Catalytic Dipolar Micelles. 3. Substrate and Surfactant Structural Effects in the Hydrolyses of Substituted Phenyl Esters in Presence and in Absence of Dipolar Cationic Micelles: Mechanistic Considerations

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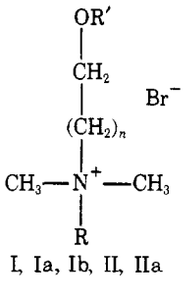
Herein are described the synthesis and kinetic parameters derived from a series of ten dipolar quaternary ammonium bromides of formula $(n\text{-}C_{10}H_{21}NR_2R')^+ Br^-$ in which R equals methyl (I, II, IV–IX) or ethyl (III) and R′ equals β,γ-dihydroxypropyl (V), α-carboxy-γ-hydroxypropyl (VI), ethyl (VII), carboxymethyl (VIII), β-methoxyethyl (Ib), and α-substituted γ-butyrolactone (IX), and the influence of the foregoing micellar systems on the rates of the base-catalyzed hydrolyses of the following substituted phenyl esters (μ = 0.8 M, KBr): 4-nitrophenyl acetate (PNPA), 4-nitrophenyl hexanoate (PNPH), 4-nitrophenyl decanoate (PNPD), 2,4-dinitrophenyl acetate (OPDNPA), 2,4-dinitrophenyl decanoate (OPDNPD), 2,4-dinitrophenyl esters of *n*-decyldimethyl(4′-carboxybutyl)ammonium bromide (OPDNPDE), phenyl decanoate (PD), 3-nitrophenyl decanoate (MNPD), 4-bromophenyl decanoate (PBPN), and 2,5-dinitrophenyl decanoate (OMDNPD), at 30 °C. Also included here is a comparative study of the reaction kinetics of the foregoing esters with nonmicellar catalysts of formula $[(CH_3)_3NR]^+ Br^-$ where R equals β-hydroxyethyl (Ia) and γ-hydroxypropyl (IIa) and $[(C_2H_5)_2CH_3NCH_2CH_2OH]^+ Br^-$ (IIIa). Two parameters for micelle formation from the surfactants I–V are presented: (1) the critical micelle concentrations (cmc), mainly from surface tension measurements; (2) the equilibrium constant of ester association into the micelle. The rates for alkaline hydrolyses were deduced from spectrophotometric measurements of the substituted phenol liberated in the course of the reaction, in the range of 295 and 450 nm. The second-order rate constants (s^{-1} M^{-1}) at 1–20 $\times 10^{-2}$ M and at pH 9.5–10.7 were computed from straight-line correlations with OH^- concentrations. All reactions in micellar systems exhibit considerable rate augmentation relative to the rate in water systems and the dependence of the rate constants with the micelle concentration. The respective β values of 0.36 and 0.31 obtained from the Brønsted plot for the hydrolysis of para- and meta-substituted phenyl esters in presence of micelles I and Ib indicate that the transition states in the catalytic reactions are highly sensitive to charge developments. Isotope effects (K_{H_2O}/K_{D_2O}) of 0.81, 0.59, and 0.76 were found for I, II, and VII, respectively. Evidence is adduced in favor of a nucleophilic mechanism involving an anionic transition state, which extrudes good leaving groups to give the products. The mechanistic pathway is discussed. The micellar models described here exhibit similarity to catalysis by relevant esterases with respect to the kinetic characteristics and mechanism.

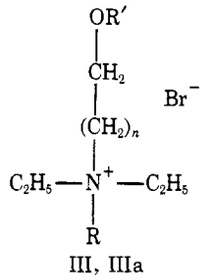
The importance of the serine hydroxyl group[1] and the carboxy residue[2] in enzymatic catalysis led to studies of systems containing these functional groups as models for enzyme–substrate intracomplex reaction.[3] Factors which might contribute to the catalytic efficiency of enzymes, such as proximity,[4] electrostatic catalysis,[5] and multifunctional catalysis,[6] were studied in the model compounds.

The similarities between the orientation of the side chain of proteins and the micellar structure[7-11] focused interest on use of micellar systems as models for enzymatic catalysis. Surfactant micelles containing groups such as imidazole,[12] amine,[13] thiol,[14] and hydroxamic[15] were found to catalyze the hydrolysis of esters.

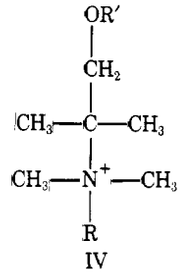
Accounts of enhanced micellar catalysis upon introduction of hydroxy groups to surfactant molecules have been recently reported.[16,17] To account for the role of the hydroxy group in the acceleration of the alkaline hydrolyses of esters, a kinetic study of the reaction in the presence of hydroxyammonium salt micelle-forming agents of structures I–VI was undertaken. We employed Ia, Ib, IIa, VII, and VIII as reference compounds. The structural variations in these cationic micelles



I, Ia, Ib, II, IIa



III, IIIa



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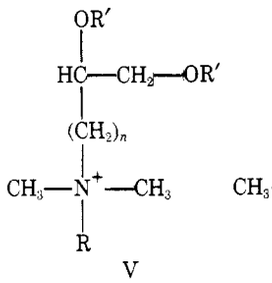

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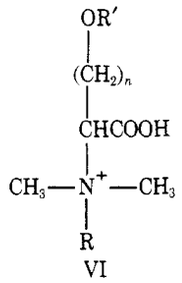
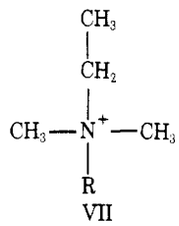


VI



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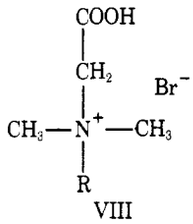
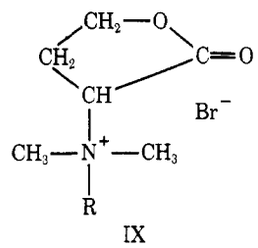


VIII



IX

I, n = 1; R = $C_{10}H_{21}$; R′ = H Ia, n = 1; R = CH_3; R′ = H Ib, n = 1; R = $C_{10}H_{21}$; R′ = CH_3
II, n = 2; R = $C_{10}H_{21}$; R = H IIa, n = 2; R = CH_3; R′ = H
III, n = 1; R = $C_{10}H_{21}$; R′ = H
IIIa, n = 1; R = CH_3; R′ = H IV, R = $C_{10}H_{21}$; R′ = H
V, n = 1; R = $C_{10}H_{21}$; R′ = H VI, n = 2; R = $C_{10}H_{21}$; R′ = H
VII, R = $C_{10}H_{21}$ VIII, R = $C_{10}H_{21}$ IX, R = $C_{10}H_{21}$

aimed at providing deeper insight into the ability of micellar systems to serve as models for enzymatic action.

Experimental Section

Surface Active Agents. All compounds were prepared according to the following general literature procedures[19] A or B

A $(CH_3)_2N(CH_2)_nCH_3 + Br(CH_2)_mX \xrightarrow{solv} CH_3(CH_2)_nN^+(CH_3)_2(CH_2)_mX \quad Br^-$

B $CH_3(CH_2)_nBr + (CH_3)_2N(CH_2)_mX \xrightarrow{solv} CH_3(CH_2)_nN^+(CH_3)_2(CH_2)_mX \quad Br^-$

where X is the head group on the cationic micelle, and the solvents used were ether, benzene, and methanol. In some cases methods A and B were carried out under neat conditions and are assigned as methods A′, B′. The preparation of *N,N*-dimethyl-*N*-decylamine [$n^{21}D$ 1.4307, bp 68 °C (1.4 Torr)] used in method A was according to Clarke et al.[20] All other reagents used were obtained from commercial sources. Examples of all four procedures follow.

***n*-Decyldimethyl(2-hydroxyethyl)ammonium bromide (I)** was synthesized either from 2-bromoethanol with dimethyldecylamine, or from 2-(dimethylamino)ethanol with freshly distilled decyl bromide, following usual methods.[21a] The reacting materials (0.1 mol each) were refluxed for 24 h in dry benzene, and the oily crude product recrystallized from acetone–ethyl acetate solution.

***n*-Decyldimethyl(2-methoxyethyl)ammonium Bromide (Ib).** Compound I was transformed to Ib by the method of Stoochnof and Benoitan[21b] with some modification. To a solution of I (0.05 mol) in 1,4-dioxane, NaH (0.06 mol) was added portionwise, and stirred for 24 h under a nitrogen environment. The solution was cooled to −10 °C and methyl bromide (100 ml) added. The reaction mixture was stirred for an additional 24 h, and then excess methyl bromide removed by evaporation at room temperature. Methanol was added to the residue, and the solution acidified (HBr). After solvent removal, the product (Ib) was extracted with dry acetone, ethyl acetate added, and the white precipitate collected after cooling.

Formation of VI from IX. The lactone (7.48 g, 0.02 mol) was dissolved in 100 ml of KOH (0.03 M) and left at room temperature for 5 days. Titration of a sample with HCl to phenolphthalein showed full hydrolysis of the lactone. It was then neutralized and used for the kinetic runs after adjusting the ionic strength.

Substituted Phenyl Esters. The mono- and dinitrophenyl esters were synthesized according to known methods as follows: *p*-nitrophenyl acetate (PNPA) (mp 79 °C) and 2,4-dinitrophenyl acetate (OPDNPA) (mp 71.5 °C) from the appropriate phenols and acetic anhydride, by the general method of Bender and Nakamura;[23] *p*-nitrophenyl hexanoate (PNPH) [bp 118 °C (0.5 Torr)], *p*-nitrophenyl decanoate (PNPD) (mp 35 °C), and 2,4-dinitrophenyl decanoate (OPDNPD) (mp 30 °C) from the respective acid chlorides and the appropriate phenols;[24] 2,5-dinitrophenyl decanoate (OMDNPD) (mp 36 °C), *m*-nitrophenyl decanoate (MNPD) (mp 36 °C), *p*-bromophenyl decanoate (PBPD) [bp 154 °C (0.1 Torr)], and phenyl decanoate (PD) [bp 125–132 °C (1–2 Torr)] using DCC as dehydrating agent.[25]

All the esters were checked by spectroscopic methods as well as by elemental analysis.

The micellar ester $CH_3(CH_2)_9N^+(CH_3)_2(CH_2)_3COOPh(NO_2)_2$-($Br^-$) ($OPDNPDE^+$) was prepared according to Bodansky and du Vigneaud.[25] Dicyclohexylcarbodiimide (0.05 mol) was dissolved in hot acetone together with equimolar quantities of 2,4-dinitrophenol and *n*-decycldimethyl(4-carboxybutyl)ammonium bromide. The crude $OPDNPDE^+$ was recrystallized from acetone–ether, bp 125–132 °C (1–2 Torr). Anal. Calcd for $C_{22}H_{37}N_3O_6Br$: C, 50.87; H, 7.13; Br, 15.41. Found: C, 50.45; H, 7.56; Br, 15.43.

Determination of Critical Micelle Concentration (cmc). Determination of cmc values of the micelle forming agents I–V was made by two methods: A, measurements of surface tension; B, measurements of refractive index. An attempt to measure the cmc of the above compounds by the determination of the specific volume was not suceessful.

Method A. Ten solutions of detergent were prepared in the range of 1×10^{-3} to 2×10^{-1} M and ionic strength of 0.8 μ. The solution was thermostated at 30 °C and the surface tension measured by a Fisher Surface Tentiomat apparatus, Model 21.

Method B. The refractive index of the solution prepared above was measured by a Zeiss refractive index apparatus. The temperature of 30 °C was attained by circulation of thermostated water through the lens block. A plot of surface tension or refractive index against the concentration of the micelle-forming compound showed a break in the curve at the cmc.

Kinetic Measurements. Rates of liberation of the phenol, *p*-nitrophenol, *m*-nitrophenol, *p*-bromophenol, 2,4-dinitrophenol, and 2,5-dinitrophenol were measured spectrophotometrically at 295, 350, 400, 310, 325, and 450 nm, respectively. A Unicam SP800 recording spectrophotometer with scale expansion and constant wavelength unit was used. The temperature of 30 °C in the cell block was attained by circulation of water from an external thermostated bath. The reaction was initiated by addition of 20 μl of ester (7.5×10^{-3} M) dissolved in acetonitrile to a thermally equilibrated solution in a stoppered 10-mm silica cell containing 3 ml of $K_2CO_3/KHCO_3$ buffer (0.035 M) and the appropriate micelle in KBr (0.8 M).[18d] The concentration of esters in solution was 5×10^{-5}. The absorbance of the solution during the kinetic run was monitored by a coupled recorder connected to the instrument. The pH of the solutions was measured before and after each run on a Radiometer pH-meter-26 with combined glass electrode type GK 2322C at 30 °C. The first-order rate constants were calculated either by means of a linear least-squares method with a CDC computer or by a regression least-squares program 18b with an Olivetti Program 101. Rates were measured at a series of micelle-forming agent concentrations $1–20 \times 10^{-2}$ M and at a series of pH values between 9.5 and 10.7 and exhibit linear dependence with hydroxide ion concentration. The second-order rates were obtained from the slope of the plot of k_{obsd} vs. OH^- concentration.

Results

The first-order rate constants for all the esters discussed are linearly dependent on the hydroxide ion concentration.

In Table II we have summarized the rate constants of the short-chain esters of various micellar systems (I–V) in a micelle concentration range of 0–0.2 M, at three cmc values. A

Table I. Analytical Data of Compounds I–IX

Registry no.	Compd	Method	Formula	Anal., % C Calcd	C Found	H Calcd	H Found	N Calcd	N Found	Br Calcd	Br Found	Crystd from[a]	Mp, °C
39995-55-6	I	A, B, B′	$C_{14}H_{32}NOBr$	54.19	54.20	10.32	10.30	4.51	4.50	25.78	25.68	F, C	152
1927-06-6	Ia	A′	$C_5H_{14}NOBr$	32.61	32.55	7.61	7.80	7.61	7.47	43.49	43.56	D	305 dec
61063-28-3	Ib	See text	$C_{15}H_{34}NOBr$	55.55	55.43	10.49	10.40	4.37	4.39	24.69	25.01	F	112
61063-29-4	II	B, B′	$C_{15}H_{34}NOBr$	55.55	55.61	10.49	10.46	4.37	4.47	24.69	24.75	F	70
61063-30-7	IIa	A′	$C_6H_{16}NOBr$	36.36	36.28	8.08	8.21	7.07	6.92	40.40	40.52	E	174–175
60535-37-7	III	B′.	$C_{16}H_{36}NOBr$	56.80	56.70	10.50	10.50	4.14	4.20	23.67	23.80	F	77
61063-31-8	IV	B′	$C_{16}H_{36}NOBr$	56.80	56.63	10.65	10.42	4.14	4.25	23.67	23.42	F	160
61063-32-9	V	B	$C_{15}H_{34}NO_2Br$	52.94	53.16	10.0	9.84	4.12	4.32	23.53	23.38		Wax
39995-56-7	VII	A	$C_{14}H_{32}NBr$	57.14	56.80	10.88	11.23	4.76	4.84	26.13	26.31	D	151
39995-54-5	VIII	A[22]	$C_{14}H_{30}NO_2Br$	51.85	51.82	9.26	8.97	4.32	4.19	24.71	24.69	D	153
61063-33-0	IX	A	$C_{16}H_{32}NO_2Br$	54.86	54.66	9.14	9.19	4.00	4.04	22.86	23.15	F	79–80

[a] C, acetone; D, methanol–ether; E, methanol; F, acetone–ethyl acetate.

Table II. Second-Order Rate Constants k' (s^{-1} M^{-1}) of PNPA, PNPH, and OPDNPA Basic Hydrolyses in Various Concentrations of Micelles I–V at 30 °C, μ = 0.8 M (KBr), Buffer 0.035 M $K_2CO_3/KHCO_3$

Ester	Micelle concn, M	Type of micelles I	II	III	IV	V
	0.00	12.0	12.0	12.0	12.0	12.0
	0.01	26.3	15.2	30.3	26.4	28.4
	0.02	72.0	19.0	87.5	45.5	46.5
	0.06	234.0	34.2	219.0	78.0	93.0
PNPA	0.08	244.0	31.0	260.0	94.0	114.0
	0.10	248.0	39.1	304.0	104.0	139.0
	0.15	270.0	42.5	350	119.0	
	0.20	280.0	44.0	399.0	135.0	
	0.00	7.9	7.9	7.9	7.9	7.9
	0.01	18.1	8.3	17.9	14.2	15.9
	0.02	61.8	10.3	106.0	27.5	41.0
	0.06	96.0	13.1	121.0	34.0	45.8
PNPH	0.08	100.0	13.5	126.0	36.0	48.0
	0.10	103.0	13.5	127.0	35.2	52.5
	0.15	108.0	13.7	136.0	40.0	
	0.20	110.0	14.2	144.0	44.0	
	00.0	64.9	64.9	64.9	64.9	64.9
	0.01	220.0	82.5	327.3	148.4	120.0
OPDNPA	0.02	610.0	111.1	840.0	296.5	264.0
	0.06	1632	210.7	2215	821.0	504.0
	0.08	1942	226	2520	930	600.0
	0.10	2150	230	2820	1020	641.0
	0.15		241	3250	1100	
	0.20		260	3450	1253	

nonlinear least-squares program was used to fit the data given in Table III with eq 1

$$k_{obsd} = \frac{k_{OH} + k_{mH}K_s(mH - cmc)}{1 + K_s(mH - cmc)} \times [OH^-] \qquad (1)$$

$$k' = k_{obsd}/[OH^-]$$

k_{mH} and k_{OH} are the second-order rates of the ester hydrolysis in the presence and the absence of the micelle, respectively. K_s is the equilibrium constant of ester association into the micelle divided by the aggregation number and mH is the monomer concentration of the micelle-forming agent, in an undissociated form. Two parameters, k_{mH} and K_s, and cmc were used on fitting data, while the cmc was constrained to the experimental region measured.

The cmc values given in Table III were determined by surface tension measurements, as well as by refractive index determinations. The above measurements indicate that all the cmc values are lower than 0.02 M.[18c]

For comparative purposes, we included in this study some kinetic measurements related to other types of dipolar micelles such as Ib, VI, VII, and VIII. The second-order rate constants k' (s^{-1} M^{-1}) measured for the long-chain ester PNPD in the presence of 0.1 M concentration of Ib, VI, VII, and VIII are 2.88, 4.3, 1.43, and 0.56, respectively (30 °C, μ = 0.8 M).

To acquire a quantitative estimate of the kinetic effect of the catalytic group in micelles I–V, kinetic measurements in analogous nonmicellar systems Ia and IIa were performed. The rate of hydrolysis of PNPA, PNPH, and OPDNPA with choline bromide (Ia) and homocholine bromide (IIa) is linearly dependent on hydroxide ion and catalyst concentration in accordance with eq 2, which is kinetically equivalent with eq 3

$$k_{obsd} = k_{AH}[ROH][OH] \qquad (2)$$

$$k_{obsd} = k_A[RO^-] \qquad (3)$$

where $k_{AH} = k_A K_a/K_w$.

Table III. Calculated Parameters K_s and Second-Order Rate Constants k_{mH} (s^{-1} M^{-1}) for Three cmc Values in the Hydrolysis of Substituted Nitrophenyl Esters Catalyzed by Micelles I–V at 30 °C, μ = 0.8 (KBr), Buffer 0.035 M K_2CO_3/ $KHCO_3$

Esters	Kinetic cmc × 10^3	I, 1–2 × 10^{-2} [a] k_{mH}	K_s	II, 0.5–1 × 10^{-2} [a] k_{mH}	K_s	III, 0.5–1 × 10^{-2} [a] k_{mH}	K_s	IV, 0.5–1 × 10^{-2} [a] k_{mH}	K_s	V, 2–2 × 10^{-2} [a] k_{mH}	K_s
PNPA	5			54.3	18.8	595	10	194	10.2	234	10.3
	10	398.2	18.9	52.2	23.3	565	11.8	178	13.3	196	17.1
	15	354	28.6			537	14.2				
PNPH	5					11		42.2	71.5	59.9	71.3
	10	113	102.8	15.6	40.4	148	94	38.9	153	54.2	161
	15							37.9	282	51.4	384
OPDNPA	5	5202	7.5			4772	14.3	1625	16.7	1112	13.3
	10	3889	13.2	355.5	16.9	3809	27.3	1430	24.8	939	21.1
	15			312	27.1					800	35.5
PNPD		78		8.3		86		39		50	
OPDNPD		505		63		700		405		276	
$OPDNPDE^+$		6000		1500		12000		3200			

[a] Experimental cmc, M.

Table IV. Third-Order Rate Constants k_{AH} (s^{-1} M^{-2}) of PNPA, PNPH, and OPDNPD Hydrolysis Catalyzed by the Nonmicellar Agents Ia, IIa, and IIIa (0.05–0.5 M), 30 °C, μ = 0.8 (KBr), Buffer 0.0035 M $K_2CO_3/KHCO_3$[a]

Ester	Ia	IIa	IIIa
PNPA	185	40.8	249
	(0.127)	(0.102)	(0.15)
PNPH	73	27.6	144
	(0.05)	(0.069)	(0.086)
OPDNPD	1450	400	1660
	(1)	(1)	(1)

[a] The numbers in parentheses are the relative rates compared to OPDNPA.

The third-order rate constants k_{AH} were derived from the plots of the second-order rate constants $k' = k_{obsd}/OH$ against concentrations of [Ia], [IIa], and [IIIa], and are assembled in Table IV.

Catalysts Ia, IIa, and IIIa exhibit similar catalytic effects on esters examined, but IIIa is shown to be a better catalyst than Ia and IIa.

The micellar catalysis is manifested from the higher rate in ester hydrolysis in presence of the catalytic (I) as compared with that of the noncatalytic (Ib) micelle, amounting to a ratio of $k'(I)/k'(Ib) = 27.1$ for PNPD. This catalysis could in principle be due to either of the two oxygen forms, the dissociated (RO^-) or the undissociated (ROH) forms of the head groups.

The rate constants due to these two forms of the head groups should obey eq 2 and 3, and can be related by the equation $k_m = k_{mH}K_w/K_a$ where k_m is a first-order rate constant.

To distinguish between these two hydrolytic pathways we examined the reaction with added nucleophile such as azide ion and *N*-decylimidazole which are not subject to general catalysis for activated esters or amides.[26,27a] The second-order rate constants for the nucleophilic catalysis of the azide ion on PNPD and $OPDNPDE^+$ in various dipolar micelles I, Ib, III, and VII are given in Table V.

The nature of the transition state in catalytic reactions has been discussed in the literature.[27] On the basis of Brønsted and Hammett criteria, the nucleophilic catalysis has been shown to be more sensitive to charge developing in the transition state (i.e., to β and ρ parameters) than in general catalysis. The changes in ρ values between the intermolecular and the intramolecular reactions were also attributed to different transition states.

Catalytic micelles I–V differ in their physical properties (hydrogen bonding, solvation, etc.) in comparison with the noncatalytic micelles Ib and VII. In the case the transition-state structure is affected by physical factors, changes in the Brønsted and Hammett plots should follow. To examine this

Table V. Second-Order Rate Constants (s^{-1} M^{-1}) of Nucleophilic Attack by Azide Ion on Substituted Phenyl Esters, 30 °C, μ = 0.8 (KBr)

	Micelles				
Ester	Ib, $k \times 10^3$	VII, $k \times 10^3$	I, $k \times 10^3$	III, $k \times 10^3$	II, $k \times 10^3$
PNPD	21[a]	19.6[a]	24[a]	32[b] 28[c]	17.4[d]
$OPDNPDE^+$		2625[e]	1850[f]		1940[e]

[a] pH 9.15. [b] pH 9.25. [c] pH 9.93. [d] pH 9.52. [e] pH 7.48. [f] pH 7.00. Buffer 0.035 M $K_2CO_3/KHCO_3$.

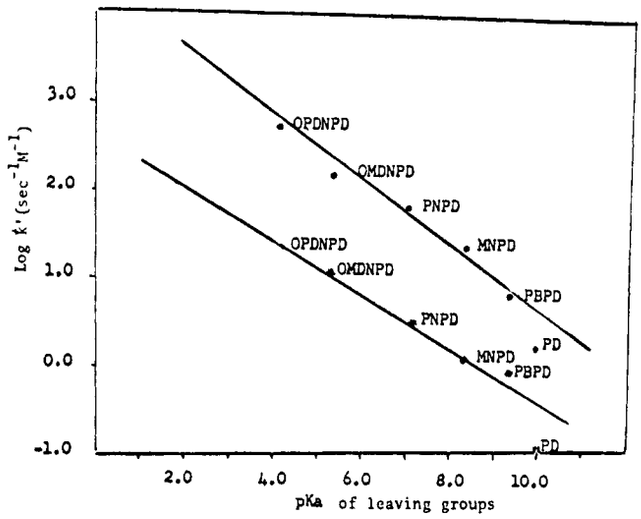


Figure 1. Brønsted plot for the hydrolysis of substituted phenyl decanoate esters in the presence of micelles I (● — ●) and Ib (★ — ★) at 30 °C, μ = 0.8 (KBr), micelle concentration 0.1 M. For pK_a values, see ref 29.

possibility the variations in rates of hydrolysis of substituted phenyl decanoates in I and Ib were investigated. The data obtained are presented in Figure 1. The β values derived from the plots in micelle I and Ib are 0.36 and 0.31, respectively. The corresponding ρ values are 1.0 and 1.1. This suggests that the nucleophilic attack of negatively charged species in the two systems are similar.

The deuterium isotope effect in the hydrolysis of PNPD (Figure 2) was studied in order to gain deeper insight on the microscopic reaction pathway. The experimental isotope effects for the second-order rate constant $k'(H_2O)/k'(D_2O)$ of micelles I, II, and VII were 0.81, 0.59, and 0.76, respectively.

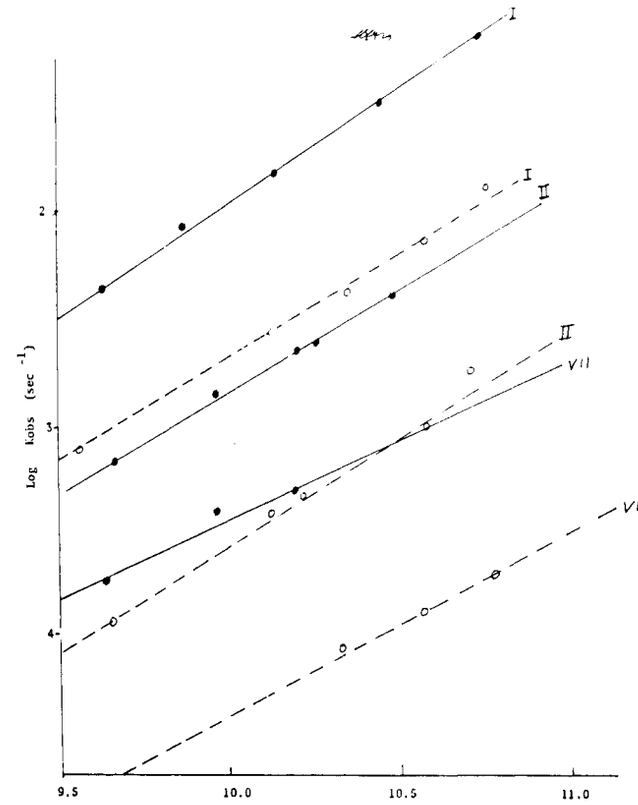


Figure 2. Log k_{obsd} vs. pH (● — ●) and pD (○ - - - ○) for the hydrolysis of PNPD in the presence of micelles I, II, and VII at 30 °C, μ = 0.8 M (KBr), buffer 0.035 M $K_2CO_3/KHCO_3$.

Table VI. Second-Order Rate Constants for Acid Hydrolysis of PNPA, PNPD, and PNPH in the Presence of Micelles I, VII at 60 °C, μ = 0.8 (KCl)

Esters	$10^5 K$ (s^{-1} M^{-1}) None	I	VII
PNPA	50.6	53.3	54.0
PNPH	41.6	13.0	12.5
PNPD		3.5	4.1

Based on the value of 0.76 found for the ratio $k(OH^-)/k(OD^-)$ (as observed for micelle VII), and assuming a ratio of 2–3 for isotope effect in the case of a general acid or general base catalysis[40] the isotope effect of a general-acid specific-base pathway can be estimated[41] and falls within the range of 1.3–2. Therefore the experimental values found for micelles I and II point to a nucleophilic attack.

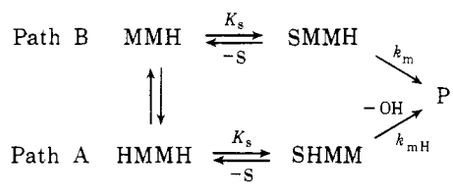
For comparison, the effect of the dipolar micelle on acid catalysis was also studied. In the acidic medium the contribution of the hydroxy group as a catalyst is diminished, suggesting that other effects such as solvation and electrostatic effects might be more pronounced. In Table VI are given the second-order rate constants of PNPA, PNPH, and PNPD hydrolysis at 60 °C. The rates were measured in the range of pH 0.5–1 and μ = 0.8 (KCl). cmc measurements as well as additional kinetic investigations in acidic media[18d] confirm the existence of a micellar system also in these acidic conditions.

Discussion

The acceleration of alkaline hydrolyses by micelles containing neighboring phenoxide on alkoxide groups can be attributed to the intramolecular assistance either of the undissociated alkoxy group or of the dissociated moiety. In the first case the acceleration can be described mechanistically by general acid–specific base catalysis, or electrophilic assistance due to hydrogen bonding in the ground state[30,31] and microscopic solvation of the transition state by hydroxy group.[32] When the oxy anion is involved (second case) the microscopic pathway could result either from nucleophilic catalysis in the formation of the less reactive esters[28a] or from general base catalysis involving water molecule.[33]

A general outline for the micellar catalysis of ester hydrolyses is shown in Scheme I.

Scheme I



In Scheme I two types of micelles are operating; MMH represents a mixed micelle aggregate containing dissociated and undissociated forms of monomers while HMMH represents an un-ionized micelle, composed only of the undissociated monomers.

When $H^+ \gg K_a$ the two pathways A and B results a first-order dependence in hydroxide ion concentration. The same rate equation can also be attributed to a different type of model in which a mixed micelle composed of undissociated and dissociated monomers is formed.

Kinetically pathways A and B are represented by the same rate equations. The data presented here strongly suggest that the hydrolyses of the substituted phenyl esters in the micellar phase do not follow pathway A.

(1) The nucleophilic attack of azide ion was measured with two esters: PNPD and OPDNPE$^+$. Since the esteric head groups are presumably located at different regions on the micellar surface, rate enhancement due to electrophilic assistance by the hydroxy head group on the micelle should not be similar. Yet the experimental results given in Table V show that the enhancement of both esters in presence of micelle I are very similar.

(2) Addition of decylimidazole (0.005–0.05 M) to 0.1 M micelle I and Ib at pH 9.54 linearly increased the hydrolytic rates of PNPD.[44] The second-order rate constants obtained are 1.0×10^{-1} and 1.1×10^{-1} s^{-1} M^{-1}, respectively. This fact argues against electrophilic assistance to the nucleophilic attack of PNPD by decylimidazole, as indicated by pathway A.

The kinetic effect of compound VIII resembles that of an anionic micelle. The rate of hydrolysis in basic solution of PNPD in 0.1 M VIII is 2.55 times slower than in 0.1 M VII, and 5.1 times slower than in 0.1 M Ib. For PNPH, the rate in 0.1 M VIII was eightfold slower than in water. If route A is operating, micelle VI is expected to exhibit inhibitory effect on the hydrolysis of PNPD, which was not the case. The fact that the rate of hydrolysis of PNPD in VI is two times slower than in II can be attributed to other factors.

This conclusion was deduced from an additional study concerning micellar catalysis by polyfunctional cationic systems, as well as by mixed micelles containing the corresponding monofunctional monomers in 1:1 molar ratio.

On the basis of estimations for the expected isotope effect in general catalysis, it is concluded that a mechanism via electrophilic assistance in the transition state of the hydroxy head group in micelles I and II is not operative. The "microscopic solvent effect" can also be ruled out since in hydrolytic reactions attributed to a "microscopic solvent effect" by vicinal hydroxy group the deuterium isotope effect ranged between the values 0.2 and 0.4.

The Brønsted β coefficients in the presence of I and Ib indicates that the reaction proceeds via an anionic transition state and that the values obtained are in accord with what was expected in a reaction between strong nucleophiles and good leaving groups. (For hydroxide ion attack on a series of substituted phenyl esters the β value is 0.3.[26a]) Since the β value for acyl transfer reaction is 1.7, the small β values obtained indicate that the transition state occurs early in the reaction pathway. In intramolecular general base transesterification systems such as 2-hydroxymethylbenzamide[35] and ethyl 2-hydroxymethylbenzoate,[33] the β coefficients obtained were 0.2 and 0.87, respectively. The difference between these values was attributed to the need for development of full negative charge in the less activated acyl group during the nucleophilic attack. If the β values observed in the micellar reaction reflect charge development in general catalysis, a specific base assistance to nucleophilic attack of the undissociated hydroxy head group would have been expected to yield β coefficients of 1.0 since the acyl group is more activated.

General base catalysis originating from an oxy ion (i.e., alcoholate ion-activated water) can also be ruled out. In the intramolecular hydrolysis of substituted phenylsalicylates Bruice[33f] has shown that the general base participation of the phenoxide ion results in a Brønsted slope of $\beta = 0$. For the case in which hydroxy micelles catalyzed the rate of hydrolysis, the attacking group is more basic than the leaving group compared to substituted phenyl salycilate esters, so that the expected β value should be near 1, which is not the case.

The same conclusion is reached by comparing the ρ paramater obtained in micellar systems with ρ values in bimolecular and monomolecular systems. For specific base and alkoxide ion catalyzed hydrolysis of substituted phenyl acetate the ρ values are 0.8–1.1[27e,36] and for phenyl 4-hydroxybutyr-

ate, ρ = 1.1.[28a] The experimental ρ values obtained in this study (i.e., ρ = 1.0 and ρ = 1.1) for catalysis in micelle Ib and I, respectively, are in accord with a nucleophilic pathway brought about by the dissociated hydroxy head group.

The conclusions we came to about the nucleophilicity of the catalysis by micelles I and II are in accord with the findings of Bunton and Diaz,[42] who attained similar results in their studies on phosphate esters' hydrolysis catalyzed by hexadecyl(2-hydroxyethyl)dimethylammonium bromide [$Br^-C_{16}H_{33}(CH_3)_2N^+CH_2CH_2OH$].

Martineck et al.[43] have found that cationic micelles of the general structure $Br^-C_{18}H_{37}(Et)_2N^+CH_2CH_2OH$ behave as nucleophilic agents, exhibiting similarity to the catalysis by serine proteinases.

Since the alkoxide ion is assumed to be the reactive species in the micellar system I–VI according to Scheme I, it should be expected that as a result of the very low concentration of these species most of the substrate will be in an unproductive surrounding. The experimental results show that the hydrolysis of substrate (i.e. [SHMM], [MMHS]) is stoichiometric. The explanation may be based either on the dynamic structure of the micelle[18] or on hydrogen exchange within the micellar phase or between the micellar phase and the bulk solution.

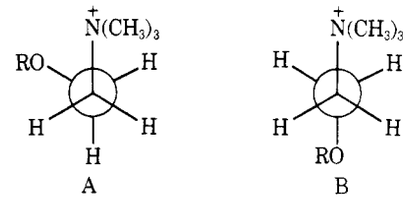
Comparison of the Models I–V. From inspection of Tables II and III several phenomena are apparent: (1) Compared of the hydrolysis of the esters in the bulk solution, all the hydroxy micelles I–V enhanced the second-order reaction rate (k_{mH}), initially by a factor of 2 in the case of micelle II and with PNPH, up to a factor of 59 in the case of micelle I with OPDNPA. (The comparison was done at cmc 1×10^{-1} M). (2) The enhancement is more pronounced with dinitrophenyl esters than with *p*-nitrophenyl esters and with micelles and III. (3) The rates are retarded as the chain length of the ester is increased; the K (association) values (K [association] = K_sN, $N \simeq 50$) are small and range between 650–1250 in the short chain esters and 2000–8000 in the hexanoate series.

Although the association constants are small, it should be mentioned that they are still greater than in compounds bearing methyl groups only on the quaternary nitrogen.[45] Lengthening the chain of the core by six carbon atoms has been shown to increase the solubility of PNPA by a factor of 3.[39] The comparison of the associated constants of hydroxylic micelles with those obtained for VII and VIII[44] shows interesting solubilization properties of micelles: (1) an apolar head group (ethyl) increases the association constant; (2) carboxylate ion separated by one carbon atom from the positively charged nitrogen center also increases the association constant (K_s for PNPH in VII and VIII is 1000 and 920, respectively); (3) the hydroxy group separated by two carbon atoms decreases the association constant. The interference of the hydroxy head group in the hydrophobic interaction is indicated by comparing K_s values with those found for PNPH and PNPA in tetradecyltrimethylammonium chloride detergent.[45] The very high ratio [K_s(PNPH)/K_s(PNPA) = 16 000:33] in TDTAC compared to the same esters in micelle I [K_s(PNPH)/K_s(PNPA) = 100:19] is in accordance with the above conclusion. The change in free energy of transfer PNPH from micelle VII to micelle I can be calculated according to eq 4.

$$\Delta(\Delta G) = -RT \ln \text{eif} K_s^{VII}/K_s^{I} \quad (4)$$

From the ratio K_s^{VII}/K_s^{I} = 10 (assuming the same aggregation number for the two micelles), the free energy of transfer can be shown to be 1380 cal/mol. Since the change in ΔG of transfer of a methylene group from water to a micellar solution is reportedly 6401 cal/mol,[12c,46] the difference in solubility of PNPH in VII as compared to I approximates the difference of hydrophobic interaction by the two methylene groups. Thus, the two methylene groups in micelle I are in a polar environment (i.e., in the outer part of the surface) and are nonpenetrating into the interior of the micelles. The difference in the free energy of solubilization found for micelle I as compared to VII cannot be explained on the basis of hydrogen bonding since kinetically the data do not conform with assistance (through hydrogen bonding) either in the ground state or in the transition state (see results of azide, Table V). The lack of hydrogen bonding by the hydroxy head groups to the ester examined here is in accordance with the free area of 102 A^2/molecule found for the hydroxy group in 2-dodecylaminoethanol hydrobromide. The additional interaction in the outer region of micelle I could instead result from different charge distribution compared to micelle VII. Molecular orbitals calculations[47] point to a very high charge delocalization. In a conformation of {50,50} only 11% of the positive charge is located on the nitrogen, while 82% of the charge is localized on the methylene groups bonded to the nitrogen. (This delocalization is one of the reasons for the roughness of the micellar surface.) The β carbon also exhibits a strong positive charge on the carbon which is ~4 times greater than that on the nitrogen. The appearance of a large positive charge on the outer hydrocarbon chain of the micelle containing a polar head group is likely to increase solvation and solute binding interactions. In esters of short carbon chain, these electrostatic interactions compensate part of the hydrophobic interaction between the solute and the hydrocarbon core of micelle I. Therefore, comparison between dipolar micelles I, Ib and micelle VII allows the anticipation that (1) the partition coefficient of the esters in the two systems are different, and (2) in a noncatalytic dipolar micelle (Ib) the transition state involved in the nucleophilic attack is relatively more stabilized than in micelle VII. With long-chain esters these effects are minimized. The twofold decrease in the second-order rate constant of the basic hydrolysis of PNPD in micelle VII as compared to that in Ib can be explained on the basis of the above argument. It is anticipated that with dipolar micelles in acidic media both solvation and destabilization of the transition state will be affected more by excess positive charge distribution than in micelle VII. Indeed, inspection of Table VI reveals that the rate constants in micelle I are very close to those in VII.

Substrate orientation in the outer part of the micellar phase is very important, especially when the nucleophile is part of the micelle monomer and hindrance to nucleophilic attack might arise. NMR analysis revealed[48] that choline, acetylcholine, and 2-methoxycholine populate almost exclusively the gauche conformation A, while ethyltrimethylammonium bromide adopts 88% of the anti form B.



The preference of conformation A is explained in terms of an interaction between the onium group and the partial negative charge on the β oxygen.[49]

Although in the micellar phase most of the positive charge is neutralized by the negatively charged ions from the bulk solution, the gauche conformation can still be dominant as a consequence of the anionic nucleophile on the β oxygen.

In micelles I–V this entails restriction in orientation of the substrate during the nucleophilic attack.

Kinetic data are in consonance with the above assumption. In contrast to the hydroxy dipolar system, the electrophilic catalysis in cationic surfactant becomes more pronounced as the chain length of the substrate increases.[45] The observed decrease in rate with the increase of the hydrocarbon chain of esters of the hydroxy dipolar micelles indicates that the hydrophobic interaction between the substrate and the interior core of the micelle expels the carbonyl group from the vicinity of the nucleophile. The relative rates k_{mH}/k_{OH} for the short chain dinitrophenyl esters (Table III) are of higher value than those of the *p*-nitrophenyl esters, indicating that the former tend to dwell in the waterlike region of the micelle, in the vicinity of the hydroxy head group. The increase in the relative rate is more pronounced in the presence of I and III than of II, IV, and V, but it is rather small in the presence of II existing presumably in a more flexible conformation. In OPDNPDE$^+$ the hydrocarbon chain of the ester is assumed to be incorporated into the micellar core where the positively charged ammonium group lies on the Stern layer and the carbonyl group points outward of the micellar surface (i.e., in the vicinity of the attacking nucleophile). Interestingly, the rates of hydrolysis of OPDNPDE$^+$ are accelerated in the presence of micelles I, II, and III (Table III) by a factor of 12–18 relative to OPDNPD, whereas in the presence of IV the factor is 5.7 only. Since in a noncatalytic micelle (Ib) the rates of hydrolysis of OPDNPDE$^+$ and OPDNPD are 1500 and 20 s^{-1} M^{-1}, respectively, evidently the effect of the ionized hydroxy head group on the nucleophilic catalysis is smaller for OPDNPDE$^+$ than for OPDNPD.

The relative rates of OPDNPD $k'(I)/k'(Ib)$ for micelles I, II, III, and IV are 505/20 = 25.2, 63/20 = 3.15, 700/20 = 35, and 405/20 = 20.2, respectively, while for the ester OPDNPDE$^+$ the relative rates for the above micelles are 4, 1, 8, and 2, respectively.

Data indicate that the catalysis by hydroxylic micelles becomes more efficient as the electrophilic center of the carbonyl ester resides in the region between the cationic and the hydroxy head group. When the residence of the carbonyl ester occurs above the micellar hydroxy head group as in the case of OPDNPDE$^+$, the catalysis, although it still exists, has rather low efficiency. The lower rate of hydrolysis of OPDNPDE$^+$ relative to OPDNPD in micelle IV can also be rationalized in terms of the micellar conformation depicted by rotamer A. In this conformation the steric interference of the dimethyl groups in the α position with the ester moiety in OPDNPDE$^+$ is greater than in OPDNPD, which is placed at the internal region of the micelle surface.

The rate constant (k') in the presence of IV is in general smaller than in I. The decrease in catalysis can be attributed to the differences in pK_a between the monomers of the two systems. From analogy between the hydroxy compounds and the carboxylic acids one can attribute an increase of 0.17 pK_a units to the dimethyl groups (the pK_a values of propionic acid and trimethylacetic acid are 4.87 and 5.04, respectively) and the relative first-order rate constants $[k_m(IV)/k_m(I)]$ should therefore be equal to 1.5-fold of the second-order rate ratio. Such an estimation shows that in the case of the long-chain ester OPDNPD and PNPD, where the ester group occupies a more restricted area than in the short-chain counterparts, the catalytic efficiency of IV is 120 and 75% of I, respectively.

The greater acceleration effect in III than in I cannot be attributed to differences in micellar volume since the same effect is noted in the case of the short-chain catalyst IIIa. We believe that replacement of the dimethyl by a diethyl group should entail a change in the microscopic environment of the oxy nucleophile which could be manifested either by a lower pK_a value of the hydroxy group or by exerting influence on the binding in the transition state.

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Registry No.—IIIa, 5455-95-8; PNPA, 830-03-5; OPDNPA, 4232-27-3; PNPH, 956-75-2; PNPD, 1956-09-8; OPDNPD, 61063-34-1; OMDNPD, 61063-35-2; PBPD, 61063-36-3; PD, 14353-75-4; OPDNPDE$^+$, 61063-37-4; hexanoyl chloride, 142-61-0; decanoyl chloride, 112-13-0; *p*-nitrophenol, 100-02-7; 2,4-dinitrophenol, 51-28-5; MNPD, 61063-38-5.

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(18) (a) No buffer effect was observed in the concentration range between 0.01 and 0.08 M, in ionic strength of 0.8 M (KBr). (b) The authors wish to thank Professor T. C. Bruice for supplying his programs for the Olivetti calculator. (c) The validity of the cmc values assembled in Table IV could be inferred from ESR measurements with spin labeling.[16b] In a forthcoming paper, Part 5, we shall present kinetic evidences establishing the reliability of the above cmc values. (d) Progress of investigations in various ionic strengths and various pH ranges will be described in following publications.
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Reaction of Atomic Fluorine with Benzotrifluoride

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A radio-frequency excited plasma has been used to generate atomic fluorine. Using a molecular beam type of reactor, monofluorination of benzotrifluoride has been achieved with yields up to 28.3%. The atomic fluorine to benzotrifluoride ratio has been found to determine which isomer(s) will be produced and to control the total overall yield of monofluorinated products.

Direct introduction of fluorine into an aromatic ring without corresponding loss of aromaticity has been an unsolved problem for years. Early attempts at direct fluorination led to explosions, the only products being tars.[1-3] Having obtained only a polymer, Bockemuller[4] concluded that under the conditions for direct liquid-phase fluorination aromatic compounds form addition products or polymers instead of the desired substitution products. In 1969, Grakauskas[5] reported the direct liquid-phase fluorination of benzene, toluene, bromobenzene, and several other aromatic compounds. Based on the distribution of ortho, meta, and para isomers of the monosubstituted fluorobenzenes, an ionic electrophilic substitution mechanism was proposed for these reactions.

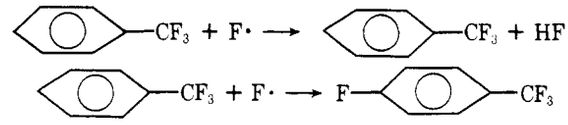
Recently, substitution of fluorine into an aromatic ring by direct reaction with atomic fluorine generated in an electrodeless radio-frequency glow discharge has been reported.[6,7] The isomer distribution of the products indicated that the introduction of fluorine into an aromatic ring via radical mechanism can occur with much more selectivity than previously thought.

Discussion

In an effort to determine the relative chemical activity of atomic fluorine with respect to molecular fluorine, reactions E and F were undertaken. The two reactions were carried out under as near identical conditions as possible except for the fact that in reaction E atomic fluorine was used and in reaction F molecular fluorine was used. Since the atomic fluorine was generated by passing molecular fluorine through a radio-frequency discharge, it was a relatively simple matter to perform experiments with and without the radio-frequency activation. In Table I it can be seen that in reaction E (where atomic fluorine was used) the yield was 28.3% monofluorinated product, while in reaction F (where molecular fluorine was used) the yield was less than 1% monofluorinated product. The use of atomic fluorine increased the percent of monofluorinated product(s) and greatly reduced polymer formation.

Figure 1 related the fluorine to substrate ratio to the recognizable fluorinated products. As the ratio was increased in the experiment, the percent recognizable product also increased.

If the original attack of the benzotrifluoride occurs as shown below, the benzotrifluoride radical produced can react in three



ways: (1) with atomic fluorine to produce monofluorobenzotrifluoride; (2) with another benzotrifluoride radical to produce bis(trifluoromethyl)biphenyl; (3) with a benzotrifluoride molecule to initiate polymerization.

Increasing the availability of the fluorine atoms with respect to benzotrifluoride radicals increases the amount of monofluorinated products and decreases the amount of polymer formed. Figure 1 shows this relationship.

In earlier atomic fluorine work Vasek and Sams[7] reported finding greater selectivity than would have been pictured from literature discussions of free-radical reactions. The findings of this study show a definite relationship between the fluorine to substrate ratio and isomer distribution. The ortho and meta