Solvation and Approximation. Solvent Effects on the Bimolecular and Intramolecular Nucleophilic Attack of Carboxyl Anion on Phenyl Esters

Thomas C. Bruice[1] **and A. Turner**[2]

Contribution from the Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106. *Received October 4, 1969*

Abstract: The rate constants for bimolecular nucleophilic attack of acetate ion upon substituted phenyl acetates as well as the rate constants for intramolecular attack of the carboxyl anion of phenyl succinates, phthalates, and 3,6-endoxo-Δ^4-tetrahydrophthalate have been determined in H_2O (w) and 1.0 *M* H_2O in DMSO (s). The values of $\rho_s/\rho_w \approx 2.2$. The greater apparent sensitivity to electronic effects in s is attributed to greater transition state stabilization of esters with electron-deficient leaving groups by solvent s as compared to w. Values of k_{intra}/k_{inter} were computed in both solvent systems employing the rate constants for acetate attack on phenyl esters as k_{inter} and the rate constants for the succinate, phthalate, and 3,6-endoxo-Δ^4-tetrahydrophthalate as k_{intra}. Transfer from solvent w to s has no appreciable effect on the magnitude of k_{intra}/k_{inter} when considering the phthalate and 3,6-endoxo-Δ^4-tetrahydrophthalate esters. The small difference in k_{intra}/k_{inter} for the succinate esters is attributed to a conformational change from transoid to cisoid on transfer from solvent w to s. This conformational change is attributed to less solvation (and decrease in steric requirements) of the carboxyl anion in s as compared to w. From these results it is concluded that carboxyl group solvation cannot contribute significantly to the large values of k_{intra}/k_{inter} (up to 10^8 *M*) when covalently rigid intramolecular models are considered. The mathematical model of Koshland is of little utility in explaining the ratios of k_{intra}/k_{inter} of this study. It is concluded that the propinquity effect is likely of great significance in determining the efficiency of certain enzymatic reactions.

An understanding of the reasons for the facility of enzymatic catalysis is truly one of the more challenging problems in chemistry. The answers to this problem are to be found in a complete elucidation of the the nature of the enzyme–substrate complex leading to catalysis and a physical–organic appreciation of the significance of the structural features of this complex. Formation of the productive enzyme–substrate complex is accompanied by the juxtapositioning of substrate and catalytic groups. Chemists have long appreciated this feature and many "model enzyme" reactions have been investigated in which catalytic functions and substrate molecules have been approximated by inclusion within the same molecule, by freezing, or through complexation and inclusion into micelles, etc.[3,4] The problem of the importance of proximity and orientation to the enzymatic rate constant has been approached, mathematically, by Koshland.[5,6] When considering the increase in rate constant brought about by converting a bimolecular reaction (eq 1) into a reaction proceeding from an intimate pair (eq 2), it was concluded that approximation and proper orientation of the reactants A and B could result only in a ratio of k_1/k_2 of *ca.* 5–50 *M* (see Discussion). A rate constant ratio of this order of magnitude is often found when the rate of a bimolecular reaction is compared to its intramolecular counterpart.

$$\mathrm{A} + \mathrm{B} \xrightarrow{k_1} \mathrm{C} \tag{1}$$

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{AB}_{\mathrm{pair}} \xrightarrow{k_2} \mathrm{C} \tag{2}$$

In many instances, however, the ratio of rate constants (k_{intra}/k_{inter}) far exceeds the anticipated values.[3,4,7] The vast majority of such cases involve nucleophilic displacement of –X from –COX. One possible contributing factor to the larger than anticipated values of k_{intra}/k_{inter} could be the necessity for desolvation of the nucleophile in the bimolecular reaction. For the intramolecular counterpart, if A and B are sufficiently juxtaposed so that solvent molecules cannot be interposed, then nucleophile desolvation may not be a portion of the energy barrier for reaction.

In this report there is provided the details of a study of the effect of solvent composition upon the value of k_{intra}/k_{inter} for the case when B = $-COO^-$ and A = $-COOPh\,(Y)_n$. The energy barrier for desolvation of a carboxyl ion is appreciable.[8]

Experimental Section

Substituted phenyl acetates were prepared by heating the phenol (3.76 g, 0.04 mol) and acetyl chloride (3.41 ml, 0.048 mol) under reflux in sodium-dried benzene (200 ml) in the presence of anhydrous potassium carbonate (16.6 g, 0.12 mol) for 18 hr. The mixture was filtered, the benzene removed under reduced pressure, and the product recrystallized from benzene–petroleum ether (bp 30–60°) giving 2,4-dinitrophenyl acetate, mp 69–70°; *p*-nitrophenyl acetate, mp 77–78°; *m*-nitrophenyl acetate, mp 53–54°.

Substituted phenyl phthalates were prepared by the method of Thanassi and Bruice.[9]

p-Methoxyphenyl hydrogen phthalate had mp 123–124°. *Anal.* Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.27; H, 4.39.

p-Bromophenyl hydrogen phthalate had mp 126–127°. *Anal.* Calcd for $C_{14}H_9O_4Br$: C, 52.36; H, 2.82; Br, 24.88. Found: C, 52.61; H, 2.98; Br, 24.75.

Phenyl hydrogen phthalate had mp 99–101° (lit.[9] mp 94–96°).

---

[1] To whom inquiries should be addressed.

[2] Postdoctoral Fellow, Department of Chemistry, University of California at Santa Barbara.

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

[4] W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill Book Co., Inc., New York, N. Y., 1969.

[5] D. E. Koshland, Jr., *J. Theoret. Biol.*, **2**, 75 (1962).

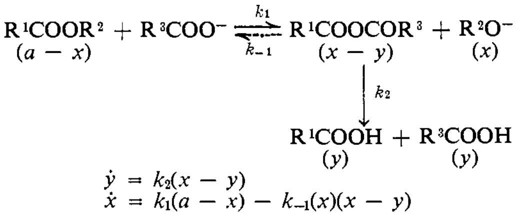
[6] D. E. Koshland, Jr., and K. E. Neet, *Ann. Rev. Biochem.*, **37**, 359 (1968).

[7] T. C. Bruice in "The Enzymes," P. D. Boyer, Ed., Vol. II, 3rd ed, Academic Press, New York, N. Y., 1970.

[8] K. D. Gibson and H. Scheraga, *Proc. Nat. Acad. Sci. U.S.*, **58**, 420 (1967).

[9] J. W. Thanassi and T. C. Bruice, *J. Amer. Chem. Soc.*, **88**, 747 (1966).

Scheme I



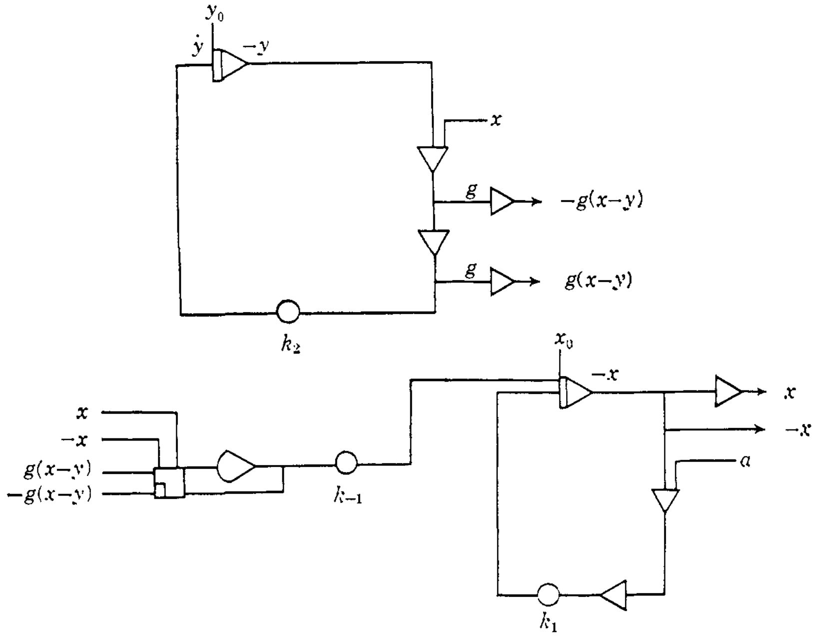
$$\underset{(a-x)}{R^1COOR^2} + R^3COO^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(x-y)}{R^1COOCOR^3} + \underset{(x)}{R^2O^-}$$

$$\xrightarrow{k_2} \underset{(y)}{R^1COOH} + \underset{(y)}{R^3COOH}$$

$$\dot{y} = k_2(x-y)$$

$$\dot{x} = k_1(a-x) - k_{-1}(x)(x-y)$$

Scheme II



Substituted phenyl succinates were prepared by the method of Bruice and Pandit[10] giving *p*-methoxyphenyl hydrogen succinate, mp 115° (lit.[10] mp 117–118°); phenyl hydrogen succinate, mp 92–94° (lit.[11] mp 98°); and *p*-bromophenyl hydrogen succinate, mp 126–127° (lit.[10] mp 125–127°).

***p*-Methoxyphenyl-3,6-endoxo-Δ^4-tetrahydrophthalate monoester** was prepared as the sodium salt by addition, under nitrogen, of an ethereal solution of sodium *p*-methoxyphenoxide (0.146 g, 0.001 mol) to an ethereal solution of the anhydride (0.166 g, 0.001 mol).[10]

Kinetic Methods. Hydrolyses were carried out under pseudo-first-order conditions, and reactions followed by determining the change in optical density due to either anhydride formation (for substituted phenyl hydrogen phthalate esters) or phenol formation (for other esters). Thus in DMSO product formation was observed at 294 mμ for *p*-methoxyphenol, 279 mμ for phenol, 290 mμ for *p*-bromophenol, 340 mμ for *m*-nitrophenol, 430 mμ for *p*-nitrophenol, 373 mμ for 2,4-dinitrophenol, and 300 mμ for phthalic anhydride, while in aqueous solution product formation was observed at 287 mμ for *p*-methoxyphenol, 274 mμ for phenol, and 300 mμ for phthalic anhydride (except *p*-methoxyphenyl phthalate hydrolysis where 304 mμ was used to minimize absorption due to phenol).

Optical densities were determined either with a Zeiss PMQ II spectrophotometer or by a Durrum stopped-flow spectrophotometer. In the former case a solution of the ester was prepared in dioxane and 1 drop added to a thermostated quartz cuvette containing the buffer solution. For stopped-flow rates, where the ester was unstable near neutral pH, a solution was prepared in DMSO or aqueous solution containing HCl. All rate constants were extrapolated to zero buffer concentrations.

It was found necessary to prepare the sodium salt of the 3,6-endoxo-Δ^4-tetrahydrophthalate ester immediately before use and to stabilize it in 1 *N* aqueous HCl. The resulting solution was then either diluted with DMSO (for kinetics in DMSO) or cooled to 0° and a portion added to 0.1 *N* HCl (thermostated at 30°) prior to a kinetic measurement (for kinetics in aqueous solution).

Good pseudo-first-order kinetics were observed except in the following cases: (i) phenyl phthalate monoesters in water, aqueous methanol, and aqueous dioxane solution, where the hydrolysis rate of the anhydride intermediate (k_2) is comparable with that of its formation (k_1) (k_1 was obtained by determining k_2 separately and by use of eq 3[12]

$$k_1 t_{\max} = 2.3(K-1)^{-1}\log K \qquad (3)$$

where $K = k_2/k_1$), and (ii) 3-nitrophenyl acetate and 4-nitrophenyl acetate in aqueous DMSO where k_{-1} is significant (Scheme I). k_1 was obtained by determining values of k_2 separately and solving for k_1 and k_{-1} on an EAI TR-20 analog computer (Scheme II). Equilibrium formation of the anhydride intermediate was confirmed in the case of these esters by addition of acetic anhydride to a solution of the phenol in aqueous DMSO (1:1 mole ratio). An immediate decrease in absorbance was observed (due to formation of the ester) followed by a slower increase to the original value (due to hydrolysis of the anhydride and reformation of the phenol).

pH measurements were made with a Radiometer pH meter type PHM 26 and an electrode system dependent on the solvent medium under examination.

In water, aqueous methanol, and aqueous dioxane solution a Radiometer GK 2021C electrode was used. True pH measurements in aqueous dioxane solution (pH) were obtained from observed readings (B) by use of eq 4[13]

$$\text{pH} = B + \Delta \qquad (4)$$

where $\Delta = \log V_M{}^\circ + \log(1/\alpha)$.

Measurements in aqueous DMSO were carried out by using an "H cell" similar to that described by Ritchie and Uschold,[14] a silver billet electrode (Beckman no. 39261), and a glass electrode filled with triply distilled mercury.[14] The latter was prepared from a Beckman E2 electrode (no. 39004) by removal of the aqueous internals together with the AgCl from the tip of the inner element. The pH meter was operated on the millivolt scale and the instrument standardized by means of *p*-toluenesulfonic acid in aqueous DMSO. Plots of millivolt reading *vs.* acid concentration gave a 60.5-mV slope over a range of acid concentrations 5×10^{-4} to 5×10^{-2} *M*. pH values were calculated from the theoretical slope of 59.1 mV.

Results

As a simple model for intramolecular carboxyl group nucleophilic catalysis of ester hydrolysis, the effect of

---

(10) T. C. Bruice and U. K. Pandit, *J. Amer. Chem. Soc.*, **82**, 5858 (1960).

(11) E. Gaetjens and H. Morawetz, *ibid.*, **82**, 5328 (1960).

(12) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, pp 166–169.

(13) L. G. Van Uitert and C. G. Haas, *J. Amer. Chem. Soc.*, **75**, 451, 455 (1953); **76**, 5887 (1954).

(14) C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, 84, 1721 (1967).

Table I. Values of k_1 and Activation Parameters for the Hydrolysis of Phenyl Hydrogen Phthalate in Aqueous Solution

10^3k_1, sec^{-1}	Temp, °C	$\Delta H^{\ddagger}$, kcal/mol[a]	$T\Delta S^{\ddagger}$, kcal/mol[a]
8.5	9.4	17.2	−2.1
25.2	19.7		
67	29.1		

[a] T = 25°.

Table II. Hydrolysis of Phenyl Hydrogen Phthalate[a]

Solvent	10^3k_1, sec^{-1}
Water	26
40 vol % aqueous methanol	25
60 vol % aqueous methanol	21
40 vol % aqueous dioxane	27
80 vol % aqueous dioxane[b]	43

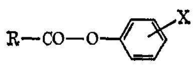
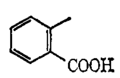
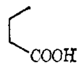
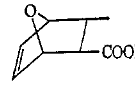
[a] T = 20°, salt concentration 0.12 M KCl + KAC. [b] Salt concentration 0.05 M.

Table III. Hydrolysis of Phenyl Hydrogen Phthalate in Aqueous DMSO[a]

H_2O, M	k_1, sec^{-1}	Relative rate
55.2	0.072	1
3.22	1.5	21
1.00	3.1	43
0.50[b]	4.2	58

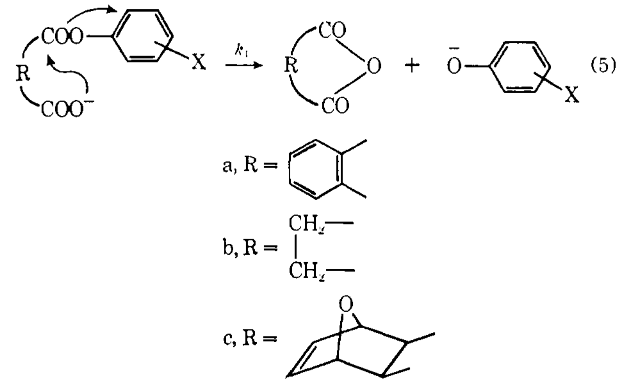
[a] T = 30°, salt concentration 0.03 M KCl + KAc. [b] Salt concentration 0.05 M.

Table IV. Hydrolysis Rates in DMSO Containing 1.00 M H_2O (T = 30°)

 R	X	$k_{1,\mathrm{DMSO}}$,[a] sec^{-1}	k_{1,H_2O}, sec^{-1}	Enhancement
	4-OCH_3	0.21	0.0318	6.6
	H	3.2	0.072	44
	4-Br	96.0	0.388	247
$-CH_3$ + CH_3COO^-	3-NO_2	0.0027[b]	9.6×10^{-7} [b,c]	2,800
	4-NO_2	0.10[b]	3.95×10^{-6} [b,c]	25,300
	2,4-$(NO_2)_2$	51[b]	4.3×10^{-4} [b,c]	119,000
	4-OCH_3	0.18	0.00107[d]	168
	H	1.8	0.0023	783
	4-Br	40.0	0.0125[d]	3,200
	4-OCH_3	177.0	0.867	204

[a] See Scheme I. Salt concentration 0.03 M. [b] l. mol^{-1} sec^{-1}. [c] At 25°, ref 14. [d] Extrapolated from values of $\Delta H^{\ddagger}$ (unsubstituted ester—this work; 4-methoxy ester—ref 9) and a Hammett $\rho\sigma$ plot.

solvent transfer on the kinetics of hydrolysis of phenyl hydrogen phthalate (eq 5a) was initially investigated.



The pH *vs.* k_{obsd} profiles that were obtained were found to be in accord with those of an earlier study[9] dictating the rate law of eq 6. From the temperature dependence

$$k_{\mathrm{obsd}} = k_1K_a/(K_a + a_H) \qquad (6)$$

of k_1, $T\Delta S^{\ddagger}$ was calculated to be −2.1 kcal mol^{-1} (Table I). On transfer from water to 80:20 (v/v) dioxane–water, the pH profile again indicated carboxyl anion participation, the value of k_1 changing by less than a factor of 2 even though the kinetic pK_a had risen from 2.78 to 8.89. A similar invariancy of k_1 with solvent composition was found with other dioxane–water mixtures and in aqueous methanol solution (Table II). In aqueous DMSO, however, an increase in k_1 was observed at high DMSO concentration (Table III).

Larger rate enhancements were observed to accompany solvent transfer for the bimolecular nucleophilic catalysis of the hydrolysis of phenyl acetates by acetate ion (Table IV). Thus, investigation of the acetate-catalyzed hydrolysis of 2,4-dinitrophenyl acetate under the pseudo-first-order conditions of excess acetate ion in aqueous DMSO revealed a 1.2×10^5 increase in rate over that in aqueous solution. In the case of this ester, the anhydride intermediate was detected by means of the addition of aniline, and the yield of acetanilide indicated that the reaction was 100% nucleophilic as is the case in aqueous solution.[15]

Analysis of the results for intermolecular reactions in aqueous DMSO solutions is more complex than in aqueous solution due to the association of acetic acid with its anion to form $H(Ac)_2^-$. However, the concentration of free acetate ion may be obtained from observed pH measurements after the method of Kolthoff and Chantooni,[16] *via* eq 7 where C_a and C_s are the analytical acid ([AcH + $H(Ac)_2^-$]) and salt ([Ac$^-$ + H·

$$[\mathrm{Ac}^-] = \frac{(C_a - C_s)}{(r - 1)} \qquad (7)$$

$(Ac)_2^-$]) concentrations, respectively, and r represents the ratio of the experimentally determined values of the

---

(15) V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.*, 515 (1968).

(16) I. M. Kolthoff and M. K. Chantooni, *J. Amer. Chem. Soc.*, **87**, 4428 (1965).

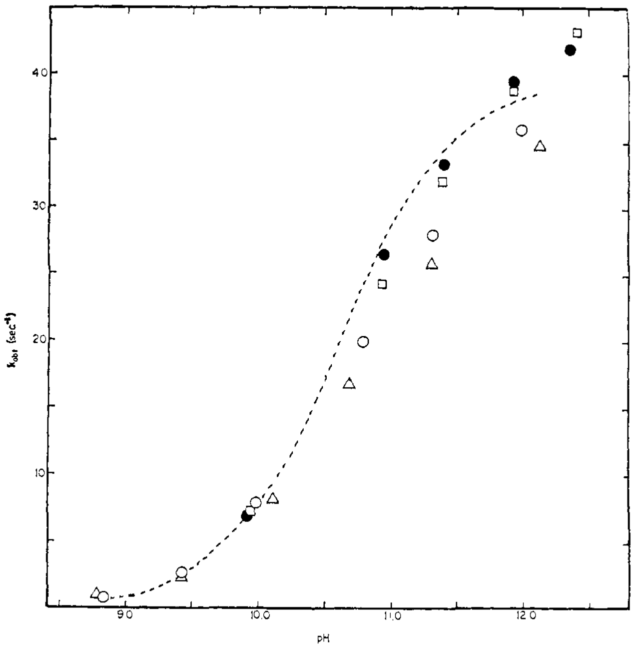


Figure 1. Hydrolysis of *p*-bromophenyl hydrogen succinate in aqueous DMSO (1.0 M H_2O): △, 0.03 M; ○, 0.015 M; □, 0.006 M; and ●, 0.003 M total formate or acetate buffer. The curve is theoretical (eq 6). Positive deviation of points at high pH is accountable as hydroxide ion catalyzed hydrolysis.

hydrogen ion activity, a_H, to those at half-neutralization. Thus, by working at two different pH's and different buffer concentrations it was shown that the catalytic species was Ac^- rather than HAc or $H(Ac)_2^-$ (*e.g.*, see Table V for 4-nitrophenyl acetate hydrolysis).

Table V. The Reaction of Acetate Ion with 4-Nitrophenyl Acetate in DMSO Containing 1.00 M H_2O (T = 30°, Salt Concentration 0.03 M KCl + KAc)

Acetate,[a] M	pH	10^3k_1,[b] sec^{-1}	k_{Ac^-}, l. mol^{-1} sec^{-1}	pH	10^3k_1,[b] sec^{-1}	k_{Ac^-}, l. mol^{-1} sec
0.03	10.68	0.317	0.101	12.12	1.52	0.099
0.015	10.78	0.213	0.123	11.98	0.833	0.100

[a] Total concentration of added acetate buffer. [b] Pseudo-first-order constants were obtained by use of an analog computer (see Experimental Section).

Like phenyl hydrogen phthalate, substituted phenyl succinates and the 3,6-endoxo-Δ^4-tetrahydrophthalate ester also exhibited rate enhancements on transfer from aqueous solution to aqueous DMSO (Table V). However, the formation of complexes (eq 8) between the

$$\begin{tikzcd}
HA + S^- \arrow[dr, shift left] & & \\
& HAS^- \arrow[ul, shift left] \arrow[dl, shift left] & (8) \\
A^- + HS \arrow[ur, shift left] & &
\end{tikzcd}$$

buffer (HA) and substrate (HS) resulted in a decrease in k_{obsd} with increase in buffer concentration which became marked at pH ≥ pK_a. This complexity (which is not important in the bimolecular reactions where the buffer anion alone is the nucleophile) was reduced to a minimum by working at low buffer concentration (0.003 M). The effect of buffer concentration upon rate is shown for a typical example in Figure 1. Rate constants for the nucleophilic acetate catalyzed hydrolysis of substituted phenyl esters in aqueous DMSO solution and in aqueous solution are provided in Table VI.

Discussion

The increase in rate constants accompanying transfer of an anion–molecule reaction (eq 9) from a protic to a

$$Y^- + RX \longrightarrow YR + X^- \qquad (9)$$

dipolar–aprotic mixed solvent cannot, at present, be simply explained.[17] The increase in rate (once initiated) for reactions of type 9 is generally found to be continuous with increasing concentration of the dipolar–aprotic component of a protic–dipolar–aprotic mixture.[18–21] Unlike transfer from protic to pure dipolar–aprotic solvent, where rate enhancement is due primarily to desolvation of Y^-,[22a] transfer from protic to mixed protic–dipolar–aprotic solvent may well involve a considerable contribution from the ability of the DMSO-containing solvation shell to stabilize the transition state.[23–25] Desolvation of anions in water–dipolar–aprotic solvent mixtures must, however, be considerable.[22b] From nmr studies of the solvation $^{35}Cl^-$ chemical shifts in DMSO–water mixtures, there appears to be nearly even competition between DMSO and water for contact with the anion.[26] Though one might anticipate that water should be preferentially pulled into the solvent shell of Cl^- *via* hydrogen bonding, it would appear that the immediate environment of Cl^- is related to the overall structural aspects of the solvent mixture. These results have been suggested[26] to be due to the fact that water hydrogen bonded to Cl^- is strongly polarized and the hydrated chloride ion is, therefore, poorly solvated by the aprotic solvent.

The present investigation deals with the influence on rate when reactions involving carboxyl ion nucleophilic attack upon phenyl esters are transferred from water to 1.0 M H_2O in DMSO. In the DMSO–H_2O mixture employed, the water molecules should exist primarily as 2:1 complexes with DMSO.[27] In this system the carboxyl anions should be considerably desolvated. As will be seen, comparison of the bimolecular reaction of eq 10 to its intramolecular counterpart (eq 5) reveals that the ratio of k_{intra}/k_{inter} may be as great as 10^8 M (water solvent). One factor which could conceivably contribute to this huge rate enhancement might be the greater solvation of the carboxyl anion in the bimolec-

---

(17) For a particularly enlightening review, see A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

(18) A. J. Parker, *Advan. Phys. Org. Chem.*, **5**, 173 (1967).

(19) D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *J. Amer. Chem. Soc.*, **83**, 3678 (1961).

(20) J. Murto, *Suomen Kemistilehti*, *B*, **34**, 92 (1961).

(21) A. J. Parker, *Australian J. Chem.*, **16**, 585 (1963).

(22) (a) R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Roxton, *J. Amer. Chem. Soc.*, **90**, 5049 (1968). (b) Parker and collaborators[22a] have determined values of log γ (these represent free energies of transfer) for transfers from protic to dipolar–aprotic solvents, and have found them to lie in the region of 4–10 for small anions (*i.e.*, they are 10^4 to 10^{10} more solvated by protic solvents).

(23) E. Tommila and M. Savolainen, *Acta Chem. Scand.*, **20**, 946 (1966).

(24) D. D. Roberts, *J. Org. Chem.*, **31**, 4037 (1966).

(25) P. O. I. Virtanan, *Suomen Kemistilehti*, *B*, **40**, 163 (1967).

(26) C. H. Langford and T. R. Stengle, *J. Amer. Chem. Soc.*, **91**, 4015 (1969).

(27) (a) E. Tommila and M. L. Murto, *Acta Chem. Scand.*, **17**, 1947 (1963). (b) In a solution of 1.0 M H_2O in DMSO the ratio of water molecules to DMSO molecules is ~1:11 so that there is an approximately fivefold excess of DMSO if all water molecules are present in a complex of DMSO–H_2O, 2:1.

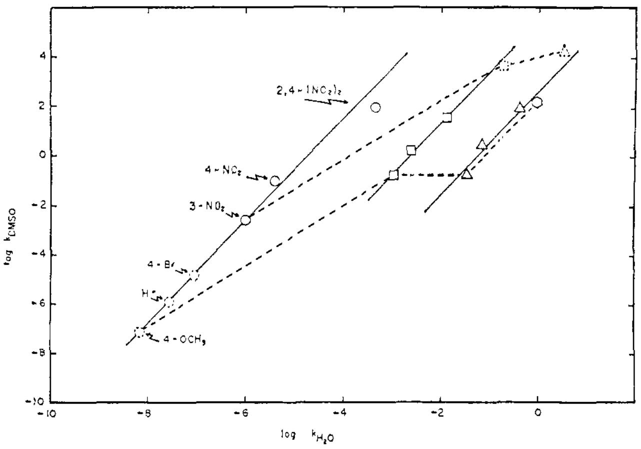
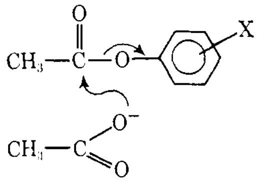


Figure 2. Plot of log k_{DMSO} *vs.* log $k_{\mathrm{H_2O}}$ for the acetate-catalyzed hydrolysis of phenyl acetates, ○; spontaneous hydrolysis of phenyl succinate ion, □; spontaneous hydrolysis of phenyl phthalate anion, Δ; and spontaneous hydrolysis of the anion of phenyl *exo*-3,6-endoxo-Δ^4-tetrahydrophthalate, ○. Solid symbols represent experimental points while dashed symbols represent extrapolated (from $\rho\sigma$ plots) rate constants. Solid lines are of slope 2.2 and represent correlation lines for the series of reactions investigated. Dashed lines connect a few esters of different series but with the same leaving groups.

ular reaction. For intramolecular reactions such as those of eq 5a and 5c, water molecules cannot be placed between the carboxyl anion and the ester carbonyl group. In comparing $k_{\mathrm{intra}}/k_{\mathrm{inter}}$ in H$_2$O to that value obtained in 1.0 M H$_2$O in DMSO, such factors as transition state stabilization, etc., should be cancelled out so that the influence of solvation can be ascertained. This is so if we make the reasonable assumption that any variation in transition state structure on transfer from H$_2$O to H$_2$O–DMSO mixed solvent is the same for carboxyl anion nucleophilic attack, be it intra- or intermolecular, as long as the leaving groups are the same.



(10)

Preliminary studies of the hydrolysis of phenyl hydrogen phthalate in aqueous methanol and aqueous dioxane indicate that the rate constant for intramolecular carboxyl anion nucleophilic attack (eq 5) is little affected by solvent transfer (Table II).[28] In contrast to the results in aqueous dioxane and aqueous methanol, reactions involving carboxyl anion participation exhibited rate enhancements on transfer from aqueous solution to aqueous DMSO (Tables III and V). The extent of the rate enhancement is found to be dependent upon the extent of the electron deficiency of the leaving group. *A priori*, alteration in the sensitivity of rate constants to electronic effects on solvent transfer most likely cannot be explained solely through the solvent dependency of ρ; new substituent constants, σ, must also be required for the dipolar-aprotic solvent.[17] It might be noted, however, that electronic effects of R- in S$_N$AR reactions of methoxide ion with 1-chloro-2-nitro-4-(R)-benzenes in DMSO–methanol are reasonably correlated with ordinary σ constants.[22] Linear free energy, $\rho\sigma$, plots for carboxyl nucleophilic attack upon phenyl esters in water provide the following values of ρ: (a) phthalate monoesters (p-OCH$_3$, p-Br, H), 2.15; (b) succinate monoesters, 2.26;[29] and (c) acetate anion with phenyl acetates [4-NO$_2$, 2,3-(NO$_2$)$_2$, 2,4-(NO$_2$)$_2$, 2,6-(NO$_2$)$_2$, 3,4-(NO$_2$)$_2$], 2.2.[30] Employing the ordinary σ values for aqueous solution, the ρ values in 1.0 M H$_2$O in DMSO were found to be (a) phthalate monoesters (p-OCH$_3$, p-Br, H), 5.26; (b) succinate monoesters (p-OCH$_3$, p-Br, H), 4.72; and (c) acetate anion with phenyl esters [3-NO$_2$, 4-NO$_2$, 2,4-(NO$_2$)$_2$], 4.5. Thus the ratio of $\rho_s/\rho_w \approx 2.2$, where s and w refer to the solvents 1.0 M H$_2$O in DMSO and H$_2$O, respectively. If $\sigma_s = \sigma_w$ then eq 11 and 12 may be combined to give (13). From eq

$$\log k_w/k_w{}^0 = \rho_w\sigma_w \qquad (11)$$

$$\log k_s/k_s{}^0 = \rho_s\sigma_s \qquad (12)$$

$$\log k_s = \frac{\rho_s}{\rho_w}\log k_w + \text{constant} \qquad (13)$$

13, for different series of reactions of esters in solvents w and s, plots of log k_s *vs.* log k_w should provide straight lines of slopes $\rho_s/\rho_w \approx 2.2$. The rate constants in Table IV are suitably described by Figure 2. In Figure 2, plots of log k_s *vs.* log k_w are reasonably correlated by lines of slope 2.2. In Figure 2 the solid points are experimental and the dashed points represent extrapolated rate constants employing the appropriate $\rho\sigma$ relationship. Recourse to the extrapolation of rate constants was necessitated because the rate constants for intra- and intermolecular carboxyl anion catalysis could not be obtained for identical leaving groups. This is so because the predominant mechanism in water for the bimolecular reaction involving poorer leaving groups is not nucleophilic but carboxylanion assisted general base catalysis[15] and in the case of the intramolecular reactions the rate constants for cases with very good leaving groups were too great to be obtained by stopped-flow spectrophotometry. Therefore, though the essential comparisons of $k_{\mathrm{intra}}/k_{\mathrm{inter}}$ necessitate the use of extrapolated rate constants they are nevertheless reasonably secure.

The rate enhancements (k_s/k_w) recorded in Table II and described by Figure 2 show, due to the ratio ρ_s/ρ_w, considerable variation within a particular series of esters. For substituted phenyl acetates they vary from ~10 for 4-methoxyphenyl acetate to ~10^5 for 2,4-dinitrophenyl acetate. An explanation of this variation may be obtained by consideration of the free energies of transfer (log ${}^w\gamma^s$) of the ground and transition states.

---

[28] The results in aqueous methanol are of interest in that they may be compared with those for aspirin hydrolysis [A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, **89**, 4853, 4857 (1967)]. The latter reaction occurs *via* a bimolecular neighboring carboxyl anion assisted general base catalyzed attack of H$_2$O or CH$_3$OH upon the ester carbonyl group. On transfer from water to 50 vol % aqueous methanol, the solvolysis rate for aspirin increases tenfold. The absence of a rate enhancement on transfer of phenyl phthalate monoanion from water to methanol–water mixtures is in accord with a unimolecular mechanism. A similar conclusion may be drawn from the entropy of activation (Table I) which is in accord with a unimolecular reaction [L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, 1, 1 (1963); T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **86**, 418 (1964)].

[29] E. Gaetjens and H. Morawetz, *J. Amer. Chem. Soc.*, **82**, 5328 (1960).

[30] The $\rho\sigma$ plot for acetate anion reacting with substituted phenyl acetates was constructed from the rate constants for reaction of acetate with the esters corrected to the per cent of the reaction established to be nucleophilic. Data are from ref 15.

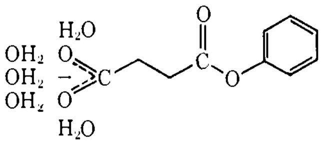
Thus, if $Y^- = Ac^-$ and RX = phenyl ester, the variation of reaction rate with solvent medium for a bimolecular reaction (eq 9) is described by eq 14.[22] Changes

$$\log k_s/k_w = \log {}^w\gamma^s{}_{Y^-} + \log {}^w\gamma^s{}_{RX} - \log {}^w\gamma^s{}_{T.S.} \quad (14)$$

in solvation of the phenyl esters with substitution may be immediately discounted as a significant factor, since $\log {}^w\gamma^s{}_{RX}$ is more negative for large polar solutes (*e.g.*, nitroaromatics)[22] and would decrease the ratio of k_s/k_w in the series 4-methoxpyhenyl acetate to 2,4-dinitrophenyl acetate. $\text{Log } {}^w\gamma^s{}_{T.S.}$ (where T.S. pertains to the transition state) must, therefore, be considerably more positive for the 4-methoxyphenyl ester transition state.

To ascertain the importance of ground state anion solvation to the ratio of k_{intra}/k_{inter} we may simply compare this value in H_2O to that in the H_2O–DMSO solvent (all comparisons of k_{intra}/k_{inter} are made from the plots of Figure 2). This is permissible since by doing so the effects of solvent transfer on the transition state stabilization are cancelled (*i.e.*, ρ_s/ρ_w values are the same for both processes). When $k_{phthalate}/k_{acetate}$ is compared it is found that the rate ratio of *ca.* 4.8×10^6 *M* ($\Delta\Delta F^{\ddagger} = -9.1$ kcal mol^{-1}) in H_2O is within experimental error the same as in 1.0 *M* H_2O in DMSO ($\Delta\Delta F^{\ddagger} = -8.9$ kcal mol^{-1}). In comparing the rate constant for acetate attack on *p*-methoxyphenyl acetate to the intramolecular nucleophilic attack of the carboxyl anion of the *p*-methoxyphenyl monester of 3,6-endoxo-Δ^4-tetrahydrophthalic acid (eq 5c) the increase in rate constant in water of 1.3×10^8 *M* ($\Delta\Delta F^{\ddagger} = -11$ kcal/mol^{-1}) is again found to be comparable to that of 2.5×10^9 *M* in 1.0 *M* H_2O in DMSO. From this result it would appear highly unlikely that solvation of acetate anion in the bimolecular reaction contributes significantly to the rate constant increase accompanying juxtapositioning of reactant species in water as long as in the intramolecular reaction the reacting groups are rigidly juxtaposed.

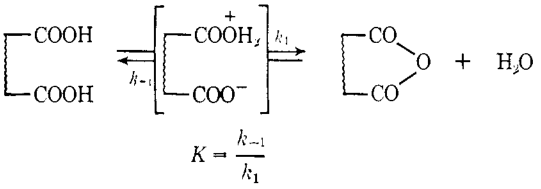
On the basis of the relative rate constants for the intramolecular nucleophilic attack of carboxyl anion upon carbophenoxy groups in glutarate, succinate, and 3,6-endoxo-Δ^4-tetrahydrophthalate monoesters (*i.e.*, decrease in $\Delta F^{\ddagger}$ of *ca.* 3 kcal/mol^{-1} associated with each single bond rotation frozen out in the transition state[10]) and the additive influence of *gem* substituents on the rate constants for the glutarate monoesters[31] it was suggested[32] that the monosuccinate and monoglutarate esters existed in an extended conformation in H_2O (**1**).



1

The conformation of **1** was suggested to be stabilized by the nonbonded interaction of the bulky heavily hydrated carboxyl anion and the ester moiety. This suggestion finds support on further inspection of Figure 2. Thus, in water the succinate esters have intramolecular rate constants about 20-fold smaller than do the phthalate esters while in 1.0 *M* H_2O in DMSO the rate constants are essentially identical indicating a much more cisoid conformation for the succinate esters in the latter solvent due to the much lessened solvation of the carboxyl anion.

The propinquity effect represented by the ratios k_{intra}/k_{inter} and described by Figure 2 may be compared with that obtainable from equilibrium studies. It is a well-established fact that carboxylic acids are in equilibrium with their anhydrides in aqueous solution[33–38] and that formation of cyclic anhydrides is an exclusive function of the free diacid species.[37] A most reasonable mechanism would be that of eq 15 in which the proton



(15)

transfer might be slow or fast. Thus, intramolecular and bimolecular anhydride formation may be related by eq 16. Values of k_{intra}/k_{inter} obtained in this way are

$$\log \frac{k_{1,\,intra}}{k_{1,\,inter}} = \log K_{inter} - \log K_{intra} + \log \frac{k_{-1,intra}}{k_{-1,inter}} \quad (16)$$

recorded in Table VI and are similar to those obtainable from Figure 2.

The model employed by Koshland[5] to calculate the kinetic importance of the proximity effect assumes (a) reactant species (nucleophilic atom, etc.) are about the size of water molecules; (b) packing of both water and reactant molecules is of the *twelve* nearest neighbors type; (c) reactant solutions are sufficiently dilute so that the probability of any more than one reactant molecule being juxtaposed to another is very small; (d) the molarity of water is 55.5; and (e) reaction occurs only through nearest neighbor pairs (eq 17).

$$A + B \rightleftharpoons AB_{pair} \longrightarrow AB \quad (17)$$

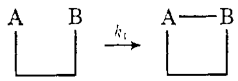
It then follows that

$$[AB_{pairs}] = \frac{[A][B]12}{55.5} \quad (18)$$

and

$$v = k_2[A][B] = k_2\frac{55.5}{12}[AB_{pairs}] \quad (19)$$

Thus, if A and B are juxtaposed within a single compound, and if orientation of the reactant species is ignored, the ratio of the rate constants k_1 to k_2 (*i.e.*, k_{intra}/k_{inter}) should be only 4.6 *M*. Means of cor-



(20)

recting for orientation are provided by Koshland.[5] The value of $k_{intra/inter}$ for k(3,6-endoxo-Δ^4-tetrahydro-

---

(31) T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, **87**, 4846, 4851 (1965).

(32) T. C. Bruice and S. J. Benkovic, *ibid.*, **85**, 1 (1963).

(33) J. Koskilkallio, *Suomen Kemistilehti.*, *B*, **29**, 5 (1956).

(34) T. Higuchi, T. Miki, A. C. Shah, and A. K. Herd, *J. Amer. Chem. Soc.*, **85**, 3655 (1963).

(35) T. Higuchi, L. Eberson, and D. J. McRae, *ibid.*, **89**, 3001 (1967).

(36) T. Higuchi and G. Flynn, unpublished work.

(37) L. Eberson, *Acta Chem. Scand.*, **18**, 1276 (1964).

(38) W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *J. Amer. Chem. Soc.*, **88**, 4464 (1966).

Table VI. Hydrolysis of Anhydrides[a]

	ΔF_H, kcal	Log (k_{-1}/k_1)	k_{-1}, sec^{-1}	$k_{\text{intra}}{}^{b}/k_{\text{inter}}$, M	$k_{\text{intra}}{}^{c}/k_{\text{inter}}$, M
Acetate[d]	−15.7	11.50	2.8×10^{-3}		
Succinate[e]	−8.3	6.00	2.6×10^{-3}	2.9×10^{5}	1.6×10^{5}
Phthalate[f]		3.66	8.9×10^{-3}[g]	2.2×10^{8}	4.8×10^{6}

[a] See eq 15. [b] From eq 16. [c] From Figure 2, by extrapolation. [d] Values of ΔF_H, log k_{-1}/k_1, and k_{-1} from ref 38. [e] Values of ΔF_H, log k_{-1}/k_1, and k_{-1} from ref 34. [f] Values of ΔF_H, log k_{-1}/k_1, and k_{-1} from ref 36. [g] This study.

phthalate)/k(acetate) = 1.3×10^{8} M. It is inconceivable that in the $[AB_{\text{pair}}] = [CH_3COO^-$ phenyl acetate$]$ only one $[AB_{\text{pair}}]$ out of each $\sim 10^{5}$ $[AB_{\text{pairs}}]$ would be properly aligned for reaction. Orientation factors of this magnitude would appear to be quite unreasonable. Thus, orientation factors in gas phase reactions are generally assumed to range from unity down to 10^{-1} to 10^{-2} The assumption of eq 18 is equivalent to the assumption of eq 21 which states that the equilibrium constant for formation of intimate

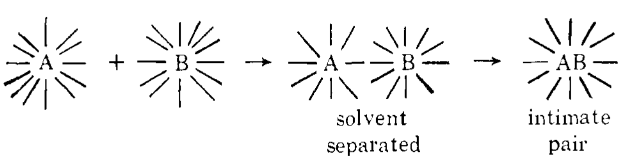
$$K = \frac{1}{4.6} = \frac{[AB_{\text{pairs}}]}{[A][B]} \tag{21}$$

pairs of reactants in solution is always about 0.2 M^{-1}. The fallacy of (21) is easily appreciated from the experimental fact that the reaction of acetate ions with phenyl acetates does not show a saturation phenomenon.

Benson[40] provides the following equation (22) for the value of K (in units of moles per liter) where r_{AB} is the

$$K = 8 r_{AB}{}^{3} N_{AV} e^{-W_{ABS}/RT} \tag{22}$$

average distance between nearest neighbors A and B and N_{AV} is Avogadro's number. The term W_{ABS} is the energy of formation of an AB_{pair} in solvent S while the collective preexponential factor may be interpreted as the entropy change in shifting 1 mole of A from a volume of 1.0 l. to the nearest neighbor volume around B. For a typical value of r_{AB} = 4 Å, W_{ABS} would have to equal about +7 kcal/mol^{-1} for $k_{\text{intra}}/k_{\text{inter}}$ to equal 10^{5} M. Therefore, the concentration of an acetate–ester$_{\text{pair}}$ in the bimolecular reaction would be infinitesimal. In applying eq 22 to the comparison of inter- and intramolecular reactions one ignores activity coefficients and restrictions of motions in the intramolecular AB_{pair}. Employing concentrations rather than activities is a tacit assumption that the molecules of A and B find no other differences in their environments on becoming an AB_{pair} other than their interaction.[40] Restriction of motion of A and B in the intramolecular (covalently approximated) AB_{pair} likely accounts for a fair portion of the value of $k_{\text{intra}}/k_{\text{inter}}$. In any case, the necessity of forming an intimate AB_{pair} from a solvent-separated AB_{pair} (eq 23), as shown experimentally in this study, is of little energetic consequence in the carboxyl anion nucleophilic attack upon phenyl esters.



(23)

In conclusion, it should be reiterated that the proximity effect may, in certain instances, be of great importance in determining the facility of product formation from enzyme–substrate complexes. It is of little consequence whether A and B are juxtaposed *via* covalent linkage (as in the intramolecular studies dealt with herein) or by noncovalent forces as in a productive ES complex. The same restrictions of movement of A with respect to B, etc., may be obtained in either case.

Acknowledgment. This study was supported by a grant from the National Institutes of Health.

---

(39) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, New York, N.Y., 1965, p 62.

(40) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter XV.