Transmission of Substituent Effects in Polar Reactions

Part 2.—Relative Rates of Halide Displacement and Ester Saponification in the Alkaline Hydrolysis of α-Haloacetate Esters

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Rate coefficients and activation energies for ester saponification in the alkaline hydrolysis of the ethyl esters of the α -haloacetic acids in aqueous solution have been determined by a pH-stat method with correction for the significant competition by displacement of halide ion for the bromo- and iodoesters. While the gross effects of the halogens relative to hydrogen may be understood by reference to the influence of direct electrostatic fields, there is evidence that the rates of ester saponification may also be enhanced by partial displacement of the halide ion in the transition state. The dissociation of methane sulphonyloxyacetic acid and the kinetics of alkaline hydrolysis of its ethyl ester have been studied in the light of this hypothesis.

In previous studies of the kinetics of ester hydrolysis in aqueous alkali $^{1, 2}$ it was found that

 $K_a(X-CH_2COOH)/K_a(CH_3COOH)$ and $k_{OH}(X-CH_2COOEt)/k_{OH}(CH_3COOEt)$

are nearly equal for most simple polar substituents. This has been used as a criterion for assuming that significant contributions to the substituent effects from neighbouring group proximity or specific solvation are absent and that direct field effects predominate over sigma-inductive interactions.

Conductimetric measurements of the rates of consumption of alkali by the ethyl esters of mono-, di- and tri-substituted haloacetic acids have been reported.³ With assumptions concerning group dipole moments and geometries, the rate coefficients were shown to be generally consistent with the direct field effects to be expected when one, two or three halogen atoms are introduced into the methyl group. However, when the rate coefficients for the mono-haloesters are compared with the dissociation constants for the corresponding acid, the reactivities of the esters of chloro-, bromo- and iodo-acetic acids are three to four times higher than expected from the linear Gibbs energy relation. The halogens showing discrepancies are those that are susceptible to bimolecular nucleophilic displacement in aliphatic systems and such $S_N 2$ substitution is commonly facilitated when the halogen is in the alpha-position relative to a carbonyl group.⁴

If nucleophilic displacement of halide ion competes with ester saponification for hydroxide ion, then the apparent second-order rate coefficient for alkali consumption will correspond to a sum for the two processes and thus could lead to a discrepancy in the direction noted above. This possibility does not appear to have been allowed for in previous studies.^{3, 5, 6} We have therefore investigated the rates of alkaline hydrolysis reactions of the ethyl esters of all four mono-haloacetic acids giving particular attention to the stoichiometry of alkali consumption and halide ion production. To

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test the hypothesis that ester saponification may itself be facilitated by the presence of a readily displaceable group in the α -position, we have examined the hydrolysis of MeSO₂O—CH₂COOEt and the dissociation of MeSO₂O—CH₂COOH.

EXPERIMENTAL

MATERIALS

Ethyl fluoroacetate and ethyl bromoacetate were both prepared by esterification of the Commercial ethyl chloroacetate (Hopkin and Williams General purpose appropriate acid.⁷ Reagent) was used. Ethyl iodoacetate was prepared by treating ethyl chloroacetate with a slight excess of 1.0 mol NaI dm^{-3} acetone at room temperature. After 24 h most of the acetone was removed under reduced pressure and water containing a little sodium thiosul-The ester was then extracted with ether and distilled under reduced pressure : phate added. b.p. (1 mmHg) = 42° C, yield 70 %.

Methane sulphonyloxyacetic acid ethyl ester was prepared by the method of Pattisson and Millington.⁸ Methane sulphonyloxyacetic acid was obtained by hydrolysis of the ester with a slight excess of ethanolic KOH. The potassium salt was filtered off, dissolved in excess hydrochloric acid and continuously extracted with ether for 12 h. The ether extract was dried, evaporated and the product recrystallized from benzene; m.p. 116-117°C, yield 50 %, (found: C, 23.5; H, 4.0; S, 20.5 %; C₄H₁₀SO₅ requires C, 23.4; H, 3.9; S, 20.8 %). The 4-chloro-2,6-dinitrophenol was used as previously prepared.¹

RATE MEASUREMENTS AND STOICHIOMETRIES

The rates of consumption of alkali by the haloacetic acid ethyl esters were measured by the pH-stat method as previously described.^{2,9} Aqueous solutions of ca. 10⁻³ mol halo-ester dm^{-3} were studied over a range of temperature at convenient values of pH.

If halide displacement occurs in the alkaline hydrolysis of a haloacetate ester the product ethyl glycollate will itself be saponified with further consumption of alkali. Two samples of ethyl fluoroacetate consumed 99.0 \pm 0.5 % of the theoretical amount confirming that substitution in this case is insignificant. Samples of all of the halo-esters were treated with excess alkali, back-titrated to neutrality with nitric acid and then solid silver nitrate was added. Ethyl chloroacetate displayed only slight signs of substitution and those only at temperatures above 40°C. With ethyl bromoacetate and ethyl iodoacetate, significant amounts of halide displacement were detected. Estimates of purity, shown in table 1, for the latter compounds were obtained by standing 0.2 g ester with 20 cm³ 0.5 mol piperidine dm⁻³ aqueous solution for 2 h and titrating the liberated halide ion by Volhard's method.

TABLE 1.—QUANTITATIVE ANALYSIS OF AQUEOUS SOLUTIONS OF ESTERS, X—CH₂COOEt, THAT ARE SUBJECT TO COMPETITIVE SAPONIFICATION AND NUCLEOPHILIC DISPLACEMENT OF X^{-a}

X—	estimate of purity ^b	temp.,°C	hydroxide ion consumption
Br—	97.9±0.4 %	25	107.9±1.0 %
		35	108.6
		45	107.7
I—	98.7±0.8 %	25	111.4±1.0 %
		35	111.6
		45	110.4
MeSO ₂ O—		25	108.5+1.0 %
-		35	110.5
		45	109.6

^a Each figure is the mean of 3 determinations.

^b Purity is estimated by halide ion loss in 0.5 mol piperidine dm⁻³ aqueous solution.

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Quantitative estimates of the extent of halide displacement occurring in the alkaline hydrolysis of the ethyl esters of bromo-, iodo- and methane sulphonyloxyacetic acids were obtained from measurements of the total alkali consumed. Aliquots (40 cm³) of 0.01 mol ester dm⁻³ aqueous solution were placed alongside 20 cm³ ca. 0.05 mol KOH dm⁻³ in divided conical flasks, brought to the required temperature and the flasks shaken to mix the contents. Preliminary rate measurements were used to compute times allowed (15 min at 25°C, 10 min at 35°C and 5 min at 45°C), to complete effectively the hydrolysis of both substrate and ethyl glycollate while minimizing further attack on the haloacetate anions or on MeSO₂OCH₂CO₂⁻. The contents of the flasks were then back-titrated with minimum delay using 0.05 mol HCl dm⁻³. The results are listed in table 1.

RESULTS

TREATMENT OF THE KINETIC MEASUREMENTS

The rate coefficients for ester hydrolysis can normally be obtained by applying Guggenheim's treatment ¹⁰ to the continuously recorded volumes of alkali supplied to maintain the pH of a reacting ester solution.⁹ For those esters undergoing simultaneous hydrolysis and substitution, this method would provide the sum of the rate constants for the two reactions, were it not for the subsequent hydrolysis of the ethyl glycollate, formed by halide displacement, which consumes additional alkali. A knowledge of the relative rate of the substitution reaction and of the rate coefficient for hydrolysis of ethyl glycollate enables allowance to be made for this extra volume.

TABLE 2.—Second-order rate coefficients for aqueous alkaline hydrolysis of esters X—CH₂COOEt that are subject to competitive saponification (A2) and displacement of X^- (S_N 2)

Results of *median* runs using pH-stat method, all with ionic strength at half reaction $ca. 5.5 \times 10^{-4}$, are shown

		TT <i>a</i>	k _{A2} +	kSN2
X	temp.,°C	pH " (approx.)	raw d dm ³ mo	corr.
HO—	25.1			1.03 c
	34.9			1.85
	44.9			3.26
Br—	25.1	9.2	35.94	36.18
	34.9	8.7	52.36	52.83
	44.9	8.4	77.83	79.35
I—-	25.1	9.5	15.33	15.63
	34.9	9.2	22.60	23.21
	44.9	8.9	35.83	37.14
MeSO ₂ O—	25.1	9.5	20.89	21.22
-	34.9	8.9	35.36	35.83
	44.9	8.6	55.92	57.20

^a Values of pH for standardization with aqueous borax and values of pK_W were obtained by interpolation from tables in R. G. Bates, *Determination of pH* (Wiley, New York, 1954), pp. 76, 404.

^b We have taken $k_{A2}^{\circ} + k_{SN2}^{\circ} = (k_1 + k_2)/[OH^-].$

^c Values of k_3 are given by $k_3 = k_{A2}^{\circ}(HO - CH_2COOEt)[OH^-]$.

d obtained from uncorrected titration volumes.

• obtained by self-consistent correction of titration record.

The reaction system is represented by

$$\begin{array}{ccc} X - CH_2COOEt \xrightarrow{k_1} X - CH_2CO_2^- \\ A & B \\ & \xrightarrow{k_2} HO - CH_2COOEt \xrightarrow{k_3} HO - CH_2CO_2^-, \\ A & C & D \end{array}$$

where k_1, k_2, k_3 are first-order rate coefficients for a given concentration of hydroxide ion. The consumption of A then follows the first-order relation

$$(n_{\rm A})_{t=0} - n_{\rm A} = (n_{\rm A})_{t=0} [1 - \exp -(k_1 + k_2)t],$$

but because of the further reaction of product C the amount of alkali supplied exceeds this by the number of moles of D that are formed. Thus

$$(n_{\rm A})_{t=0} - n_{\rm A} = n_{\rm OH}(\text{supplied}) - n_{\rm D},$$

with

$$n_{\rm D} = (n_{\rm A})_{t=0} \{k_2/(k_1 + k_2)[1 - \exp(-(k_1 + k_2)t] - k_2/[k_3 - (k_1 + k_2)][\exp(-(k_1 + k_2)t) - \exp(-(k_3 t)]]\}.$$

From the uncorrected chart record of volumes of alkali in each pH-stat run a first estimate of $k_1 + k_2$ was obtained by least-squares analysis of a Guggenheim plot. Estimates of k_1 and k_2 were then obtained by assuming, on the basis of data in table 1, that k_2/k_1 is constant over the temperature range involved and is 0.13 for ethyl iodoacetate and 0.10 for the other two esters. The appropriate value of k_3 , available from our previous work,¹ was then used to correct the amounts of alkali consumed to allow for the further reaction of ethyl glycollate. Analysis of the corrected data by the Guggenheim method then led to an improved estimate of $k_1 + k_2$ and the procedure was repeated to selfconsistency. A typical set of results is shown in table 2.

In the above treatment we have neglected the reaction $X-CH_2CO_2^-+OH^- \rightarrow HO-CH_2CO_2^-+X^-$ because the carboxylate group hinders S_N^2 attack on bromoacetate ion ¹¹ (cf. bromomethane ¹²) and presumably this holds also for the other substituted methanes, which are themselves attacked by OH⁻ at a rate too slow to affect our analysis under the conditions employed. Of the substituents involved, those most readily displaced by OH⁻ from the corresponding methane are ¹³ MeSO₂O- and bromine ¹⁴ ($k_{S_{N2}} 4 \times 10^{-3}$ and 2×10^{-3} dm³ mol⁻¹ s⁻¹ respectively at 45°C).

All kinetic measurements are summarized in table 3. The second-order rate coefficients k_{A2}° refer to ester saponification at zero ionic strength.² Activation energies E_A and pre-exponential factors A were obtained from Arrhenius plots by the method of least squares, which also gives $k_{A2}^{\circ}(298.15 \text{ K})$, the "most probable" value of the rate coefficient at 25°C. 75 % confidence limits are quoted.

ACID DISSOCIATION MEASUREMENTS

The pK_a of methane sulphonyloxyacetic acid was determined by a spectrophotometric method similar to that previously described for isocyanoacetic acid.¹ The absorbances of aqueous mixtures of the acid and 4-chloro-2,6-dinitrophenol were measured at λ_{max} (446 nm) for the phenolate anion at $25\pm1^{\circ}$ C with a Shimadzu QR-50 spectrophotometer. The pH and all other parameters necessary for the evaluation of pK_a were thus obtained, activity coefficients being calculated from the Debye-Hückel expression. The results are shown in table 4.

x—	temp. °C	no. of runs	pH (approx.)	104 <i>1</i> (half- reaction)	k ^o dm³ mol ^{−1} s ^{−1}	<i>E</i> A kJ mol⁻1	log A dm ³ mol ⁻¹ s ⁻¹	k ^o _{A2} (298.15 K) dm³ mol ^{−1} s ^{−1}
Н	25.0	2	11.4	66	0.108 ± 0.009	47.6 ^d	7.38 ^d	
F	0.7	2	11.5	8.7	$\textbf{3.54} \pm \textbf{0.24}$	38.4±0.6	$\textbf{7.88} \pm \textbf{0.11}$	13.8 ± 0.2
	25.0	7	10.0 a	6.9	13.9±0.3			
	29 .6	4	9.6	5.2	17.5±0.4			
	36.0	4	9.3	5.5	$\textbf{23.4} {\pm} \textbf{0.4}$			
	41.2	4	9.2	7.5	$\textbf{31.4} \pm \textbf{1.0}$			
Cl—	0.7	2	11.0	5.1	8.41 ± 0.4	35.2 ± 0.8	$7.64{\pm}0.15$	29.6 ±0.5
	25.0	2	10.0	5.7	29.9 ±0.6			
	41.2	2	9.3	5.3	$61.2\pm\!0.8$			
Br—	25.1	5	9.2	5.5	32.7 ±0.7 ^b	31.4±1.3	7.01 ±0.23	32.7±0.7
	34.9	5	8.7	5.5	49.2 ±2.4			
	44.9	5	8.4	5.5	71.9 ± 2.2			
I—	25.1	5	9.5	5.5	13.8 ±0.2 ^c	33.6±0.9	7.02 ± 0.15	13.7±0.2
	34.9	5	9.2	5.5	20.7 ± 0.6			
	44.9	5	8.9	5.5	32.0 ± 0.5			
MeSO ₂ O	- 25.0	5	9.5	5.5	19.4±0.3 ^b	39.3±0.4	8.18±0.08	19.5±0.1
-	34.9	5	8.9	5.5	32.5 ± 0.2			
	44.9	5	8.6	5.5	52.3 ± 0.3			

TABLE 3.—KINETIC PARAMETERS FOR THE AQUEOUS ALKALINE SAPONIFICATION OF ESTERS OF THE TYPE X—CH₂COOEt

^a pH range 9.5-10.5, in all other cases quoted value, ± 0.1 ; ^b assuming $k_{SN2}/k_{A2} = 0.10$; ^c assuming $k_{SN2}/k_{A2} = 0.13$; ^d see table 5, footnote e.

Table 4.—Results of spectrophotometric study of dissociation of methane sulphonyloxyacetic acid (HA) with 4-chloro-2,6-dinitrophenol (HInd) in aqueous solution at $25\pm1^\circ$ C

C _{HA} mmol dm ⁻³	CHInd mmol dm ⁻³	decadic absorbance ($l = 10 \text{ mm}$, $\lambda = 446 \text{ nm}$)	pKa	
1.428	0.1185	0.425	2.53	
0.892	0.1185	0.493	2.49	
0.714	0.1185	0.529	2.56	
0.892	0.0948	0.400	2.56	
0.714	0.0948	0.426	2.55	
0.714	0.0592	0.268	2,52	
0.357	0.0592	0.316	2.57	
0.357	0.0474	0.256	2.70	

mean value of $pK_a(MeSO_2OCH_2COOEt, aq., 298 \text{ K}) = 2.56 \pm 0.04$

DISCUSSION

The present estimates of rate coefficients $k_{A2}^{\circ}(X-)$ for the halo-esters X-CH₂COOEt in aqueous solution at 25°C, are listed in table 5. Those for ethyl fluoroacetate and ethyl chloroacetate are in good agreement with results reported by other workers.^{3, 5, 6} This also applies for ethyl bromoacetate and ethyl iodoacetate

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HE DISSOCIA-			Nepe cos σι 4πεoR2	1-1 mol-1
IH EFFECTS ON TH			<i>pe</i> (XCH ₃), ^d	10-30 0 20
IVL ACETATE WI	OLARITIES	$X(\mathbf{X},s^2p^7)$ c	Pauling	mite
ONIFICATION OF ETH	/ITIES AND GROUP H	$-\mathbf{R}T \ln [K_a(X-)/$	$X_a(H)]$	kI mol-1
ENS ON THE RATE OF SAPO WITH ELECTRONEGATIVI		$E_{\mathbf{A}}(\mathbf{X}) - E_{\mathbf{A}}(\mathbf{H})$	1-Inml-1	
EFFECTS OF HALOGE	F ACETIC ACID AND	$-\mathbf{R}T$ in [k $^{\circ}_{\mathbf{A2}}(\mathbf{X}-)/$	k ⁰ A2(H—)]	1-1-1-1
SUBSTITUENT	IO NOIL		$k^{\circ}_{A2}(X-)/$	
COMPARISON OF S			к _{А2} (298 К) а	1-3 [-] mol -] -]
TABLE 5(group	×

$K_a(H-)$ b Pauling $p_e(X-CH_3)^a$ $4\pi\epsilon_0 R^2$	kJ mol ⁻¹ units 10 ⁻³⁰ C m kJ mol ⁻¹	0 2.28 0 0	-12.4 3.90 6.06 -37.6	-10.8 3.00 6.47 -40.0	-10.6 2.68 5.97 -37.1	-9.1 2.60 5.33 -33.1	-12.5 a
$E_{\mathbf{A}}(\mathbf{X})-E_{\mathbf{A}}(\mathbf{H})$	kJ mol ⁻¹	<i>ə</i> 0	-9.2	- 12.4	-16.2	- 14.0	-8.3
$k_{A2}^{\circ}(H-)]$	kJ mol ⁻¹	0	-11.9	- 13.8	14.1	-11.9	-12.8
$k_{A2}^{\circ}(\mathbf{X}-)/$	$k_{A2}^{\circ}(H-)$	1	124	267	294	123	176
$k_{A2}^{0}(298 \text{ K}) a$	dm ³ mol ⁻¹ s ⁻¹	0.111 e	13.8	29.6	32.7	13.7	19.5
group	x	ļ	ļ	1	3r		MeSO,O-

a this work

b see G. Kortüm, W. Vogel and K. Andrussow, Dissociation Constants of Organic Acids in Aqueous Solution (Butterworths, London).

^c see J. Hinze, M. A. Whitehead and H. H. Jaffe, J. Amer. Chem. Soc., 1963, 85, 148. ^d see A. L. McClellan, Tables of Experimental Dipole Moments (W. H. Freeman and Co., San Francisco, 1963). ^e E. Tommila, A. Koivisto, J. P. Lyyra, K. Antell and S. Heimo, Ann. Acad. Sci. Fennicae All Chemica, 1952, 47, p. 1.

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when the previously reported values are reduced by ca. 10 % to allow for the simultaneous halide displacement. The results of Barthel, Bäder and Schmeer ³ are then in particularly good agreement with the values shown in table 5.

SUBSTITUENT EFFECTS ON STANDARD GIBBS ENERGY CHANGES

While the rate coefficient for saponification of ethyl fluoroacetate conforms to the linear Gibbs energy relation with the dissociation constant of the corresponding acid the values of $-RT \ln \{k_{A2}^{\circ}(X-)/k_{A2}^{\circ}(H-)\}$ remain significantly larger in magnitude than $-RT\{\ln K_a(X-)/K_a(H-)\}$ for the chloro-, bromo- and iodo-derivatives, as shown in table 5, even after the rate coefficients have been corrected for halide displacement. The electronegativity differences, $X(X,s^2p^7)-2.28$, for the halogens compared with hydrogen, differ widely from fluorine to iodine while the substituent effects show a much smaller percentage variation. The group dipoles p_e as measured by reference to the methyl derivatives, and the geometrical parameters R and $\cos \theta$, as calculated from the average position of the charge at the reaction site, cf. the centre of the C-X bond (ref. (3), table 2), do not vary greatly down the series. The field effect of an uncharged polar substituent on a process involving the development of a unit *negative* charge is expressed, in accordance with the Bjerrum-Eucken formulation,¹⁵ by

$$\delta \Delta G_{\text{field}}^{\circ(\mp)} = V_{\text{field}} = Nep_e \cos \theta / 4\pi \varepsilon_0 R^2$$

The relative magnitudes of $p_e \cos \theta/R^2$ are ³ generally consistent with the relative rates of alkaline hydrolysis of the mono-, di- and tri-haloacetic acid ethyl esters. However, we have listed the corresponding quantities for the mono-haloacetate series in table 5, with D, the effective dielectric constant, put equal to unity. Since we expect that systems of such similar structure should have closely similar values of effective dielectric constant, the saponification rate for ethyl fluoroacetate appears relatively low while that of ethyl bromoacetate appears high (col. 4/col. 9). On the other hand, the dissociation constants for the haloacetic acids ¹⁶ (cf. col. 6) follow the sequence to be expected if electronegativity differences play a small but significant part by sigmainductive relay * over and above the effects of direct electric fields.

SUBSTITUENT EFFECTS ON STANDARD ENTHALPY CHANGES

When the substituent effects of the halogens on the Arrhenius activation energy for acetate ester hydrolysis, $E_A(X-)-E_A(H-)\equiv\delta\Delta H^{\circ \neq}$, are compared with the changes in standard Gibbs energy of activation (table 5, col. 4), fluorine shows a ratio of 0.77, comparable with the highest values that could be interpreted as arising mainly from direct electrostatic interaction between substituent and reaction site for those substituents previously considered.¹ For both bromine and iodine $\delta\Delta H^{\circ \neq}/\delta\Delta G^{\circ \neq}$ is markedly greater than unity (1.15 and 1.18 respectively) while chlorine shows an intermediate ratio at 0.90.

The above anomalies in standard Gibbs energies and enthalpies of activation for saponification of the ethyl esters of chloro-, bromo- and iodo-acetic acids appear to be correlated with the facility of substitution by the $S_N 2$ mechanism for the halogens in aliphatic systems. In table 6, columns 3 and 4, the apparent discrepancies between saponification rates and acid strengths are compared with the relative rates of halide displacement ^{13, 14} for the methyl derivatives on the scale of Gibbs energy. Fluorine has been chosen as the reference substituent for clarity of presentation and because it

^{*} Our previous studies ¹ indicate that a unit increase in substituent electronegativity leads to a reduction of ca. 1 kJ mol⁻¹ in the standard Gibbs energy change for such a process.

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displays no significant departure from the linear Gibbs energy relation referred to above.

It appears that the additional enhancement of reactivity in ester saponification is most marked when the more readily displaced halogens are present and we therefore

TABLE 6.—COMPARISON OF RATE COEFFICIENTS FOR HALIDE DISPLACEMENT WITH DISCREPANCIES BETWEEN SAPONIFICATION RATES AND PARENT ACID STRENGTHS FOR ETHYL ESTERS OF THE HALO-ACETIC ACIDS IN AQUEOUS SOLUTION AT 25°C

	$10^{2}k_{S_N2}$ (X-ester) ^a	10 ⁷ k _{SN2} (X-CH ₃) ^b	$-RT \ln [k_{A2}^{\circ}(X-) K_{a}(F-)/$
x—	dm ³ mol ⁻¹ s ⁻¹	dm ³ mol ⁻¹ s ⁻¹	$k_{A2}^{\circ}(F-) K_a(X-)]$ kJ mol ⁻¹
F	с	<i>ca</i> . 5	0
Cl—	с	66.7	-6.0
Br—	330 ^d	1435	-13.6
I—	180 d	636	-11.6
MeSO ₂ O	195 d	ca. 3800	5.4

^a this work; ^b see ref. (13) and (14); ^c too small to be estimated by the technique employed in other cases; d probable error ± 10 %.

believe that the high rate coefficients for saponification of chloro-, bromo- and iodoacetic acid ethyl esters can be understood by postulating a form of neighbouring group participation in which the transition state for breakdown of the tetrahedral intermediate involves partial displacement of the halide ion, as represented by (I), the oxygen of the developing alkoxide ion being located in the region of approach for backside attack on the methylene group. A similar mechanism may operate, though to a lesser extent, to increase the relative stabilities of the haloacetate anions, as indicated by (II).



The study of the effects of $MeSO_2O_{--}$, another group that is prone to displacement by nucleophils, was designed to test the hypothesis of anchimeric assistance of ester hydrolysis by partial displacement of the α -substituent. The results included in tables 5 and 6 provide some confirmation but are not definitive. Thus,

MeSO₂O-CH₂COOEt

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is 5.5 times more reactive than MeSO₂NH-CH₂COOEt when a factor of ca. 1.5 is expected from comparison of the effects of HO— and H_2N —⁹; the loss of MeSO₃ is greatly facilitated by the presence of -COOEt, but the discrepancy between substituent effects on k_{A2} and on K_a is in this case small. The MeSO₂O— group may be oriented in many different ways and thus small variations in the observed effects cannot be interpreted unambiguously.

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