

# Micellar Effects upon Aromatic Nucleophilic Substitution by Amines<sup>1</sup>

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**Abstract:** The reaction between 2,4-dinitrofluorobenzene and aniline at 25.0° is catalyzed by cationic micelles of cetyltrimethylammonium bromide and chloride (CTABr and CTACl), and by uncharged micelles of the polyether, Igepal, and slightly by anionic micelles of sodium lauryl sulfate, NaLS. Similar but smaller effects are found for the corresponding reactions of 2,4-dinitrochlorobenzene at 85.0°. CTACl is a better catalyst than CTABr for the reaction of hydroxide ion with 2,4-dinitrofluorobenzene, but there is little difference for the reaction of aniline. Cationic micelles assist (up to *ca.* 30-fold) and anionic micelles inhibit the reactions of glycinate, glycyglycinate, and glycyglycyglycinate with 2,4-dinitrofluorobenzene at 25.0° even though the negative charge is not on the reactive center of the amine. Smaller micellar effects are found for the reaction of glycyglycinate ion with 2,4-dinitrochlorobenzene at 85.0°. Added salts inhibit the micellar catalysis of the reaction between the glycyglycinate ion and 2,4-dinitrofluorobenzene, but have small effects on the corresponding reaction with aniline.

Micellar effects upon reactions of ions and ion-molecule reactions have been studied very extensively,<sup>2-8</sup> but much less work has been done on reactions between molecules.<sup>9,10</sup> Richards and his coworkers found that the rate of the reaction between anisylthioethane and iodine cyanide was unaffected by the anionic detergent, sodium lauryl sulfate, NaLS, even though the thioethane was taken up by the micelles; also the reaction of glycinamide with 2,4-dinitrofluorobenzene was unaffected by anionic micelles.<sup>10</sup> Cationic micelles of cetyltrimethylammonium bromide, CTABr, catalyzed the reactions of glycyglycinate ion and glycinamide with 2,4-dinitrofluorobenzene, but this catalysis was not studied in detail, because of experimental difficulties, although inhibition of the reaction of glycyglycinate ion by NaLS was observed.<sup>10</sup> Some nucleophilic displacements upon fluorobenzenes are multistep reactions in which an addition complex may go forward to products or revert to reagents, and the decomposition of the intermediate can be general base catalyzed.<sup>11,12</sup> These complexities are generally absent in the corresponding reactions of the chlorobenzenes, except in special cases,<sup>11-13</sup> and therefore we were interested in examining the reactions of an uncharged amine and of anions of amino acids or peptides with chloro- and fluoro-2,4-dinitrobenzene in the presence of ionic and uncharged micelles, so that we could

compare them with the corresponding reactions of hydroxide or thiophenoxide ion.<sup>8,14</sup> We were interested in finding out whether micelles could catalyze reactions between uncharged molecules by bringing the reagents together, and whether attack by the anion of an amino acid or peptide upon an uncharged substrate was influenced by the electrostatic effects which govern micellar catalysis and inhibition of ion-molecule reactions,<sup>2-10</sup> even though the reactive amino group is uncharged, and the negative charge some distance away from the reactive center. It should be noted that micellar catalysis has been observed in reactions between uncharged substrates, halobenzenes, or carboxylic esters, and negatively charged nucleophiles in which the reactive center is uncharged, but is relatively close to the negative charge.<sup>10,15</sup> In order to vary the separation of the negative charge from the nucleophilic center we used glycinate, glycyglycinate, and glycyglycyglycinate ions as nucleophiles. As Richards and his coworkers have noted micellar studies can be used as models for some aspects of the reactions of proteins with electrophiles.<sup>10</sup>

We also compared the catalytic efficiencies of cetyltrimethylammonium chloride and bromide (CTACl and CTABr) for the reactions of aniline and hydroxide with 2,4-dinitrofluorobenzene in order to examine the effects of the counterion on these two reactions, and to supplement existing studies of salt effects on micellar catalysis.<sup>4,8,16</sup>

## Experimental Section

**Materials.** The purification of most of the reagents has been described.<sup>7,8</sup> Glycine, glycyglycine (Aldrich), and glycyglycyglycine (Sigma) were dried in a vacuum oven. Aniline (Baker and Adamson) was distilled before use. Cetyltrimethylammonium bromide (CTABr) and sodium lauryl sulfate were purified by the method of Duynstee and Grunwald.<sup>3</sup> Cetyltrimethylammonium chloride (Eastman) was vacuum dried at 80° for several days and was used immediately after drying.

**Kinetics.** The reactions were followed spectrophotometrically using a Gilford spectrophotometer with a water-jacketed cell com-

(1) Support of this work by the Arthritis and Metabolic Diseases Institute of the U. S. Public Health Service and the National Science Foundation is gratefully acknowledged.

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partment at 25.0°, using methods already described. Reactions at 25.0° were followed directly in the spectrophotometer, but samples were taken for the reactions at 85.0°. The wavelengths used were 3580 Å for the reactions of hydroxide ion, 3650 Å for the reactions of aniline, 3625 Å for reactions of glycinate ion, and 3550 Å for the reactions of the peptides. Precipitates formed with the reactions of glycyglycinate ion in the uncharged detergent, Igepal 24, which is a dinonylphenol condensed with 24 ethylene oxide units and which is designated as DNPE, and reactions with this reagent were therefore not examined in solutions of this detergent.

Solutions of glycine, glycyglycine, and glycyglycyglycine were neutralized with sodium hydroxide before use, and the pH was adjusted to the required value. The concentration of the amino acids was generally 0.025 M, and that of aniline was generally 0.05 M for reactions of 2,4-dinitrofluorobenzene and 0.055 M for reactions of 2,4-dinitrochlorobenzene. These concentrations were much greater than those of the halobenzenes ( $10^{-5}$ – $10^{-4}$  M) and the reactions followed good first-order kinetics up to at least 2 half-lives. The second-order rate constants,  $k_2$ , are in  $\text{l. mol}^{-1} \text{sec}^{-1}$ , and were obtained by dividing the observed first-order rate constant,  $k_\psi$ , by the nucleophile concentration.

Our value of  $k_2$  for the reaction of glycyglycine and 2,4-dinitrofluorobenzene at pH 9.5 and 25.0° in the absence of detergent is larger than that calculated from the results of Richards and his coworkers,<sup>10</sup> probably because of differences in the ionic strength of the solution and the composition of the buffer and its pH.

The second  $pK_a$  of glycyglycine is 8.25 and that of glycyglycyglycine is 8.09<sup>17</sup> and therefore the former should be present almost completely as the anion at pH 9.5, and the latter at pH 9.0, especially in the presence of cationic micelles which should assist ionization.<sup>18</sup> The rate constants were not increased by small increases in pH. For glycine the second  $pK_a$  is 9.78, and therefore we had to use higher pH's of 10.5 and 10.8 for the reactions with 2,4-dinitrofluorobenzene. The reaction between hydroxide ion and 2,4-dinitrofluorobenzene begins to contribute to the over-all reaction at these pH's.<sup>9</sup> In the absence of detergent  $k_\psi \sim 3.6 \times 10^{-5} \text{sec}^{-1}$  for the hydroxide ion reaction at pH 10.5, and  $7.6 \times 10^{-5} \text{sec}^{-1}$  at pH 10.8 (calculated from data obtained at higher pH's). In the presence of 0.035 M CTABr the values of  $k_\psi$  for the reaction in the absence of glycine is  $557 \times 10^{-5} \text{sec}^{-1}$  at pH 10.5. Therefore the hydroxide ion reaction makes 1–2% contribution to the over-all rate in 0.025 M glycine at pH 10.5 in the absence of detergent, and ca. 5% in 0.035 M CTABr.

The rate of reaction of 2,4-dinitrofluorobenzene and glycinate ion at 25.0° in CTABr is close to the limit ( $t_{1/2} \sim 10 \text{sec}$ ) which can be obtained using conventional methods, and the rate constants are less accurate for this reaction than for others. Within experimental error a pH change from 10.5 to 10.8 does not affect the values of  $k_2$ , showing that uncertainties caused by incomplete ionization of the nucleophile and contributions of the reaction with hydroxide ion are not particularly important.

The relative reactivities of fluoro- and chloro-2,4-dinitrobenzenes toward amines are much greater than toward hydroxide ion, and therefore we restricted the pH to 9.0 for the reaction of the glycyglycinate and 2,4-dinitrochlorobenzene at 85.0°, to avoid incursion of the hydroxide ion reaction. The reactions with 2,4-dinitrochlorobenzene were therefore not studied in detail, and the results for them are less satisfactory than for the fluorobenzene.

## Results

**Reactions of the Glycinate Ions.** In the absence of detergent, glycinate ion is five times as reactive as glycyglycinate which is slightly more reactive than glycyglycyglycinate toward 2,4-dinitrofluorobenzene (Table I), because the inductive effect of the carboxylate group increases the basicity, and presumably the nucleophilicity, of the amino group.<sup>18</sup> In some reactions of amines with halobenzenes a general base removes a proton from the amino group in the rate-limiting step,<sup>11–13</sup> and it seemed possible that the carboxylate group in the peptides might act as a general base in a cyclic transition state, but this possibility seems to

(17) R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," Butterworth, London, 1965, Appendix 12.1.

(18) G. S. Hartley and J. W. Roe, *Trans. Faraday Soc.*, **36**, 101 (1940); P. Mukerjee and K. Banerjee, *J. Phys. Chem.*, **68**, 3567 (1964).

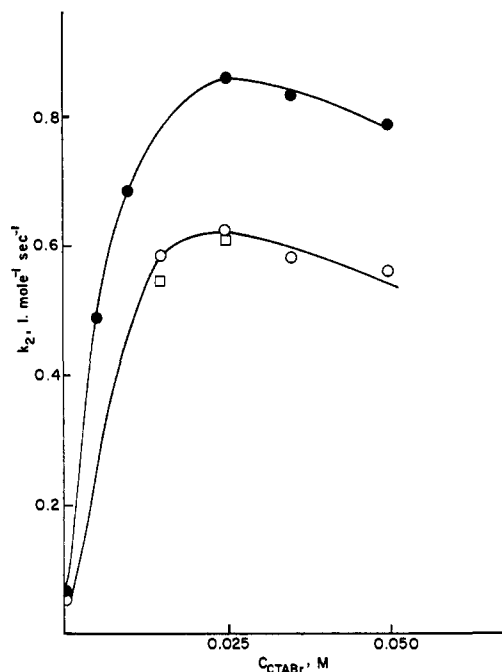


Figure 1. Catalysis of the reactions of glycyglycinate and glycyglycyglycinate ions with 2,4-dinitrofluorobenzene at 25.0°: ●, glycyglycinate ion at pH 9.5; ○, glycyglycyglycinate ion at pH 9.0; □, at pH 9.5.

be excluded by the reactivity sequence for the glycinate ions (Table I), and a slow proton transfer is improbable in water.

Table I. Second-Order Rate Constants for Reaction of Glycinate Ions with 2,4-Dinitrofluorobenzene<sup>a</sup>

Nucleophile	$\text{NH}_2\text{CH}_2\text{CO}_2^-$	$\text{NH}_2\text{CH}_2\text{-CONHCH}_2\text{-CO}_2^-$	$\text{NH}_2\text{-CH}_2\text{CONH-CH}_2\text{CO}_2^-$
$k_2, \text{l. mol}^{-1} \text{sec}^{-1}$	0.17 <sup>b</sup>	0.034 <sup>c</sup>	0.028 <sup>d</sup>

<sup>a</sup> In water at 25.0° in the absence of detergents with 0.025 M nucleophile. <sup>b</sup> At pH 10.5 in 0.015 M carbonate buffer. <sup>c</sup> At pH 9.5 in 0.015 M borate buffer. <sup>d</sup> At pH 9.0 in 0.015 M borate buffer.

The catalysis by CTABr of the reactions of these glycinate ions with halobenzenes is typical of anion-molecule, as opposed to intermolecular reactions (Table II

Table II. Micellar Catalysis of the Reaction Between Glycinate Ion and 2,4-Dinitrofluorobenzene<sup>a</sup>

$\text{Concn}_{\text{CTABr}}, M$	$k_2, \text{l. mol}^{-1} \text{sec}^{-1}$
	0.17
0.0010	0.21
0.0075	2.28
0.0154	2.91
0.025	3.65
0.025	3.82 <sup>b</sup>
0.035 <sup>c</sup>	4.71
0.035	4.62 <sup>b</sup>
0.050	3.98

<sup>a</sup> At 25.0° at pH 10.5 in 0.015 M carbonate buffer and 0.025 M glycinate ion unless specified. <sup>b</sup> pH 10.8. <sup>c</sup> In the absence of glycinate ion  $k_\psi = 5.57 \times 10^{-5} \text{sec}^{-1}$  at pH 10.5.

and Figure 1). Richards and his coworkers showed that the anionic detergent inhibited the reaction of glycyglycinate ion with 2,4-dinitrofluorobenzene.<sup>10</sup> We

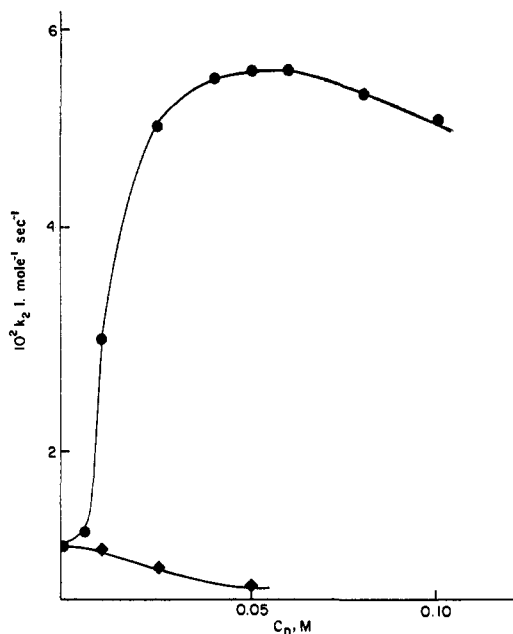


Figure 2. Micellar effects upon the reaction between glycyglycinate ion and 2,4-dinitrochlorobenzene at 85.0°: ●, with CTABr; ◆, with NaLS.

confirmed these results using pH 9.5 (Table III), but the inhibition was less than that observed earlier.<sup>10</sup> The difference was probably caused by incomplete ionization of glycyglycinate at pH 9.0, and an anionic detergent should decrease the extent of ionization.

Table III. Inhibition of the Reaction of Glycyglycinate Ion with 2,4-Dinitrofluorobenzene<sup>a</sup>

Concn <sub>NaLS</sub> , M	0.01	0.025	0.050
$10k_2$ , l. mol <sup>-1</sup> sec <sup>-1</sup>	0.335	0.293	0.191

<sup>a</sup> At pH 9.5 with NaLS in 0.015 M borate buffer.

For reactions of glycinate and glycyglycinate ions with 2,4-dinitrofluorobenzene in CTABr we obtained *ca.* 30-fold rate enhancements, and *ca.* 22-fold for the glycyglycyglycinate ion (Figure 1 and Table II), showing that the inductive effects which influence the nucleophilicities of the anions in water are also at work for reaction in the micellar phase. The values of  $k_2$  for the reactions of glycyglycinate and glycyglycyglycinate ions with 2,4-dinitrofluorobenzene in CTABr decrease with increasing anion concentration (Table IV).

Table IV. Variation of  $k_2$  with Concentration of Peptide<sup>a</sup>

Concn <sub>NH<sub>2</sub>·R</sub>	Reagent	
	NH <sub>2</sub> CH <sub>2</sub> CONH-CH <sub>2</sub> CO <sub>2</sub> <sup>-b</sup>	NH <sub>2</sub> (CH <sub>2</sub> CONH) <sub>2</sub> -CH <sub>2</sub> CO <sub>2</sub> <sup>-c</sup>
0.025	0.335 <sup>d</sup>	0.279 <sup>d</sup>
0.010	10.5	
0.025	8.60	6.24
0.050	8.18	4.92
0.072		4.12

<sup>a</sup> Values of  $10k_2$ , l. mol<sup>-1</sup> sec<sup>-1</sup> at 25.0° in 0.025 M CTABr unless specified. <sup>b</sup> At pH 9.5. <sup>c</sup> At pH 9.0. <sup>d</sup> In the absence of detergent.

This result seems to be typical for micellar-catalyzed reactions, and the decrease of  $k_2$  which we observe here

is very similar to that found for reactions of hydroxide ion with halobenzenes in CTABr.<sup>8</sup> There is no evidence for aggregation of the glycinate ions. Saturation of the micelles by the reagent, and an increase in the aggregation number of the micelle with increasing ionic strength,<sup>19,20</sup> would give the observed decrease in  $k_2$ .<sup>21</sup>

Micellar effects upon the reaction of glycyglycinate ion with 2,4-dinitrochlorobenzene are smaller than those found for the fluorobenzene. Because of the higher temperature (85.0°) there is less incorporation of the substrate into the micelles, and therefore both catalysis and inhibition should be smaller than at lower temperatures, as is observed. With 2,4-dinitrochlorobenzene in CTABr a 6-fold rate enhancement is found (Figure 2), as compared with *ca.* 30-fold for 2,4-dinitrofluorobenzene at 25.0° (Figure 1). The reaction between 2,4-dinitrochlorobenzene and glycyglycinate ion at 85.0° is, as expected, inhibited by NaLS (Figure 2). We assume that incomplete ionization of glycyglycinate will not be a problem at this higher temperature.

**Micellar Effects upon the Reactions with Aniline.** 2,4-Dinitrofluorobenzene is much more reactive than the chlorobenzene toward amines,<sup>11,12</sup> and therefore we examined the reactions of the fluorobenzene at 25.0° and of the chlorobenzene at 85.0°. Nonetheless the general kinetic patterns are similar, with CTABr giving modest, 3–8-fold rate enhancements, and NaLS having smaller effects (Figures 3 and 4). The uncharged detergent DNPE is a catalyst and is as effective as CTABr for the reaction between aniline and 2,4-dinitrochlorobenzene (Figure 4).

For the reaction between hydroxide ion and 2,4-dinitrochlorobenzene in the presence of CTABr the values of  $k_2$  are almost independent of  $C_{OH^-}$  in the range 0.005–0.025 M, and then decrease.<sup>8</sup> Similar results were obtained with glycyglycinate and glycyglycyglycinate ions and 2,4-dinitrofluorobenzene (Table IV). For the reaction between 2,4-dinitrofluorobenzene and aniline  $k_2$  decreases slightly with increasing aniline concentration for CTABr, NaLS, and DNPE (Table V). These

Table V. Micellar Effects upon Reaction of 2,4-Dinitrofluorobenzene with Aniline<sup>a</sup>

Detergent	Concn <sub>PhNH<sub>2</sub></sub> , M		
	0.025	0.050	0.075
CTABr	29.5	26.2	22.8
NaLS	9.3	8.8	8.0
DNPE	14.3	13.8	12.1

<sup>a</sup> Values of  $10^3k_2$ , l. mol<sup>-1</sup> sec<sup>-1</sup> at 25.0° with 0.04 M detergent. In the absence of detergent  $k_2 = 3.0 \times 10^{-2}$  l. mol<sup>-1</sup> sec<sup>-1</sup>.

effects could arise because electrolytes increase the aggregation numbers of ionic micelles,<sup>19,20</sup> and therefore decrease the number of micelles present at a given detergent concentration, and incorporation of aniline or other organic molecules into a micelle should also in-

(19) E. W. Anacker and M. M. Ghose, *J. Phys. Chem.*, **67**, 1713 (1963); *J. Amer. Chem. Soc.*, **90**, 3161 (1968).

(20) P. H. Elworthy, A. T. Florence, and C. B. Macfarlane, "Solubilization by Surface-Active Agents," Chapman and Hall, London, 1968, Chapter I.

(21) A similar saturation effect has been observed in the acid cleavage of  $\alpha$ -phenylvinyl diethyl phosphate in NaLS.<sup>22</sup>

(22) C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, **91**, 6072 (1969).

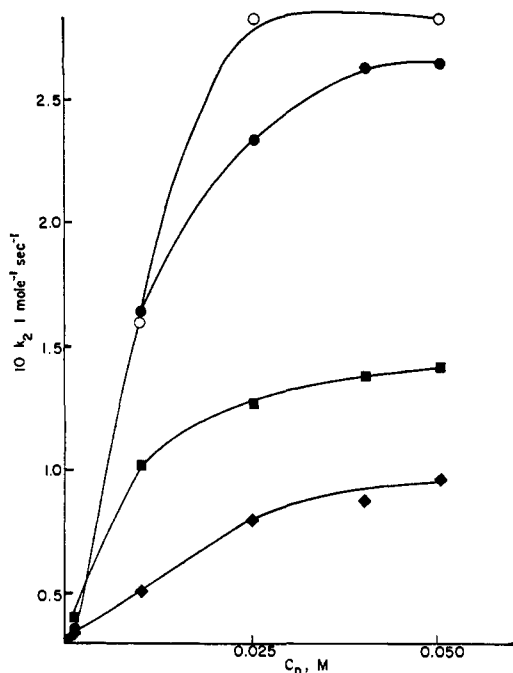


Figure 3. Micellar effects upon the reaction between aniline and 2,4-dinitrofluorobenzene at 25.0°: ○, CTACL; ●, CTABr; ■, DNPE; ◆, NaLS.

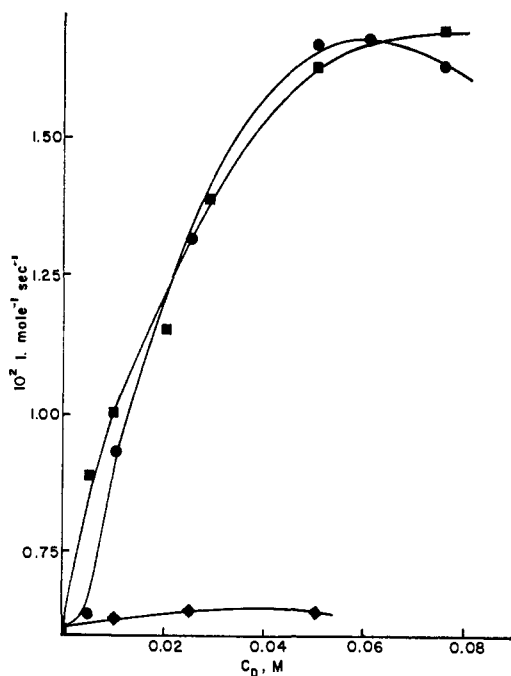


Figure 4. Micellar effects upon the reaction between aniline and 2,4-dinitrochlorobenzene at 85.0°: ●, CTABr; ■, DNPE; ◆, NaLS.

crease the aggregation number.<sup>20</sup> In addition we may be beginning to see a saturation effect, so far as reactions in the micellar phase are concerned.<sup>22</sup>

**Effect of the Counteranion.** Added electrolytes inhibit micellar catalysis of ionic or ion-molecule reactions at least in part by decreasing the interaction between the micelle and the ionic reagent.<sup>4,7,8,15</sup> However, they increase aggregation numbers by stabilizing ionic micelles,<sup>19,20</sup> and therefore reduce the concentration of micelles. Both effects should inhibit catalysis of

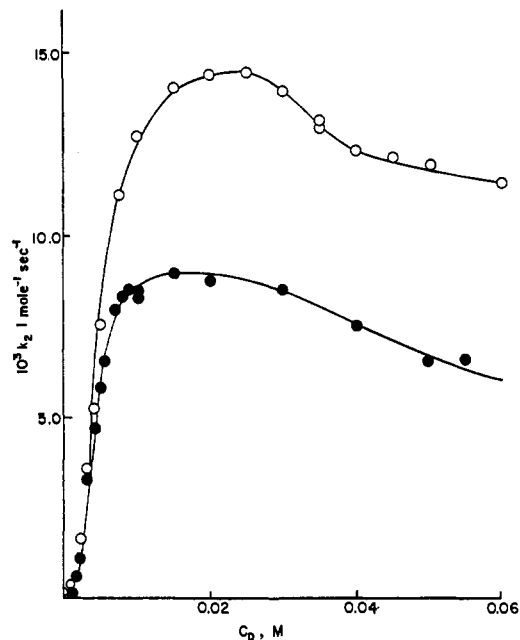


Figure 5. Micellar catalysis of the reaction between hydroxide ion and 2,4-dinitrochlorobenzene at 25.0°: ●, CTABr; ○, CTACL.

an ion-molecule reaction by an ionic micelle, but only the second effect should be important so far as catalysis of an intermolecular reaction is concerned. Comparison of the catalytic effects of CTACL and CTABr upon the reactions of 2,4-dinitrofluoro- and chlorobenzene with hydroxide ion and 2,4-dinitrofluorobenzene with aniline suggests that both inhibition effects of electrolytes are at work (Figures 3 and 5 and Table VI).

Table VI. Catalysis by CTACL and CTABr of the Reaction between Hydroxide Ion and 2,4-Dinitrofluorobenzene<sup>a</sup>

Conc <sub>D</sub> , M	Detergent	
	CTACL	CTABr
0.010	6.06	5.17
0.025	9.02	7.03
0.050	8.51	6.34

<sup>a</sup> Values of  $k_2$ , l. mol<sup>-1</sup> sec<sup>-1</sup> at 25.0° in 0.01 M NaOH. In the absence of detergent  $k_2 = 0.12$  l. mol<sup>-1</sup> sec<sup>-1</sup>.

The rate maxima tend to be reached at lower concentrations of CTACL than CTABr, suggesting that more micelles are present at a given concentration of the chloride than the bromide, as would be expected in view of the more effective interaction between the cationic micelle and the low charge density bromide as compared with the chloride ion. However this cannot be the only effect, because whereas the maximum rate for the aniline reaction in CTACL is only 7% greater than that in CTABr (Figure 3), the corresponding figures for the hydroxide ion reactions are 60% (Figure 5 and Table VI). Therefore we conclude that the major cause of electrolyte inhibition is exclusion of the ionic reactants from the neighborhood of the micelle, in agreement with earlier suggestions.<sup>4,7,8,22,23</sup>

Added salts inhibit the CTABr catalysis of the reaction of glycylglycinate ion and 2,4-dinitrofluorobenzene

(23) O. H. Griffith and A. S. Waggoner, *Accounts Chem. Res.*, **2**, 17 (1969).

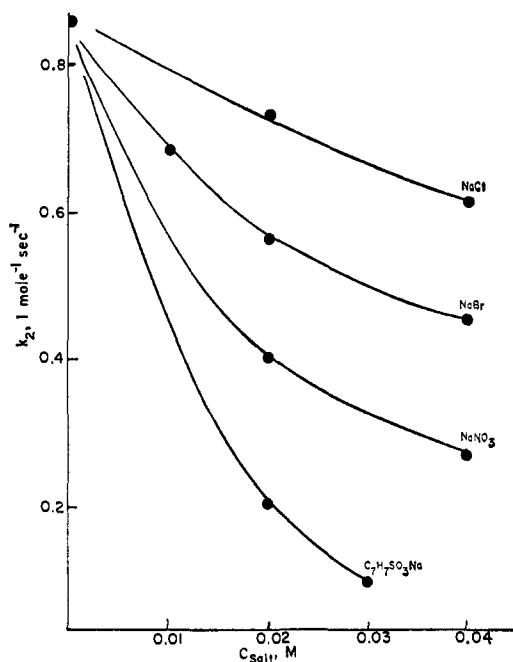


Figure 6. Salt inhibition of the CTABr-catalyzed reaction between glycyglycinate ion and 2,4-dinitrofluorobenzene; at 25.0° in 0.025 M CTABr.

(Figure 6). The rate decrease in the sequence no salt > NaCl > NaBr > NaNO<sub>3</sub> > *p*-C<sub>7</sub>H<sub>7</sub>SO<sub>3</sub>Na is typical, and agrees with other evidence that inhibition increases with decreasing charge density of the counterion.<sup>4,7,8,22,23</sup>

In marked contrast to the large salt effects upon the reaction of glycyglycinate ion are the very small effects of salts upon the aniline reaction (Table VII) which con-

Table VII. Salt Effects upon the CTABr-Catalyzed Reaction of Aniline with 2,4-Dinitrofluorobenzene<sup>a</sup>

Salt	Concn <sub>salt</sub> , M	10 <sup>2</sup> k <sub>2</sub> , l. mol <sup>-1</sup> sec <sup>-1</sup>
NaCl	0.02	23.4
NaCl	0.04	23.8
NaBr	0.02	24.2
NaBr	0.04	22.4
NaNO <sub>3</sub>	0.04	22.2
<i>p</i> -C <sub>7</sub> H <sub>7</sub> SO <sub>3</sub> Na	0.02	23.2
<i>p</i> -C <sub>7</sub> H <sub>7</sub> SO <sub>3</sub> Na	0.03	22.2
<i>p</i> -C <sub>7</sub> H <sub>7</sub> SO <sub>3</sub> Na	0.03	17.0

<sup>a</sup> At 25.0° with 0.05 M aniline in 0.025 M CTABr.

firm our supposition that salts are not having large effects upon the catalytic properties of the cationic micelles.

## Discussion

**Micellar Effects upon the Reactions of Glycinate Ions.** The observed inhibitions of the reactions between glycyglycinate ion and 2,4-dinitrofluoro- and chlorobenzenes by NaLS (Table III, Figure 2, and ref 10) are typical of anion-molecule reactions. The smaller inhibition of the reaction of glycyglycinate ion with 2,4-dinitrochlorobenzene is probably related to the higher temperature used for the chloro- as opposed to the fluoro-benzene reactions. In the same way CTABr catalyzes the reaction of glycinate ions with 2,4-dinitrofluorobenzene 20-30-fold at 25.0°, as compared with 6-fold

for 2,4-dinitrochlorobenzene at 85.0° (Table II and Figures 1 and 2).

In other micellar-catalyzed or inhibited anion-molecule reactions the reactive center of the nucleophile has been negatively charged.<sup>2-6,8,10</sup> So far as inhibition by anionic micelles is concerned the position of the negative charge in the nucleophile is of no consequence, because the micelle acts by protecting the substrate from the anionic nucleophile. However catalysis requires not only that the cationic micelle brings the substrate and the anionic nucleophile together in the micellar phase, but it must bring them together with an orientation such that they can form the activated complex without losing the binding with the micelle.<sup>15</sup>

It seems surprising at first sight that a negative charge which is six atoms away from the reaction center in the glycyglycinate ion and nine away in the glycyglycylglycinate ion can act almost as effectively as one which is at the reaction center, as in most anionic nucleophiles, or close to it, as in the glycinate ion, and these observations suggest that the nucleophile is held electrostatically by the carboxylate group at one position on the micellar surface, with the amino group attacking the substrate at another position on the micellar surface. In addition hydrophobic interactions of the methylene group with the micelle and ion-dipole interactions involving the amide residues should help to bind the peptide anions to the cationic micelle.

There is evidence that solutes have considerable mobility in the micellar phase,<sup>23</sup> and we would expect this to be the situation for those polar solutes which reside in the water-rich outer layer of micelles.<sup>24</sup>

Other examples of reactions in which strong hydrophobic or ionic bonding between a nucleophile and a cationic micelle is maintained during formation of the transition state are the reactions of myristyrylhistidine with *p*-nitrophenyl acetate,<sup>9</sup> and aryl phosphate dianions with *p*-nitrophenyl diphenyl phosphate.<sup>15</sup> In all these reactions groups remote from the reaction center have considerable effects upon reactions occurring in a micellar phase,<sup>5,6</sup> and we can see analogies between this behavior and that found in some enzymic reactions whose rates can be controlled by substituents remote from the reaction center of a substrate or inhibitor.<sup>25</sup>

**Catalysis of the Aniline Reactions.** The cationic detergents CTABr and CTACl catalyze the reactions between aniline and the halobenzenes (Figures 3 and 4). The catalysis is considerably larger (*ca.* eightfold) with the fluoro- than with the chlorobenzene (*ca.* threefold) because the temperatures of the two sets of experiments were different and the catalysis should be greater at the lower temperature because the cationic micelle should lower the activation energy,<sup>3,26</sup> and in addition the solubility of the reagent in the micellar phase should decrease with increasing temperature. For the hydroxide ion reactions of both 2,4-dinitrofluoro- and chlorobenzenes in CTABr similar 60-100-fold rate enhance-

(24) J. Clifford, *Trans. Faraday Soc.*, **61**, 1276 (1965); J. C. Eriksson and G. Gilberg, *Acta Chem. Scand.*, **20**, 2019 (1966).

(25) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," John Wiley & Sons, Inc., New York, N. Y., 1967; B. R. Baker, *Accounts Chem. Res.*, **2**, 129 (1969).

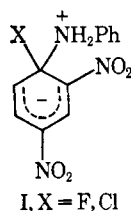
(26) For the reaction between hydroxide and fluoride ions and *p*-nitrophenyl diphenyl phosphate CTABr actually increases the activation energy,<sup>9</sup> but this case appears to be special because of the very high solubility of the substrate in the micellar as compared with the aqueous phase, and the expected decrease of the activation energy is found for reactions of 2,4-dinitrofluoro- and chlorobenzenes.

ments were observed, showing that the difference in substrates is of little importance.

The nonionic detergent DNPE enhances the reaction rate between aniline and 2,4-dinitrofluoro- and chlorobenzene, but the effects of NaLS are much smaller (Figures 3 and 4). For intermolecular reactions such as those between iodine cyanide and anisylthioethane, and glycineamide and 2,4-dinitrofluorobenzene, kinetic micellar effects have to date been small,<sup>10</sup> although large effects have been observed with the bulky nucleophile, myristylhistidine.<sup>9</sup>

Bringing the reactants together into the micellar phase should of itself increase the reaction rate, provided that the reactants are not held so rigidly that they cannot form a transition state in the micellar phase. For the reactions between triaryl phosphates and aryl phosphate anions,<sup>15</sup> and for the reactions of the glycinate ions, the reagents can form a transition state without disturbing the binding to the micelle, and we assume that this is true in the present case.

Medium effects could also be important, except that it is assumed that reactions in micellar phases generally take place in the outer, polar, water-rich layer of the micelles. However the dielectric constant in the water around the micelle is thought to be about half that in water, based on changes in charge transfer spectra.<sup>27</sup> Reactions between amines and halonitrobenzenes are retarded by a decreasing solvent polarity, as predicted by qualitative solvent theory, but the effects are not large.<sup>28</sup> Another effect could depend on the interaction between the charged groups of the micelle and the dipolar transition state, whose structure should be similar to that of the intermediate I.<sup>11,12</sup> In I the negative



charge is delocalized over the dinitrophenyl group, whereas the positive charge is localized upon the ammonium group, whose hydrogens should be strongly hydrogen bonded to water. In other experiments it has been shown that low density charges interact more strongly with ionic micelles than do high density charges,<sup>7,8,15</sup> and in the present reaction, I, and therefore the transition state, should interact more strongly with a cationic than with an anionic micelle. To this extent charge interactions between the transition state and the micelle should assist reaction in CTABr and CTACl, hinder it in NaLS, and be absent in DNPE, and

(27) P. Mukerjee and A. Ray, *J. Phys. Chem.*, **70**, 2144 (1966).

(28) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951); J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, **77**, 5051 (1955).

the over-all effect should be the sum of this effect and that caused by concentration of the reagents in the micellar phase, and could lead to the observed kinetic effects of the ionic detergents, although this explanation does not explain why the nonionic detergent DNPE is so effective catalytically for the reaction of aniline with 2,4-dinitrochlorobenzene. One possibility is that the forming ammonium group in the transition state is hydrogen bonded to ether oxygen atoms of the non-ionic micelles. There is evidence for hydrogen bonding between a phenolic hydroxyl group and polyoxyethylene micelles.<sup>29</sup>

**The Effects of the Counteranion.** The effects of added salts upon the catalysis by micelles of CTA are explicable on the assumption that anions exclude ionic nucleophiles from the micellar surface, but do not have this effect upon uncharged nucleophiles which in any event should enter the micellar phase rather than stay in the Stern layer.<sup>23,24</sup> The only exception to this generalization is provided by sodium tosylate which inhibits the reaction of aniline with 2,4-dinitrofluorobenzene in CTABr (Table VII). An anion of low charge density, such as tosylate, should interact strongly with CTA micelles, and so change their properties, and the solutions become very viscous with 0.03 *M* sodium tosylate.

Although added salts inhibit the reactions of 2,4-dinitrofluorobenzene with both hydroxide and glycyglycinate ions (Figure 6 and ref 8) their effect is larger for the hydroxide ion reaction,<sup>8</sup> e.g., 0.02 *M* sodium chloride cuts the rate of the hydroxide ion reaction by 35% and that of the glycyglycinate reaction by 15%, and for 0.02 *M* sodium bromide the corresponding values are 46% and 37%, and for 0.02 *M* sodium nitrate, 66% and 53%.

This difference is readily understandable because a large anion, such as glycyglycinate, should be held more strongly to a cationic micelle than the small hydroxide ion, and its reactions should therefore be inhibited less by an inhibiting anion.

Comparison of the catalytic efficiencies of CTACl and CTABr allows us to compare the effects of the counteranions without adding additional cations to the solution. For the reaction between hydroxide and 2,4-dinitrochlorobenzene the maximum rate in CTABr is ca. 55% of that in CTACl (Figure 5), whereas it is ca. 77% for the corresponding reaction of 2,4-dinitrofluorobenzene (Table VI). These rate differences are very similar to those which we observe between the inhibitions by sodium chloride and bromide for the reactions of hydroxide ion with 2,4-dinitrochloro- and fluorobenzenes in CTABr,<sup>8</sup> suggesting that the sodium ions are having little effect upon the anion inhibition of catalysis by a cationic micelle.

(29) T. Nakagawa and K. Shinoda, "Colloidal Surfactants," K. Shinoda, T. Nakagawa, B.-I. Tamamushi, and T. Isemura, Ed., Academic Press, New York, N. Y., 1968, p 141.