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(29) When the reaction solution was kept at 25 °C in benzene, conditions previously used to good advantage in the reaction of **1** with arylthiosulfonates (see ref 16), dark-colored intractable material resulted. Therefore the typical procedure consisted in mixing the reactant at 25 °C and cooling immediately thereafter.

# Reactions of Activated Arenesulfonates with Oxygen and Nitrogen Nucleophiles. Hydroxide Ion and Micellar Catalysis

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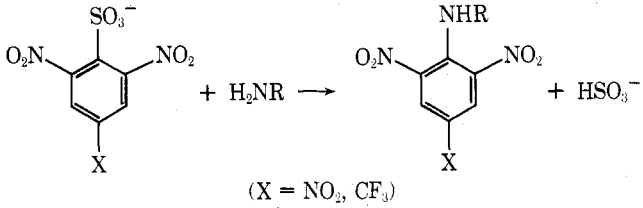
The reactions of 2,4,6-trinitrobenzenesulfonate ion (TNBS) and 2,6-dinitro-4-trifluoromethylbenzenesulfonate ion (TFBS) with $OH^-$ are catalyzed by $OH^-$ as are the reactions with aniline and glycinate ion, and the kinetic parameters have been evaluated in terms of a mechanism in which a tetrahedral intermediate decomposes to products spontaneously or with hydroxide ion catalysis. Decomposition of the tetrahedral intermediate can be followed spectrophotometrically for reaction of TNBS with $OH^-$ in aqueous $Me_2SO$. At relatively low pH (<10.5), cationic micelles of cetyltrimethylammonium bromide (CTABr) catalyze the reactions of TNBS by the following factors: glycinate, 6; leucinate, 38; phenylglycinate, 174; aniline, 30. The reaction of glycineamide is slightly inhibited by CTABr. In CTABr the hydroxide ion catalysis of reactions of TNBS with aniline or $OH^-$ is considerably less than at relatively low pH. The reaction of phenoxide ion with TNBS is catalyzed by a factor of 2000 by CTABr.

Activated arenesulfonates, e.g., 2,4,6-trinitrobenzenesulfonate ion (TNBS) and 2,6-dinitro-4-trifluorobenzenesulfonate ion (TFBS), react readily with primary and secondary amines and are useful protein modifying agents.[1] The reaction of TNBS with amino acid anions is reportedly cleanly second order.[1a,b] Aromatic nucleophilic substitution by uncharged




(X = $NO_2$, $CF_3$)

and anionic nucleophiles is catalyzed by cationic micelles,[2-5] which also speed formation of the tetrahedral intermediate.[6,7] Addition to give the tetrahedral intermediate is generally rate limiting for reactions of halonitrobenzenes in polar hydroxylic solvents.[13,14]

The polarities of micellar surfaces are similar to those of many proteins,[10] so that nucleophilic aromatic substitution catalyzed by a micelle should be a better model for protein modification than reaction in water, and the effects of cationic micelles of cetyltrimethylammonium bromide (CTABr) upon reactions of TFBS and 2,4-dinitrofluorobenzene were examined.[15] For both reagents micellar catalysis increases with increasing hydrophobicity of the nucleophile, as is generally found,[8-12] but the effect is much more marked for reactions of TFBS.

In this paper we extend the investigation to reactions of TNBS and we show that for reactions with hydroxide and glycinate ion and aniline there is a base-catalyzed reaction suggesting that the breakdown of the tetrahedral intermediate can become rate limiting, which complicates discussion of the micellar catalysis. However, reaction of phenoxide ion with TNBS is very strongly catalyzed by CTABr, showing the role of substrate hydrophobicity in a non-base-catalyzed nucleophilic aromatic substitution.

## Experimental Section

**Materials.** The preparation of the surfactants and most of the reagents followed methods already described.[4,5,15] The tertiary amines were treated with tosyl chloride to remove secondary or primary amines and then distilled.

**Kinetics.** All the reactions were followed spectrophotometrically in water, at 25.0 °C, using Gilford spectrophotometers[15] at the following wavelengths: amino acid derivatives, 420 nm; phenoxide ion, 446 nm; $OH^-$, 430 nm; aniline, 435 nm.

The nucleophile was in large excess over the arenesulfonate, which was $1–4 \times 10^{-5}$ M, and the integrated first-order rate constants, $k_\psi$, are in $s^{-1}$, and the second-order rate constants, $k_2^{obsd}$, $M^{-1}\ s^{-1}$, were calculated by dividing $k_\psi$ by the reagent concentration. It was necessary to use low concentrations of TNBS because otherwise there was precipitation during reactions with aniline in the absence of surfactant. The rate constants for reactions with amines in water were unaffected, within experimental error, by up to threefold changes in reagent concentration or for reaction with aniline by increases in pH from 7.5 to 10.

The pH was such that the amino acids were wholly in the reactive anionic form, and 0.027 M carbonate buffer was used, except for re-

Table I. Reactions of Amines in the Absence of Surfactant[a]

| Reagent | $k_2$, $M^{-1}$ $s^{-1}$ TNBS | TFBS |
|---|---|---|
| Glycinate | 6.41 | 0.15[b] |
| Leucinate | 4.86 | 0.029[b] |
| Phenylglycinate | 8.47 | 0.061[b] |
| Glycineamide | 1.45 | 0.037[b] |
| Aniline[c] | 2.99 | 0.00105 |

[a] At 25.0 °C in aqueous solution. [b] Reference 15. [c] pH 7.5.

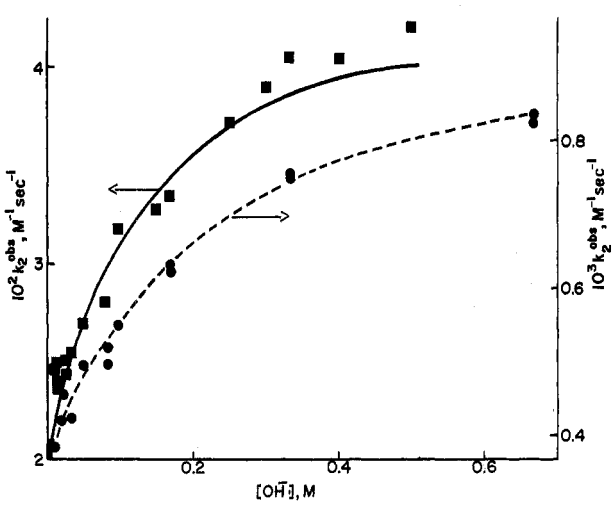



**Figure 1.** Effect of $OH^-$ upon the second-order rate constants of $OH^-$ with TNBS (solid line) and TFBS (broken line). The lines are calculated.

actions with tertiary amine buffers. Redistilled, deionized, $CO_2$-free water was used for the kinetic solutions.

The amines and phenoxide ion are so much more reactive than hydroxide ion that its reaction can be neglected. The reaction of phenoxide ion with TNBS was shown to give the phenoxy ether initially, by comparison of the spectra obtained by repetitive scanning of the reaction mixture with authentic material prepared from picryl chloride.[16] The phenoxy ether readily hydrolyzes under the reaction conditions,[13] so reaction was followed at 446 nm, which is an isosbestic point. There was a small change in the spectra of the products of reaction with the amines, but it was so much slower than attack of the amines on TNBS that it did not complicate the rate measurements.

## Results and Discussion

Reactions of amino acid anions with TNBS are cleanly second order, and are not catalyzed by weak bases,[1a,b] but the reaction of TFBS with hydroxide ion is of greater than first order with respect to hydroxide ion,[15] suggesting that attack of hydroxide ion is assisted by a second hydroxide ion. We subsequently found that reactions of aniline and glycinate anion are catalyzed by added hydroxide ion, suggesting that an initially formed tetrahedral intermediate decomposes spontaneously at low pH (pH <10) but with hydroxide ion catalysis at high pH. Most of our experiments with amines were at pH such that there was no hydroxide ion catalysis, and these will be considered first.

**Reactions of Amines in the Absence of Surfactants.** The second-order rate constants for reactions of amines with TNBS and TFBS at relatively low pH are in Table I. TFBS and 2,4-dinitrofluorobenzene have similar reactivities toward amines,[15] but TNBS is much more reactive because of powerful electron withdrawal by the *p*-nitro group. Hydroxide ion catalysis of amine reactions will be discussed after consideration of the reactions of TNBS and TFBS with hydroxide ion.

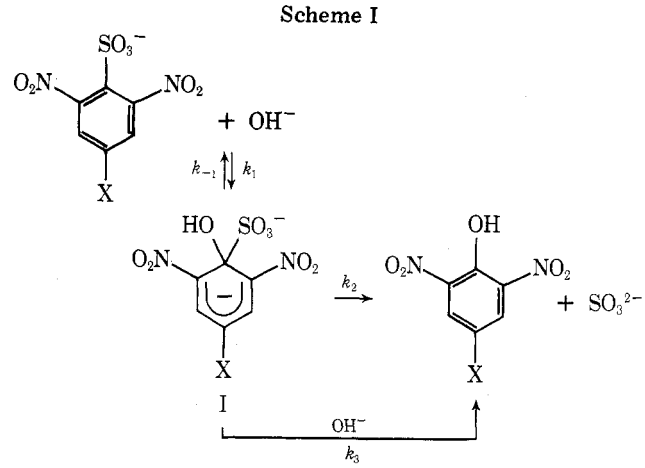
**Reactions with Hydroxide Ion.** The second-order rate constants for reactions of TNBS and TFBS with hydroxide ion increase with increasing hydroxide ion concentration, but tend to level off at relatively high concentrations of hydroxide ion (Figure 1). These results were unexpected because in polar hydroxylic solvents nucleophilic aromatic substitutions with oxygen nucleophiles are typically second-order reactions,[13] but reactions with amines are often base catalyzed,[13,14,17] suggesting that the high order with respect to hydroxide ion in reactions of these activated arenesulfonates is due to intervention of a base-catalyzed reaction (Scheme I).

Table II. Analysis of the Rate Constants for Reactions with Hydroxide Ion[a]

| Substrate | $k_1$, $M^{-1}$ $s^{-1}$ | $k_2/k_{-1}$ | $k_3/k_2$, $M^{-1}$ $s^{-1}$ | $k_3/k_{-1}$, $M^{-1}$ $s^{-1}$ |
|---|---|---|---|---|
| TNBS | $4.5 \times 10^{-2}$ | 0.8 | 19 | 15 (15) |
| TFBS | $1.0 \times 10^{-3}$ | 0.6 | 11 | 6.4 (6.9) |

[a] The values in parentheses are estimated from the initial slopes of plots of $k_2^{obsd}$ against $[OH^-]$.

Scheme I




X = $CF_3$, $NO_2$

Applying the steady-state approximation gives

$$k_2^{obsd} = k_1(k_2 + k_3[OH^-])/(k_{-1} + k_2 + k_3[OH^-]) \quad (1)$$

where $k_2^{obsd}$ is the second-order rate constant with respect to $OH^-$ and the arenesulfonate, and neglecting electrolyte effects of NaOH upon the individual rate constants.

Equation 1 can be rearranged to

$$k_2^{obsd}/(k_1 - k_2^{obsd}) = (k_2/k_{-1}) + (k_3[OH^-]/k_{-1}) \quad (2)$$

which should give a linear relation between the left-hand term and $[OH^-]$ if the correct value of $k_1$ is used. We chose arbitrary values of $k_1$ and selected that which gave the best linear fit, and thus calculated $k_2/k_{-1}$ and $k_3/k_{-1}$ (Table II).

Equation 1 reduces to eq 3 when $[OH^-] \rightarrow 0$

$$k_2^{obsd} = k_1k_2/(k_{-1} + k_2) \quad (3)$$

and the extrapolated values of $k_2^{obsd}$ (Figure 1) agree reasonably well with the predicted values.

Another test of equation is to use the initial slope of a plot of $k_2^{obsd}$ against $[OH^-]$. Differentiation of eq 1 gives

$$\frac{k_3}{k_1k_{-1}}\frac{dk_2^{obsd}}{d[OH^-]} = \frac{k_3}{k_{-1} + k_2 + k_3[OH^-]} \quad (4)$$

From the experimental value of $dk_2^{obsd}/d[OH^-]$ (Figure 1) and the estimated values of $k_1$ and $k_2/k_{-1}$ (Table II) we calculate the values of $k_3/k_{-1}$, given in parentheses in Table II, which are in satisfactory agreement with the values obtained using eq 2.

Added salts increase $k_2^{obsd}$, and NaCl has a larger effect

Table III. Salt Effects upon Reaction of TNBS with Hydroxide Ion

| | Salt[a] | |
|---|---|---|
| [OH⁻], M | NaCl | $NaClO_4$ |
| 0.005 | 2.08 | 3.68 |
| 0.025 | 2.48 | 3.81 | 3.22 |
| 0.167 | 3.39 | 4.29 | 3.68 |
| 0.333 | 3.69 | 4.26 |

[a] Reactions with added salt are at $I = 1$.

Table IV. Reaction of TNBS in Tertiary Amines[a]

| $[Et_3N]$, M | [NMP], M | $10^2$ [OH⁻], M[b] | $10^4$ $k_\psi$, s⁻¹ | $10^2$ $k_\psi/[OH^-]$, $M^{-1}$ s⁻¹ |
|---|---|---|---|---|
| 0.0497 | | 0.45 | 1.26 | 2.8 (2.1) |
| 0.249 | | 1.04 | 3.08 | 3.0 (2.4) |
| 0.489 | | 1.46 | 4.12 | 2.8 (2.4) |
| | 0.0521 | 0.37 | 0.80 | 2.1 (2.1) |
| | 0.267 | 0.85 | 1.91 | 2.3 (2.3) |
| | 0.512 | 1.20 | 2.52 | 2.1 (2.4) |

[a] At 25.0 °C and [TNBS] = $3.9 \times 10^{-5}$ M; the values of $k_\psi/[OH^-]$ in parentheses are interpolated for reaction with NaOH. [b] Calculated from $pK_a$ of the amines.

Table V. Reaction of TNBS in Tertiary Amine Buffers[a]

| $R_3N$ | $[R_3N]/[R_3\overset{+}{N}H]$ | $[R_3N]$, M | $10^4$ $k_\psi$, s⁻¹ |
|---|---|---|---|
| $Et_3N$ | 4 | 0.032 | 2.09 |
| | | 0.064 | 2.65 |
| | | 0.128 | 3.01 |
| NMP | 2 | 0.032 | 0.77 |
| | | 0.064 | 0.81 |
| | | 0.128 | 0.92 |
| NMP | 4 | 0.032 | 1.19 |
| | | 0.064 | 1.39 |
| | | 0.128 | 1.65 |

[a] At 25.0 °C and [TNBS] = $3.9 \times 10^{-5}$ M at $I = 1$ (NaCl).

than $NaClO_4$, but carrying out the reaction at an ionic strength of 1 does not eliminate the dependence of $k_2^{obsd}$ on hydroxide ion (Table III).

The decomposition of the intermediate (I) to products probably requires loss of a proton from the hydroxyl group, and this ionization should be subject to a positive salt effect. Because NaCl and $NaClO_4$ have different salt effects, we see no simple way of allowing for the effects of NaOH as an electrolyte,[18] because it has to be present in relatively high concentration, and the rate constants in Table I may include a contribution due to an (undetermined) electrolyte effect. However, the high order with respect to hydroxide ion is not eliminated by working at constant ionic strength.

The decomposition of the intermediate (I) could be general base or specific hydroxide ion catalyzed. The usual test of carrying out the reaction in buffers of a given pH is not readily applicable at these high concentrations of hydroxide ion, but we used triethylamine and *N*-methylpyrrolidine (NMP) as sources of hydroxide ion, and found no catalysis by the tertiary amine.

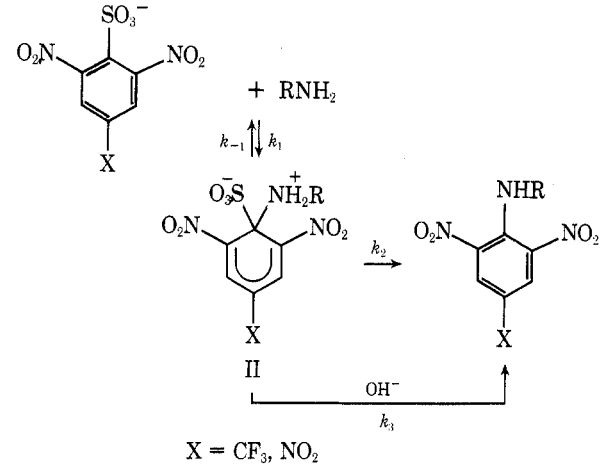
The reaction of TNBS was followed using a range of concentrations of tertiary amine (Table IV), and the concentrations of hydroxide ion were calculated from the values of $pK_a$ of 10.65 and 10.46 for triethylamine and *N*-methylpyrrolidine, respectively,[23] neglecting activity effects. (This neglect is probably not too serious because the ionic strengths of the solutions are low.) The second-order rate constants, $k_\psi/[OH^-]$, calculated in this way, agree reasonably well with the second-order rate constants, $k_2^{obsd}$, determined from reaction in sodium hydroxide (Figure 1). When reaction was carried out using fixed buffer ratios and ionic strength of 1 (with NaCl), the first-order rate constants increased, but not markedly, with amine concentration (Table V). The variations in $k_\psi$ with buffer concentration could well be due to the different concentrations of ammonium ions because there is no reason to believe that sodium and trialkylammonium ions will have the same salt effects; in fact there is evidence which suggests the opposite because the bulky anionic transition states could interact favorably with the bulky ammonium ions.[3b,19-22] It is difficult to carry out buffer dilution experiments if high buffer concentrations have to be used.

These experiments with tertiary amines suggest that the reaction is not general base catalyzed, but this conclusion is tentative because kinetic salt effects could complicate the situation and if the Bronsted coefficient, $\beta$, is close to unity the tertiary amines may not be basic enough to contribute to the catalysis by hydroxide ion, although often hydroxide ion is less basic kinetically than expected from its formal $pK$ value,[24] so that proton loss from I could be concerted with product formation.

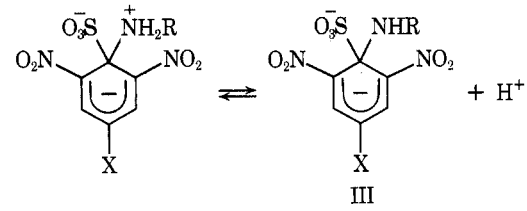
These hydroxide ion reactions involve dianionic tetrahedral intermediates, and dianionic Meisenheimer complexes have been observed in addition of hydroxide ion to 1,3,5-trinitrobenzene.[25]

**Hydroxide Ion Catalysis of Reactions with Amines.** Both TNBS and TFBS react much more rapidly with primary amines than with hydroxide ion, but the attack of amines is catalyzed by hydroxide ion (Tables VI and VII). The reaction is formulated in Scheme II, which is similar to Scheme I for reaction with hydroxide ion.

**Scheme II**




In the above scheme it is possible that decomposition of the intermediate (II) to products involves the ionization




followed by slow decomposition of the dianion (III), or a concerted process (cf. ref 13, 14, 17).

The kinetics can be treated using the method outlined for reaction with hydroxide ion, with the simplification that the amines, which are in relatively low concentration, do not act as base catalysts.

Rearrangement of eq 1 gives

Table VI. Hydroxide Ion Catalysis of Reactions of TNBS and TFBS with Aniline[a]

| | $k_2^{obsd}$, $M^{-1}$ $s^{-1}$ | |
|---|---|---|
| [NaOH], M | TNBS[b] | TFBS[c] |
| 0 | 2.99 (3.00) | 0.00105 (0.00105) |
| 0.010 | 5.87 (5.82) | |
| 0.015 | 6.92 (7.05) | |
| 0.020 | | 0.0035 (0.0034) |
| 0.025 | 9.18 (9.18) | 0.0040 (0.0040) |
| 0.033 | 10.5 (10.7) | 0.0047 (0.0050) |
| 0.040 | | 0.0056 (0.0058) |
| 0.050 | 13.7 (13.7) | 0.0077 (0.0070) |
| 0.084 | | 0.0115 (0.0108) |
| 0.100 | 18.7 (19.2) | |
| 0.150 | 24.2 (21.6) | |
| 0.167 | | 0.0227 (0.0195) |
| 0.333 | | 0.0420 (0.0355) |

[a] At 25.0 °C the values in parentheses are calculated (Table VIII). [b] 0.01 M $PhNH_2$. [c] 0.0333 M $PhNH_2$.

Table VII. Hydroxide Ion Catalysis of Reactions of TNBS with Glycinate Ion[a]

| [NaOH], M | $k_2^{obsd}$, $M^{-1}$ $s^{-1}$ |
|---|---|
| 0 | 6.41 (6.41) |
| 0.015 | 8.35 (8.34) |
| 0.023 | 9.16 (9.24) |
| 0.040 | 11.0 (10.8) |
| 0.090 | 14.3 (14.1) |
| 0.140 | 15.8 (16.4) |

[a] At 25.0°C with 0.01 M glycinate ion; the values in parentheses are calculated (Table VIII).

$$\frac{1}{k_2^{obsd}} = \frac{1}{k_1} + \frac{k_{-1}}{k_1(k_2 + k_3[OH^-])} \quad (5)$$

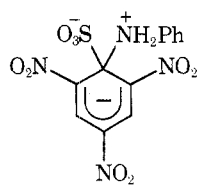
If $k_2^{OH}$ and $k_2^0$ designate the values of the observed second-order rate constant, $k_2^{obsd}$, in the presence and absence of hydroxide ion, we obtain

$$\frac{k_2^{OH}}{k_2^{OH} - k_2^0} = \frac{k_1 k_2}{k_{-1} k_2^0}\left(1 + \frac{k_2}{k_3[OH^-]}\right) \quad (6)$$

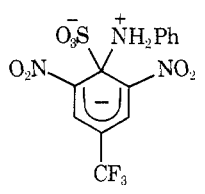
[In this formulation the observed rate constants are corrected for the minor contribution from a direct reaction of $OH^-$ with the substrate (Figure 1)].

Plots of $k_2^{OH}/k_2^{OH} - k_2^0$) against $1/[OH^-]$ are linear for reactions of aniline with TNBS and TFBS (Figure 2), and from the slope and the intercept we estimate $k_2/k_3$, and insertion of these values into eq 5 then gives $k_1$ and $k_{-1}/k_2$. The values of the various kinetic parameters are given in Table VIII, and the calculated values of $k_2^{obsd}$ agree reasonably well with the observed values (Tables VI and VII).

These results suggest that in the absence of added strong base the intermediates return to starting material much more readily than go to product, and the various kinetic parameters depend markedly on the structure of the reagents. Considering first the reactions with aniline, the values of $k_2/k_{-1}$ and $k_3/k_{-1}$ are much larger for the reaction with TNBS than with TFBS, probably because the strong electron withdrawal by the 4-nitro group allows easier proton loss from IV than from V, but the values of $k_3/k_2$ are very similar.



IV



V

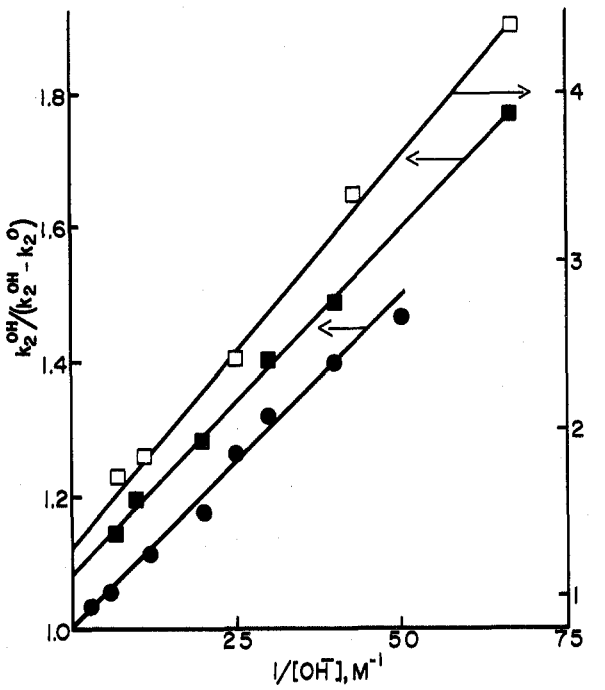
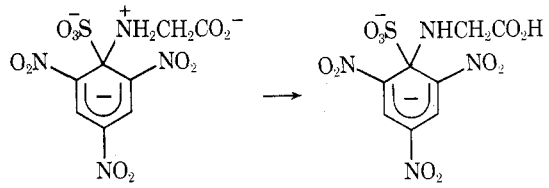



**Figure 2.** Analysis of the hydroxide ion catalyzed reactions of aniline (solid points) and glycinate ion (open points) with TNBS (■, □) and TFBS (●).

The pattern is different again for reaction with glycinate ion, where $k_2/k_{-1}$ is larger than for reaction with aniline. This difference was unexpected because the −I effect of the phenyl group should make IV a stronger acid than VI. The difference could be due to an intramolecular proton transfer to the carboxylate moiety of VI, because although the carboxylate ion



VI

is a weak base it is in a favorable position to accept a proton from the ammonium ion, and this intramolecular proton transfer could occur more readily than an intermolecular transfer to water.[26] This suggestion is consistent with the observation that $k_3/k_{-1}$ is similar for reactions of TNBS with aniline and glycinate ion (Table VIII), because $k_3$ involves proton transfer to $OH^-$.

This explanation suggests that the proton loss from the ammonium ion in the intermediate (VI) is part of the rate-limiting step of product formation and, by implication, that this is also true for reaction with aniline. The values of $k_3/k_2$ for reaction with aniline are smaller than expected if they were controlled by the equilibrium basicities of water and hydroxide ion (assuming that proton loss is a prerequisite for decomposition of the intermediates to products). Intramolecular proton transfer from an ammonium ion moiety to an *o*-nitro group has been considered as a route to the decomposition of tetrahedral intermediates, especially for reactions in nonpolar solvents.[14] Consistently, TNBS is more reactive than TFBS, but the difference is most marked for the reactions with aniline, not because the rates of nucleophilic attack are so different, but because the values of $k_2/k_{-1}$ and $k_3/k_{-1}$ are much lower for reaction of TFBS (Table VIII).

**Formation of Tetrahedral Intermediates.** The difference between the kinetic forms of the reactions of halobenzenes and

Table VIII. Analysis of the Base-Catalyzed Reactions with Amines

| Substrate | Amine | $k_2^0$, $M^{-1}$ $s^{-1}$ | $k_1$, $M^{-1}$ $s^{-1}$ | $k_2/k_{-1}$ | $k_3/k_{-1}$, $M^{-1}$ $s^{-1}$ | $k_3/k_2$, $M^{-1}$ $s^{-1}$ |
|---|---|---|---|---|---|---|
| TNBS | Aniline | 2.99 | 32.7 | 0.10 | 11.4 | 113 |
| TFBS | Aniline | 0.00105 | 0.123 | 0.01 | 1.05 | 105 |
| TNBS | Glycinate | 6.41 | 24.8 | 0.35 | 10.0 | 29 |

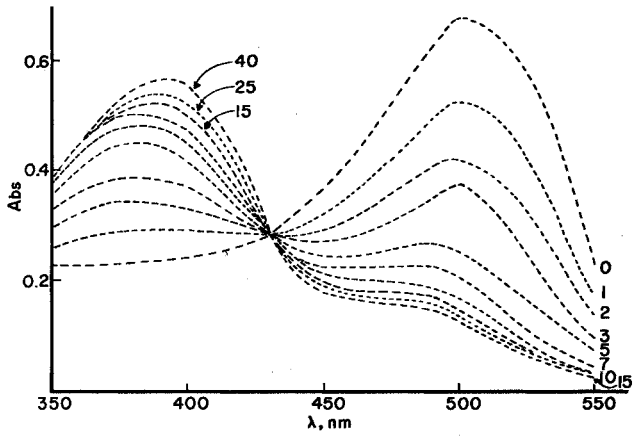



**Figure 3.** Repetitive scans of the spectrum of TNBS ($3.9 \times 10^{-5}$ M) and 0.333 M NaOH in DMSO–$H_2O$ (65:35 v/v) at 25 °C. The times are in minutes.

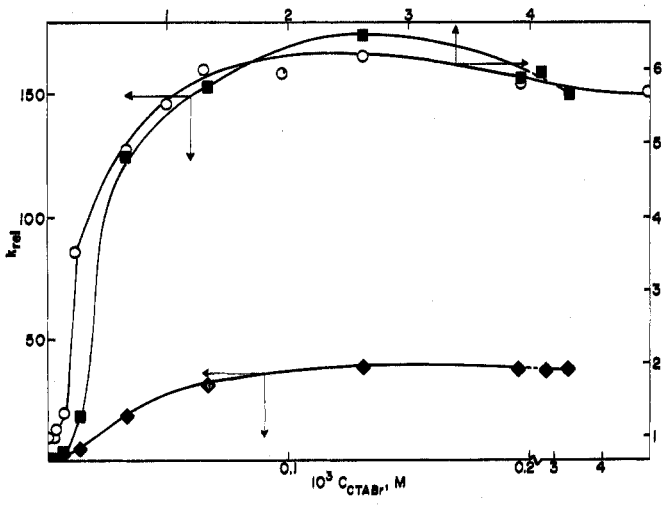



**Figure 4.** Micellar catalysis by CTABr of the reactions of $8.08 \times 10^{-4}$ M leucinate (♦), $1.44 \times 10^{-4}$ M phenylglycinate (■), and $10^{-3}$ M glycinate ion (○).

these activated arenesulfonates arises because the sulfite dianion should be a poorer leaving group than a halide ion and the strong electron withdrawal by the substituents in TNBS and TFBS should stabilize a tetrahedral intermediate.

Repetitive scans of the reaction mixtures in water gave no evidence for buildup of an intermediate, but we saw spectral evidence for intermediate formation between TNBS and $OH^-$ in aqueous DMSO.

In the reaction of TNBS with 0.333 M NaOH in $Me_2SO$–$H_2O$ 65:35 (v/v) at 25 °C there was an immediate appearance of a peak with $\lambda_{max}$ at 505 nm which gradually disappeared giving picrate ion, $\lambda_{max}$ 390 nm (Figure 3).

These observations show that activated arenesulfonates are useful substrates for dissection of the various steps of aromatic substitution, even for reagents such as $OH^-$ and solvents such as water, which generally give (rate limiting) nucleophilic addition.

**Micellar Effects on Reactions with Amino Acids.** Most of the amine reactions were followed at pH <10.5 where catalysis by hydroxide ion should be very small and with such low concentration of amine that its contribution as a base should be negligible. Most of the work was done using amino acid anions (Figure 4), and the pattern of micellar catalysis was similar to that observed earlier for reactions with TFBS,[15] but different from that with fluoro- or chloro-2,4-dinitrobenzene, where catalysis increased with increasing hydrophobicity of the amino acid, but not markedly so.[24] The micellar rate enhancements are summarized in Table IX. Cationic micelles of CTABr inhibit the reaction of glycineamide with TNBS (Table X), and the inhibition is more marked than with TFBS.[15] The micellar catalysis by CTABr tends to be larger for reactions of TFBS than for TNBS (ref 15 and Table IX), in line with the greater hydrophobicity of TFBS.

Table IX. Second-Order Rate Constants for Reactions of TNBS and TFBS in CTABr[a]

| Reagent | TNBS, $k_2^{obsd}$ | TFBS,[b] $k_2^{obsd}$ |
|---|---|---|
| Glycinate | 44 (6) | 8.7 (5.8) |
| Phenylglycinate | 1470 (174) | 14.8 (247) |
| Leucinate | 186 (38) | 2.7 (93) |
| Glycineamide | (<1) | (<1) |

[a] At 25.0 °C, the values in parentheses are rate enhancements by the micelle. [b] Reference 15.

Table X. Reaction of TNBS with Glycineamide in CTABr[a]

| $10^3$ [CTABr], M | $k_2$, $M^{-1}$ $s^{-1}$ |
|---|---|
| | 1.45 |
| 0.65 | 0.78 |
| 1.30 | 0.86 |
| 2.61 | 0.81 |
| 3.26 | 0.79 |
| 4.56 | 0.86 |

[a] At 25.0 °C with 0.0185 M Glycineamide at pH 9.5 (0.027 M carbonate).

All the kinetic evidence suggests that nucleophilic addition is the slow step for reaction with the halodinitrobenzenes in water,[13] whereas for reactions of the arenesulfonate, it is decomposition of a tetrahedral intermediate, and one can explain the different patterns of micellar catalysis in these terms. Increasing the hydrophobicity of the amine will increase the micellar catalysis of the formation of the tetrahedral intermediate by nucleophilic attack upon either the fluorobenzene or the arenesulfonate. But reaction of the arenesulfonate involves a partitioning of the intermediate which can go on to products or revert to reactants, and drawing the intermediate more deeply into the Stern layer of the micelle should assist decomposition to product by increasing the rate of ionization of the ammonium ion,[29] because of unfavorable coulombic interactions between it and the cationic head groups of the micelle (Scheme III). Thus the bulkier the group R the more

Scheme III

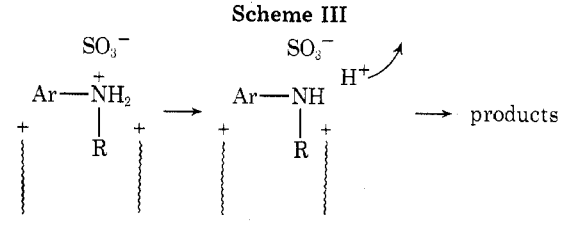


Table XI. Micellar Catalysis of the Reaction of TNBS with Aniline[a]

| $10^4$ [CTABr], M | $k_2^{obsd}$, $M^{-1}$ $s^{-1}$ | $10^4$ [CTABr], M | $k_2^{obsd}$, $M^{-1}$ $s^{-1}$ |
|---|---|---|---|
| | 3.21 | 10.0 | 94.0[c] (30) |
| | 2.97[b] | 10.0 | 87.4[c,e] (28) |
| | 3.15[c] | 10.0 | 92.2[d] (29) |
| | 3.21[d] | 20 | 88.9 (28) |
| 2.0 | 23.5 (7.3) | 20 | 98.2[b] (32) |
| 4.0 | 86.8[b] (29) | 40 | 87.1 (27) |
| 5.0 | 96.7 (30) | 40 | 86.8[b] (29) |
| 9.0 | 106 (33) | 40 | 86.2[d] (27) |

[a] At 25.0°C with $1.3 \times 10^{-5}$ M substrate and $3.33 \times 10^{-3}$ M aniline in 0.027 M carbonate buffer at pH 8.5 unless specified; the values in parentheses are rate enhancement. [b] $1.67 \times 10^{-3}$ M aniline. [c] pH 7.5. [d] pH 10.1. [e] $4 \times 10^{-5}$ M substrate.

Table XII. Micellar Catalysis of the Reaction of TFBS with Aniline[a]

| $10^4$ [CTABr], M | pH 8.5 | pH 10.1 |
|---|---|---|
| | 0.11 | 0.11 |
| 6.67 | 9.74 (87) | 10.4 (93) |
| 10.0 | 9.79 (87) | 10.8 (96) |
| 20.0 | 9.79 (87) | 10.4 (93) |
| 30.0 | 9.50 (85) | |
| 40.0 | 9.10 (82) | 9.40 (84) |

[a] Second-order rate constants, $10^2$ $k_2^{obsd}$, $M^{-1}$ $s^{-1}$ at 25.0 °C with $10^{-5}$ M substrate and $3.33 \times 10^{-2}$ M aniline. The values in parentheses are rate enhancements by the micelle.

Table XIII. Effects of Hydroxide Ion on Reactions of Aniline in CTABr[a]

| [NaOH], M[b] | $k_2^{obsd}$, $M^{-1}$ $s^{-1}$ TFBS[c] | TNBS[d] |
|---|---|---|
| (7.5) | | 94.0[d] |
| (10.1) | 0.11 | 92.2[d] |
| 0.005 | | 120 |
| 0.010 | 0.32 | 136 |
| 0.010 | | 146[e] |
| 0.010 | | 127[f] |
| 0.020 | | 151 |
| 0.025 | 0.43 | |
| 0.025 | 0.44[g] | |
| 0.025 | 0.34[e] | |
| 0.025 | 0.34[h] | |
| 0.033 | | 165 |
| 0.050 | 0.50 | 181 |
| 0.100 | | 199 |
| 0.167 | 0.61 | |

[a] At 25.0 °C with $10^{-3}$ M CTABr unless specified. [b] The values in parentheses are pH in 0.027 M carbonate buffer. [c] In 0.033 M aniline. [d] In $1.67 \times 10^{-3}$ M aniline unless specified. [e] In $2 \times 10^{-3}$ M CTABr. [f] In $4 \times 10^{-3}$ M CTABr. [g] In $0.67 \times 10^{-3}$ M CTABr. [h] In $3 \times 10^{-3}$ M CTABr.

readily should the tetrahedral intermediate go on to products, so that hydrophobicity of the amine assists both steps of the reaction with the arenesulfonates, but only the initial addition to the halobenzenes, because then the second step is fast.

**Micellar Effects on Reaction with Aniline.** At low pH the reactions of TNBS and TFBS with aniline are catalyzed effectively by micellized CTABr (Tables XI and XII), and the catalysis is larger than that of approximately tenfold for reaction with 2,4-dinitrofluorobenzene.[4] The micellar catalysis is not affected by small changes in reactant concentration or pH, and as expected in terms of reagent hydrophobicity the catalysis is greater for TFBS than for TNBS.

Table XIV. Micellar Effects upon the Reaction of TNBS with Hydroxide Ion[a]

| [OH⁻]M | $10^3$ [CTABr], M 0.65 | 2.61 | 3.26 | 4.56 |
|---|---|---|---|---|
| 0.0132 | 33.9 (15) | 43.2 (23) | 50.4 (22) | 50.7 (22) |
| 0.159 | | | 14.1 (4.3) | |
| 0.238 | | | 11.2 (3.3) | |

[a] Values of $10^2$ $k_2^{obsd}$, $M^{-1}$ $s^{-1}$ at 25.0°C; the values in parentheses are relative to reaction in the absence of CTABr.

The reactions with aniline in water are strongly catalyzed by hydroxide ion (Table VI), but surprisingly this base catalysis is smaller when reaction is carried out in sufficient CTABr to incorporate the substrate (Table XIII). Because incorporation of reactants into the Stern layer of a micelle can markedly increase their concentration in that layer and so speed reaction, a reaction in which three reagents generate the transition state should be catalyzed more by a micelle than an otherwise similar bimolecular reaction. For example, micellar catalysis of a two-proton benzidine rearrangement is much greater than that of a one-proton benzidine rearrangement.[31]

These reactions of the arenesulfonates in the presence of hydroxide ion are an exception to this generalization, probably because the unfavorable coulombic interactions between the first formed tetrahedral intermediate and the cationic head groups speed decomposition of the intermediate through assisting spontaneous proton loss from the ammonium ion (Scheme III).

The rate increase with added hydroxide ion is greater for the reaction of TFBS with aniline than for that of TNBS (Tables VI and XIII), whether reaction is carried out in water or CTABr, but for both arenesulfonates the base catalysis is markedly reduced by CTABr, and the effect of hydroxide ion changes little with small variations in the concentration of CTABr. We did not attempt to estimate the various kinetic parameters for these reactions in CTABr (cf. Table VIII), because the overall effect of hydroxide ion is relatively small, and there is also a problem because of uncertainties in the distribution of $OH^-$ between the micelles and bulk solvent.

**Micellar Effects upon Reactions with Hydroxide Ion.** Although micellized CTABr strongly catalyzes the reaction of hydroxide ion with 2,4-dinitrofluorobenzene,[3b] it is less effective for the reactions with TNBS and TNFS even in dilute alkali, and the catalysis decreases markedly as the hydroxide ion concentration is increased (Tables XIV and XV and ref 15). This behavior is unusual; for example, the catalysis by CTABr of the reactions of hydroxide ion with 2,4-dinitrofluoro- and chlorobenzene decreases only slightly as the concentration of hydroxide ion is increased.[3]

Micellar catalysis is generally larger for reactions of higher order, but this is not the case for these arenesulfonate reactions with either aniline or hydroxide ion (cf. Table XIII).

These differences between reactions in water and in CTABr could arise because (1) the micelle speeds the spontaneous decomposition of the dianionic intermediate, Scheme I, so that the hydroxide ion catalyzed decomposition competes less effectively, or (2) the micelle suppresses the hydroxide ion catalyzed decomposition of the intermediate (I). Insofar as cationic micelles increase acid ionization, the first explanation seems the more probable, but it is difficult to give a quantitative discussion because we do not know how the distribution of hydroxide ion between water and micelles depends on hydroxide ion concentration. (For discussions of this general problem of reagent distribution in kinetic and other studies see ref 1, 12, 32, and 33.)

Table XV. Micellar Effects upon the Reaction of TFBS with Hydroxide Ion[a]

| [OH⁻], M | 10³ [CTABr], M | 0.65 | 1.30 | 3.04[b] | 3.26 | 4.56 |
|---|---|---|---|---|---|---|
| 0.0264 | | 6.89 (15) | 6.67 (15) | | 6.10 (13) | 5.01 (11) |
| 0.0833 | | | | 3.70 (7.3) | | |
| 0.167 | | | | 2.94 (4.7) | | |
| 0.333 | | | | 1.63 (2.2) | | |

[a] Values of $10^3\ k_2^{obsd}$, $M^{-1}\ s^{-1}$ at 25.0 °C; the values in parentheses are relative to reaction in the absence of CTABr. [b] From ref 15.

Table XVI. Micellar Catalysis of the Reaction of Phenoxide Ion with TNBS[a]

| 10³ [CTABr], M | $k_2^{obsd}$, $M^{-1}\ s^{-1}$ | $k_{rel}$ |
|---|---|---|
| | 0.0059 | |
| 0.333 | 6.00 | 1020 |
| 0.400 | 8.57 | 1450 |
| 0.467 | 11.2 | 1900 |
| 0.533 | 11.7 | 1980 |
| 0.600 | 10.9 | 1850 |
| 0.667 | 9.85 | 1670 |
| 0.800 | 9.06 | 1540 |
| 1.00 | 7.96 | 1350 |
| 1.34 | 6.69 | 1130 |
| 2.00 | 4.63 | 790 |

[a] At pH 10 (0.01 M borate) at 25.0 °C with $2 \times 10^{-5}$ M TNBS and $6.67 \times 10^{-4}$ M phenol. The reaction was followed at 446 nm.

**Reaction of TNBS with Phenoxide Ion.** Micelles of CTABr are very effective catalysts of the attack of phenoxide ion upon 2,4-dinitrofluorobenzene,[5] and a similar, but much larger, catalysis was found with TNBS (Table XVI). Phenol is partially ionized under the experimental conditions, and the second-order rate constants are calculated in terms of the phenoxide ion concentration, allowing for the micellar effect upon the apparent dissociation constant.[5]

The rate maximum is found at a relatively low concentration of CTABr, pointing to strong interactions between the reactants and micelles of CTABr, and the rate enhancement is approximately tenfold larger than that found with 2,4-dinitrofluorobenzene.[5] These observations are as expected for micellar catalysis of a reaction between two relatively hydrophobic reagents.[8-12]

**Micellar Catalysis of Reactions of Arenesulfonates and Halobenzenes.** These reactions of activated arenesulfonates with amines or hydroxide ion are two-step reactions in which decomposition of a tetrahedral intermediate appears to be rate limiting, and is base catalyzed, whereas nucleophilic addition on halodinitrobenzenes appears to be rate limiting. It is therefore difficult to compare the origins of the micellar catalyses; for example, the catalysis of the reactions of the halobenzenes increases with increasing hydrophobicity of the nucleophile, but not markedly so, but the dependence of the catalysis on hydrophobicity of the nucleophile is much more striking for reactions of the activated arenesulfonates.[2-5,15] For reactions of the arenesulfonates, the more hydrophobic the nucleophile the more deeply it is drawn into the Stern layer, and the more readily the tetrahedral intermediate, e.g., IV or V, loses a proton and goes on to product, but only the first effect is important for reactions of the halobenzenes.

However, we can compare micellar effects upon non-base-catalyzed nucleophilic aromatic substitutions by using a nucleophile such as phenoxide ion. The reaction of 2,4-dinitrofluorobenzene with phenoxide ion is catalyzed 230-fold by micelles of CTABr,[5] whereas for this reaction of TNBS the catalysis is by a factor of 2000 (Table XV), showing the high sensitivity of the micellar catalyzed reactions of the arenesulfonates to hydrophobicity of the nucleophile.

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**Registry No.**—Glycinate, 23297-34-9; leucinate, 17332-93-3; phenylglycinate, 58013-93-7; glycineamide, 598-41-4; aniline, 62-53-3; TNBS, 16655-63-3; TFBS, 59016-58-9; hydroxide ion, 14280-30-9; NaCl, 7647-14-5; $NaClO_4$, 7775-09-9; $Et_3N$, 121-44-8; NMP; 120-94-5; CTABr, 57-09-0; phenoxide ion, 3229-70-7; 2,4-dinitrofluorobenzene, 70-34-8.

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