

## Alkaline Hydrolysis of Methyl Carboxylates, Alkyl Acetates, and Alkyl Carboxylates. Steric Effects in Carboxylic Acid Derivatives and Related Systems<sup>1</sup>

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The second-order alkaline hydrolysis rate constants for nine methyl carboxylates (RCOOMe), nine alkyl acetates (MeCOOR'), and nine identically substituted alkyl carboxylates (RCOOR', R = R') have been determined in 40% aqueous *p*-dioxane at 20 and 50 °C. The variation in reactivity in these series is controlled predominantly by steric effects of the R and R' groups. These effects are as significantly represented in terms of  $E_s$  as in terms of  $\nu_R$  for variable substitution in the acyl portion of ester molecules. Similar results are observed when previously reported data on a variety of other acyl substituted carboxylic acid derivatives are evaluated in terms of  $E_s$  and  $\nu_R$ . The effect of variable substitution in the nonacyl portion of ester molecules is as adequately represented in terms of  $E_s^c$ -type parameters as in terms of  $\nu$ -type parameters. However, for most carboxylic derivatives RCXGR' (X = O or S and G = O, S, or NH), the influence of nonacyl groups on acyl group properties is in general more significantly represented in terms of corrected steric parameters ( $E_s^c$ -type) than in terms of individual  $\nu_{GR'}$  parameters where  $\nu$  values change as G changes. Thus, the necessity for sets of steric parameters derived from a variety of defining basis sets appears to be questionable.

The study of steric substituent effects and their influence on molecular properties have been of interest for a considerable period of time.<sup>2-4</sup> The quantification of these effects was proposed originally by Taft<sup>2</sup> in terms of the steric substituent parameter  $E_s$  as determined from rate studies on the acid hydrolysis of acyl substituted esters (RCOOR', R' is constant). In an attempt to refine the steric substituent parameter, Hancock and his co-workers<sup>5</sup> determined a set of steric parameters ( $E_s^c$ ) corrected for hyperconjugation effects and applicable to the alkyl portion of carboxylate esters. The application of the  $E_s$  and  $E_s^c$  parameters to a variety of chemical systems has since provided a considerable amount of information regarding the influence of steric effects, and many of these studies have provided useful quantitative relationships in terms of these parameters.<sup>3</sup> More recently, Charton<sup>6a</sup> has demonstrated the linearity of Taft's original  $E_s$  values with van der Waals radii and has defined<sup>6b</sup> new steric substituent constants ( $\nu_x$ ) in terms of the van der Waals radii of the X groups. These new values have then been used to assess the effect of steric factors on a variety of rate, equilibria, and physical data.<sup>7a,b</sup> However, while the latter results are of interest, no assessment of the validity or necessity of the more established steric parameters has been attempted relative to the new  $\nu_x$  values. Such an assessment is particularly important relative to carboxylic acid derivatives which are the defining basis set for all of the steric parameters. That is, while all  $E_s$ -type parameters are derived from acyl substituted carboxylate esters,  $\nu_x$  values were calculated initially for groups substituted only in the acyl portion of carboxylate esters with additional sets of values ( $\nu_{GX}$ ) being required for the nonacyl portion of these derivatives and for each different type of nonacyl G moiety. Thus, it appeared to be of interest to investigate the applicability of the various steric parameters via data on closely related carboxylate systems under identical reaction conditions. The present paper reports the results of such a study based on our determinations of the alkaline hydrolysis rate constants in 40% aqueous *p*-dioxane at 20 and 50 °C for a series of identically substituted alkyl acetates (MeCOOR'), methyl carboxylates (RCOOMe, R = R' of acetates), and alkyl carboxylates (RCOOR', R = R'). Also included for comparison is the evaluation in similar terms of

previously reported data on other carboxylic acid derivatives.

### Results and Discussion

The second-order alkaline hydrolysis rate constants ( $\log k$ , L mol<sup>-1</sup> min<sup>-1</sup>) at 20 and 50 °C in 40% aqueous *p*-dioxane for the methyl carboxylates, alkyl acetates, and alkyl carboxylates are reported in Table I along with a number of steric parameters for various R and R' groups.

**Effect of Variable Steric Factors in the Acyl Portion of Carboxylic Acid Derivatives.** Inspection of the data in Table I for the methyl carboxylates (RCOOMe) indicates a relative order of reactivity in accord with the variable steric factors of the R groups as represented by  $E_s$  or  $\nu_R$ . Correlation analyses<sup>3,8</sup> of these data give eq 1 and 2 (for data at 20 °C) and eq 3 and 4 (for data at 50 °C).

$$\log k = 0.83 + 0.93E_s, r^2 = 99.3\%, s = 0.045 \quad (1)$$

(<0.001)

$$\log k = 1.86 - 1.99\nu_R, r^2 = 99.1\%, s = 0.052 \quad (2)$$

(<0.001)

$$\log k = 1.55 + 0.91E_s, r^2 = 98.3\%, s = 0.071 \quad (3)$$

(<0.001)

$$\log k = 2.56 - 1.95\nu_R, r^2 = 98.0\%, s = 0.075 \quad (4)$$

(<0.001)

The significance of the various equations is essentially identical and indicates that variable steric effects in the acyl portion of this particular series are as adequately represented in terms of  $E_s$  as in terms of  $\nu_R$ . Additional confirmation of this result is provided by the correlations reported in Table II which involve rate data for the formation or hydrolysis of a variety of carboxylic acid derivatives RCOGR' (R variable, R' constant, G = O, S, or NH). That is, inspection of these data reveals that the effect of variable steric factors from the acyl portion of carboxylic acid derivatives is independent of the nature of G and can be represented as significantly by  $E_s$  as

**Table I. Second-Order Alkaline Hydrolysis Rate Constants ( $\log k$ ,  $L \text{ mol}^{-1} \text{ min}^{-1}$ ) at 20 and 50 °C in 40% Aqueous *p*-Dioxane and Steric Parameters for R and R' for Methyl Carboxylates (RCOOMe), Alkyl Acetates (MeCOOR'), and Alkyl Carboxylates (RCOOR')**

R or R'	log $k$ for RCOOMe at		log $k$ for MeCOOR' at		log $k$ for RCOOR' (R = R) at		$E_s(R)^a$	$E_s(R')^b$	$E_s^c(CH_2R')^c$	$\nu_R^d$	$\nu_{OR}^e$			
	registry no.	20 °C	50 °C	registry no.	20 °C	50 °C						registry no.	20 °C	50 °C
Me	79-20-9	0.9028	1.6555		0.9028	1.6555		0.9028	1.6555	0	0	-0.38	0.52	0.36
Et	554-12-1	0.7651	1.4600	141-78-6	0.5858	1.2718	105-37-3	0.3879	1.0660	-0.07	-0.38	-0.67	0.56	0.48
<i>n</i> -Pr	623-42-7	0.4754	1.2648	109-60-4	0.4530	1.1300	105-66-8	-0.0981	0.6086	-0.36	-0.67	-0.70	0.68	0.56
<i>i</i> -Pr	547-63-7	0.3560	1.0483	108-21-4	-0.1267	0.6175	617-50-5	-1.1440	-0.4468	-0.47	-1.08	-1.24	0.76	0.75
<i>n</i> -Bu	624-24-8	0.4267	1.1045	123-86-4	0.3788	1.0649	591-68-4	-0.2574	0.4486	-0.39	-0.70	-0.71	0.68	0.58
<i>i</i> -Bu	556-24-1	-0.0795	0.6726	110-19-0	0.2742	0.9927	589-59-3	-0.8755	-0.1728	-0.93	-1.24	-0.74	0.98	0.62
<i>s</i> -Bu	868-57-5	-0.2012	0.5419	105-46-4	-0.4167	0.3412	869-08-9	-2.2205	-1.2931	-1.13	-1.74	-1.36	1.02	0.86
<i>t</i> -Bu	598-98-1	-0.5700	0.1838	540-88-9	-1.4553	-0.5383	16474-43-4	-3.7768	-3.1838	-1.54	-2.46	-2.05	1.24	1.22

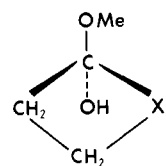
<sup>a</sup> Reference 2. <sup>b</sup> Reference 5. <sup>c</sup> Calculated from  $E_s^c(R')$  assuming -O- equivalent to -CH<sub>2</sub>-. <sup>d</sup> Reference 7. <sup>e</sup> Reference 19.

**Table II. Results of Correlation Analysis of Rate Data for the Formation and Hydrolysis of Carboxylic Acid Derivatives, RCOGR' (R variable, R' constant, G = O, S, or NH)<sup>a</sup>**

set	parameter coefficient	$r^2$ , %	$s$	$t_s$	$n^b$
1X <sup>c</sup>	-1.83	98.8	0.047	<0.001	9
1Y	0.984	99.6	0.029	<0.001	9
2X <sup>d</sup>	-1.95	99.9	0.016	<0.001	17
2Y	0.90	99.1	0.054	<0.001	17
3X <sup>e</sup>	-1.25	97.5	0.061	<0.001	6
3Y	-0.59	98.7	0.044	<0.001	6
4X <sup>f</sup>	-2.20	99.0	0.052	<0.001	9
4Y	0.93	99.0	0.051	<0.001	9
5X <sup>g</sup>	-2.59	97.5	0.157	<0.001	8
5Y	1.28	98.5	0.122	<0.001	8
6X <sup>h</sup>	-2.59	98.6	0.137	<0.001	8
6Y	1.28	98.7	0.129	<0.001	8
7X <sup>i</sup>	-1.75	96.8	0.091	<0.001	9
7Y	0.93	96.9	0.090	<0.001	9
8X <sup>j</sup>	-1.87	94.8	0.082	<0.001	10
8Y	0.86	93.4	0.093	<0.001	10
9X <sup>k</sup>	-2.13	98.0	0.083	<0.001	8
9Y	0.99	98.0	0.084	<0.001	8

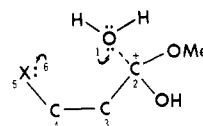
<sup>a</sup> Correlations using  $\nu$  are designated X and those using  $E_s$  are designated Y. <sup>b</sup> Number of compounds in data set. <sup>c</sup> RCOOEt + H<sub>2</sub>O in 70% MeAc-H<sub>2</sub>O at 44.7 °C/HCl from G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940). <sup>d</sup> RCOOH + MeOH at 50 °C/MeOH-HCl from H. A. Smith, *J. Am. Chem. Soc.*, **61**, 254 (1939); **62**, 1136 (1940). <sup>e</sup> RCOOC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub><sup>-4</sup> + H<sub>2</sub>O at 30 °C/H<sub>2</sub>O from T. H. Fife and D. M. McMahon, *ibid.*, **91**, 7481 (1969). <sup>f</sup> RCOOMe + H<sub>2</sub>O in MeOH-H<sub>2</sub>O at 25 °C/HCl from M. H. Palomaa et al., *Ber.*, **69B**, 1338 (1936); **68**, 887 (1935); *Suom. Kemistil. B.*, **19**, 85 (1946); *ibid.*, **19**, 53 (1946). <sup>g</sup> RCOOEt + HO<sup>-</sup> in 70% MeAc/H<sub>2</sub>O at 35 °C from G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940). <sup>h</sup> RCOOEt + HO<sup>-</sup> in 85% EtOH-H<sub>2</sub>O at 25 °C from H. A. Smith et al., *J. Am. Chem. Soc.*, **61**, 1172 (1939); **62**, 1556, 2324, 2733 (1940); **64**, 2362 (1942). <sup>i</sup> RCONH<sub>2</sub> + H<sub>3</sub>O<sup>+</sup> in H<sub>2</sub>O at 75 °C from A. Bruylants and F. Kezdy, *Rec. Chem. Prog.*, **21**, 213 (1960); P. D. Bolton, *Aust. J. Chem.*, **19**, 1013 (1966). <sup>j</sup> RCONH<sub>2</sub> + HO<sup>-</sup> in H<sub>2</sub>O at 75 °C from P. D. Bolton and G. L. Jackson, *Aust. J. Chem.*, **24**, 969 (1971). <sup>k</sup> RCOSMe + HO<sup>-</sup> in 40% dioxane-H<sub>2</sub>O at 35 °C from J. P. Idoux, P. T. R. Hwang, and C. K. Hancock, *J. Org. Chem.*, **38**, 4239 (1973).

by  $\nu_R$ . An additional point of interest concerning the comparison of  $E_s$  and  $\nu_R$  involves R groups of the type XCH<sub>2</sub>CH<sub>2</sub> where X = O, S, Cl, and I. Such groups have been described<sup>13</sup> as having "unexpectedly large  $\nu_R$  values" (compared to XCH<sub>2</sub> and X(CH<sub>2</sub>)<sub>3</sub> groups) due to the importance of a structure such as I in which the protonated ester is assumed to be stabilized and thus less reactive to attack by a water molecule.



I

However, when such groups are viewed in terms of  $E_s$ , this explanation is unnecessary. For carboxylic acids and esters, Newman<sup>14</sup> has demonstrated that the six number of a substituent (i.e., the number of atoms in the six position from the carbonyl oxygen atom as atom number one) makes a large contribution to the total steric effect of that substituent and is thus an important factor in considering the esterification of carboxylic acids and the hydrolysis of the corresponding esters. The  $E_s$  value for a substituent, as defined by Taft,<sup>2</sup> is the total steric effect for a substituent and includes the steric six-number effect. The influence of a six-number effect on reactions which involve addition to a carbonyl function has been expanded<sup>15</sup> to include the attacking group so that groups in the substrate which interfere with the addition reaction are separated from the attacking group in the transition state by four atoms. Thus the influence of XCH<sub>2</sub>CH<sub>2</sub> groups is not unexpectedly large but rather, as shown in structure II, is



II

expected when considered in terms of a six-number effect between unshared electron pairs on the oxygen of a water molecule as position 1 and unshared electron pairs on X as position 6. For XCH<sub>2</sub> and X(CH<sub>2</sub>)<sub>3</sub> groups in an aliphatic chain with normal bond lengths and bond angles,<sup>16,17</sup> unshared electron pairs on X would occupy the less effective 5 or 7 positions. Other interesting examples of the influence of six-number effects on esterification by alkylation of carboxylate salts<sup>17</sup> and on esterification of alkyl substituted acetic acids<sup>18</sup> have recently been reported.

**Effect of Variable Steric Factors in the Nonacyl Portion of Carboxylic Acid Derivatives.** Inspection of the data in Table I for the alkyl acetates (MeCOOR') indicates that the relative order of reactivity (with the exception of R' = *i*-Bu) is identical to that for the methyl carboxylates while the absolute reactivity of any particular acetate is less in each case (with the exception of R = R' = *i*-Bu) than that of the corresponding carboxylates. As expected, the quantitative analysis of the acetate data in terms of  $E_s$  or  $\nu_R$  leads to poorer overall correlations than that in terms of  $E_s^c$  (Table III). However,

**Table III. Results of Correlation Analysis of Alkyl Acetate Data (Table I) with  $E_s$ ,  $\nu_{R'}$ , and  $E_s^c$** 

steric parameter	parameter coeff	$r^2$ , %	$s$	$t_s$
$E_s$	1.24 <sup>a</sup>	81.9	0.34	0.003
	1.15	82.1	0.31	0.003
$\nu_{R'}$	-2.66	81.3	0.35	0.004
	-2.45	81.5	0.32	0.004
$E_s^c$	0.91	92.9	0.21	<0.001
	0.84	93.7	0.18	<0.001

<sup>a</sup> The first set of values in each case is for data at 20 °C and the second set is for data at 50 °C.

the latter correlation is considerably improved when the variable steric factors of the  $R'$  group are assessed in terms of  $E_s^c(\text{CH}_2R')$  (eq 5 and 6, 20 and 50 °C, respectively).

$$\log k = 1.42 + 1.37E_s^c(\text{CH}_2R'), r^2 = 98.5\%, s = 0.098 \quad (5)$$

(<0.001)

$$\log k = 2.05 + 1.26E_s^c(\text{CH}_2R'), r^2 = 98.3\%, s = 0.095 \quad (6)$$

(<0.001)

The latter constant is simply calculated from  $E_s^c(R')$  assuming that the interposition of an oxygen between the carbonyl carbon and the  $R'$  group is approximately equivalent to that of a  $\text{CH}_2$  group. In a similar manner,  $\nu_{OR'}$  values have been determined by Charton<sup>19</sup> for the  $R'$  group in the nonacyl portion of an ester. Analysis of the alkyl acetate data in terms of  $\nu_{OR'}$  (eq 7 and 8, 20 and 50 °C, respectively) also leads to significantly improved correlations relative to that with  $\nu_{R'}$ .

$$\log k = 1.96 - 2.77\nu_{OR'}, r^2 = 99.7\%, s = 0.042 \quad (7)$$

(<0.001)

$$\log k = 2.55 - 2.55\nu_{OR'}, r^2 = 99.8\%, s = 0.028 \quad (8)$$

(<0.001)

Similarly, either  $E_s^c(\text{CH}_2R')$  or  $\nu_{OR'}$  provides the best representation of variable steric effects from the nonacyl portion of a carboxylate ester for the acid-catalyzed hydrolysis of alkyl acetates (set 1, Table IV) and for the formation of alky benzoates (set 2, Table IV). However, because of corresponding differences in bond lengths and bond angles, the use of  $E_s^c(\text{CH}_2R')$  or  $\nu_{OR'}$  does not adequately represent variable steric effect changes from the  $R'$  group for other carboxylic acid derivatives,  $\text{RCOGR}'$ , in which  $R$  is constant,  $R'$  is variable, and  $G \neq \text{O}$ . For example, for  $N$ -monosubstituted amides ( $G = \text{NH}$  in  $\text{RCOGR}'$ ) we have demonstrated previously<sup>20</sup> that  $R'$  groups exert a steric influence on the acyl portion of the molecule which is not accounted for solely by  $E_s^c$ . That is, groups in the seven position of  $R'$  (from the carbonyl oxygen as position one) affect the acyl portion of these molecules and provide an additional factor of importance when considering properties associated with the acyl portion. In a similar manner,  $\nu_{NHR'}$  constants have been determined<sup>21</sup> for the  $R'$  group in the nonacyl portion of amides. Correlation analysis of a variety of chemical and physical properties of  $N$ -monosubstituted amides ( $\text{RCONHR}'$ ,  $R$  constant,  $R'$  variable) in terms of  $E_s^c + \text{H-7-no}$  (the seven position effect of  $R'$  in terms of the number of hydrogen atoms in the seven position of  $R'$ ) or in terms of  $\nu_{NHR'}$  are reported in Table IV (sets 3–8). In general, variable steric effects from the  $R'$  portion of these molecules are as or more meaningfully represented in terms of  $E_s^c + \text{H-7-no}$  than in terms of  $\nu_{NHR'}$ . Presumably, one could determine  $\nu_{GR'}$  values for the  $R'$  group of any  $\text{RCXGR}'$  derivative, but those values would be applicable only to the defining basis set or to closely related systems. For example, a case in point is the correlations reported in set 8 of Table IV for the  $^1\text{H}$  NMR substituent chemical shifts (SCS) of the acyl

**Table IV. Results of Correlation Analysis of Rate and Physical Data for Carboxylic Acid Derivatives,  $\text{RCOGR}'$  ( $R$  constant,  $R'$  variable,  $G = \text{O}, \text{NH},$  or  $\text{S}$ )**

set	steric parameters	parameter coeff	$r^2$ , %	$s$	$t_s$	$n^a$
1 <sup>b</sup>	$E_s^c(\text{CH}_2R')$	0.47	98.5	0.045	<0.001	5
	$\nu_{OR'}$	-0.94	99.5	0.026	<0.001	5
2 <sup>c</sup>	$E_s^c(\text{CH}_2R')$	1.15	93.1	0.16	<0.001	10
	$\nu_{OR'}$	-2.32	89.9	0.20	<0.001	10
3 <sup>d</sup>	$E_s^c + \text{H-7-no}$	0.64 + 0.051	97.1	0.060	<0.001 + 0.005	8
	$\nu_{NHR'}$	-1.33	97.3	0.052	<0.001	8
4 <sup>e</sup>	$E_s^c + \text{H-7-no}$	0.90 + 0.056	98.4	0.056	<0.001 + 0.010	6
	$\nu_{NHR'}$	-1.94	98.4	0.049	<0.001	6
5 <sup>f</sup>	$E_s^c + \text{H-7-no}$	2.25 + 0.42	91.5	0.36	<0.001 + 0.003	8
	$\nu_{NHR'}$	-3.97	70.7	0.61	0.008	8
6 <sup>g</sup>	$E_s^c + \text{H-7-no}$	-1.53 + 0.48	90.4	0.49	<0.001 + <0.001	14
	$\nu_{NHR'}$	-2.43	77.1	0.57	0.001	10
7 <sup>h</sup>	$E_s^c + \text{H-7-no}$	-4.52 + 0.52	99.8	0.17	<0.001 + <0.001	5
	$\nu_{NHR'}$	15.38	98.6	0.42	<0.001	5
8 <sup>i</sup>	$E_s^c + \text{H-7-no}$	2.62 + 0.70	90.0	0.64	0.005 + 0.005	6
	$\nu_{NHR'}$	-3.79	38.7	1.35	0.200	6
9 <sup>j</sup>	$E_s^c$	0.30	92.0	0.076	<0.001	8
	$\nu_{SR'}$	-0.87			defining basis set for $\nu_{SR'}$	
10 <sup>k</sup>	$E_s + E_s^c$	0.99 + 0.42	99.0	0.12	<0.001 + 0.001	7
	$\nu + \nu_{SR'}$	-2.00 + 1.27	99.5	0.09	<0.001 + <0.001	7

<sup>a</sup> Number of compounds in data set. <sup>b</sup>  $\text{MeCOOR}' + \text{H}^+$  in  $\text{H}_2\text{O}$  at 30.1 °C from T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. 1, W. A. Benjamin, New York, N.Y., 1966, p 272. <sup>c</sup>  $\text{ROH} + 4\text{-O}_2\text{NC}_6\text{H}_4\text{COCl}$  in  $\text{Et}_2\text{O}$  at 25 °C from J. F. Norris and A. A. Ashdown, *J. Am. Chem. Soc.*, **47**, 837 (1925); **49**, 2340 (1927). <sup>d</sup>  $\text{MeCONHR}' + \text{H}_3\text{O}^+$  in  $\text{H}_2\text{O}$  at 75 °C from P. D. Bolton, J. Ellis, R. D. Frier, and P. C. Nancarrow, *Aust. J. Chem.*, **25**, 303 (1972). <sup>e</sup>  $\text{MeCONHR}' + \text{HO}^-$  in  $\text{H}_2\text{O}$  at 75 °C from T. Yamana, Y. Mizukami, A. Tsuji, Y. Yasuda, and K. Masuda, *Chem. Pharm. Bull.*, **20**, 881 (1972). <sup>f</sup>  $\text{MeCOOMe} + \text{RNH}_2$  in dioxane 5 M in  $(\text{CH}_2\text{OH})_2$  from E. M. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950). <sup>g</sup>  $^1\text{H}$  NMR substituent chemical shifts for the acyl methyl protons of  $\text{MeCONHR}'$  from J. P. Idoux, J. M. Scandrett, and J. A. Sikorski, *ibid.*, **99**, 4577 (1977). <sup>h</sup> Angle of rotation  $\phi$  about the  $\text{N}_1\text{-C}_\alpha$  bond of  $\text{MeCON}_1(\text{H})\text{-C}_\alpha\text{HR}'\text{CONHMe}$  from M. T. Cung, M. Marraud, and J. Neel, *Jerusalem Symp. Quantum Chem. Biochem.*, **5**, 69 (1973). <sup>i</sup>  $^1\text{H}$  NMR substituent chemical shifts for the acyl methyl protons of  $\text{MeCSNHR}'$  from J. P. Idoux and A. Davis, unpublished results. <sup>j</sup>  $\text{MeCOSR}' + \text{HO}^-$  in 40% dioxane- $\text{H}_2\text{O}$  at 35 °C from J. P. Idoux, P. T. R. Hwang, and C. K. Hancock, *J. Org. Chem.*, **38**, 4239 (1973). <sup>k</sup>  $\text{RCOSR}' + \text{HO}^-$  in 40% dioxane- $\text{H}_2\text{O}$  at 35 °C from reference in footnote j.

methyl protons of a series of N-monosubstituted thioacetamides (MeCSNHR'). That is, the variation in SCS in this series is adequately represented in terms of  $E_s^c + H-7$ -no for R' while evaluation in terms of  $\nu_{\text{NHR}'}$  constants gives a very poor correlation. In addition, a comparison of these data with those of set 6 in Table IV provides a direct assessment of the influence of 7-position R' groups in these systems. The latter effects are obviously not accounted for by  $\nu_{\text{NHR}'}$  and thus tend to be obscured by correlation analysis using  $\nu_{\text{NHR}'}$ . If the G heteroatom in RCXGR' is sulfur (MeCOSR', set 9 and RCOSR', set 10), there is an increase in distance between the acyl center and R' due to the larger van der Waals radius of the connecting sulfur atom. Thus, 7-position influence of R' becomes minimal and correlations simply in terms of  $E_s^c$  provide a good indication of the effect of R' groups which can then be compared directly to other RCXGR' systems.

The examples cited above establish the usefulness of  $E_s^c$ -type parameters but more importantly serve to emphasize the use of correlation analysis as only a "guide" or "tool" in assessing the influence of variable steric effects without at the same time neglecting the comparison of individual groups or systems.

**Effect of Simultaneous Variable Steric Factors in the Acyl and Nonacyl Portion of Carboxylic Acid Derivatives.** Inspection of the data in Table I for the alkyl carboxylates (RCOOR', R = R') indicates, as expected from analysis of the corresponding MeCOOR' and RCOOMe derivatives, that simultaneous, variable steric factors from the acyl and nonacyl portions of the molecules have a magnified effect on the reactivities. Correlation analyses of these data give eq 9 and 10 (for the data at 20°) and eq 11 and 12 (for data at 50°) and confirm the earlier assessments in terms of  $E_s$  and  $\nu_R$  for R and  $E_s^c(\text{CH}_2\text{R}')$  and  $\nu_{\text{OR}'}$  for R'.

$$\log k = 1.49 + 1.31E_s + 1.61E_s^c(\text{CH}_2\text{R}'),$$

$$(<0.001) \quad (<0.001)$$

$$R^2 = 99.9\%, s = 0.064 \quad (9)$$

$$\log k = 3.31 - 1.72\nu_R - 4.14\nu_{\text{OR}'}, R^2 = 99.6\%, s = 0.12$$

$$(0.008) \quad (<0.001) \quad (10)$$

$$\log k = 2.26 + 1.22E_s + 1.71E_s^c(\text{CH}_2\text{R}'),$$

$$(<0.001) \quad (<0.001)$$

$$R^2 = 99.7\%, s = 0.096 \quad (11)$$

$$\log k = 4.02 - 1.48\nu_R - 4.42\nu_{\text{OR}'}, R^2 = 99.9\%, s = 0.034$$

$$(<0.001) \quad (<0.001) \quad (12)$$

However, while the significance of the various equations is statistically high and essentially identical, the differences between the coefficients of  $\nu_R$  and  $\nu_{\text{OR}'}$  in eq 10 and 12 are substantially larger than the corresponding differences from eq 2 and 7 and from eq 4 and 8. Thus, based solely on eq 10 and 12, one would predict a substantial difference in the importance and degree of simultaneous, variable steric effects from the acyl and nonacyl portions of these esters. A similar assessment in terms of  $E_s$  and  $E_s^c(\text{CH}_2\text{R}')$  from eq 9 and 11 leads to more reasonable acyl/nonacyl contributions when compared to eq 1 and 5 and eq 3 and 6.

### Summary

The comparative correlations reported in this study demonstrate that the influence of variable steric effects in the acyl portion of a carboxylic acid derivative can be assessed as well in terms of  $E_s$  as in terms of  $\nu$ . However, certain substituents (e.g., flexible  $\text{XCH}_2\text{CH}_2$ , X = O, S, Cl, and I) appear to have an exalted steric influence when considered in terms of  $\nu$  values. For these groups, their influence is better treated in terms of  $E_s$  and individual considerations of six-number effects. On the other hand, the influence of variable steric effects

originating from the nonacyl portion of a carboxylic acid derivative and the influence of simultaneously variable steric effects from the acyl and nonacyl portions of these derivatives are more properly treated in terms of  $E_s$ -type parameters. In particular, the validity and importance of  $E_s^c$ -type parameters, as proposed by Hancock,<sup>5</sup> appear to be clearly established. These parameters have the additional advantages (relative to the various  $\nu$  values) of having been derived from a single, common defining basis set and of being applicable to the study of variable steric effects in non-carboxylic acid systems.<sup>3</sup> Thus, the necessity for sets of steric parameters derived from a variety of defining basis sets appears to be questionable. More importantly, the nature of the correlations reported in this study serves to emphasize the fact that correlation analysis should be relied upon only as a "guide" or "tool" in assessing variable steric effects and should not be relied upon to replace the direct comparison of groups or systems whereby more meaningful indications of differences and/or deviations can often be obtained.

### Experimental Section

The esters used in this study were either obtained commercially or were prepared by well known procedures. All of the esters were purified by distillation to constant boiling points in agreement with previously reported values.<sup>22</sup>

The second-order alkaline hydrolysis rate constants reported in Table I are the average of at least three determinations and were determined conductometrically as described previously in detail.<sup>5</sup> The average deviation from the mean of replicate rate constant values did not exceed 1.5% except in the following cases: at 20 °C, EtCOEt (1.6%), *s*-BuCOO-*s*-Bu (3.2%), *t*-BuCOO-*t*-Bu (3.8%); at 50 °C, *n*-PrCOOMe (2.0%), *i*-PrCOOMe (3.4%), *n*-BuCOOMe (2.1%), MeCOO-*n*-Bu (2.8%), EtCOEt (2.7%), *n*-PrCOO-*n*-Pr (1.6%).

The statistical calculations were performed on an IBM 360-75 computer using the Ohio State University interactive regression program MULREG.

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## Solvolysis of 2-Oxiryl-2-propyl *p*-Nitrobenzoate. Evidence on the Mode of Stabilization of the Oxirylcarbinyl Cation

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The effect of a neighboring oxiryl group on the stability of an adjacent developing cationic center is minor in comparison to a cyclopropyl group. Thus, a neighboring oxiryl group increases the rate of solvolysis by a factor of 10 over an acyclic analogue. By comparison, a neighboring cyclopropyl provides a rate enhancement of  $10^5$  over an acyclic control.

There has been considerable interest in the solvolytic behavior of heterocyclic analogues of cyclopropylcarbinyl systems. The effect of a neighboring oxirane has been studied by several workers.<sup>1-6</sup> The oxirane ring can theoretically stabilize an adjacent cationic center by conjugative stabilization through its strained bonds and/or by participation of the nonbonded electrons on oxygen.<sup>1-6</sup>

However, the degree to which a neighboring oxirane group stabilizes an adjacent cationic center is in doubt. Reports have varied from a lack of significant participation to an oxirane group being almost as effective as a cyclopropyl group in stabilizing a cationic center.<sup>1,5,6</sup> Therefore, a comparison of the rates of solvolysis of the 2-oxiryl-2-propyl system with a suitable reference system, 2-methyl-3-methoxy-2-butyl, which allows for the estimation of inductive effects and the participation by lone pair electrons on a  $\beta$  oxygen, and the 2-cyclopropyl-2-propyl system with the 2,3-dimethyl-2-butyl system was undertaken.

### Results

**Synthesis.** 2-Oxiryl-2-propyl *p*-nitrobenzoate (1) was prepared by the epoxidation of 2-methyl-3-buten-2-yl *p*-nitrobenzoate with *m*-chloroperbenzoic acid at 0 °C in methylene chloride. At higher temperatures the oxiryl ring is opened by the *m*-chlorobenzoic acid which is formed in the reaction.

**Rates.** Rates of solvolysis were determined titrimetrically in 80:20 acetone-water (v/v) by the procedure previously reported.<sup>7</sup> The compounds followed first-order kinetics except for 2-oxiryl-2-propyl *p*-nitrobenzoate (1) which exhibited a decrease in rate after 20% reaction. Therefore, the initial rate constant was determined during the first 20% of the reaction. This deviation was due to side reactions as described below in the product study. The rate data appear in Table I.

**Products of Solvolysis.** Oxiranes undergo facile reactions with both electrophilic and nucleophilic reagents. As noted in the synthesis of 1, the presence of benzoic acid derivatives leads to opening of the oxiryl ring. Thus, during solvolysis of 1,  $\geq 50\%$  rearranges to a secondary *p*-nitrobenzoate (via NMR). The formation of relatively unreactive secondary esters results in a decrease in rate.

Kinsman has reported that solvolysis of 2-oxiryl-2-propyl dinitrobenzoate gives a complex mixture of products.<sup>9</sup> Between 65 and 80% rearranges to 2,2-dimethyl-3-oxetanyl dinitrobenzoate. The products arising from solvolysis are 2,2-dimethyl-3-oxetanol and polymer (polyether). 2-Oxiryl-2-

propanol rearranges to triols under solvolytic conditions; however, none was reported in the reaction products.<sup>9</sup>

These results suggest that 2-oxiryl-2-propyl derivatives react via ring expansion to give secondary esters (ion pair return) and oxetanols (hydrolysis by an ionizing mechanism in which the dinitrobenzoate acts as a leaving group).<sup>3,9</sup>

### Discussion

The strained bonds in an oxiryl group have been reported to be almost as effective as the strained bonds of the cyclopropyl group in stabilizing a cationic center.<sup>1,5</sup> However, the strain energy in the oxiryl group is substantially less than in a cyclopropyl group.<sup>10</sup>

If neighboring group stabilization is important in a system, the rate of solvolysis must be greater than the unassisted rate of solvolysis estimated from reference compounds.<sup>11</sup> Clearly the choice of a reference system which reacts without stabilization is critical.<sup>7,12</sup> The isopropyl group is a suitable model system for the cyclopropyl group because of similar steric requirements.<sup>13</sup> On the other hand, the isopropyl group is a

Table I. Rate Constants in 80% Acetone

<i>p</i> -nitrobenzoate	temp, °C	$k_1$ , s <sup>-1</sup>	$\Delta H^\ddagger$ , kcal mol <sup>-1</sup>	$\Delta S^\ddagger$ , eu
2,3-dimethyl-2-butyl <sup>a</sup> (3)	25.0	$2.15 \times 10^{-10b}$	28.5	-7.3
2-cyclopropyl-2-propyl <sup>a</sup> (2)	25.0	$3.75 \times 10^{-5}$	20.8	-9.0
2-methyl-3-methoxy-2-butyl (4)	150.0	$1.97 \times 10^{-5}$		
	125.0	$1.66 \times 10^{-6}$		
	25.0	$1.32 \times 10^{-12b}$	32.5	-3.8
2-oxiryl-2-propyl (1)	150.0	$1.49 \times 10^{-4c}$		
	125.0	$1.31 \times 10^{-5c}$		
	25.0	$1.33 \times 10^{-11b}$	(32)	(-1)

<sup>a</sup> Reference 8. <sup>b</sup> Calculated from data at other temperatures.

<sup>c</sup> Initial (20%) rate constants.