Isotope Exchange and Solvolysis in the Basic Methanolysis of Aryl Esters. Molecular Interpretation of Free Energies, Enthalpies, and Entropies of Activation[1,2]

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Abstract: The free energies of activation for methoxide-catalyzed methanolysis of aryl acetates and carbonates in methanol are not linearly related to the free energies of ionization of the corresponding phenols; instead the rate process becomes less sensitive to substituent as the electron-withdrawing power of the substituent increases. This is not due to a change in rate-determining step from phenoxide elimination of the tetrahedral intermediate with poor leaving groups to carbonyl addition with good leaving groups, because methoxyl-labeled aryl methyl carbonates, $CH_3*OCO_2C_6H_4X$, undergo basic methanolysis without methoxyl exchange regardless of the character of X (X = *p*-CHO, H, *p*-CH_3O). A plot (slope 1.8) of free energies of activation *vs.* $(0.80F + R)$, where F and R are the field effect and resonance constants of Swain and Lupton, is linear, consistent with the attribution of the curvature in the other plots to greater importance of the resonance interaction in the equilibrium than in the rate process. Alternatively, the length of the transition-state nucleophile–carbonyl bond may increase with electron withdrawal in the leaving group. The substituent effect appears neither in the enthalpy of activation alone nor in the entropy of activation alone, but rather both vary and there is not a linear relation between them. The substituent points in the enthalpy–entropy plane may be represented by vector sums of isergonic ("isokinetic") relations, one having a slope of 330°K, presumably resulting from substituent effects on solvation, and one having a very large slope, presumably resulting from substituent effects on internal energy. The solvation effects essentially disappear from the free energies of activation at 298° (near 330°) and the free energy relations thus arise from internal energy interactions.

Carbonyl displacement reactions, such as the cleavage of esters and amides, are of wide prevalence in biochemistry[6] and are important for fundamental physical organic chemistry.[7] They have been extensively investigated from a mechanistic point of view.[8,9] Important studies of the relation of structure to reactivity in the cleavage of esters have been reported by several groups in the recent past.[10-12] An interesting uniformity in these reports is the observation of nonlinear correlations of free energy of activation with the free energy of ionization of the conjugate acid of the leaving group or nucleophile. Ryan and Humffray required a linear combination of σ and σ^- constants to give a linear correlation of their free energies of activation for hydrolysis of aryl esters in 56 wt % acetone–water solvent (in effect, they used $(0.7\sigma + 0.3\sigma^-)$ for aryl benzoates[10b] and $(0.8\sigma + 0.2\sigma^-)$ for aryl acetates[10a]). Kirsch, Clewell, and Simon[11] conducted a careful and complete study of substituent effects in both the aryl center and leaving group for basic hydrolysis of aryl benzoates in 33% acetonitrile–water. They confirmed a rather general observation[6] that, in order to linearize Hammett plots for leaving-group substituents, a special value of σ for *p*-NO_2 is required which is intermediate between its ordinary σ value (0.778) and its σ^- value (1.27). The best-fit value of this special constant was 0.89, which corresponds to $(0.78\sigma + 0.22\sigma^-)$. A closely reasoned argument by Kirsch, Clewell, and Simon supports their view that the enhanced value of σ required for the *p*-NO_2 substituent results from ground-state destabilization because of cross-conjugation of ether–oxygen lone-pair electrons between the carbonyl group and the nitro group. Bruice and Benkovic[13] had earlier explained the observation by noting that the mechanism is an over-all two-step process and that the first step, attack on carbonyl, might require σ, while the second step, elimination of the leaving group, might require σ^-.

Jencks and Gilchrist[12] studied displacement reactions in aqueous solution at the carbonyl groups of four aryl acetates (the pK_a of the leaving-group conjugate acids varied from 2 to 10) with a series of oxyanion nucleophiles ranging from methoxyacetate ion to hydroxide ion (conjugate acid pK_a's from 3.4 to 15.75). Plots of log k for displacement *vs.* pK_a for nucleophile conjugate acid were nonlinear, the selectivity becoming smaller as the basicity of the nucleophile increased. It was noted that this behavior is in accord with a change in rate-determin-

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[2] Catalysis in Ester Cleavage. II. For part I, see R. L. Schowen and C. G. Behn, *J. Am. Chem. Soc.*, **90**, 5839 (1968).

[3] Predoctoral Fellow of the National Institutes of Health.

[4] Holder of a Research Career Development Award of the National Institute of General Medical Sciences.

[5] Undergraduate Research Participant of the National Science Foundation and the Kansas Heart Association.

[6] T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966.

[7] J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 12.

[8] W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964), reviews related, pertinent data.

[9] S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

[10] (a) J. J. Ryan and A. A. Humffray, *J. Chem. Soc., B*., 842 (1966); (b) A. A. Humffray and J. J. Ryan, *ibid.*, 468 (1967).

[11] J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, 33, 127 (1968).

[12] W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968).

[13] T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964).

Table I. Rate Constants for Methoxide Ion Catalyzed Methanolysis of $RCO_2C_6H_4X^{a,b}$

		Temp, °C								
		A	B	C	D	E	F	G	H	I
X	R	k, M^{-1} sec^{-1}								
p-NO_2	CH_3O	9.8	13.7	22.0	26.2	31.3	33.6	39.3		
p-CHO	CH_3O	0.97	1.97	3.64	5.03	7.72	10.4	14.8		
p-$COCH_3$	CH_3O	1.42	2.23	3.49	4.58	6.34	8.89			
p-CO_2CH_3	CH_3O	1.81	2.21	3.00	3.76	4.70	6.14	7.81	8.69	
p-OCO_2CH_3	CH_3O	0.65	1.25	2.34	2.90	4.46	6.47			
p-Br	CH_3O	0.72	1.09	1.74	2.46	3.51	4.65			
p-Cl	CH_3O	1.39	1.52	2.37	2.84	3.11	3.53	4.08	4.84	5.08
p-$NHCOCH_3$	CH_3O	0.32	0.38	0.55	0.81	1.25	1.91			
H	CH_3O	0.12	0.27	0.38	0.75	1.09	1.76			
p-Cyclohexyl	CH_3O	0.16	0.24	0.34	0.50	0.77	1.18			
p-CH_3	CH_3O	0.33	0.44	0.55	0.75	0.84	0.90	1.10	1.20	1.39
p-CH_3O	CH_3O	0.20	0.49	0.61	0.91	1.29				
p-O^-	CH_3O	0.034	0.041	0.065	0.092					
p-CO_2CH_3	CH_3	3.37	5.28	7.54	9.97	15.9				
p-Br	CH_3	2.06	3.02	4.70	6.17	10.4				
H	CH_3	0.58	0.84	1.09	1.55	2.15	3.94			
p-CH_3	CH_3	0.39	0.59	0.99	1.36	2.15	3.21			
p-CH_3O	CH_3	0.38	0.61	1.12	1.68	2.57	3.80			

[a] Standard deviations of second-order rate constants were less than ±1%. [b] Ionic strength maintained at 0.4 M with added lithium chloride.

Table II. Key to Reaction Temperatures (°C) from Table I[a]

X	R	A	B	C	D	E	F	G	H	I
p-NO_2	CH_3O	16.5	21.7	30.5	33.5	36.5	38.4	40.6		
p-CHO	CH_3O	3.9	12.7	19.3	23.4	29.8	34.0	38.6		
p-$COCH_3$	CH_3O	8.7	14.7	21.1	25.3	29.8	35.7			
p-CO_2CH_3	CH_3O	14.7	17.3	20.7	24.4	27.8	31.3	34.3	36.8	
p-OCO_2CH_3	CH_3O	3.3	12.3	18.3	24.4	28.8	34.3			
p-Br	CH_3O	8.7	14.9	21.1	25.3	29.7	35.8			
p-Cl	CH_3O	19.3	22.0	27.0	30.0	32.0	34.0	36.0	38.0	
p-$NHCOCH_3$	CH_3O	10.9	14.0	19.2	23.6	29.4	36.0			
H	CH_3O	3.2	12.6	16.7	25.6	31.0	38.5			
p-Cyclohexyl	CH_3O	9.1	14.2	18.9	23.4	29.4	36.1			
p-CH_3	CH_3O	18.9	22.0	26.0	31.1	31.9	34.0	36.0	37.9	39.9
p-CH_3O	CH_3O	14.1	25.0	30.0	33.3	38.5				
p-O^-	CH_3O	20.7	23.8	34.0	38.7					
p-CO_2CH_3	CH_3	2.7	8.8	13.5	18.1	26.2				
p-Br	CH_3	2.9	9.5	16.5	20.4	27.8				
H	CH_3	3.3	7.9	13.4	17.2	24.9	31.1			
p-CH_3	CH_3	2.7	8.3	16.0	20.3	27.8	34.2			
p-CH_3O	CH_3	2.9	9.6	18.0	24.7	31.1	37.8			

[a] Precision of temperature control was ±0.01° and reported temperatures are accurate to ±0.1°.

ing step from carbonyl addition with good nucleophiles to leaving-group expulsion with poor nucleophiles, or with variations in transition-state structure from reactant-like with good nucleophiles to less reactant-like for poor nucleophiles (as predicted by the Hammond postulate[14] and similar concepts[15] or by the Swain–Thornton reacting-bond rule[16]). No completely definite choice among these was possible.

Therefore we now have several explanations available for curvature in such structure–reactivity free-energy correlations: (a) a change in rate-determining step (or a change in the balance of several contributing steps) is occurring as reactant structure is varied; (b) a change in the structure of the activated complex with reactant structure is altering the structural sensitivity of the reaction; (c) a difference in the balance of several substituent-interaction mechanisms[17] (*e.g.*, resonance and inductive effects) requires a more complex correlation equation than a linear one.[18,19]

We report in this paper results on free energies, enthalpies, and entropies of activation for the methoxide-catalyzed methanolysis[20] of aryl esters, together with data on methoxide exchange in methyl-labeled aryl methyl carbonates, which we believe will illuminate this problem.

[14] G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

[15] (a) J. E. Leffler, *Science*, **117**, 340 (1953); (b) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 4319 (1962).

[16] (a) E. R. Thornton, *ibid.*, **89**, 2915 (1967); (b) C. G. Swain and E. R. Thornton, *ibid.*, **84**, 817 (1962).

[17] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1962.

[18] Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Japan*, **32**, 971 (1959).

[19] C. G. Swain and E. C. Lupton, Jr., *J. Am. Chem. Soc.*, **90**, 4328 (1968).

[20] To speak of the apparently simple attack of methoxide ion on an ester substrate as methoxide *catalysis* may seem strange, but in the case of esters of weakly acidic alcohols the methoxide ion is not consumed. In all cases, it is difficult to distinguish methoxide-assisted attack of methanol (with very large Brønsted β) from simple "uncatalyzed" reaction of methoxide.

Table III. Activation Energetics for Methoxide-Catalyzed Methanolysis of $RCO_2C_6H_4X$ in Methanol[a,b]

X	ΔG_{298}^*, kcal/mol	ΔH^*, kcal/mol	ΔS_{298}^*, eu
	A. R = CH_3O		
p-NO_2	15.80 ± 0.01	9.58 ± 0.06	−20.8 ± 0.2
p-CHO	16.47 ± 0.01	12.87 ± 0.08	−12.0 ± 0.2
p-$COCH_3$	16.56 ± 0.01	11.24 ± 0.05	−17.9 ± 0.2
p-CO_2CH_3	16.64 ± 0.01	12.12 ± 0.09	−15.6 ± 0.3
p-Br	16.94 ± 0.01	11.78 ± 0.17	−17.3 ± 0.5
p-Cl	17.04 ± 0.01	11.51 ± 0.18	−18.6 ± 0.5
p-OCO_2CH_3	17.14 ± 0.01	11.88 ± 0.24	−17.6 ± 0.7
p-$NHCOCH_3$	17.52 ± 0.01	12.13 ± 0.16	−18.1 ± 0.5
H	17.67 ± 0.01	12.51 ± 0.08	−17.3 ± 0.2
p-Cyclohexyl	17.81 ± 0.01	12.47 ± 0.06	−17.9 ± 0.2
p-CH_3	17.85 ± 0.01	11.57 ± 0.14	−17.1 ± 0.4
p-CH_3O	17.89 ± 0.01	12.80 ± 0.29	−17.1 ± 0.9
p-O^-	19.32 ± 0.01	9.0 ± 0.8	−34.8 ± 2.5
	B. R = CH_3		
p-CO_2CH_3	15.85 ± 0.01	10.28 ± 0.11	−18.7 ± 0.3
p-Br	16.19 ± 0.01	10.15 ± 0.17	−20.3 ± 0.5
H	16.92 ± 0.01	10.36 ± 0.27	−22.0 ± 0.8
p-CH_3	17.10 ± 0.01	10.68 ± 0.03	−21.5 ± 0.1
p-CH_3O	17.13 ± 0.01	10.72 ± 0.03	−21.5 ± 0.1

[a] Standard states are 1 *M* for solutes and pure liquid for methanol. [b] Error limits are standard deviations.

Results

Kinetics. The reaction of methanol with aryl esters, catalyzed by methoxide ion, to yield the corresponding phenol and methyl ester (eq 1) was first order in methoxide ion and first order in substrate ester. The second-order rate constants at a number of temperatures are given in Table I (a key to the temperature used for each reaction appears in Table II).

At each temperature, first-order rate constants were obtained at about seven methoxide concentrations, from 0.001 to 0.1 *M*, for each compound, the ionic strength being maintained in all runs at 0.4 *M* by added lithium chloride. The first-order rate constants showed excellent linearity in base concentration. Runs at lower ionic strength showed no dependence, to within the experimental error, of the rates on the concentration or identity of added inert salt.

$$CH_3OH + RCO_2Ar \xrightarrow{CH_3O^-} RCO_2CH_3 + ArOH \qquad (1)$$

Energetics of Activation. The free energies of activation, ΔG^*, were calculated from the Eyring equation, eq 2, in which k is the second-order rate constant. The standard deviations were calculated from eq 3. The enthalpies of activation, ΔH^*, were determined from the slope of eq 4 and the entropies of activation, ΔS^*,

$$\Delta G^* = -RT \ln (kh/\mathbf{k}T) \qquad (2)$$

$$\sigma(\Delta G) = (\sigma(k)/k)/RT \qquad (3)$$

$$\ln (k/T) = (\Delta H^*/R)(1/T) + (\ln (\mathbf{k}/h) + \Delta S^*/R) \qquad (4)$$

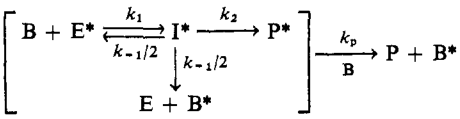
from its intercept by the method of least squares.[21] Standard deviations were calculated for each quantity. The results are given in Table III.

Isotope-Exchange Experiments. Isotope-exchange measurements can be used to define the rate-determining step in the methanolysis of aryl methyl carbonates in the following way. Scheme I portrays the kinetic consequences of combining CH_2TOCO_2Ar (E^*) with methoxide ion (B) in methanol. The labeled tetrahedral intermediate I^* is supposed to decompose to E^* and to unlabeled ester E at equal rates ($k_{-1}/2$), thus neglecting the probably small secondary tritium isotope effect. The other route open to I^* is expulsion of ArO^- to form labeled dimethyl carbonate (P^*), which itself exchanges methoxyl groups with solvent in a base-catalyzed process with a rate constant k_p which can be evaluated in independent experiments. Our experiments were carried out under such conditions that the conversion of aryl ester, concurrently with exchange, to P^* (in other words, the entire bracketed process in Scheme I) was complete within 2–20 sec, depending on the aryl substituent. Our observations were of the subsequent, comparatively slow exchange of P^*. This reaction follows the simple first-order rate law of eq 5, so that P_0^* (and thus the molar specific activity of P at zero time, *i.e.*, at the time of its formation by the "burst" reaction (in brackets))

$$P_t^* = P_0^* e^{-k_p[B]t} \qquad (5)$$

can be determined by extrapolation. This molar specific activity was always equal within experimental error to the molar specific activity of E^* for the three esters (Ar = p-$CHOC_6H_4$, C_6H_5, and p-$CH_3OC_6H_4$) studied. Thus k_2 is so much greater than $k_{-1}/2$ so that essentially no radioactivity is lost from E^* in the course of its conversion to P^*. From considerations of experimental error we can estimate possible magnitudes of k_{-1}/k_2, given in Table IV. The details of the methodology are given in the Experimental Section.

Scheme I



(21) H. D. Young, "Statistical Treatment of Experimental Data," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter IV.

Table IV. Fractionation of the Tetrahedral Intermediate in Methoxide-Catalyzed Methanolysis of p-$XC_6H_4OCO_2CH_3$

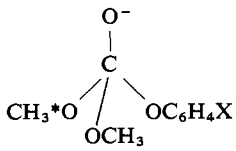
X	k_{-1}/k_2	f_{-1}[a]	f_2[b]
CH_3O	0.07 ± 0.12	0.06 ± 0.11	0.94 ± 0.11
H	0.12 ± 0.12	0.10 ± 0.11	0.90 ± 0.11
CHO	−0.03 ± 0.12	−0.02 ± 0.11	1.02 ± 0.11

[a] Fraction of tetrahedral intermediate which reverts to reactants. [b] Fraction of tetrahedral intermediate which proceeds to products.

Discussion

In the discussion of these findings, we wish to deal with three aspects of their significance: (a) the fractionation of the tetrahedral intermediate between reactant and product and its implications for the structures of the two activated complexes[22] along the reaction pathway; (b) the nonlinearity of the free-energy relation connecting phenol ionization and base-catalyzed phenyl–ester solvolysis and the possible origins of this nonlinearity; and (c) the substituent-induced variations in both enthalpy and entropy of activation for these reactions and the molecular interpretation of these variations.

Fractionation of the Tetrahedral Intermediate. The use of a label to determine the degree to which the tetrahedral intermediate in carbonate methanolysis (I) reverts to reactants has certain advantages over the similar technique of ^{18}O exchange in the hydrolysis of esters.[23] In that case, proton equilibration between the oxygen of the nucleophilic hydroxyl and the oxygen of the ester carbonyl group is necessary before the two positions become chemically equivalent, as is required if a comparison of hydrolysis and exchange rates is to measure the fractionation of the tetrahedral intermediate between reactants and products. Bender and Thomas found, however, from the quite different substituent effects on hydrolysis and exchange indications that the proton-shift process is kinetically significant[24] and thus one cannot in general be sure how accurately these measurements probe the decomposition preference of the intermediate. This difficulty is fully avoided in methoxyl exchange *vs.* methanolysis, where the two methoxyls are equivalent immediately upon vibrational relaxation of the adduct.



I

Although all our exchange measurements showed the reversion rate of I to reactants to be within experimental error of zero, compared to its rate of transformation to products, we can obtain from estimates of the experimental error in the measurements maximum values of k_{-1}/k_2. This procedure (*cf.* Table IV) yields k_{-1}/k_2 = 0.19 (X = p-CH_3O), 0.24 (X = H), and 0.09 (X = p-CHO). From these numbers, the minimum differences in free energy of the addition activated complex (T_1) and the elimination activated complex (T_2) are found to be $G_1{}^* - G_2{}^* = 1.0$ (X = p-CH_3O), 0.8 (X = H), and 1.4 (X = p-CHO) kcal/mol. These values are compared with the free energies of activation for the rate-determining addition step (Table III) in Figure 1, a partial free-energy diagram for the reaction.

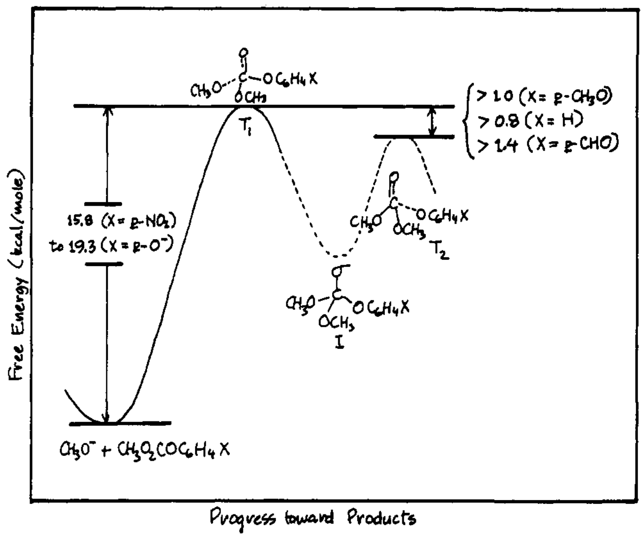


Figure 1. Partial free-energy diagram for the methoxide-catalyzed methanolysis of methyl acetates and carbonates at 25°.

As is to be expected from the relative stabilities of the phenoxide and methoxide ions (as measured by their basicities), T_2 is stabler than T_1. In fact, by a comparison of the minimum values of k_{-1}/k_2 with $K_{CH_3O^-}/K_{ArO^-}$, the relative basicities of the two leaving groups, a rough measure of the Brønsted α value and thus of the resemblance[25] of T_1 and T_2 to I can be found. Since the pK_a's of the phenols (see below) are 14.3 (X = H) and 12.1 (X = p-CHO), and the autoprotolysis pK of methanol[26] is 16.92, using units of M^2, or 18.3, using units of M, the corresponding minimum values of β (from $\beta_{min} = -\log(k_{-1}/k_{2max})/(18.3 - pK_a)$) are about 0.2 in all cases. Hammond's postulate leads one to expect values of less than 0.5, corresponding to a closer resemblance of T_1 and T_2 to I (to which they are energetically closer) than to

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[22] No data reported here exclude a single-step concerted displacement as the mechanism of this reaction. However, Johnson (*J. Am. Chem. Soc.*, **86**, 3819 (1964)) showed by the absence of a third-order acid–base-catalyzed term in the kinetics of the pyridine-catalyzed ethanolysis of ethyl trifluoroacetate, and by the exclusion of a contribution from pyridinium–ethoxide ion catalysis on the ground that an unreasonably large rate constant would be required, that the ethanolysis reaction follows a two-step route. The second of these observations exempts Johnson's conclusion from the criticism leveled by Burwell and Pearson (*J. Phys. Chem.*, **70**, 300 (1966)), *viz.*, that isotope-exchange reactions need not follow symmetrical routes on potential surfaces but may proceed by two equal-rate, mirror-image, unsymmetrical paths. One of these (and thus half the reaction) would in Johnson's case necessarily have been the excluded pyridinium–ethoxide catalysis. An indicatory piece of evidence, more clearly consistent with a two-step than with a one-step pathway, is the observation (from ^{18}O isotope effects) that the activated-complex carbonyl stretching frequency in the methoxide-catalyzed methanolysis of aryl benzoates is decreased to 1300 ± 200 cm^{-1} (C. G. Mitton and R. L. Schowen, *Tetrahedron Letters*, 5803 (1968)).

[23] A recent, particularly elegant example of the use of the ^{18}O exchange *vs.* hydrolysis technique is given by M. L. Bender and H. d'A. Heck, *J. Am. Chem. Soc.*, **89**, 1211 (1967).

[24] M. L. Bender and R. J. Thomas, *ibid.*, **83**, 4189 (1961). Although the conclusions reached by Bender and Thomas must now be reevaluated in the light of newer studies by Shain and Kirsch (*ibid.*, **90**, 5848 (1968)), the possibility of kinetically significant proton transfer still haunts, in principle, the ^{18}O exchange *vs.* hydrolysis method.

[25] Reference 17, pp 157–158.

[26] E. Grunwald and E. Price, *J. Am. Chem. Soc.*, **86**, 4517 (1964).

either reactants or products. The results here do not disagree with this, but do tend to show the leaving group bonds to be at least one-fifth broken at T_1 and T_2.

Free-Energy Relations. A plot (Figure 2) of the substituent effect on ΔG^* for the methanolysis reaction ($\delta_x\Delta G^*$) *vs.* the corresponding quantity for ionization of phenols ($\delta_x\Delta G^\circ$) under the same conditions is not linear but rather the slope decreases as reactivity, or electron-withdrawing power of the substituent, increases. This is quite in agreement with previous work on similar systems.[6,10-12]

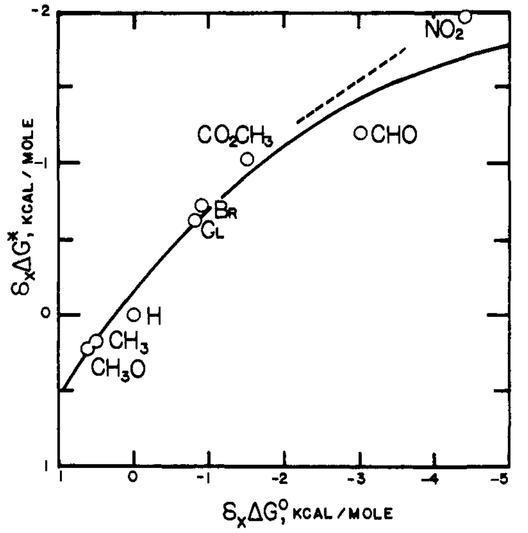

Figure 2. Substituent effect on the free energy of activation for methoxide-catalyzed methanolysis of $CH_3OCO_2C_6H_4X$ at 25° ($\delta_x\Delta G^*$) *vs.* substituent effect on the free energy of ionization of HOC_6H_4X under the same conditions ($\delta_x\Delta G^\circ$).

One of the explanations offered earlier[13] for such phenomena might be stated for this particular situation as follows. The first step of the reaction, which ought to be more nearly rate determining for good leaving groups, shows a small correlation slope because no negative charge is appearing on the leaving group in the activated complex (T_1). The second step, on the other hand, should show a larger slope because in T_2, negative charge appears in the leaving groups; this step should contribute more to determining the rate for poor leaving groups, for which the energy of T_2 will rise toward that of T_1. If m_1 is the slope for the case in which the first step is clearly rate determining and m_2 the corresponding value for the second step clearly rate determining, then at intermediate points the observed slope m_0 is given[27] by eq 6, where f_{-1} is the fraction of I which reverts to reactants and f_2 the fraction of I which proceeds on to products. Since we

$$m_0 = f_{-1}m_2 + f_2m_1 \qquad (6)$$

have maximum values for f_{-1} and f_2 at three points along the curve (at X = p-CH_3O, H, p-CHO) and m_0's can be estimated from the tangents, some statement is possible about conceivable values of m_1 and m_2 if this explanation—a shift with substituent of the relative importance of the two steps in determining the rate—is in fact correct.

In order to be conservative, we assume that for p-CH_3O, f_{-1} has its maximum value of 0.19; that for p-CHO, $f_{-1} = 0$; that m_0 at p-CHO has the maximum value shown by the dashed line in Figure 2 (0.35) and that m_0 at p-CH_3O is the slope of the solid line at that point (0.67). Equation 6 then yields $m_1 = 0.35$ and $m_2 = 2.0$. Thus if a shift in rate-determining step is actually under observation the *minimum* value for $\delta_x\Delta G^*/\delta_x\Delta G^\circ$ for conversion of reactants to T_2 is 2.0; combining this with our above estimate that the leaving-group bond is 20–50% broken in T_2, we find that complete deacylation of phenols (corresponding to T_2 with 100% bond breakage) would have to exhibit a substituent effect at least four to ten times larger than complete deprotonation (ionization) of phenols.

Although deacylation in water shows a substituent effect 1.72 times larger than deprotonation,[28] a factor of more than 4–10 seems much too large and we believe constitutes a strong argument against this explanation. The first step in this process is apparently rather clearly rate determining throughout.

A second explanation involves the idea that substituents exert two qualitatively different effects on molecular energies, usually classified as *inductive* and *resonance* interaction mechanisms. When the latter is not a chief mode of action of the substituent, a good linear correlation of free energies of activation and of phenol ionization is found (as in the left side of Figure 2), but when resonance effects come strongly into play (as with p-NO_2 and p-CHO), then the effect in the rate process, where no net negative charge is appearing directly in the leaving group, is smaller than that in the ionization process. A fall-off in $\delta_x\Delta G^*/\delta_x\Delta G^\circ$ with such substituents then results. An alternative formulation involving cross-conjugation in the reactant state, advanced by Kirsch, Clewell, and Simon,[11] was mentioned above.

The widely used idea of two interaction mechanisms, the inductive and resonance effects, for substituent action has been lent strong support by the recent finding of Swain and Lupton[19] that the entire plethora of substituent constants may be replaced by a single set of two constants for each substituent, which they term F (for field or inductive effect) and R (for resonance effect). They show that all substituent-constant sets so far defined are representable as linear combinations of F and R ($\sigma = fF + rR$). The fraction $\psi|r|/(\phi|f| + \psi|r|)$, where ϕ and ψ are weighting factors to correct for observed ranges of f and r, was used to derive the "per cent resonance" (% R) characteristic of any set of substituent constants. This is of course determined by the nature of the chemical or physical process used to define the substituent scale in question. Now if the % R for basic phenyl ester solvolysis is different from that for deprotonation of phenols, and if this gives rise to the nonlinear free energy relation, then it should be possible to linearize the free energy curve for the activation process by plotting *vs.* an appropriate linear combination of F and R. Such a plot is in fact linear, as shown in Figure 3 if $(0.80F + R)$ is used; this corresponds, from the formula of Swain and Lupton,[19] to % R = 46. This is to be compared with % R = 56 for σ^- values (phenol ionization in water).

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(27) R. L. Schowen and K. S. Latham, Jr., *J. Am. Chem. Soc.*, **89**, 4677 (1967).

(28) J. Gerstein and W. P. Jencks, *ibid.*, **86**, 4655, (1964).

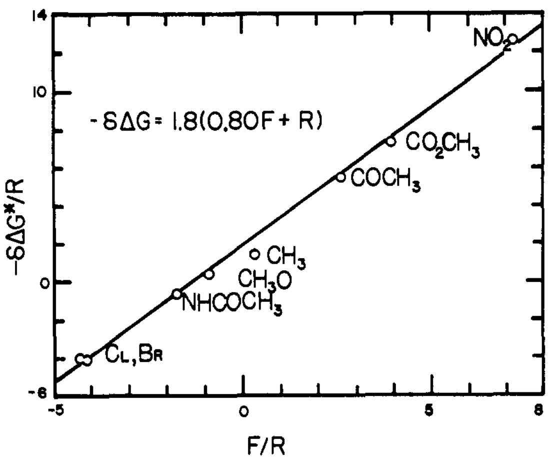

Figure 3. Graphical demonstration of the linear dependence of the substituent effect on the free energy of activation for methoxide-catalyzed methanolysis of $CH_3O_2CO_6H_4X$ at 25° ($\delta_x\Delta G^*$) on $(0.80F + R)$ where F and R are the field (inductive) and resonance constants of Swain and Lupton.[19]

A *caveat* about the ascription of these nonlinearities merely to resonance involving the substituent itself is in order here. Swain and Lupton[19] noted that σ and σ^- both show about the same $\% R$ (53 ± 0 and 56 ± 4, respectively, for *para* substitution) so that the enhanced substituent effects seen in phenol deprotonation or aniline protonation for such substituents as nitro and cyano may come as much from the field effects as from resonance interactions by these groups. The field effect of any group will of course be enhanced by resonance relay of electron density through the remainder of the system to the vicinity of the substituent; this factor may be the crucial characteristic of the cases requiring σ^-. It may also be the point of importance in cases requiring linear combinations of σ and σ^-.

Since Swain and Lupton have shown that all substituent-constant sets are expressible as linear combinations of their F and R, and have given the appropriate coefficients f and r for the various sets, a useful, uniform method of reporting data correlated in this fashion suggests itself. Any data linear in any substituent-constant set will be characterized if three parameters are specified: (i) the $\% R$ of the set required; (ii) the value of r used; (iii) the slope of the plot. For example, our data show $\% R = 46$, $r = 1$, slope $= 1.8$. Of course the value chosen for r is arbitrary, and if all workers were to agree on a common value, say unity, then only $\% R$ and slope would need to be stated.

Finally, it may be noted that the curvature of the free energy plot is qualitatively in the direction for a change in transition-state structure predicted by Hammond's postulate[14] or the reacting bond rule of Swain and Thornton.[16] The idea that the appearance of driving force in a chemical reaction should shift the structure of the activated complex toward a resemblance to the substances on the unfavorable side of the equilibrium has recently been cast in quantitative form by Marcus,[29] who showed that the shifts should produce free energy relations of quadratic form, concave downward. With a total of eight points and some scatter, it would be easy to construct a parabolic curve to fit our plot in Figure 2. It is thus entirely possible that the shape of the free energy relation in this and related reactions arises from a lengthening of the activated-complex nucleophile-to-carbonyl bond with electron withdrawal.[30]

Enthalpies and Entropies of Activation. The entire discussion of free energies of activation has been conducted as if these quantities were representatives of internal potential-energy changes of activation. As Hepler[31] and Willi[32] explained some time ago, this is frequently a justifiable procedure. Our determination of the enthalpies and entropies of activation for a wide range of structures in this reaction allows us to examine this assumption for validity and in addition to develop a molecular interpretation of the structurally induced variations observed for these quantities.

Table III shows no regularity or trend with substituent in either ΔH^* or ΔS^*, although within the acetate and carbonate series the regularities in ΔG^* discussed above are readily apparent. Furthermore, a plot of ΔH^* *vs.* ΔS^* yields no discernible relation. This may be taken as an indication[33] that more than a single interaction mechanism is contributing to the variations in enthalpy and entropy of activation. For simplicity we shall attempt to use no more than two such mechanisms to explain the data. Following Hepler,[31] we take these to be *external* effects of the substituent, *i.e.*, effects on the energy and entropy of the solvation sphere, and *internal* effects, chiefly those changes in potential energy to which the action of substituents is usually attributed. The observed substituent effects on enthalpy and entropy of activation are then taken as the sum of solvation and internal changes (eq 7 and 8) and it is further assumed that each of these interaction mechanisms is characterized by its own isergonic ("isokinetic") relation (eq 9 and 10). Then, by a simple combination of these equations it

$$\delta_x\Delta H^* = \delta_x\Delta H_e^* + \delta_x\Delta H_i^* \tag{7}$$

$$\delta_x\Delta S^* = \delta_x\Delta S_e^* + \delta_x\Delta S_i^* \tag{8}$$

$$\delta_x\Delta H_e^* = \beta_e\delta_x\Delta S_e^* \tag{9}$$

$$\delta_x\Delta H_i^* = \beta_i\delta_x\Delta S_i^* \tag{10}$$

becomes clear (eq 11) that the locus of any substituent point in the $\Delta H^* - \Delta S^*$ plane may be found by moving from the point for the unsubstituted compound along a vector[33] which is the sum of a solvation vector (eq 9) and an internal-energy vector (eq 10). Now the internal-energy interaction mechanism is expected to show a very large isergonic temperature, β_i, because only small entropy changes are likely to accompany the considerable changes in electronic energy levels induced by the substituent. The electronic entropy of all these molecules is zero and only internal-rotational entropy changes are likely to be correlated with $\delta_x\Delta H_e^*$; these contributions can probably

$$\delta_x\Delta H^* = \beta_e\delta_x\Delta S_e^* + \beta_i\delta_x\Delta S_i^* \tag{11}$$

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[29] R. A. Marcus, *J. Phys. Chem.*, **72**, 891 (1968).

[30] Entropies of activation for the methoxide-catalyzed methanolysis of substituted aryl benzoates have been interpreted by Jones and Sloan (*Tetrahedron Letters*, 831 (1966)) as indicating an opposite trend in activated-complex bond lengths. Alternative interpretations of the entropies may, however, be possible.[27]

[31] L. G. Hepler, *J. Am. Chem. Soc.*, **85**, 3089 (1963); *cf.* L. G. Hepler and J. W. Larsen, *J. Org. Chem.*, **33**, 3961 (1968).

[32] A. V. Willi, *Chimia* (Aarau), **15**, 558 (1961).

[33] Reference 17, pp 343–353.

be neglected in comparison with the translation–rotation terms from the solvation interaction mechanism. Thus we take β_i as essentially infinite, $\delta_x\Delta S_e^* \approx \delta_x\Delta S^*$, and convert eq 11 to eq 12. The latter shows that if the above arguments are correct, then the locus of any substituent

$$\delta_x\Delta H^* = \beta_e\delta_x\Delta S^* + \delta_x\Delta H_i^* \qquad (12)$$

in the $\Delta H - \Delta S^*$ plane will deviate from the line $\delta\Delta H^* = \beta_e\delta\Delta S^*$ by a vertical amount equal to $\delta_x\Delta H_i^*$. To test the entire hypothesis it remains only to choose a value of β_e, the isergonic temperature for the solvation interaction mechanism. This value is likely to be near room temperature[31-34] and we find the data are best explained by taking $\beta_e \approx 330°K$. Figure 4 shows a plot of ΔH^* *vs.* ΔS^* for both the carbonate and acetate data sets; lines of slope 330°K are drawn through the points for the two unsubstituted compounds. The vertical arrows should then represent $\delta_x\Delta H_i^*$. Notice that points for all electron-donating substituents lie above the line, corresponding to an increase in the internal energy of activation, while for all electron-withdrawing groups the points lie below the line, indicating a lowering of the internal energy of activation. Furthermore, the greater the electron-donating or -withdrawing power of the substituent, the greater is the distance of its point from the line. This model is thus qualitatively and quantitatively satisfactory as a basis for molecular interpretation of enthalpies and entropies of activation in this reaction.

The power of the model is also sufficient to validate the discussion of the free energies of activation in potential-energy terms. Using eq 12 and $\beta_e \approx 330°K$ to write an expression for $\delta_x\Delta G^*$, we find eq 13. Clearly at

$$\delta_x\Delta G^* = \delta_x\Delta H_i^* + (330 - T)\delta_x\Delta S^* \qquad (13)$$

temperatures near 330°, $\delta_x\Delta G^* \approx \delta_x\Delta H_i^*$ and thus, as Hepler[31] noted for the Hammett equation, remote substituent effects on free energy tend (near room temperature) to approximate the effects on internal energy.

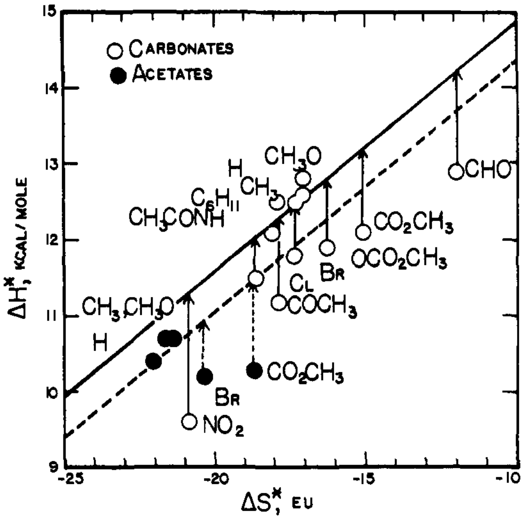
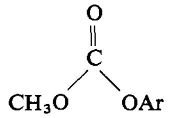
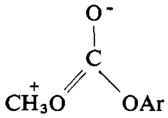


Figure 4. Enthalpies of activation *vs.* entropies of activation for the methoxide-catalyzed methanolysis of $p\text{-}XC_6H_4OCO_2CH_3$ (○) and $p\text{-}XC_6H_4O_2CCH_3$ (●). The lines (—, carbonates; ----, acetates) represent $\delta_x\Delta H^* = 330\delta\Delta_xS^*$. The vertical arrows then give $\delta_x\Delta H_i^*$.

Acetates *vs.* Carbonates. Figure 5 shows that the substituent effects on reactivity are equal in the acetate and carbonate series, their free energies being strictly linear. From the analysis given above, we expect the constant difference in free energy of activation between similar compounds in the two series (ΔG^* for acetates always smaller by 0.72 kcal/mol) to arise from internal differences, rather than from solvation changes which entropy–enthalpy compensation removes from the free energy at room temperature. However, the constant internal difference could be a difference in internal energy of activation or in internal entropy of activation. In the latter case, since it is constant along the substituent series, $\delta_x\Delta S_i^* = 0$ is still a valid assumption. Figure 6 portrays the two possibilities in the form of a $\Delta H^* - \Delta S^*$ plot. For the same substituent, each carbonate point may be connected to its corresponding acetate point by either the solid vectors (solvation plus an enthalpy difference) or the dashed vectors (solvation plus an entropy difference). No choice is possible on the basis of our data. An enthalpy difference might be rationalized as originating in greater resonance stabilization of the carbonate esters (shown), while a more negative internal entropy of activation (by about 2–3 eu) might be visualized as due to greater internal-rotational freedom in the acetate activated complex.





Conclusions

We interpret these data as excluding a change in the balance of rate determination between addition and elimination steps as the origin of nonlinear structure–reactivity correlations in the systems studied by us. The substituent effects of enthalpy and entropy may be viewed as superpositions of effects of solvation (isergonic temperature about 330°K) and of internal energy. The solvation effects disappear from the free energy due to enthalpy–entropy compensation near room temperature, so that free energy changes may be interpreted as changes in internal potential energy in the classical way. The free energies of activation are linear *vs.* $(0.8F + R)$, which is consistent with the importance of more than one substituent interaction mechanism. The nonlinearity of the plot of $\delta_x\Delta G^*$ *vs.* $\delta_x\Delta G°$ for phenol ionization may result either for this reason or because substituents induce changes in activated-complex structure.

Experimental Section

Materials. *p*-Bromophenol (Eastman White Label), methyl *p*-hydroxybenzoate (Matheson Coleman and Bell), *p*-hydroxybenzaldehyde (Eastman White Label), *p*-hydroxyacetophenone (J. T. Baker Chemical Co., Baker Grade), *p*-chlorophenol (Eastman Kodak Co., practical, recrystallized from petroleum ether 30–60° fraction), *p*-hydroxyacetanilide (prepared from *p*-aminophenol of unknown origin, using the Lumiere–Barbier method,[35] mp 168°, lit.[36] 168°), *p*-cyclohexylphenol (unknown source, mp 130.0–130.9°

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(34) For arguments and some applications, see R. L. Schowen, *J. Pharm. Sci.*, **56**, 931 (1967).

(35) R. Adams and J. R. Johnson, "Laboratory Experiments in Organic Chemistry," The Macmillan Co., New York, N. Y., 1960, p 329.

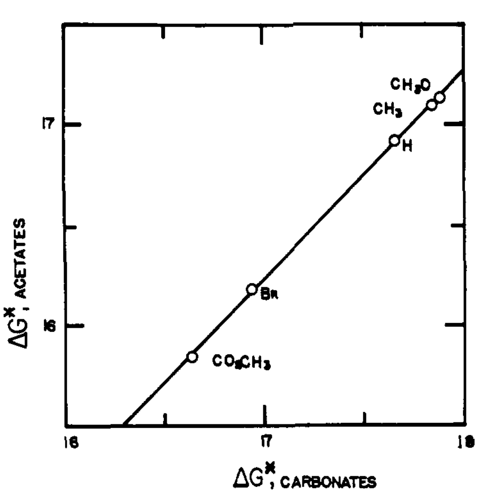

Figure 5. The substituent effects on free energies of activation for methoxide-catalyzed methanolysis of aryl acetates and aryl carbonates are equal.

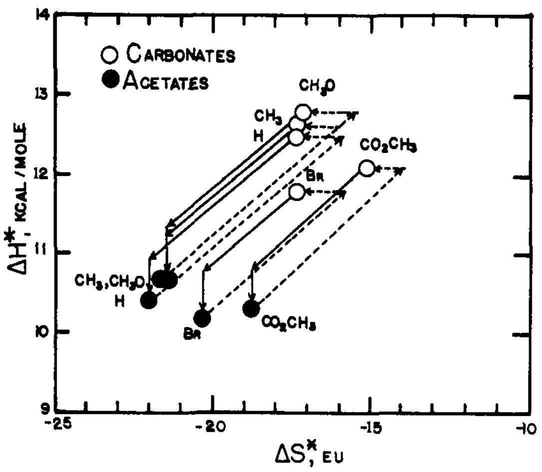

Figure 6. ΔH^* *vs.* ΔS^* for methoxide-catalyzed methanolysis of p-$XC_6H_4OCO_2CH_3$ (○) and p-$XC_6H_4O_2CCH_3$ (●). The solid vectors ascribe the nonsolvation component of their differing activation energetics to a larger internal enthalpy of activation for carbonates; the dashed vectors ascribe it to a more negative internal entropy of activation for carbonates.

after sublimation, lit.[37] 129.2–131.4°), p-methoxyphenol (Matheson Coleman and Bell), hydroquinone (Matheson Coleman and Bell), p-nitrophenol (Eastman Yellow Label, recrystallized from petroleum ether), and p-methoxyphenol (Matheson Coleman and Bell) were used in preparation of esters as described below. Anhydrous lithium perchlorate (G. F. Smith Chemical Co. and Foote Mineral Co.), anhydrous lithium chloride (Fisher Certified Reagent), p-tolyl acetate (Aldrich Chemical Co.), p-methoxyphenyl chloroformate, phenyl chloroformate, methyl chloroformate, and dimethyl carbonate (all four Eastman White Label) were used as obtained.

Esters. All carbonate esters were prepared according to the method of Carpino, *et al.*[38] Methyl chloroformate (Eastman White Label) was added slowly to the appropriate phenol and quinoline, with all reagents in equimolar quantities, methylene chloride or chloroform being used as the solvent. The reaction flask was generally cooled with an ice bath. Aqueous washings (acidic, basic, and then neutral) were followed by sodium sulfate drying of the organic layer, evaporation of the solvent, and vacuum distillation or repeated crystallization as appropriate. Physical properties of p-$XC_6H_4OCO_2CH_3$: NO_2, mp 110.0–110.5°, lit.[39] 109–111°; H, bp 210° (736 mm), lit.[39] 212–215° (760 mm); Cl, bp 85° (0.63 mm);[40] CH_3, bp 82° (0.75 mm);[40] CO_2CH_3, mp 66.0–67.5°, lit.[41] 70–71°; CHO, mp 35.5–35.7°; OCO_2CH_3, mp 113–114°, lit.[42] 115°; cyclohexyl, mp 58.5–59.5°; $NHCOCH_3$, mp 115–116°; $COCH_3$, mp 86.9–88.2°, lit.[41] 88–89°; Br, mp 34.5–35.3°; CH_3O, mp 34.5–36.0°. Infrared and nmr spectra for all compounds were consistent with expectation for pure compounds of the indicated identity.

The aryl acetates were prepared by adding a slight excess of acetyl chloride to a methylene chloride solution of the appropriate phenol. The mixture was allowed to reflux for about 3 hr. Then the excess acetyl chloride and the solvent were distilled off. The esters were purified by distillation or crystallization. Physical properties of p-$XC_6H_4O_2CCH_3$: H, bp 34° (0.05 mm); Br, bp 67–69° (0.05–0.10 mm); CO_2CH_3, mp 81.0–81.6°; CH_3, bp 49.50 (0.05 mm); CH_3O, bp 65–66° (0.05 mm).

Phenol Acidities in Methanol. The pK_a values were determined by the spectrophotometric method of Stearns and Wheland,[43] as previously described.[27] We find 13.2 for p-$CH_3O_2CC_6H_4OH$ and 12.1 for p-$OHCC_6H_4OH$. Values for p-XC_6H_4OH of 14.70 (CH_3O), 14.63 (CH_3), 14.26 (H), and 13.69 (Cl) were taken from ref 27 and of 13.60 (Br)[44] and 11.2 (NO_2)[45] from the literature.

Scintillation Counting. All liquid scintillation counting was carried out using xylene (Fisher Certified Reagent) scintillation solutions, prepared by dissolving 32.7 g of 2,5-diphenyloxazole ("PPO," Packard Instrument Co., Inc., scintillation grade) and 1.95 g of 1,4-bis-2-(4-methyl-5-phenyloxazole)benzene ("dimethyl POPOP," Packard scintillation grade) in 3.8 l. of xylene. Relative activities were determined using the Beckman Liquid Scintillation System.

Kinetics. The solvolysis kinetics were determined spectrophotometrically using a Cary Model 14 recording spectrophotometer. Temperature was controlled by using a thermostated cell holder; the reactions were initiated by injection of 0.50 ml of sodium methoxide solution from a thermostated syringe into the cell containing 1.0 ml of the ester solution. The recorder was turned on immediately and the first-order exponential trace was obtained. Our second-order rate-constant program causes the IBM 7040 or GE 625 computer first to calculate the observed first-order rate constants by a least-squares regression treatment of the integrated first-order rate law. The first-order rate constants thus obtained are similarly treated as a function of sodium methoxide concentration to yield second-order rate constants. A final least-squares fit of these to the Eyring equation produces the activation parameters.

The standard sodium methoxide solutions (about 0.4 *M* in nearly all cases) were prepared by weighing about 10 g of clean sodium and storing under xylene. Then portions are thoroughly washed, first in bulk methanol and then in reagent grade methanol, and quickly transferred to a 1-l. polyethylene bottle filled with methanol (Matheson Coleman and Bell or Baker Analyzed Reagent). The resulting solution is standardized against dried potassium biphthalate (Baker and Adamson Primary Standard) using a Heath-Built pH recording electrometer. The less concentrated base solutions were prepared by pipetting aliquots of the standard base solution into volumetric flasks and diluting to the mark with a lithium chloride solution of the same concentration as the standard base solution. The thermal expansion coefficients of the methoxide and salt solutions were determined so that the actual methoxide concentrations at the various experimental temperatures could be calculated.

Isotope Exchange. The kinetics of the methoxyl-exchange reaction of the labeled carbonates was determined as follows. Equal volumes of a stock solution of ester (about 0.020 *M*) and

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[36] C. D. Hodgman, Ed., "Handbook of Chemistry and Physics," 41st ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1959, p 766.

[37] Reference 36, p 1374.

[38] L. A. Carpino, D. Collins, S. Göwecke, J. Mayo, S. D. Thatte, and F. Tibbetts, *Org. Syn.*, **44**, 22 (1964).

[39] I. B. Douglas and G. H. Warner, *J. Am. Chem. Soc.*, **78**, 6070 (1956).

[40] Analysis by vpc on a DEGS column at 150° (flow rate 40 cc/min) showed only a single peak.

[41] P. Brown and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 2711 (1967).

[42] V. Syniewski, *Ber.*, **28**, 1874 (1895).

[43] R. S. Stearns and G. W. Wheland, *J. Am. Chem. Soc.*, **69**, 2025 (1947).

[44] C. H. Rochester and B. Rossall, *J. Chem. Soc. B*, 743 (1967).

[45] B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Am. Chem. Soc.*, **88**, 1911 (1966). Marc Jacobson, in our laboratory, has found 10.9.

of the standard base solution (about 0.20 *M*) were thermostated separately at 25°. At zero time, the two solutions were mixed rapidly. Then 4.00-ml aliquots were removed at appropriate times with a 5.00-ml syringe and were injected rapidly into separatory funnels containing 20.0 ml of 0.020 *M* aqueous hydrochloric acid and 15.00 ml of xylene. Then 2.00 ml of the stock ester solution is added and the procedure continued as above.

The distribution coefficients of the esters between the aqueous methanol layer and xylene were determined by pipetting 20.0 ml of 0.020 *M* hydrochloric acid, 2.00 ml of methanol, 2.00 ml of the standard 0.20 *M* sodium methoxide solution, and then 15.00 ml of a 0.020 *M* labeled ester solution was added to 10.00 ml of the scintillation solution and the radioactivity was measured. By comparison of this activity with that of 10.00 ml of the unextracted ester–xylene solution, added to 10.00 ml of scintillation solution, the fraction of the ester which remains in the xylene layer after the aqueous washing is determined. Plots of the apparent activity *vs.* concentration of ester in the scintillation solution for dimethyl carbonate, methyl phenyl carbonate, and methyl *p*-formylphenyl carbonate were linear and intersected the origin. However, the plot for methyl *p*-methoxyphenyl carbonate was significantly curved and it was therefore necessary to correct for the self-quenching in order to determine accurately the zero-time activity for the exchange experiments.

The observed activity, *a*, of the final scintillation solution (in excess of background) is then given by eq 14, where the coefficients γ represent the fraction of the species present in the scintillation solution after extraction and the other symbols are defined in the Results section above (Scheme I). The concentrations refer to the reaction solution. To obtain

$$a = \gamma_E[E^*] + \gamma_P[P^*] \qquad (14)$$

the time dependence of *a*, we require $E^*(t)$ and $P^*(t)$. The former is readily found from Scheme I to be given by eq 15–16. The latter is described by the solution of the linear first-order differential eq 17, which is given[46] by eq 18. Experiments were carried out

$$[E^*] = [E_0^*]\exp(-(k_e + k_s)[CH_3O^-]t) \qquad (15)$$

$$k_e = k_{-1}/(2k_{-1} + 2k_2)$$
$$k_s = k_2/(k_{-1} + k_2) \qquad (16)$$

$$d[P^*]/dt = k_s[CH_3O^-][E^*] - k_p[CH_3O^-][P^*] \qquad (17)$$

$$[P^*] = \frac{k_s[E_0^*]}{k_s + k_e - k_p}\{\exp(-k_p[CH_3O^-]t) - \exp(-(k_e + k_s)[CH_3O^-]t)\} \qquad (18)$$

$$a = [E_0^*]\left\{\gamma_E - \frac{\gamma_p k_s}{k_s + k_e - k_p}\right\} \times \exp(-(k_e + k_s)[CH_3O^-]t) + \frac{\gamma_p k_s[E_0^*]}{k_s + k_e - k_p}\exp(-k_p[CH_3O^-]t) \qquad (19)$$

such that $\exp\{-(k_e + k_s)[CH_3O^-]t\} < 10^{-3}$ at times for measurement of activity; that this condition was fulfilled was shown by the linearity of semilogarithmic plots of activity *vs.* time, all of which yielded slopes equal to $(-k_p[CH_3O_-])$, k_p having been determined in an independent experiment. Such plots obey therefore eq 20; from their intercepts can be calculated $k_e/k_s = k_{-1}/2k_2$ which is the only unknown in that quantity. Data and results for typical experiments are given in Table V. The value of γ_p is 0.66 and of γ_E is 1.00 in all cases.

$$\ln(a\gamma_E/a_0\gamma_p) = -k_p[CH_3O^-]t - \ln\left\{1 + \frac{k_e}{k_s} - \frac{k_p}{k_s}\right\} \qquad (20)$$

Table V. Rate of Loss of Nonionic Radioactivity during Solvolysis of $CH_3{}^*OCO_2C_6H_4X$ in Methanol at 25°

X = H		X = *p*-CH$_3$O		X = *p*-CHO	
time, min	*a*, cpm	time, min	*a*, cpm	time, min	*a*, cpm
2.30	7,084	1.91	13,773	1.64	12,211
3.56	5,263	3.60	9,151	3.01	9,292
4.90	3,834	4.98	6,609	4.34	7,118
6.25	2,814	6.16	4,929	6.04	5,023
7.48	2,145	7.62	3,541	7.61	3,714
8.55	1,708	9.05	2,590	9.33	2,713
9.65	1,345	11.94	1,456	10.71	2,111
a_0 = 17.900		a_0 = 29,600		a_0 = 24,500	
k_p/k_s = 0.105		k_p/k_s = 0.093		k_p/k_s = 0.007	

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[46] G. B. Thomas, Jr., "Calculus," Addison-Wesley Publishing Co., Cambridge, Mass., 1953, pp 541–542.