yield 0.45 g. A small sample was recrystallized from water for analysis to give a product with a melting point of 243–244°.

Anal. Calcd. for $C_8H_{11}N_5O$: C, 49.7; H, 5.7; N, 36.2. Found: C, 49.6; H, 5.6; N, 35.8.

2-Amino-3-methyl-6-methoxypurine was similarly prepared from VIII and sodium methoxide in refluxing methanol. The crude product was recrystallized from water to give a 50% yield, m.p. >300°.

Anal. Calcd. for $C_7H_9N_5O \cdot H_2O$: C, 42.6; H, 5.6; N, 35.5. Found: C, 42.3; H, 5.5; N, 35.2.

3-Methyl-2-methylthio-6-purinone (III).—2-Mercapto-3-methyl-6-purinone[15] (5 g.) was placed in 50 ml. of water, and just enough solid potassium hydroxide added to dissolve all the solid. The solution was cooled to 25° and 7 g. of methyl iodide added. The solution was stirred vigorously for 2 hr. at room temperature and finally treated with charcoal and filtered and the *p*H adjusted to 7 with glacial acetic acid. After cooling, the precipitate was filtered and the solid reprecipitated to yield 4.1 g. of product, m.p. >300°.

Anal. Calcd. for $C_7H_8N_4OS$: C, 42.9; H, 4.1; N, 28.6. Found: C, 43.0; H, 3.8; N, 28.4.

2,6-Diamino-3-methylpurine (IX, R_1, R_2 = H).—2-Amino-6-chloro-3-methylpurine (VIII, 0.25 g.) was added to 100 ml. of absolute ethanol and the solution refluxed for 8 hr. A stream of anhydrous ammonia was passed through the refluxing solution during the entire reaction period. The solution was then set on the steam-bath and the volume reduced to 50 ml. The solution was allowed to cool at 15° for 12 hr. and the solid filtered to yield 0.2 g. of product. A small sample was recrystallized from a methanol–ethyl acetate mixture for analysis and gave a product melting at >300°.

Anal. Calcd. for $C_6H_6N_6 \cdot HCl$: C, 36.0; H, 4.5; N, 42.0. Found: C, 36.2; H, 4.3; N, 41.9.

2-Amino-6-(*n*-butylamino)-3-methylpurine (IX, R_1 = H, R_2 = n-C_4H_9). **Method 1.**—2-Amino-6-chloro-3-methylpurine (VIII, 0.5 g.) was added to 30 ml. of *n*-butylamine and the solution stirred at room temperature for 1 hr. The solution then was evaporated to dryness in a stream of air, and the residue was triturated with 35 ml. of acetone at room temperature. The precipitate was filtered to yield 0.35 g. of a solid which was recrystallized from chloroform for analysis and gave a product melting at 255–258°.

Anal. Calcd. for $C_{10}H_{16}N_6$: C, 54.6; H, 7.3; N, 38.2. Found: C, 55.0; H, 6.5; N, 38.2.

Method 2.—2-Amino-3-methyl-6-methylthiopurine (VI, R = CH_3) (0.5 g.) was added to 25 ml. of *n*-butylamine (40% aqueous), and the solution was refluxed on the steam-bath for 2 hr. The excess *n*-butylamine was removed *in vacuo* on the steam-bath and 10 ml. of water added to the residue. The *p*H of the solution was adjusted to 6 and the solution evaporated to dryness in a stream of air. The residue was recrystallized from chloroform to give a product identical with that prepared by method 1 as judged on the basis of ultraviolet spectra.

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

Hydroxyl Group (V)[1] and Imidazole (X)[2] Catalysis. The General Base Catalysis of Ester Hydrolysis by Imidazole and the Influence of a Neighboring Hydroxyl Group

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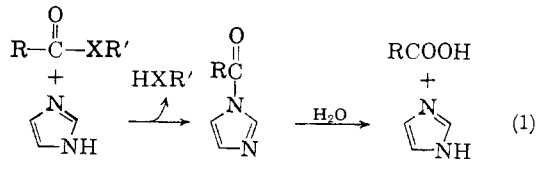
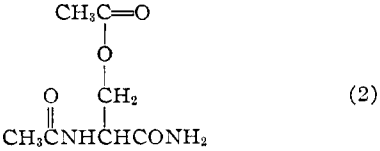
Imidazole has been found to be a catalyst for the hydrolysis of alkyl acetyl esters (CH_3COOR') in which the pK_a' of HOR' is less than pK_w. The catalytic coefficient for imidazole catalysis in these cases has been found to be associated with a deuterium solvent kinetic isotope effect (*i.e.*, k^H/k^D) of 2 to 4. It is suggested that the mechanism represents an imidazole general base or general acid-catalyzed hydrolysis. The rate of alkaline hydrolysis of the cyclopentyl ester of dichloroacetic acid has been shown to be only about half as sensitive to facilitation by a neighboring hydroxyl group as previously found for the corresponding acetyl ester. In addition, the rate of imidazole general base-catalyzed hydrolysis of cyclopentyl dichloroacetate has been found to be completely insensitive to the presence of a neighboring hydroxyl group.

The mechanism of the imidazole catalysis of the hydrolysis of the ester bond (R–CO–XR') has been found to be dependent on the nature of the group R– and the conjugate acid of the leaving group HXR'. When R– represents an alkyl or aryl group and HXR' phenol, a substituted phenol or a thiol then nucleophilic catalysis (1) invariably has been noted.[2,4,5]



(1)

When R– represents a particularly electron withdrawing substituent group as $CHCl_2$–, CH_3OCO– etc.[6,7] and HXR' an alcohol, then the catalysis occurs by way of general base or general acid mechanisms in which N-acetylimidazole is not an intermediate. A general base mechanism has also been noted in one case in which R– is not electron withdrawing and HXR' represents an alkoxide ion of pK_a' less than pK_w. This ester is the enzymologically important N,O-diacetylserine amide[8] (2).



(2)

The pK_a' of the leaving group (N-acetylserine amide) has been established recently as being

(1) For Hydroxyl Group Catalysis. IV, see T. C. Bruice and Fritz-Hans Marquardt, *J. Am. Chem. Soc.*, **84**, 365 (1962).

(2) For Imidazole Catalysis. IX, see T. C. Bruice and J. J. Bruno, *ibid.*, **84**, 2128 (1962).

(3) Post-doctoral Fellow, Department of Chemistry, Cornell University.

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13.6.[9] For acetyl esters in which HXR′ represents an alcohol of $pK_a > pK_w$ (*i.e.*, ethyl or methyl acetate) there can be detected no catalysis of hydrolysis by imidazole.[5]

The purpose of the present study has been to establish whether esters of the general structure CH_3COOR' in which HOR′ represent alcohols of $pK_a < pK_w$ undergo imidazole-catalyzed hydrolysis and to determine also whether the mechanism of the hydrolysis is nucleophilic or the general base type. In addition, we have also investigated the influence of a neighboring hydroxyl group on the rates of alkaline and imidazole general base catalysis of the hydrolysis of dichloroacetyl esters. It has been demonstrated previously that a neighboring hydroxyl group facilitates the alkaline hydrolysis of acetyl esters (for pertinent references on this topic see ref. 10).

Experimental

Compounds.—**The imidazole** employed was Eastman Kodak Co. (white label) and was dried *in vacuo* over P_2O_5. **Pentaerythritol monoacetate** was that of a previous study.[9] **The 2-methoxyethyl acetate** [b.p. 141–142° (740 mm.), $n^{22}D$ 1.4007; lit.[11] b.p. 144–145° (760 mm.). *Anal.* Calcd. for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.60; H, 8.50], **2-chloroethyl acetate** [b.p. 141–142° (740 mm.), $n^{22}D$ 1.4232; lit.[12] b.p. 143–145°, $n^{17}D$ 1.4255] and **2,2-dichloroethylacetate** [b.p. 154–155° (740 mm.), $n^{24}D$ 1.4450. *Anal.* Calcd. for $C_4H_6Cl_2O_2$: C, 30.60; H, 3.85. Found: C, 30.78; H, 3.81] were prepared by slowly adding an equivalent amount of acetyl chloride to the appropriate alcohol under anhydrous conditions, while stirring and cooling. After pumping off residual hydrogen chloride, the esters were distilled through a vacuum-jacketed Vigreux column.

Cyclopentyl dichloroacetate was prepared by adding 28.0 g. (0.19 mole) of dichloroacetyl chloride in an equal volume of ether to 15.0 g. (0.174 mole) of cyclopentanol in a solution of pyridine (13.8 g., 0.174 mole) and anhydrous ether (200 ml.). The addition was made dropwise under anhydrous conditions with constant stirring while cooling in an ice-bath. After completion of addition, the ice-bath was removed and the reaction mixture stirred overnight. The ethereal solution was decanted from the precipitated pyridine hydrochloride and washed with water, aqueous sodium bicarbonate and again with water. The ethereal solution was next dried over anhydrous sodium sulfate, the ether removed by flash evaporation and the residual liquid distilled. In this manner there was obtained 26.7 g. (78%) of product, b.p. 99° (13 mm.), $n^{25}D$ 1.4680.

Anal. Calcd. for $C_7H_{10}O_2Cl_2$: C, 42.64; H, 5.07; Cl, 36.04. Found: C, 42.66; H, 5.22; Cl, 35.88.

***trans*-2-Methoxycyclopentanol.**—Cyclopentene oxide (15.0 g., 0.18 mole) was added to a solution of 150 ml. of methanol in which 2.1 g. (0.09 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. 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 solvent removed by flash evaporation and the residual liquid distilled. There was thus obtained 12.5 g. (59.8%) of product, b.p. 96° (27 mm.), $n^{25}D$ 1.4513; lit.[13] b.p. 175° (760 mm.), $n^{20}D$ 1.4534.

***trans*-2-Methoxycyclopentyl Dichloroacetate.**—To *trans*-2-methoxycyclopentanol (12.5 g., 0.18 mole) and pyridine (8.53 g., 0.18 mole) in 200 ml. of anhydrous ether there was added dropwise with vigorous stirring and under anhydrous conditions, 15.9 g. (0.18 mole) of dichloroacetyl chloride. When addition was completed, the reaction mixture was stirred overnight, the ethereal solution decanted from the precipitated pyridine hydrochloride and washed with water. The ethereal solution then was dried over anhydrous sodium sulfate and the solvent removed by flash evaporation. Distillation of the residual liquid yielded 15.0 g. (61.2%) of product, b.p. 103° (6 mm.), $n^{24.5}D$ 1.4668.

Anal. Calcd. for $C_8H_{12}O_3Cl_2$: C, 42.29; H, 5.28; Cl, 31.27. Found: C, 42.49; H, 5.47; Cl, 31.24.

***trans*-2-Hydroxycyclopentyl Dichloroacetate.**—Dichloroacetyl chloride (31.5 g., 0.214 mole) in 50 ml. of chloroform was slowly added in a dropwise manner with vigorous stirring to a solution of 21.8 g. (0.214 mole) of *trans*-1,2-cyclopentanediol in 250 ml. of chloroform. During the addition a stream of nitrogen was continuously bubbled through the reaction mixture. After addition was complete the mixture was stirred for 5 hours, and washed with water, aqueous sodium bicarbonate and water. After drying the chloroform solution over anhydrous sodium sulfate, the solvent was removed by flash evaporation and the residual liquid distilled to yield the ester, 30.1 g., 68.7%, b.p. 124° (4 mm.), $n^{25.5}D$ 1.4843.

Anal. Calcd. for $C_7H_{10}O_3Cl_2$: C, 39.44; H, 4.69; Cl, 33.33. Found: C, 39.60; H, 4.74; Cl, 33.10.

Apparatus.—Spectrophotometric measurements were taken with a Ziess PMQII spectrophotometer. All *p*H measurements were made on a Radiometer model 22 *p*H meter at the same constant temperature as employed in the kinetic runs. Hydrolytic constants determined at constant *p*H without buffer were determined with the aid of a *p*H-Stat assembly as previously described.[14] The *p*H measurements for the kinetic experiments performed at 95° were determined at 99° by a Metrohm ℉ type H, high temperature electrode in an apparatus described previously.[1]

Kinetic Measurements. (A) Imidazole Catalysis of Ester Hydrolysis.—In these experiments the disappearance of ester was followed by the hydroxamic acid method[15] as previously described.[16] In all cases the esters were at a concentration of about 10^{-2} *M* and sufficient imidazole was employed to serve as both catalyst and buffer.

The hydrolysis of the acetyl esters was followed in aqueous solutions adjusted to a calculated ionic strength of 1.0 *M* with KCl and at pH$_{95°}$ of 6.75. One-ml. aliquots of the ester–imidazole solution were pipetted into 15 × 150 mm. screw-cap (neoprene-lined) Pyrex vials. At the desired time intervals, tubes were removed from the constant temperature bath, quenched and assayed for remaining ester by the hydroxamate procedure. The hydroxamate reaction was carried out at 95° after addition of 2 ml. of the stock hydroxylamine solution and tightly recapping the vials. The optimum times for full development were determined in separate experiments. For pentaerythritol monoacetate and 2-methoxyethyl acetate in both H_2O and D_2O a development time of 2 hours was employed. One hour development time was employed for 2-chloroethyl acetate and only 20 minutes for 2,2-dichloroethyl acetate. All reactions were followed to at least 50% completion, and found to invariably follow pseudo-first-order kinetics. The pseudo-first-order rate constants (k_{obs}) were obtained from the slopes of plots of log (O.D.$_i$/O.D.$_t$) *vs.* time.

The imidazole catalysis of the hydrolysis of the dichloroacetyl esters was studied in 50–50 dioxane–water (v./v.) solvent adjusted to a calculated ionic strength of 0.5 *M* with KCl and in water adjusted to a calculated ionic strength of 1.0 *M* with KCl. Again, the imidazole was at sufficient concentration to serve as both catalyst and buffer. The disappearance of ester from solution was again followed by the hydroxamic acid procedure.[16] For the reactions run at 30°, the ester–imidazole solutions were made up in 25-ml. glass-stoppered, volumetric flasks which were then thermostated at 30 ± 0.1°. At the desired time intervals, 1.0-ml. aliquots of solution were withdrawn with a pipet from the reaction solution and placed into 15 × 150 mm. screw-cap (neoprene-lined) Pyrex vials containing 2 ml. of the hydroxylamine stock solution and in the case of *trans*-2-meth-

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oxycyclopentyl dichloroacetate and cyclopentyl dichloroacetate, 1.0 ml. of dioxane. The hydroxamic acid was then developed at 70° in a constant temperature water-bath employing the following development times.

Ester	Conditions for kinetic runs	Develop. time, min.
V	50–50 dioxane–H_2O, 30°	60
	50–50 dioxane–H_2O, 70°	40
VI	50–50 dioxane–H_2O, 30°	30
	50–50 dioxane–H_2O, 70°	20
VII	50–50 dioxane–H_2O, 30°	30
	50–50 dioxane–H_2O, 70°	20
	H_2O, 30°	6
	D_2O, 30°	30

Reactions were followed to 50% completion and the pseudo-first-order rate constants calculated as previously described.

For the runs at 70° with the dichloroacetyl esters, the operational procedure detailed for the acetyl esters was employed.

B. *p*H dependence of the aqueous hydrolysis of dichloroacetyl esters was determined in water on a *p*H-Stat at a calculated ionic strength of 1.0 *M* (with KCl). All runs were followed to completion and found to be pseudo-first order. The pseudo-first-order rate constants (k_{obs}) were determined by the method of Guggenheim.[17]

C. D_2O Solvent Kinetic Isotope Effect.—The rates of hydrolysis of the esters in D_2O were determined by the same procedures used for the reactions in water. Care was taken to ensure that all solutions remained anhydrous. In the determination of a_D, the glass-electrode correction formula of Fife and Bruice[18] was employed. The ion product of D_2O at 30° was taken to be 0.224×10^{-14} [16] and the value at 95° was calculated to be 6.35×10^{-14} from the values of $K_{D_2O} = 0.154 \times 10^{-14}$ [19] and $K_w = 1.008 \times 10^{-14}$ [20] at 25° and the value of $K_w = 41.6 \times 10^{-14}$ at 95°, by assuming that the change in K_{D_2O} is proportional to the change in K_w. The autoprotolysis constant of water at 95° was obtained by interpolation of the data of Harned and Robinson (between 0° and 60°) and Noyes and Kato ($K_w = 48 \times 10^{-14}$ at 100°).[21]

***p*K Determinations.**—The pK_a of imidazole in H_2O at 99 ± 0.1° was found to be 6.02 by the method of half-neutralization and serial dilution. The pK_a of imidazole in D_2O at 99 ± 0.1° by the same procedure was determined to be 6.43. In the D_2O experiments the glass electrode correction for the Metrohm type H electrode was used in determining a_D.[18] The apparent pK_a of imidazole in 50–50 dioxane–water was determined at 30° and 70° by the method of half-neutralization and by titration on the autotitrator. The values were found to be 6.45 and 5.95, respectively.

Infrared Spectra.—The carbon tetrachloride 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 0.0025 *M* and 0.001 *M* concentration and 1-cm. cells were employed. The hydroxyl frequencies of *trans*-2-hydroxycyclopentyl dichloroacetate in the range 2.6 to 2.85 mμ 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.

Results

In the reaction of imidazole with the various esters studied, the rates of ester disappearance were found to be pseudo-first-order and dependent on the concentration of imidazole in the base form and also on the acidity of the medium

$$k_{obs} = k_{IM}C_{IM_T}[K_a/(K_a + a_H)] + k_{OH}K_w/a_H + k_0$$
$$k_{obs} = k_{IM}C_{IM} + k_{OH}K_w/a_H + k_0 \qquad (3)$$

where C_{IM_T} equals the combined concentrations of imidazole in its free base and conjugate acid form (*i.e.*, $C_{IM_T} = C_{IM} + C_{IMH^{\oplus}}$), K_a is the dissociation constant of IMH^+, K_w the autoprotolysis constant for water and a_H the hydrogen ion activity as determined by the glass electrode. From 3 it follows that plots of the experimentally observed pseudo-first-order rate constants for hydrolysis (k_{obs}) *vs.* C_{IM} should be linear and of slope equal to k_{IM} and intercept equal to $k_{OH}(K_w/a_H) + k_0$. In Fig. 1 are plotted the values of k_{obs} *vs.* C_{IM} for the acetyl esters studied in H_2O and D_2O (95°), and in Table I are recorded the second-order rate constants for imidazole catalysis of ester hydrolysis in H_2O-(k_{IM}^H) and in D_2O(k_{IM}^D) as well as the second-order rate constants for $OH^{\ominus}$(k_{OH^-}) and $OD^{\ominus}$(k_{OD^-}) catalysis of hydrolysis. In Fig. 2 are plotted the determined values of k_{obs} for the hydrolysis of *trans*-2-hydroxycyclopentyl dichloroacetate *vs.* C_{IM} at two *p*H values in water and one *p*D value in D_2O. The values of k_{IM}, $k_{OH^{\ominus}}$ and $k_{OD^{\ominus}}$ calculated from Fig. 2 are also included in Table I. From an examination of Table I it can be seen that the deuterium solvent isotope effects for the imidazole-catalyzed hydrolysis are 2 or greater. This would tend to substantiate a general base-catalyzed hydrolysis in each case. The values of $k_{OH^{\ominus}}/k_{OD^{\ominus}}$ listed in Table I are seen to vary from 0.2 to 0.5 and are in agreement with the expected kinetic isotope ratios for a reaction involving nucleophilic attack of $OH^{\ominus}$ and $OD^{\ominus}$ on the ester carbonyl group. Thus, the ratio of K_w/K_{D_2O} is 6.5 and the second-order rate constants for nucleophilic displacement reactions at the ester bond are known to follow the relationship $\log k_r = \alpha pK_a + D$.[4d] If we assume that the value α is approximately a constant dependent only on the nature of the ester,[4d] then it follows that the deuterium solvent isotope effect for nucleophilic attack at the ester bond by $OH^{\ominus}$ and $OD^{\ominus}$ should be given by 4. Assuming the

$$\frac{k_{OH^-}}{k_{OD^-}} = \left(\frac{K_{D_2O}}{K_w}\right)^{\alpha}\frac{D_{H_2O}}{D_{D_2O}} \qquad (4)$$

intercept constants D for H_2O and D_2O are common.

$$k_{OH^{\ominus}}/k_{OD^{\ominus}} = (0.154)^{\alpha} \qquad (5)$$

Reasonable values of α for ester hydrolysis fall in the range 0.4 to 0.9 giving values of $k_{OH^{\ominus}}/k_{OD^{\ominus}}$ of 0.7 to 0.2. These values are significantly smaller than those for nucleophilic displacement of the SN1 and SN2 variety on the sp^3-carbon[22-24] and reflect the known[4d,25] differences in these mechanisms and requirements for nucleophilicity.

In Fig. 3 are presented the *p*H-rate profiles for the hydrolysis of the dichloroacetyl esters at 60° in water. The portions of the profiles in the alkaline region possess a slope of 1.0 and represent alkaline hydrolysis. For the most labile ester, *trans*-2-hydroxycyclopentyl dichloroacetate (VII), it was possible to determine the rate constants for hydrolysis on the acid side of neutrality (*p*H 6.25 at 60°). It should be noted that though the dichloroacetyl esters are quite labile to $OH^{\ominus}$-catalyzed hy-

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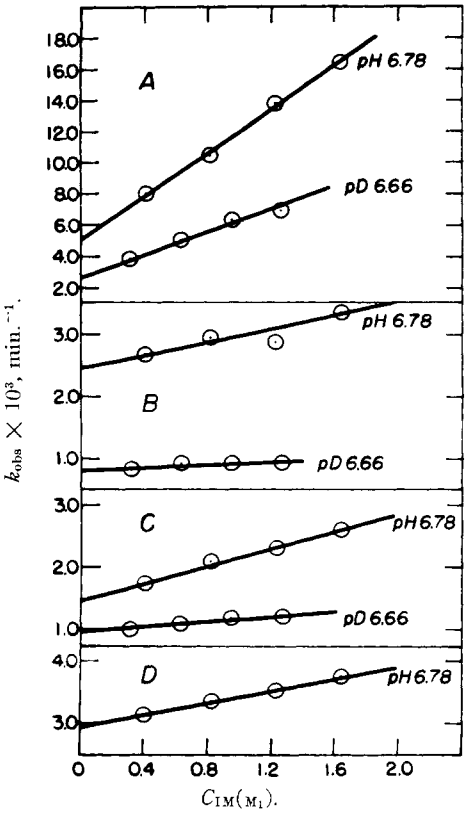


Fig. 1.—Plots of the determined pseudo-first-order rates (k_{obs}) of hydrolysis against the concentration of imidazole free base (C_{IM}) for reactions studied in H_2O and D_2O: A, 2,2-dichloroethyl acetate; B, monoacetyl pentaerythritol; C, 2-methoxyethyl acetate; D, 2-chloroethyl acetate.

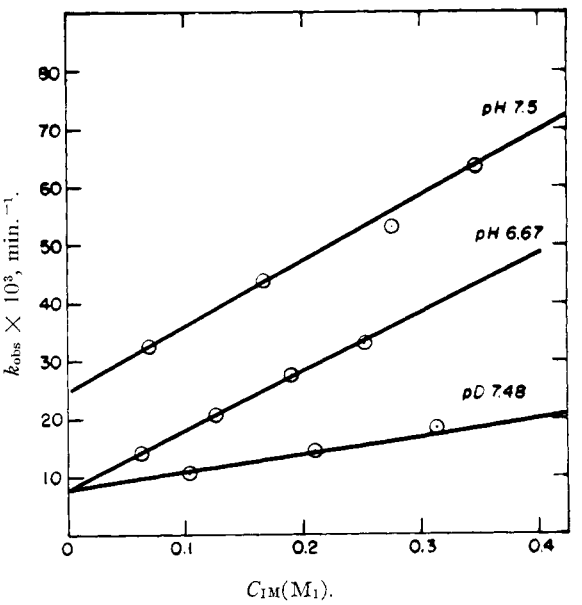


Fig. 2.—Plots of the observed pseudo-first-order rate constants (k_{obs}) for the hydrolysis of *vic-trans*-hydroxycyclopentyl dichloroacetate *vs.* the concentration of imidazole free base (C_{IM}) in water at 30° (μ = 1.0 *M*) at *p*H 7.5 and 6.67 and in deuterium oxide at 30° and *p*D 7.48.

drolysis, they are comparatively resistant to $H_3O^{\oplus}$ catalysis. In the acid region, the profile for VII exhibits a definite plateau rate indicating a mechanism for hydrolysis which is insensitive to $H_3O^{\oplus}$ and $OH^{\ominus}$ concentration.[26] The rate constant for this water solvolysis is $k_0 = \sim 1.9 \times 10^{-3}$ min.$^{-1}$. The known susceptibility of dichloroacetyl esters to general base catalysis suggests that the value of k_0 represents a general base catalysis in which water behaves as the general base. Unfortunately, because of the slow rate of hydrolysis in the plateau region, no accurate deuterium solvent isotope effect could be determined for k_0 on the *p*H-Stat. The values of k_{OH} determined from the profiles of Fig. 3 are given in Table II.

$$k_{obs} = k_{OH}K_w/a_H + k_0 \qquad (6)$$

In Figs. 4 and 5 are plotted the values of k_{obs} for the imidazole catalysis of the hydrolysis of the dichloroacetyl esters in 50% dioxane–water (v/v.) at 30° and 70°. The values of k_{IM}, k_{OH} and as-

TABLE I

DEUTERIUM SOLVENT ISOTOPE EFFECTS ON THE IMIDAZOLE AND HYDROXIDE ION CATALYSIS OF A SERIES OF ALIPHATIC ESTERS

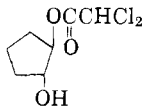
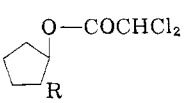
Ester	$k_{IM}^{H_2O}$ (l. mole^{-1} min.$^{-1}$ × 10^4)	$k_{IM}^{D_2O}$ (l. mole^{-1} min.$^{-1}$ × 10^4)	k_{IM}^{H}/k_{IM}^{D}	T, °C.	k_{OH} (l. mole^{-1} min.$^{-1}$ × 10^{-3})	k_{OD} (l. mole^{-1} min.$^{-1}$ × 10^{-3})	$k_{OH^{\ominus}}/k_{OD^{\ominus}}$	T, °C.
Cl_2CHCH_2OAc (I)	69.5	37.1	1.9	95	1.98	9.0	0.2	95
$(HOCH_2)_3CCH_2OAc$ (II)	5.3	1.25	4.3	95	0.99	2.8	.4	95
$ClCH_2CH_2OAc$ (III)	4.85			95	1.17			
$CH_3OCH_2CH_2OAc$ (IV)	7.0	2.2	3.2	95	0.58	3.3	.2	95
	1070	321	3.3	30	53.8	102	.5	30

TABLE II

EFFECT OF A NEIGHBORING HYDROXYL GROUP ON THE ALKALINE HYDROLYSIS OF CYCLOPENTYL DICHLOROACETATES



Ester, R =	k_{OH} (H_2O, μ = 1.0, T = 60°), l. mole^{-1} min.$^{-1}$	k_{rel}	k_{obs} (50% dioxane–H_2O v./v., *p*H meter reading 7.12, T = 70°), min.$^{-1}$	k_{rel}
V, H	1.48×10^4	1.0	8.0×10^{-4}	1.0
VI, OCH_3	1.74×10^5	11.8	7.0×10^{-3}	8.8
VII, OH	3.09×10^5	20.9	1.76×10^{-2}	22.0

(26) R. Skrabal, *Monatsh.*, **71**, 298 (1938), has previously noted a *p*H insensitive ratio of hydrolysis for other acyl activated esters.

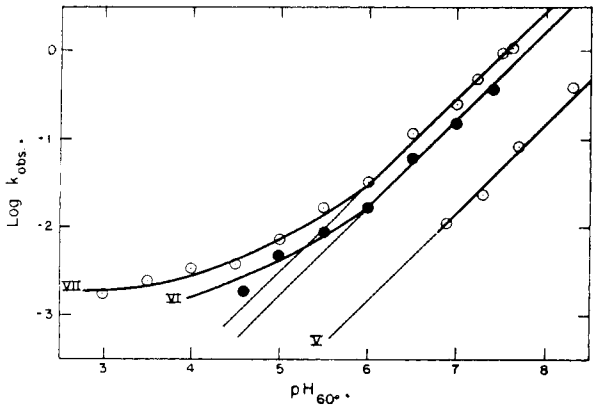


Fig. 3.—pH–rate profiles (60°) for the hydrolysis of the dichloroacetyl esters V, VI and VII in water (μ = 1.0 M).

sociated ΔH^* and ΔS^* values have been determined and are recorded in Tables II, III and IV.

TABLE III

EFFECT OF A NEIGHBORING HYDROXYL GROUP ON THE IMIDAZOLE GENERAL BASE-CATALYZED HYDROLYSIS OF CYCLOPENTYL DICHLOROACETATES

50% dioxane-water (v./v.), μ = 0.5 M

	T = 30°		T = 70°	
Ester	k_{IM}, l. mole^{-1} min.$^{-1}$	k_{rel}	k_{IM}, l. mole^{-1} min.$^{-1}$	k_{rel}
V	8.69×10^{-4}	1.0	1.09×10^{-2}	1.0
VI	4.7×10^{-3}	5.4	4.28×10^{-2}	3.9
VII	5.78×10^{-3}	6.6	3.88×10^{-2}	3.6

TABLE IV

ACTIVATION PARAMETERS FOR THE HYDROXIDE ION AND IMIDAZOLE CATALYSIS OF THE HYDROLYSIS OF DICHLOROACETYL ESTERS

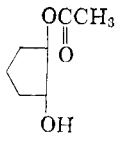
	50% dioxane-water (v./v.), μ = 1.0		H_2O, μ = 1.0	
	k_{IM}[a]		k_{OH}[b]	
Ester	ΔS^*, e.u.	ΔH^*, kcal./mole	ΔS^*, e.u.	ΔH^*, kcal./mole
V	−40.2	12.2		
VI	−42.0	10.6		
VII	−46.7	9.1	−6.0	10.9

[a] The activation parameters from the imidazole-catalyzed rates have been determined from the true second-order rate constants and are corrected for the heat of ionization of imidazole. These are therefore, true values; ΔS^* calculated at 70° with rate constants in units of l. mole^{-1} sec.$^{-1}$. [b] Calculated from the true second-order rate constants at 30° and 60°. These values have been corrected for the heat of ionization of water and are true constants; ΔS^* calculated at 60° with rate constants in l. mole^{-1} sec.$^{-1}$.

TABLE V

INFRARED ABSORPTION FOR DICHLOROACETYL ESTERS IN CCl_4

Ester	>C=O, cm.$^{-1}$	—O—H, cm.$^{-1}$
V	1768	
	1746	
VI	1770	
	1748	
VII	1758	3617(s)
	1739	3583(m)
	1731	3620(w)
		3547(broad)



The infrared absorption of the ester carbonyl groups of V, VI and VII as well as the O–H stretching frequency for VII were determined in CCl_4 at high dilution and are recorded in Table V. The split carbonyl peak undoubtedly is due to the presence of rotamers and finds a parallel in the studies of the carbonyl absorption of some substituted ethyl acetates.[27] The split hydroxyl stretching absorption noted for VII may be attributed to intramolecular hydrogen bonding of the hydroxyl and ester carbonyl group.[28] Comparison of the O–H stretching frequency of VII with that for the corresponding acetyl ester, as determined in a previous study[10] (Table V), indicates that the hydrogen bond is much weaker (position of absorption) in the case of VII and present to a smaller extent (relative intensity). However, since the base line density of the normal (3617) and hydrogen bonded (3547) peaks are of an approximate ratio of 2:1, an appreciable fraction of the molecules of VII must be considered to be internally hydrogen bonded.

Discussion

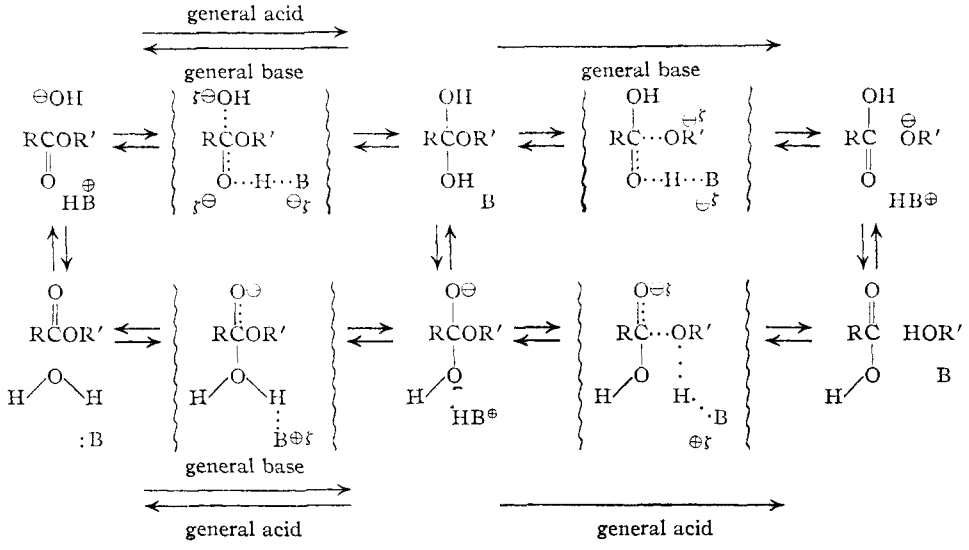
For acetyl esters, CH_3COOR', catalysis of hydrolysis by imidazole in water previously has been shown to be nucleophilic when HOR′ represents phenol and substituted phenol and imperceptible when HOR′ represents $HOCH_3$ or C_2H_5OH. In this study we find that the rate constants for imidazole catalysis are easily measurable if HOR′ represents an aliphatic alcohol of $pK_a < pK_w$. Nucleophilic catalysis of the hydrolysis of phenyl acetates by imidazole is not associated with a deuterium solvents isotope effect. However, we find the imidazole catalysis of the hydrolysis of aliphatic esters is associated with a deuterium solvent isotope effect of 2.0 or greater. Presumably, the latter reactions involve a transition state in which a bond to hydrogen is undergoing cleavage. Most probably the associated mechanism is of the general base or general acid type represented by the possible mechanisms of Chart I, though it could be of the nucleophilic type but requiring a donation of a proton from water in the transition state. However, it should be noted that nucleophilic catalysis by nitrogen bases has never been noted to be subject to a deuterium solvent isotope effect.[7] These results now place the finding of a deuterium isotope effect of 1.9 for the imidazole-catalyzed hydrolysis of N,O-diacetylserine amide (2) in proper perspective. The pK_a' of the hydroxyl group of N-acetylserine amide is known to be 13.6.[9]

The general base mechanism for the catalysis of hydrolysis of the alkyl esters of dichloroacetic acid by weak bases has been firmly established by Jencks and Carriuolo.[6] It has also been well established that a neighboring hydroxyl group facilitates the alkaline hydrolysis of alkyl esters of acetic acid (see ref. 10 for a review of recent literature). It is of mechanistic interest to inquire whether a neighboring hydroxyl group can also facilitate the imidazole

(27) T. L. Brown, *J. Am. Chem. Soc.*, **80**, 3513 (1958).

(28) (a) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957); (b) R. West, J. J. Korst and W. S. Johnson, *J. Org. Chem.*, **25**, 1976 (1960).

CHART I



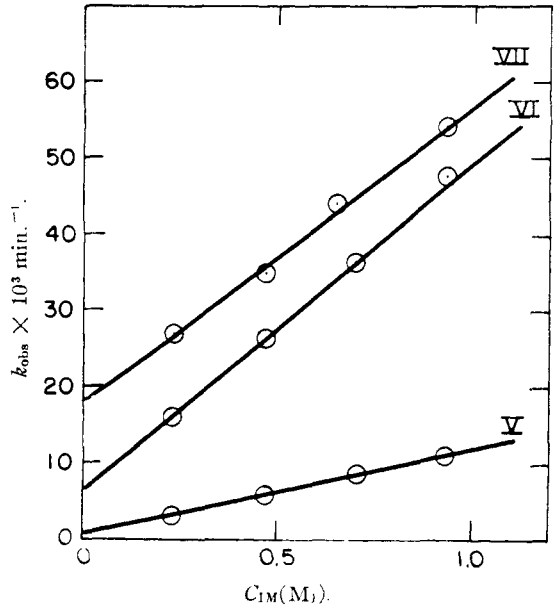


Fig. 4.—Plot of the observed pseudo-first-order rate constants (k_{obs}) *vs.* total imidazole concentration for the hydrolysis of esters V, VI and VII at 70° in 50% dioxane–water (v./v.) and at a *p*H meter reading of 7.12.

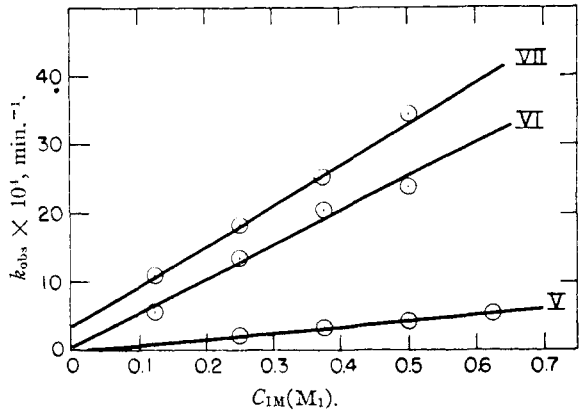


Fig. 5.—Plots of the pseudo-first-order rate constants *vs.* total imidazole concentration for the hydrolysis of esters V, VI and VII at 30° in 50% dioxane–water (v./v.) and at a *p*H meter reading of 6.45.

general base-catalyzed hydrolysis of dichloroacetyl esters. In addition, a comparison of the extent of neighboring hydroxyl group facilitation in the alkaline hydrolysis of acetyl and dichloroacetyl esters provides data on the importance of electronic factors in determining the extent of facilitation. Inspection of Table II reveals that the rate of alkaline hydrolysis of cyclopentyl dichloroacetate is increased 11.8 times by substitution of a *trans*-vicinal methoxyl group and 20.9 times by substitution of a *trans*-vicinal hydroxyl group. The relative rates do not appear to be solvent dependent and possess about the same values in 50% dioxane–water (v./v.) as in water (Table II). Because the electronic effect of methoxyl and hydroxyl groups are identical[29] we might consider that the *trans*-vicinal hydroxyl group provides a two-fold facilitation of the alkaline hydrolysis of the dichloroacetyl ester. The extent of facilitation is less than previously determined for the acetyl ester of cyclopentanol whose rate of alkaline hydrolysis was increased 5.5 times when a *trans*-vicinal methoxyl group was replaced by a *trans*-vicinal hydroxyl group. The lessening of the facilitation on increasing the positive nature of the carbonyl carbon of an ester is to be expected on the basis that stabilization of the transition state associated with the $OH^{\ominus}$ attack on the carbonyl group by hydrogen bonding should be less as the ester group becomes more electron deficient. The lessening of internal hydrogen bonding in the ground state of ester VII as compared to the analogous acetyl ester (Table IV) reflects what might be anticipated for the transition state.

(29) 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.

For the imidazole general base-catalyzed hydrolysis of the dichloroacetyl esters, there is seen to be no facilitation by a neighboring hydroxyl group. Inspection of Table III reveals that at 30° and 70° the same rate enhancement is obtained upon substitution of a *trans*-hydroxyl and *trans*-methoxyl group vicinal to the ester bond in cyclopentyl dichloroacetate. Neighboring hydroxyl group facilitation in the alkaline hydrolysis of cyclopentyl acetate is subject to a marked compensation in ΔS^* and ΔH^*. It would of course be quite conceivable that a neighboring hydroxyl group could participate in the imidazole general base-catalyzed hydrolysis of cyclopentyl dichloroacetate without altering ΔF^* significantly if any change in ΔH^* were completely compensated for by a change in $T\Delta S^*$. Inspection of Table IV reveals that all changes in ΔH^* and $T\Delta S^*$ amount to no more than 1 kcal. The apparent compensation in the present study could arise simply from a random error of 1 kcal. in ΔF^*. It may be noted that the values of ΔH^* for the imidazole general base-catalyzed hydrolysis of cyclopentyl dichloroacetate are comparable to that for hydroxide ion catalysis but that a much more negative ΔS^* is associated with the imidazole catalysis. This would be in accord with a greater solvent striction in the imidazole reaction.

Acknowledgment.—We wish to thank the National Institutes of Health and the National Science Foundation for the support of this research.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF NEW YORK UNIVERSITY, NEW YORK 53, N. Y.]

Optically Active 9,10-Dihydro-4,5-dimethylphenanthrene[1]

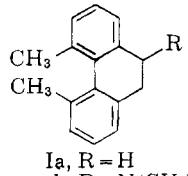
BY KURT MISLOW AND HARVEY B. HOPPS

RECEIVED APRIL 2, 1962

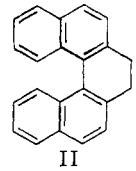
(−)-(R)-9,10-Dihydro-4,5-dimethylphenanthrene has been prepared. The optical stability and optical rotatory dispersion characteristics are discussed.

Our interest in securing optically active 9,10-dihydro-4,5-dimethylphenanthrene (Ia) was stimulated by related work in these laboratories[2,3] and by the recorded failure of a previous attempt in the same direction.[4]

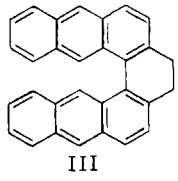
Precedent exists for stereoisomerism in cognate systems. Thus, the bridged binaphthyl[5] and bianthryl[6] analogs II and III are optically stable, the



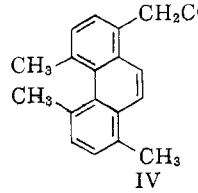
Ia, R = H
b, R = $N(CH_3)_2$



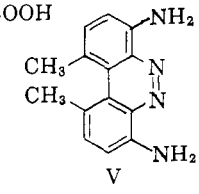
II



III



IV



V

overcrowded aromatic compounds IV[7] and V[8] have been obtained in optically active, albeit optically unstable, form, and the separation of diastereomeric forms of Ib has been claimed.[4]

The desired compound was obtained by ring closure of (−)-(R)-2,2′-bis-(bromomethyl)-6,6′-dimethylbiphenyl with phenyllithium at ice-bath temperatures. In order to remove unreacted starting material, the crude product was treated with silver nitrate in aqueous acetone at 0–5°. Chromatography on silica gel at 0–5° gave a 30% yield of (−)-(R)-Ia, identical in every respect, other than rotation, with authentic racemic material.

Racemization studies on (−)-Ia are summarized in Table I. The rate constants follow the Arrhenius equation $k_1 = 10^{12.8} \exp(-23.1/RT)\text{sec.}^{-1}$. The Arrhenius parameters are of an order of magnitude frequently encountered in bridged biphenyls.[9]

TABLE I

RACEMIZATION OF Ia IN BENZENE

Temp., °C.	28.1	42.1	54.4
α_{435} at t_0[a]	−11.77°	−10.15°	−8.01°
$k_1 \times 10^4$, sec.$^{-1}$	1.07	5.87	23.6
$t_{1/2}$, min.	108	19.7	4.9

[a] c 0.986, l 2, t_0 taken as the time of the first measurement, usually about 3 minutes after the sample has been brought to the desired temperature.

The two methyl groups in Ia appear to be far less effective as blocking groups than the two benzo groups in II: the binaphthyl racemizes according to the expression[9] $k_1 = 10^{13.4} \exp(-30.8/RT)\text{sec.}^{-1}$. In the transition state the two methyl groups can bend out of the way more readily than the rigid aromatic framework in II; similar considerations have been advanced to account for the relative

(1) Grateful acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, and to the Alfred P. Sloan Foundation for fellowship support (K.M.).

(2) K. Mislow, *Angew. Chem.*, **70**, 683 (1958).

(3) K. Mislow, *Ann. N. Y. Acad. Sci.*, **98**, 457 (1962).

(4) G. Wittig and H. Zimmermann, *Chem. Ber.*, **86**, 629 (1953).

(5) D. M. Hall and E. E. Turner, *J. Chem. Soc.*, 1242 (1955).

(6) G. W. Badger, P. R. Jefferies and R. W. L. Kimber, *ibid.*, 1837 (1957).

(7) M. S. Newman and A. S. Hussey, *J. Am. Chem. Soc.*, **69**, 3023 (1947).

(8) W. Theilacker and F. Baxmann, *Ann.*, **581**, 117 (1953).

(9) D. M. Hall and M. M. Harris, *J. Chem. Soc.*, 490 (1960).