stirring. The reaction mixture was quenched by the addition of 5–10 ml. of methanol and after dilution with ether, washing and drying of the ether layer and evaporation of the solvent the residue was distilled through a 5-in. Vigreux column and the fraction b.p. 50–51° (1.8 mm.) collected. Preparations of the compound are summarized in Table IV.

Optically Active *sec*-Butyllithium.—2-Octyllithium (0.058 mole, 73 ml. of 0.802 *N* solution) in pentane was added over 8 min. from a hypodermic syringe to 9.16 g. (0.029 mole) of di-*sec*-butylmercury ((−)(±)-X), $[\alpha]^{21}D$ −12.6°, in 200 ml. of pentane while stirring at −7 to −5°. The solution was then stirred at −10 to −7° for 22 min. and added to Dry Ice over 12 min. After warming to room temperature the mixture was diluted with an equal volume of ether and extracted with 5% aqueous sodium hydroxide and then with water. Acidification of the aqueous extracts with sulfuric acid (congo red) and extraction with ether gave after drying and evaporation of the ether 8.46 g. of oil with $\alpha^{21}D$ − 0.06 ± 0.04° (0.5-dm. tube, neat). Gas phase chromatography at 175° on a didecyl phthalate column in a Perkin–Elmer Vapor Fractometer, model 154B, showed the presence of 2-methylbutyric acid (4.7 mole %) and 2-methylcaprylic acid (95.3 mole %). Distillation at 1.6 mm. gave 0.22 g. of 2-methylbutyric acid, b.p. 45–50°, $\alpha^{21}D$ −1.30 ± 0.03°; 0.60 g. of an intermediate fraction, b.p. 50–90°, $\alpha^{21}D$ −0.19 ± 0.03°; and 6.61 g. of 2-methylcaprylic acid, b.p. 90–95° $\alpha^{21}D$ −0101 ± 0.03°. The vapor chromatograph of the 2-methylbutyric acid fraction showed that it was contaminated by about 5% of a mixture of 2-octanol and 2-methylcaprylic acid. It was purified further by extraction of an aqueous solution of its sodium salt with ether. The resulting acid showed the presence of no impurities on gas phase chromatography and had $\alpha^{22}D$ −1.32 ±0.03° (0.5-dm., neat) and $[\alpha]^{22}D$ −2.84° (d^{22} 0.931). Distillation of the neutral portion of the reaction mixture after drying over magnesium sulfate gave 7.47 g. (82%) of di-*sec*-butylmercury, $\alpha^{22}D$ −10.82 ± 0.03° (0.5-dm., neat), $[\alpha]^{22}D$ −12.3°. This and other results obtained similarly are summarized in Table III.

***sec*-Butyl-α-naphthylmercury.**—α-Naphthylmagnesium bromide, made from 29.6 g. (0.143 mole) of α-naphthyl bromide and 6.58 g. (0.271 g.-atom) of magnesium turnings in 170 ml. of ether and 30 ml. of benzene, was added over 15 min. to a solution of 40.0 g. (0.119 mole) of *sec*-butylmercuric bromide in 100 ml. of ether. After 1 hr. under reflux the mixture was poured into 400 ml. of ice-water, the ether layer washed with water, dried over magnesium sulfate and the ether distilled. The remaining orange colored oil was chromatographed on 250 g. of alumina. Elution with hexane gave 31.4 g. of a yellow oil and benzene–ether mixtures eluted 9.6 g. (24% recovery), m.p. 41–43°; mixed with *sec*-butylmercuric bromide, m.p. 41–43°. From the oil 9.5 g. of naphthalene, m.p. 74–79°, was sublimed during 15 hours at 1 mm. as the material was slowly heated to 140°. The remaining oil (21.9 g., 48%) crystallized on cooling; m.p. 39–42°. Recrystallization from 95% ethanol gave 17.8 g. (39%) of white platelets, m.p. 42–43°. A portion recrystallized from methanol had m.p. 42–43°. A similar product could also be obtained from the reaction of α-naphthyllithium and *sec*-butylmagnesium bromide.

Anal. Calcd. for $C_{14}H_{16}Hg$: C, 43.7; H, 4.2. Found: C, 43.7; H, 4.3.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY, ITHACA, N. Y.]

Hydroxyl Group Catalysis. III.[1] The Nature of Neighboring Hydroxyl Group Assistance in the Alkaline Hydrolysis of the Ester Bond

BY THOMAS C. BRUICE AND THOMAS H. FIFE[2]

RECEIVED NOVEMBER 22, 1961

The extent and nature of internal hydrogen bonding, the rates of alkaline hydrolysis and associated activation parameters as well as the solvent deuterium isotope effects on the rates of alkaline hydrolysis were determined for a number of cyclopentane and norbornane acetates and diol monoacetates. The neighboring hydroxyl group in all sterically favorable instances assists alkaline hydrolysis. The assistance is not associated with a deuterium solvent kinetic isotope effect divergent from that for the specific base-catalyzed hydrolysis of an aliphatic ester. Furthermore, there is no clear-cut alteration of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ that can be associated with neighboring hydroxyl group facilitation. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the alkaline hydrolysis of the esters studied exhibit compensation and the isokinetic temperature is −17°. Arguments are presented, on the basis of steric, ground state hydrogen bonding and kinetic considerations, that the most likely mechanism for neighboring hydroxyl group facilitation involves internal solvation of the transition state for attack of OH^- at the ester carbonyl group.

Introduction

The purpose of the present investigation has been to determine the nature of the neighboring aliphatic hydroxyl group facilitation of OH^- catalyzed ester hydrolysis. Possibly the first report of hydroxyl group facilitation of nucleophilic displacement at the ester bond was that of Henbest and Lovell[3] who studied the solvolysis of 3-acetoxy-5-hydroxy steroids of the cholestane and coprostane series in aqueous methanolic potassium carbonate solution (20°). They found that the axial esters were, unexpectedly,[4] hydrolyzed faster than the equatorial esters if *cis* to the 5-hydroxyl group. Similar facilitation of the base-catalyzed methanolysis of the C_7- and C_{16}-O-acetates of germine by hydroxyl groups at C_{14} and C_{20} and the C_{16}-O-acetate of cevine by a hydroxyl group at C_{20} was reported by Kupchan, Johnson and co-workers.[5-7] These studies, representing apparent cases of neighboring hydroxyl group facilitation in cyclohexane-1,3-diol monoacetates, were of a qualitative nature and do not allow the calculation of rate constants. In a preliminary communication, Kupchan, Slade and Young[8] describe studies on the hydrolysis of cholestane-3β,4β,-diol monoacetates. The neighboring hydroxyl group was reported to increase the rate of ester hydrolysis in these vicinal cyclohexanediol monoacetates by 8 to 9 times over that noted in corresponding cyclohexane monoacetates (30°). Zachau and Karau[9] investigated the rates of alkaline hydrolysis of monoglycyl derivatives of *cis*-

(1) Presented in part as a communication in *Tetrahedron Letters*, No. **8**, 263 (1961).

(2) Research Fellow, Department of Chemistry, Cornell University.

(3) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

(4) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(5) S. M. Kupchan, W. S. Johnson and S. Rajagopalan, *Tetrahedron*, **7**, 47 (1959).

(6) S. M. Kupchan and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 3864 (1956).

(7) S. M. Kupchan and C. R. Narayanan, *ibid.*, **81**, 1913 (1959).

(8) S. M. Kupchan, P. Slade and R. J. Young, *Tetrahedron Letters* No. **24**, 22 (1960).

(9) H. G. Zachau and W. Karau, *Ber.*, **93**, 1830 (1960).

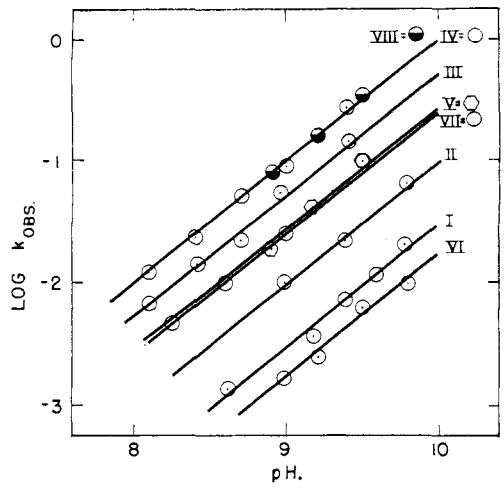
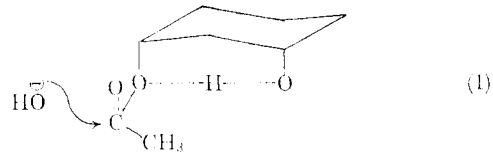


Fig. 1.—Plots of the logarithm of the observed first-order rate constants (log k_{obs}) for hydrolysis obtained at 78°; μ = 1.0 M *vs.* *p*H for various esters studied.

and *trans*-tetrahydrofuran-3,4-diols as well as 3-hydroxytetrahydrofuran. The *trans*-hydroxyl group was found to increase the rate of alkaline hydrolysis 2.3 times, whereas the *cis*-hydroxyl group provided a 6.7-fold increase in rate (30°). The neighboring hydroxyl group facilitation has also been studied in the case of the saponification of methyl 2-hydroxycyclohexanecarboxylates. However, because of the complexity of the esters employed (yohimbine, corynanthine, methyl reserpate, etc.)[10] little of a quantitative nature can be made of these results.

On the basis of qualitative infrared analysis, Henbest and Lovell[3] favored a hydrogen bonded structure, involving the ether oxygen, to account for the hydroxyl group assistance for what has now been called the Henbest–Kupchan effect.[11] Transition states involving a like disposition of



(I)

atoms have been favored by Kupchan and co-workers[5-8] for hydroxyl group facilitation in 1,3-diol monoacetates, whereas Zachau and Karau[9] have proposed the facilitation in vicinal 1,2-diol monoglycinates to be due to hydrogen bonding to the ester carbonyl oxygen. Johnson, *et al.*,[11] have substantiated the infrared results of Henbest and Lovell in a recent study involving various polycyclic 1,2-diol monoacetates, but point out that though hydrogen bonding in the ground state may be determined *via* infrared analysis to be to the ether oxygen the kinetically important species could be that with hydrogen bonding to the carbonyl group.

A not completely dissimilar case of apparent intramolecular general acid catalysis of C–O bond scission by an aliphatic hydroxyl group was proposed, at an early date, by Woodward[12] to account for the ready β-elimination of glycolic acid from strychninolic acid by 1.0 N NaOH at room temperature.

(10) M. J. Allen, *J. Chem. Soc.*, 4904 (1960); 4252 (1961).

(11) R. West, J. J. Korst and W. S. Johnson, *J. Org. Chem.*, **25**, 1976 (1960).

Results

In Fig. 1 there are presented the partial *p*H–rate profiles for the hydrolysis of the esters I-VIII at 78° in aqueous 1.0 N KCl. In the *p*H range investigated, the observed *pseudo*-first-order rates of hydrolysis (k_{obs}) are a linear function of hydroxide ion concentration. In Fig. 2 are plotted the values of log k_{obs} (determined at a constant *p*H of 9.5) *vs.* $1/T$ for various esters. From the data of Figs. 1 and 2 the values of the rate constants for alkaline hydrolysis, k_{OH}, at 78° as well as the activation parameters have been calculated. The various constants are recorded in Table I. The activation parameters have been calculated from the true value of k_{OH} (*i.e.*, $k_{obs}K_w/a_H$) and do not contain the ΔH of ionization of water. Because of the solubility characteristics of the ester VI its activation parameters were determined in 50–50 propanol–H_2O (v./v) at an ionic strength of 0.05 M with KCl. For comparison, the activation parameters of I were also determined in propanol–water. Because the value of K_w is not known in this mixed solvent the activation parameters were simply calculated from the observed pseudo-first-order rate constant of hydrolysis at a *p*H-meter reading of 9.7. The values so determined for I and VI are included in Table I in the column labeled (PW). They may not be compared to the values determined in water because of the method of calculation, but do serve to show that the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for the hydrolysis of I and VI are comparable.

The positions of the infrared absorption maximum of the ester carbonyl group (taken at concentrations of 0.001 M in CCl_4 using 1-cm. cells) as well as the O–H stretching maximum (at concentrations of 0.005 M in CCl_4 using 1-cm. cells) for the esters I–VII were determined and are recorded in Table II.

Discussion

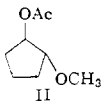
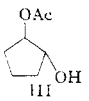
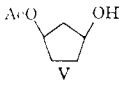
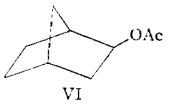
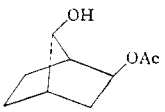
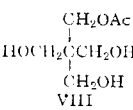
Hydrogen Bonding.—Inspection of the position of the carbonyl and O–H absorption frequencies of the esters studied (Table II) reveals some internal hydrogen bonding by all the esters possessing neighboring hydroxyl groups except V. Considering the infrared data for hydrogen bonding we may conclude: (a) In the cyclopentane series, the electronic effect of a vicinal *trans*-hydroxyl group on $\nu_{C=O}$ is negligible (I *vs.* II). (b) A vicinal *trans*-hydroxyl group decreases the value of $\nu_{C=O}$ by 9 cm.$^{-1}$ and the hydroxyl stretching frequency is displaced to a lower value by 73 cm.$^{-1}$ from the normal OH stretching frequency of 3620 cm.$^{-1}$ (III). A very weak OH band at 3620 cm.$^{-1}$ and a strong band at 3547 cm.$^{-1}$ can be observed for III, showing the hydroxyl group to be mainly in an internally hydrogen bonded form. From the direction of the carbonyl shift[3] and the *trans* configuration of ester and –OH group, the hydrogen bond-

(12) R. B. Woodward, quoted by Holmes in "The Alkaloids," Academic Press, Inc., New York, N. Y., 1952, Vol. II, p. 517.

TABLE I

RATES OF HYDROLYSIS AND VALUES OF $\Delta H^{\ddagger}$ AND $T\Delta S^{\ddagger}$ AT 78°

Solv. H_2O; $\mu = 1.0$ M with KCl[a]

Ester	k_{OH}, l. mole^{-1} min.$^{-1}$	k_{rel}	$\Delta H^{\ddagger}$ kcal. mole^{-1} H_2O	$\Delta H^{\ddagger}$ kcal. mole^{-1} PW	$T\Delta S^{\ddagger}$ kcal. mole^{-1} H_2O	$T\Delta S^{\ddagger}$ kcal. mole^{-1} PW
 I	9.3	1.0	11.3	23.9	−10.7	−3.79
 II	31.6	3.4	11.9		− 9.2	
 III	174	18.7	13.6		− 6.28	
 IV	309	33.2	16.8		− 2.70	
 V	85.1	9.2	10.9		− 9.51	
 VI	5.0	1.0		23.9		−3.9
 VII	79.4	15.9	10.7		− 9.79	
 VIII	316.2		11.2		− 6.56	

[a] Certain of the kinetic constants contained herein differ from those reported in our preliminary communication. Revisions of data are based on rate measurements performed over a greater range of temperature and pH.

ing must be to ester carbonyl oxygen. (c) The hydroxyl group when *vic-cis* is mostly non-hydrogen bonded, since the major O–H absorbance is at the normal position of 3618 cm.$^{-1}$ (IV). An O–H absorbance (v.w.) at 3543 cm.$^{-1}$ indicates the presence of some hydrogen bonded species in IV and from the shift of the carbonyl frequency to higher values the hydrogen bond must involve the ether oxygen of the ester bond[3,11]. (d) Unlike the *cis*- and *trans-vic* diol monoacetate of cyclopentane the *cis*-1,3-diol monoacetate V exhibits no measurable internal hydrogen bonding. (e) Inspection of the positions of O–H absorbance in VII indicates partial internal hydrogen bonding and from the positive shift of the carbonyl absorption, the hydrogen bonding involves the ether oxygen of the ester bond.[3,11]

A summary of the nature and extent of internal hydrogen bonding of I-VII is included in Table II. In water at 78° the extent of hydrogen bonding (if any) must be considerably less than that determined in CCl_4 at 25° and we may therefore

TABLE II

CARBONYL AND HYDROXYL GROUP ABSORPTION IN THE INFRARED AS A MEASURE OF HYDROGEN BONDING[a]

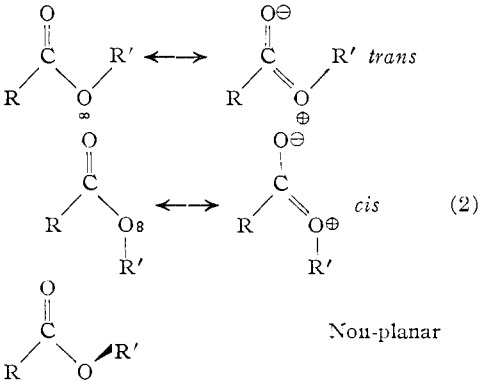
Solv. CCl_4; $T = 25°$

Ester	>C=O	Absorption max. cm.$^{-1}$ —OH	H-type bond	Extent
I	1740	.....	.....	
II	1742	.....	.....	
III	1731	3620(w) 3547(broad)	—O—H···O=C<	Major
IV	1747	3618(s) 3543(v.w.)	—O—H···O—CO—	Minor
V	1739	3620(s)	.....	None
VI	1738	.....	.....	None
VII	1748	3618(s) 3540(w)	—O—H···—OCO—	Minor

[a] Only one band was observed for the carbonyl stretching frequency of VII. Since we are working with a mixture of isomers, however (see Experimental), presumably more than one band is present. The direction of the shift of the carbonyl band could only be due to the internally hydrogen bonded isomer corresponding to structure VII since any other isomer present would not be hydrogen bonded and would therefore have a normal carbonyl frequency.

consider the extent of internal hydrogen bonding recorded in Table II to be the upper limit under the conditions of solvolysis.

The results of the infrared study are in complete agreement with expectations. The ester bond can exist in either the planar *cis* and *trans* conformations or in non-planar conformations. Resonance in the ester group is possible in the planar *cis* or *trans* forms but becomes drastically reduced as planarity is lost. Because of the electrostatic re-



(2)

pulsion of filled orbitals,[13] the planar *trans* conformation is much more stable than the planar *cis*.[14] Therefore, in order to have hydrogen bonding of the type dealt with herein, it is essential to have the ester bond in the planar *trans* conformation. With this limitation, hydrogen bonding can only be to the ether oxygen in the case of the esters IV and VII. Thus, from examination of Stuart Briegleb models it becomes obvious that hydrogen bonding to the carbonyl oxygen in the esters IV and VII would require the ester group to be in a non-planar conformation with the prohibitive expenditure of much of its resonance energy (15–18 kcal./mole).[15]

(13) D. Cooke, *J. Am. Chem. Soc.*, **80**, 49 (1958).

(14) R. J. B. Marsden and L. E. Sutton, *J. Chem. Soc.*, 1383 (1936).

(15) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 99.

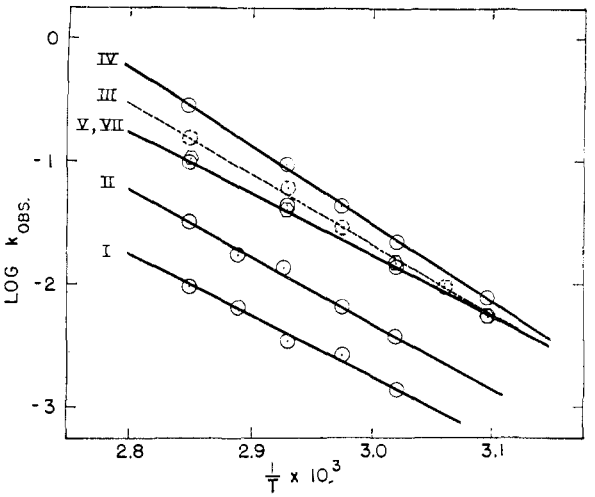


Fig 2.—Plots of the logarithm of the observed first-order rate constant (min.$^{-1}$) for hydroxide ion catalysis of the esters I through V and VII. The values of k_{obs} were obtained at constant pH values of 9.5 for I, II, V and VII and 9.4 for III and IV. ⬡ = V, ◯ = III.

For the ester III, on the other hand, bonding to the ether oxygen is impossible because of the fixed *trans* disposition of acetyl and hydroxyl groups. Inspection of Stuart-Briegleb models reveals, however, that hydrogen bonding to the ester carbonyl would be greatly favored because the ester group would, in such a case, have the energetically favored *trans* planar conformation (Fig. 3). In the case of the *cis*-1,3-diol monoacetate V internal hydrogen bonding to the ether oxygen is sterically possible as shown by the internal hydrogen bonding exhibited by the diol. Hydrogen bonding of the hydroxyl and ester carbonyl groups is also sterically possible as seen by examination of Stuart-Briegleb models. The order of internal hydrogen bonding in the cyclopentane diol monoacetates is then III > IV > V = O. The lack of hydrogen bond in V is in sharp contrast to the strong hydrogen bond seen in diaxial 1,3-diol monoacetates of cyclohexane.[3,11]

Rates of Alkaline Hydrolysis.—The increase in rate of alkaline hydrolysis (78°) of cyclopentyl acetates of threefold obtained by substituting a methoxy group alpha to the acetoxy group (I *vs.* II) is about that expected on the basis of the inductive effect of the methoxy group.[16a,b] However, the increase in rate of alkaline hydrolysis (78°) of cyclopentyl or *exo*-2-norbornyl acetates on the substitution of an hydroxyl group into the α- or β-position (III, IV, V *vs.* I and VII *vs.* VI) is greater than could be explained on the basis of an inductive effect.[16] The alkaline hydrolysis of pentaerythritol acetate (VIII), though characterized by a rate constant greater than those for the other esters investigated in this study, owes much of the ease of its hydrolysis to the lower pK_a' of pentaerythritol.[17]

(16) (a) "Tables of the Chemical Kinetics of Homogeneous Reactions," Circular 510 National Bureau of Standards (1951), Tables 212, 441; (b) R. W. Taft, in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 556.

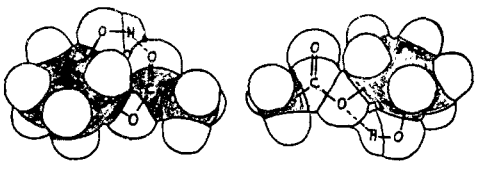


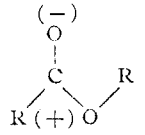
Fig. 3.—The *trans*-planar nature of the ester bond in the —O---H---O=C< and —O---H---O—CO— internally hydrogen bonded structures of the *trans*- and *cis*-monacetyl cyclopentane-1,2-diols, respectively.

In the alkaline hydrolysis of esters (2) the rate-determining step is the nucleophilic attack of $OH^{\ominus}$

$$OH^{\ominus} + R_1COR_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R_1C(O^{\ominus})(OH)R_2 \xrightarrow{k_3} RCO^{\oplus} + HOR \quad (2)$$

(k_1)[18] and any large rate enhancements must be ascribed to an increase in this rate constant.[19] Since the mechanism of Henbest and Lovell postulates assistance to the leaving group (k_3) as a rationale to the Henbest-Kupchan effect, it is most likely incorrect. Also, the extent of facilitation is not greatly dependent on the type (*i.e.*, to the ether or carbonyl oxygen) of possible internal hydrogen bonding nor its extent, and the facilitation in esters III and V cannot be explained by the Henbest-Lovell mechanism (1).

Other possible rationales for the Henbest-Kupchan effect follow. Facilitation could be due to hydrogen bonding to either the ether or carbonyl oxygens in the ground state. This would increase the positive character of the carbonyl carbon and therefore also increase k_1. This explanation must also be discarded since the proposed effect should be much more important at the carbonyl oxygen where the hydrogen bond would favor the dipolar resonance form of the esters (3). However, the *trans*-



(3)

vic-diol monoacetate III exhibits strong hydrogen bonding between carbonyl and hydroxyl groups (Table II) but less facilitation than the *cis* isomer IV which exhibits weak hydrogen bonding between the hydroxyl group and the ether oxygen. Of greater significance is the fact that the ester V exhibits no measurable internal hydrogen bonding, but its hydrolysis is facilitated.

The facilitation might be assumed to be associated with general base catalysis by the neighboring hydroxyl group (4). Under conditions where $OD^{\ominus} = OH^{\ominus}$ the ratio of k^H/k^D can be calculated for this mechanism to be[20,21]

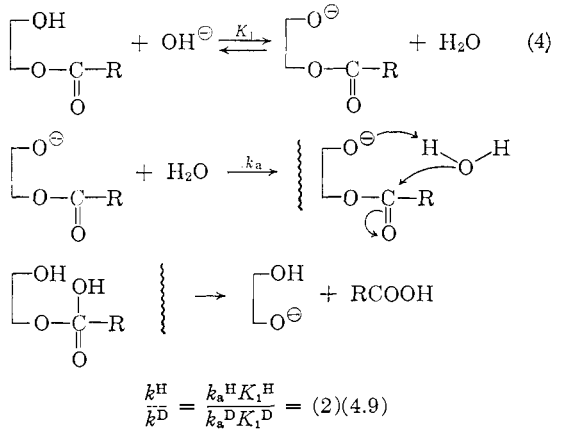
(17) T. C. Bruice, T. H. Fife, J. J. Bruno and N. Brandon, *Biochemistry*, 1, 7 (1962).

(18) M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).

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

(20) The ratio of K_1^H/K_1^D was approximated from the data presented by R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 188.

(21) F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).

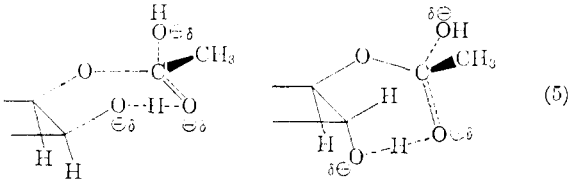


(4)

$$\frac{k^H}{k^D} = \frac{k_a{}^H K_1{}^H}{k_a{}^D K_1{}^D} = (2)(4.9)$$

For the general base-catalyzed mechanism a kinetic solvent isotope ratio greater than 2.0 would clearly be anticipated. In Table III the values of k^H/k^D for the hydrolysis of the esters III, IV, V, VIII as well as several normal aliphatic esters are recorded. In all cases the ratios of k^H/k^D are between 0.4 to 0.2 (78°, 95°). These values compare most favorably to those expected of the normal $B_{AC}2$ specific base-catalyzed hydrolysis of an ester.[21] We may, therefore, rule out the possible involvement of general base catalysis as the basis of the Henbest–Kupchan effect.

An alternate hydrogen bonding mechanism would involve a hydrogen bond in the transition state rather than the ground state. If the transition state resembled more closely the tetrahedral intermediate, then hydrogen bonding to the carbonyl oxygen would be possible for both the *cis*- and *trans*-esters of cyclopentane-1,2-diol monoacetate (III and IV) as well as the esters V, VII and VIII (5). The kinetic solvent isotope effect



(5)

ratio for this mechanism would be expected, *a priori* to be about 0.5 as a result of the involvement of simultaneous specific base-general acid catalysis. The data of Table III is not sufficient to differentiate between a simple specific base mechanism and a specific base–general acid catalysis. The specific base-general acid mechanism fits well with the known facts concerning the Henbest–Kupchan effect. Thus, the most reasonable mechanism for the Henbest–Kupchan effect is that in which a neighboring hydroxyl group solvates the transition state for nucleophilic attack of the hydroxyl ion on the ester carbonyl group.

The possibility exists that the internal solvation of the critical transition state by the neighboring hydroxy group is due to more subtle factors which we may label, for lack of better terms, as a microscopic solvent change. Thus, the proximity of the hydroxyl group to the ester bond may change the microscopic medium surrounding the ester bond (*i.e.*, by the binding and/or orienting of water

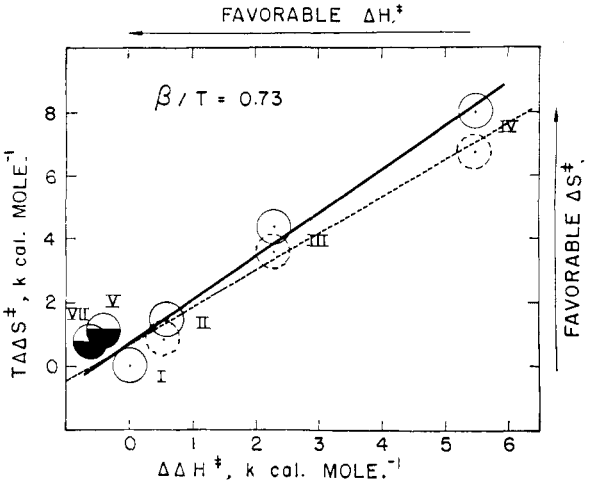


Fig. 4.—Plot of $\Delta\Delta H^{\ddagger}$ *vs.* $T\Delta\Delta S^{\ddagger}$ at 78° for the esters I through V and VII. Cyclopentylacetate was employed as the standard. The dashed line represents the same plot derived from data obtained by extrapolation of Fig. 2 to 25° and calculation of the activation parameters at this temperature. The circles were drawn with a radius of ±250 cal./mole in $\Delta\Delta H^{\ddagger}$.

molecules). It may be noted that for the hydrolysis of ethyl acetate, transfer from water to ethanol-water (μ = 0.2 *M*, *D* = 50)[22] is accompanied by a rate increase (78°) and large positive changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. This characteristic is shared by the esters III and IV as compared to I. Theoretical interpretations of what might be expected of a microscopic solvent change are made most difficult since the rates of ionic reactions are not correlatable to the dielectric constant of the media,[22,23] alterations in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ brought about by macroscopic changes in solvent composition are not at all understood,[24] and in particular for the alkaline hydrolysis of esters the alteration of $\Delta F^{\ddagger}$ with solvent composition is not[25] in accord with the Hughes–Ingold theory of solvent action[26] as developed from the solvolysis of alkyl halides.

The tendency for $\Delta H^{\ddagger}$ to change in such a manner as to minimize any alteration in $\Delta F^{\ddagger}$ brought about by changes in $\Delta S^{\ddagger}$ (compensation) is a common phenomenon.[27,28] From the isokinetic equation of Leffler[27]

$$\Delta H^{\ddagger} = \Delta H_0{}^{\ddagger} + \beta\Delta S^{\ddagger} \qquad (6)$$

one may readily derive

$$\frac{\Delta\Delta H^{\ddagger}}{T\Delta\Delta S^{\ddagger}} = \frac{\beta}{T} \text{ or } \frac{\Delta\Delta F^{\ddagger}}{T\Delta\Delta S^{\ddagger}} = \frac{\beta}{T} - 1 \qquad (7)$$

The term β/T may be called the compensation

(22) The activation parameters for ethyl acetate hydrolysis were extrapolated to 78° from the kinetic data of J. E. Potts and E. S. Amis, *J. Am. Chem. Soc.*, **71**, 2112 (1949).

(23) E. S. Amis and G. Jaffe, *J. Chem. Phys.*, **10**, 598 (1942).

(24) See, for example, S. Winstein and A. H. Fainberg, *J. Am. Chem. Soc.*, **79**, 5937 (1957).

(25) M. L. Bender and W. A. Glasson, *ibid.*, **81**, 1590 (1959).

(26) E. C. Hughes and C. K. Ingold, *J. Chem. Soc.*, 252 (1935); C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 345.

(27) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

(28) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 508.

TABLE III

KINETIC DEUTERIUM ISOTOPE EFFECTS FOR THE ALKALINE HYDROLYSIS OF ACETYL ESTERS

Ester	T, °C.	k^H/k^D[a]
III	78	0.4[b]
IV	78	.4[b]
V	78	.3[b]
VIII	78	.3[b]
	95	.4[c]
$CHCl_2CH_2OCOCH_3$	95	.2[c]
$CH_3OCH_2CH_2OCOCH_3$	95	.2[c]

[a] Based on the average of at least three rate determinations in H_2O and three rate determinations in D_2O. [b] This study. [c] From unpublished data of J. J. Bruno and T. C. Bruice.

factor and when $\beta/T < 1.0$, $T\Delta\Delta S^{\ddagger}$ determines the alteration of $\Delta F^{\ddagger}$, etc. In Fig. 4, $\Delta\Delta H^{\ddagger}$ has been plotted against $T\Delta\Delta S^{\ddagger}$ (78°) for the esters I, II, III, IV, V and VII with I as standard. From inspection of Fig. 4 it is obvious that the extent of compensation ($\beta/T = 0.73$) is the same for neighboring hydrogen, methoxyl or hydroxyl groups.[28a] This strongly suggests that the nature of the compensation is not related to the neighboring hydroxyl group but only to the $B_{AC}2$ mechanism (78°) for the hydrolysis of these aliphatic ester bonds. Because the standard ester, cyclopentyl acetate, exhibits a negative departure from the compensation plot of Fig. 4 all the esters listed owe their greater rates of hydrolysis to a favorable value of $T\Delta S^{\ddagger}$ while the esters II, III and IV possess unfavorable values of $\Delta H^{\ddagger}$ (compared to I) and the esters V and VII favorable values of $\Delta H^{\ddagger}$. As in all cases of reactions exhibiting compensation the extent of facilitation (cyclopentyl acetate as standard) is temperature dependent and at 25° the facilitation by a vicinal hydroxyl group is only ~4-fold, whereas for a β-substituted hydroxyl group the facilitation is essentially temperature independent, the change of relative rates in going from 78° to 25° being due to an alteration of β/T from 0.73 to 0.58.

Experimental

Materials. Cyclopentyl Acetate.—To cyclopentanol (25.0 g., 0.29 mole) was added an excess of acetic anhydride containing 1 drop of concentrated sulfuric acid per 10 ml. of solution. The mixture was cooled and then allowed to remain at room temperature for 24 hr. The mixture was poured into water and extracted with three 100-ml. portions of ether. The combined ether extracts were washed with water, aqueous sodium bicarbonate and water and were dried over anhydrous sodium sulfate. The ether was evaporated and the liquid residue distilled at atmospheric pressure. There was obtained 26 g. (71%) of cyclopentyl-acetate, b.p. 151° (760 mm.), $n^{25.2}D$ 1.4282 [lit.[29] b.p. 50° (12mm.), $n^{25}D$ 1.4288].

cis-**2-Hydroxycyclopentyl acetate** was prepared according to the procedure of Owen and Smith[30]; b.p. 104–106° (20 mm.), $n^{25}D$ 1.4569 [lit. b.p. 104–106 (20 mm.), $n^{17}D$ 1.4576]. The same compound was also prepared by monoacetylation of *cis*-1,2-cyclopentanediol[30] (3.0 g., 0.029 mole) with acetyl chloride (2.27 g., 0.29 mole) using chloroform as solvent. The acetyl chloride was added dropwise with very rapid stirring. The product was purified by distillation and chromatography on silica gel.

trans-**2-Hydroxycyclopentyl acetate** was prepared from cyclopentene oxide and acetic acid according to the procedure of Owen and Smith[30]; b.p. 95–97° (20 mm.), $n^{25}D$ 1.4539 [lit. b.p. 93–97° (20 mm.), $n^{20}D$ 1.4553]. The product was further purified by chromatography on silica gel. The same compound was also prepared by monoacetylation of *trans*-1,2-cyclopentanediol[30] (4.0 g. 0.039 mole) with acetyl chloride (3.0 g., 0.039 mole) using chloroform as the solvent. The acetyl chloride was added slowly dropwise with very rapid stirring.

trans-**2-Methoxycyclopentanol.**—Cyclopentene oxide (9.0 g., 0.146 mole) was added to a solution of 75 ml. of methanol in which 1.7 g. (0.073 g. atom) of sodium had been dissolved. The mixture was refluxed for 4 hours. About one-half of the methanol was distilled through a Vigreux column and the remaining solution was added to an equal volume of water and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate. The ether was evaporated and the product was distilled. In this manner the product was obtained in 29.2% (4.9 g.) yield; b.p. 96° (27 mm.), $n^{25.2}D$ 1.4513 [lit.[31] b.p. 175° (760 mm.), $n^{20}D$ 1.4534].

trans-**2-Methoxycyclopentyl Acetate.**—*trans*-2-Methoxycyclopentanol (4.5 g., 0.039 mole) was dissolved in a mixture of 20 ml. of acetic anhydride and 80 ml. of glacial acetic acid in a 250-ml. volumetric flask and heated in a 75° bath for 12 hours. The solution was diluted with 5 volumes of water and extracted four times with 100-ml. portions of petroleum ether (b.p. 30–60°). The petroleum ether extract was washed with water, aqueous sodium bicarbonate and water and was dried over anhydrous sodium sulfate. The solvent was removed by flash evaporation and the residue distilled. There was obtained 4.0 g. (64.9%) of product, b.p. 101° (44 mm.), $n^{25}D$ 1.4337.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.76; H, 8.86. Found: C, 60.86; H, 9.04.

exo-**Norborneol** was prepared according to the procedure of Schmerling[32]; m.p. 126° (lit. m.p. 126°).

exo-**Norbornyl acetate** was prepared by treatment of *exo*-norborneol with acetic anhydride and acetic acid as described by Winstein and Trifan.[33] The product boiled at 91° (24 mm.), $n^{25}D$ 1.4568 (lit. $n^{25}D$ 1.4565).

exo-**2-Acetoxy-*syn*-7-hydroxynorbornane** (VII) was prepared by reaction of norbornylene with peracetic acid as adapted from literature procedures.[34] In a 1-l. three-necked flask equipped with a stirrer and thermometer was placed 250 ml. of glacial acetic acid, 28 ml. of 30% hydrogen peroxide and 3 drops of concd. sulfuric acid. Norbornylene (28.2 g., 0.30 mole) was added in small portions over a period of 1 hour. The temperature of the reaction was not allowed to exceed 40°. The reaction was stirred at 40° for 1 hour and then allowed to stand overnight at room temperature. The acetic acid was removed by flash evaporation and the residue taken up in ether and washed with aqueous sodium bicarbonate and water. The ether was flash evaporated and the residue distilled. The portion boiling at 114° (4.2 mm.) amounted to 9.0 g. (26.4%) and was col-

(28a) The values of β have been suggested to be employable to ascertain changes in mechanism (see ref. 27). However, the constant does not appear to be sensitive to the presence or absence of a few hydrogen ions in the transition state (the acid and alkaline hydrolysis of alkylacetates in 62% acetone have a $\beta/T = 0.99 \pm 0.03$ at $T = 7°$ and 47° as calculated from the data of ref. 27). Also, β/T is apparently not sensitive to steric factors (for the esterification of *o,m,p*-substituted benzoic acids in methanol $\beta/T = 0.839$ at $T = 37°$ as calculated from the data of ref. 27).

(29) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).

(30) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4026 (1952).

(31) M. Mousseron and R. Granger, *Compt. rend.*, **205**, 327 (1937).

(32) L. Schmerling, *J. Am. Chem. Soc.*, **78**, 2819 (1956).

(33) S. Winstein and D. Trifan, *ibid.*, **74**, 1160 (1952).

(34) H. Kwart and W. G. Vosburgh [*ibid.*, **76**, 5400 (1954)] treated norbornylene with performic acid and after saponification obtained a diol melting at 174–176° which was assumed to be *exo*-2-*syn*-7-norbornanediol on the basis of negative tests for vicinal diol and infrared studies which indicated strong intramolecular hydrogen bonding. The same diol was prepared by treating 2,3-norbornene oxide with mineral acid. A non-classical carbonium ion mechanism was proposed to explain the rearrangement. Melting points ranging from 174–176° to 194° have been reported for this diol. Krieger [for references and a discussion see H. Krieger, *Suomen Kemi.*, **B31**, 340 (1958)] treated norbornylene with performic acid under conditions identical to those employed by Kwart and Vosburgh. He obtained a product melting 186–188° which was shown to be a mixture by separation into two isomeric diols (m.p. 180–181° and 199–200°) upon treatment with carbon disulfide. These compounds were assigned structures corresponding to the *syn* and *anti* isomers of *exo*-2,7-norbornanediol.

lected; $n^{25}D$ 1.4748. The material was further purified by chromatography on silica gel in the attempt to remove any diacetate which might be present.

Anal. Calcd. for $C_7H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.40; H, 8.21.

It might be anticipated that the product would be a mixture of the isomeric *syn*-(VII) and *anti*-hydroxyacetates corresponding to the two diols isolated by Krieger[34] in the reaction of norbornylene with performic acid. The component associated with the facilitated rate of alkaline hydrolysis is assigned structure VII on the basis of the other data reported in this paper showing that proximity of a neighboring hydroxyl group produces a rate enhancement in alkaline hydrolysis of esters.

***cis*-1,3-Cyclopentanediol**[35] was prepared by the method of Saegebarth[36]; b.p. 114° (5 mm.), $n^{25}D$ 1.4791 [lit. 86–87° (0.5 mm), $n^{25}D$ 1.4832]. The diol gave a negative periodate test for vicinal diol. The infrared spectrum at high dilution (0.005 *M* and 0.0025 *M*) showed the presence of intramolecular hydrogen bonding, exhibiting two bands at 3620 and 3551 cm.$^{-1}$ whose ratio was independent of concentration.

***cis*-3-Hydroxycyclopentylacetate** was prepared by slow dropwise addition with vigorous stirring and under anhydrous conditions of a solution of acetyl chloride (1.57 g., 0.02 mole) in ether to a solution of *cis*-1,3-cyclopentanediol (2.04 g., 0.02 mole) and pyridine (5.0 g.) in 100 ml. of anhydrous ether. Pyridine hydrochloride precipitated as the reaction progressed. When the addition was completed the reaction mixture was stirred slowly overnight. The ether solution was decanted and the residue triturated with 200 ml. of ether. The ether solutions were combined and the remaining pyridine removed by washing with dilute hydrochloric acid. The ether solution was then washed with aqueous sodium bicarbonate and water and dried over anhydrous sodium sulfate. The ether was removed by flash evaporation and the residue distilled to yield 1.9 g. (66.0%) of material boiling at 110–111° (9 mm.), $n^{25}D$ 1.4520.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.33; H, 8.33. Found: C, 58.16; H, 8.57.

Pentaerythritol monoacetate was prepared according to the procedure of Marans, Elrick and Preckel[37]; m.p. 68.5–69.5° (lit.[37] m.p. 65–66°).

Infrared Spectra.—The carbon tetrachloride used as solvent was distilled over P_2O_5 just prior to use. A Perkin–Elmer model 21 spectrophotometer equipped with a NaCl prism was used for measurement of the carbonyl frequencies. Solutions of 0.001 *M* concentration and 1-cm. cells were employed. The hydroxyl frequencies in the range 2.6 to 2.85 μ were measured with a Beckman DK spectrophotometer equipped with a quartz prism. The solutions were 0.005 *M* and 0.0025 *M* in concentration and a 1-cm. cell was employed. The position of the hydroxyl stretching frequencies were also determined in the range 2.6 to 3.2 μ with a Perkin–Elmer model 21 spectrophotometer equipped with a NaCl prism and using 0.005 *M* solutions and a 3-cm cell. No additional bands beyond 2.85 μ could be found for any of the compounds studied. The band due to hydrogen bonded hydroxyl in the spectrum of *cis*-2-hydroxycyclopentyl acetate was very weak and gave the appearance of a broad shoulder on the main peak. To obtain a definite peak the area of the band due to free hydroxyl, considering it to be a symmetrical peak, was subtracted from the spectrum.

Kinetics.—All the rate constants reported herein were determined on a *p*H-Stat. The assembly consisted of a Radiometer TIIIa autotitrator and a Radiometer Titrigraph equipped as previously described.[38] Samples employed were 2.0 to 1.5 ml. in volume. Before each run the cell was flushed with prehumidified nitrogen. The microtitration cell as assembled was air tight. All runs were made in 1.0 *M* KCl to maintain constant ionic strength and were followed to completion. The pseudo-first-order rate constants were calculated by the method of Guggenheim.[39] The possibility of an epoxidation reaction occurring during the hydrolysis of III is considered improbable by the fact that $\Delta\Delta H^{\ddagger}$ and $T\Delta\Delta S^{\ddagger}$ for III fit on the compensation plot of Fig. 3. Such a reaction is not considered likely under the mild alkaline conditions employed in the present study.

Deuterium Solvent Isotope Effect.—Hydrolytic rate constants were determined at 78° (μ = 1.0 *M*) in D_2O (99.7%) and H_2O under conditions of identical acidity (*p*H meter reading of 9.4 in H_2O and 9.22 in D_2O).[40] Second-order rate constants k_{OH} and k_{OD} were calculated from the relationships $k_{obs} = k_{OH}(K_w/a_H)$ and $k_{obs} = k_{OD}(K_{D_2O}/a_D)$. The value of K_{D_2O} at 78° was estimated from the value of K_{D_2O} at 25°[41] and the assumption that K_{D_2O} varies with temperature as does K_W. The ratio k_{OH}/k_{OD} was then determined.

Acknowledgments.—This work was supported by grants from the National Institutes of Health and the National Science Foundation.

(35) L. N. Owen and P. N. Smith [*J. Chem. Soc.*, 4043 (1952)] prepared the two isomeric *cis*- and *trans*-1,3-cyclopentane-diols by treatment of the corresponding *cis*- and *trans*-3,5-dibromocyclopentenes with tetraethylammonium acetate in acetone, conditions considered to be favorable to SN2 substitution in allylic systems [W. G. Young, H. K. Hall and S. Winstein, *J. Am. Chem. Soc.*, **64**, 2157 (1942)]. This was the only method which gave products free from the 1,2-isomer. It was found that all the earlier methods in the literature for the preparation of 1,3-cyclopentanediols gave mixtures. W. E. Young, H. K. Hall and S. Winstein [*J. Am. Chem. Soc.*, **78**, 4338 (1956)] showed that the previously assigned configurations of the isomeric 3,5-dibromocyclopentenes had been reversed and therefore concluded that the configurations of the two corresponding 1,3-cyclopentanediols reported by Owen and Smith were also reversed. The work of Saegebarth,[36] however, indicates that the assignment of configuration made by Owen and Smith are correct. Saegebarth prepared *cis*-1,3-cyclopentanediol (bishydroboration of cyclopentadiene) and found that the physical properties of this compound as well as the melting points of its derivatives were in agreement with those of the compound assigned the *cis* configuration by Owen and Smith (*i.e.*, prepared from *trans*-1,3-cyclopentene dibromide). Therefore, an inversion of configuration must have occurred. Owen and Smith do not report any infrared hydrogen bonding studies on their compounds. There can be no doubt that the diol prepared by Saegebarth is *cis*-1,3-cyclopentanediol. The compound gives a negative periodate test, shows from infrared studies that strong intramolecular hydrogen bonding is present and allows formation of a *p*-nitrobenzyledeneacetal in 80% yield.

(36) K. A. Saegebarth, *J. Org. Chem.*, **25**, 2212 (1960).

(37) N. S. Marans, D. E. Elrick and R. F. Preckel, *J. Am. Chem. Soc.*, **76**, 1304 (1954).

(38) T. C. Bruice and T. H. Fife, *ibid.*, **83**, 1124 (1961).

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