infty] = k_{obsd}t \quad (7)$$

(45) The measurement temperature is well above the melting point of pure sulfolane; the melting point was depressed for convenience of handling at room temperature.

V is the digitized output voltage (proportional to absorbance) and *t* is the channel number multiplied by the time base, i.e., the spacing of the digital sampling of *V*. The "time base" varied from 10 μs for the fastest reaction (X = Me; eq 2) to 50 ms for the slowest (X = 3,4-Cl_2; eq 2). All reactions were followed to t_∞ but the pseudo-first-order plot was defined over typically 90% reaction using ca. 7–10 data points. The initial concentrations of phenacyl and trimethylphenacyl bromide were ca. 5×10^{-3} M and those of the thiophenoxide anions were ca. 5×10^{-5} M, ensuring excellent pseudo-first-order kinetics. Because all the thiophenoxide anions are very air sensitive (yielding the disulfides), they were generated in situ by adding excess triethylamine or DBU (ca. 20–100-fold) or a few KOH pellets to a freshly made volumetric solution of the appropriate thiol; additionally, all the solutions were kept rigorously dried by the addition of calcium hydride to the volumetric flasks and even to the stopped-flow storage syringes.

Equilibria. The equilibrium constants of eq 1 were determined by a procedure analogous to that for the rate studies (vide supra) except that the initial concentrations of reactants were comparable at ca. 0.01–0.05 M. The limiting factor here is the solubility of the sodium benzenesulfonates in sulfolane, which cannot go much above 0.05 M even with excess crown ether.

The equilibrium constants, *K*, are defined according to the expression

$$K = \frac{ac^2}{bc + b - ac} \quad (8)$$

a and *b* are the initial concentration of ester and nucleophile, respectively, and *c* is the ratio of the concentration of product ester over starting ester at equilibrium and is obtained directly from the peak areas after applying a small correction for the ratio of the extinction coefficients of the two esters at 250 nm.

For X = Me and OMe, the equilibrium constants were determined in the forward direction as written in eq 2. For X = 3,4-Cl_2, the equilibrium constant was determined in the reverse direction, again with comparable initial concentrations of the nucleophile and ester; the value obtained, *K* = 0.0216, is given as the inverse in Table I. For X = CF_3, Cl, and F, the equilibrium constants were determined in the reverse direction against the 3,4-dichloro anion. The values are *K* = 0.562, 0.048, and 0.021, respectively. Dividing each of these by 0.0216 gives the equilibrium constants quoted in Table I for X = CF_3, Cl, and F, respectively.

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