nitrogen temperature and the tube sealed. After heating the tube at 150° for 58 hr the contents were poured into water and the brown precipitate that was produced was isolated by filtration and dried. Recrystallization from 95% ethanol gave carbazole (0.140 g, 0.837 mmol, 83%) which was identified by its melting point and infrared characteristics.

The Hydrolysis of Bis(4-Nitrophenyl) Carbonate and the General Base Catalyzed Hydrolysis of o-(4-Nitrophenylene) Carbonate

Thomas H. Fife* and Diane M. McMahon

Department of Biochemistry, University of Southern California, Los Angeles, California 90033

The rates of hydrolysis of o-(4-nitrophenylene) carbonate have been measured in H_2O at 30°. The values of k_{obsd} for spontaneous hydrolysis are independent of pH from pH 1 to pH 7. In this pH region a water-catalyzed reaction is occurring with a D_2O solvent isotope effect (k_{H_2O}/k_{D_2O}) of 2.35. As acid concentration is increased from 1.0 M to 5.29 M, the rate of hydrolysis decreases. This behavior is similar to that observed previously for bis(4-nitrophenyl) carbonate. Hydrolysis is catalyzed by a series of general base catalysts. A linear plot of log k_B vs. the pK_a of the catalyzing base is obtained with a slope of 0.30. The point for imidazole fits well on this line with catalysts of much lower basicity including H_2O. The value of $k_{Im}^{H_2O}/k_{Im}^{D_2O}$ is 3.49, indicating proton transfer in the transition state. In contrast, nucleophilic catalysis takes place in the imidazole-catalyzed hydrolysis of bis(4-nitrophenyl) carbonate. Formation and decomposition of an intermediate could be observed in that reaction. Reasons for the mechanism change with the cyclic ester are discussed.

The imidazole-catalyzed hydrolysis of esters having a leaving group of low basicity, such as p-nitrophenyl acetate, has been shown to take place with nucleophilic attack by imidazole at the carbonyl of the ester.[1,2] It was thought that it would be of considerable interest to determine the effect on rate and mechanism of constraining an ester with a good leaving group in a cyclic cis configuration since constraint of this type could take place in an enzymatic reaction, and indeed has been suggested for α-chymotrypsin.[3] As part of a general investigation on steric effects on the mechanisms of hydrolysis of esters and amides, both enzymatic and nonenzymatic,[4] we have therefore studied the hydrolysis of the cyclic ester o-(4-nitrophenylene) carbonate (I) and, for comparison purposes, the analogous noncyclic bis(4-nitrophenyl) carbonate (II). The hydrolysis of

I   II
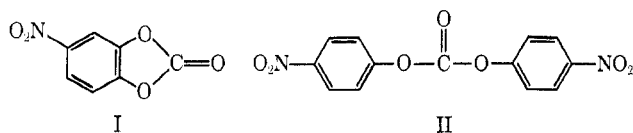
bis(4-nitrophenyl) carbonate in various acid solutions where the reaction involves water catalysis has been studied,[5] but kinetic studies of carbonate ester hydrolysis in buffer solutions have not been previously reported.

Experimental Section

Materials.—o-(4-Nitrophenylene) carbonate was prepared from 4-nitrocatechol and phosgene by the same procedure previously

utilized for the preparation of bis(4-nitrophenyl) carbonate.[5] The pale yellow crystals melted at 99–100°. *Anal.* Calcd for $C_7H_3NO_5$: C, 46.42; H, 1.67; N, 7.72. Found: C, 46.47; H, 1.71; N, 7.67. The infrared spectrum was consistent with structure I. There was no absorption band present due to phenolic OH. Complete hydrolysis in HCl or in buffered solutions gave 1 equiv of 4-nitrocatechol per equiv of ester, as determined spectrophotometrically.

N-(p-Nitrophenoxycarbonyl)imidazole was prepared by adding dropwise 5.0 g (0.025 mol) of p-nitrophenyl chloroformate in dry benzene to 3.4 g (0.05 mol) of imidazole in refluxing dry benzene. The mixture was stirred for 2 hr, cooled, and filtered. Upon evaporation of the benzene a solid residue was obtained which was recrystallized from benzene. The material melted at 128–129°. *Anal.* Calcd for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02. Found: C, 51.62; H, 3.01; N, 17.94.

p-Nitrophenyl chloroformate was obtained from K and K Laboratories. Acetonitrile was Eastman Kodak Spectrograde and was further purified by distillation from P_2O_5 and K_2CO_3. Deuterium oxide (99.8%) was obtained from Bio-Rad Laboratories. Hydrochloric acid was Baker Reagent grade. The concentration of HCl solutions was determined by titration of standard base. Imidazole was obtained from Eastman Kodak and was recrystallized from benzene. All other chemicals were reagent grade.

Kinetic Measurements.—The rates of hydrolysis of o-(4-nitrophenylene) carbonate at 30° in H_2O were followed by measuring the appearance of 4-nitrocatechol at 335 mμ or the monoanion at 410 mμ with a Gilford 2000 recording spectrophotometer. The hydrolysis of bis(4-nitrophenyl) carbonate was followed by measuring the appearance of p-nitrophenol at 330 mμ or p-nitrophenoxide ion at 400 mμ. The spectrum of the solution upon completion of the reaction was identical with that of p-nitrophenol or 4-nitrocatechol in the appropriate buffer solution.

In spectrophotometric determinations the ester was dissolved in acetonitrile and 50 μl of this solution was added with a Hamilton syringe to 3 ml of solution in the cuvette with stirring. The reactions were followed to completion, and infinity points were stable. Constant temperature ($\pm0.1°$) was maintained by circulating water from a Precision Scientific Lo-Temptrol 154 circulating water bath around the cell compartment. The temperature inside the cell compartment was determined with a probe supplied with the Gilford instrument. Pseudo-first-

* Author to whom correspondence should be addressed.
(1) M. L. Bender and B. W. Turnquest, *J. Amer. Chem. Soc.*, **79**, 1652, 1656 (1957).
(2) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957).
(3) T. C. Bruice, *J. Polym. Sci.*, **49**, 101 (1961).
(4) For previous papers, see (a) T. H. Fife, *J. Amer. Chem. Soc.*, **87**, 4597 (1965); (b) J. A. Fee and T. H. Fife, *J. Org. Chem.*, **31**, 2343 (1966); (c) J. A. Fee and T. H. Fife, *J. Phys. Chem.*, **70**, 3268 (1966); (d) T. H. Fife and J. B. Milstien, *Biochemistry*, **6**, 2901 (1967); (e) J. B. Milstien and T. H. Fife, *J. Amer. Chem. Soc.*, **90**, 2164 (1968).

(5) T. H. Fife and D. M. McMahon, *ibid.*, **91**, 7481 (1969).

order rate constants (k_{obsd}) were calculated with an Olivetti–Underwood Programma 101 programmed to calculate a least squares evaluation of the slope and intercept of a plot of ln $[(OD_\infty - OD_0)/(OD_\infty - OD_t)]$ vs. time. Correlation coefficients were invariably in the range 0.9990 to 0.9999. A twofold variation in substrate concentration produced no change in the observed rate constants.

The most probable reaction scheme in acidic solution is that illustrated in eq 1 for hydrolysis of bis(4-nitrophenyl) carbonate. Formation of the monoester, the step governed by k_1, must be

(1)
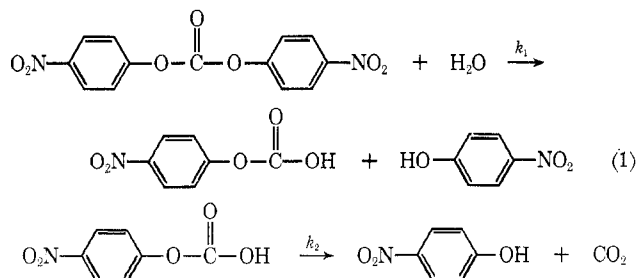
rate determining for spontaneous hydrolysis, considering the reaction to be irreversible, since excellent first-order kinetics were always observed and an initial rapid release of p-nitrophenol was not detected.[5] Complete hydrolysis of II invariably gave 2 equiv of p-nitrophenol per equiv of diester. Identical rate constants were obtained in the presence or absence of 10^{-4} M p-nitrophenol. Good first-order kinetics would not be observed if decomposition of monoester was rate determining unless the first step in the sequence was exceedingly rapid. In that case, however, there would be a burst of 1 equiv of p-nitrophenol which was not observed.

Further evidence for k_1 being rate determining is provided by the very rapid spontaneous hydrolysis of p-nitrophenyl chloroformate (see Results). In that reaction mono(4-nitrophenyl) carbonate can reasonably be assumed to be formed as an intermediate. The chloroformate hydrolyzes to p-nitrophenol at a much faster rate than observed for either I or II at all acid concentrations.

The excellent first-order kinetics and stable infinity points observed in the hydrolysis of o-(4-nitrophenylene) carbonate indicate that ring opening is very probably rate determining. A monoester intermediate would, of course, have an appreciable extinction coefficient at the wavelengths employed, but as with II, a rapid reaction followed by a slower change in absorbance was not observed. A fast initial release of product followed by a slower reaction was not observed in any case in acid or buffer solutions, except for II in imidazole buffers.

The pH measurements were made with a Radiometer Model 22 pH meter. To determine pD, the glass electrode correction equation of Fife and Bruice was employed.[6]

Results

In Table I rate constants are given for hydrolysis of p-nitrophenyl chloroformate in various acidic solutions at 30°. These rate constants are much greater than observed for either I or II at the same acid concentrations. The hydrolysis of p-nitrophenyl chloroformate was too fast to measure at 30° in 0.125 M formate or acetate buffers. The rate constants for hydrolysis of p-nitrophenyl chloroformate in imidazole buffers are much smaller than for spontaneous hydrolysis. An intermediate is therefore being formed which hydrolyzes relatively slowly.

The hydrolysis of bis(4-nitrophenyl) carbonate is subject to marked buffer catalysis. In Table II the second-order rate constants at 50° and μ = 0.5 are presented. In Figure 1 is shown a plot of k_{obsd} vs. total formate buffer concentration at constant pH and ionic strength. The slope increases as the pH is increased. Thus, formate ion is the active species. Formate

(6) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

TABLE I

RATE CONSTANTS (k_{obsd}, MIN^{-1}) FOR HYDROLYSIS AT 30° OF p-NITROPHENYL CHLOROFORMATE, *N*-(4-NITROPHENOXYCARBONYL)IMIDAZOLE, AND THE INTERMEDIATE PRODUCED IN THE IMIDAZOLE-CATALYZED HYDROLYSIS OF BIS(4-NITROPHENYL) CARBONATE

	p-Nitro-phenyl chloroformate	*N*-(4-Nitro-phenoxy-carbonyl)-imidazole	Intermediate
5.29 M HCl	0.438		
3.53 M HCl	1.165		
2.03 M HCl	2.75		
1.36 M HCl	3.31		
0.1 M HCl	6.17		
0.001 M HCl	6.22	2.64	
0.001 M Imidazole[a]			0.0292
0.002 M Imidazole[a]			0.0415
0.004 M Imidazole[a]		0.055	0.054
0.006 M Imidazole[a]		0.06	0.0589
0.01 M Imidazole[a]	0.147	0.149	0.151
0.02 M Imidazole[a]	0.378	0.362	0.392
0.04 M Imidazole[a]	1.18	1.09	1.08
0.064 M Imidazole[a]	2.30	2.26	2.35
0.08 M Imidazole[a]	3.32	3.35	3.56

[a] Total imidazole concentration at pH 7.17, μ = 0.5 M with KCl.

TABLE II

RATE CONSTANTS FOR CATALYSIS OF THE HYDROLYSIS OF BIS(4-NITROPHENYL) CARBONATE AT 50°, μ = 0.5 M WITH KCl

Catalyst	pK_a, 50°	Solvent	k_B l. mol^{-1} min^{-1}
H_2O	−1.74	H_2O	0.00305[a]
$H_2PO_4^-$	2.10	H_2O	0.163[b]
HCOO$^-$	3.60	H_2O	0.182
HCOO$^-$	4.04	D_2O	0.112
CH_3COO^-	4.60	H_2O	0.304
Pyridine	4.99	H_2O	16.4
HPO_4^{2-}	6.70	H_2O	11.34[c]
Imidazole	7.10[d]	H_2O	1450[e]
Imidazole	7.54[d]	D_2O	1500[e]
sym-Collidine	7.10	H_2O	0.783

[a] $k_0/55.5$. [b] Determined in H_3PO_4–$H_2PO_4^-$ buffers. [c] Corrected for catalysis by $H_2PO_4^-$. [d] Measured at 30°. [e] Rate constant for intermediate formation at 30°.

buffer catalysis is reduced in D_2O, ($k_{HCOO^-}^{H_2O}/k_{HCOO^-}^{D_2O}$ = 1.63). The intercept in Figure 1 is also considerably less in D_2O than in H_2O ($k_0^{H_2O}/k_0^{D_2O}$ = 2.65). It was previously shown[5] that spontaneous hydrolysis is a pH-independent reaction with k_{H_2O}/k_{D_2O} = 2.88 for hydrolysis in 0.1 M HCl and 0.1 M DCl. In a plot of log k_B vs. the pK_a of the catalyzing base, differing types of bases do not fit well on a single straight line.

Imidazole is undoubtedly acting as a nucleophile in the hydrolysis of bis(4-nitrophenyl) carbonate since an intermediate can be detected in the reaction. At 50° there is a very rapid initial release of p-nitrophenoxide ion although the extent of this reaction could not be determined quantitatively because of the subsequent hydrolysis of the intermediate. However, by working at lower temperature and low total imidazole concentration (0.001 M–0.01 M), the initial burst of p-nitrophenoxide ion can be measured. At 30°, pH 7.17 and 6.74, and a substrate concentration of 2 × 10^{-5} M, approximately 1 equiv of p-nitrophenoxide per equiv of
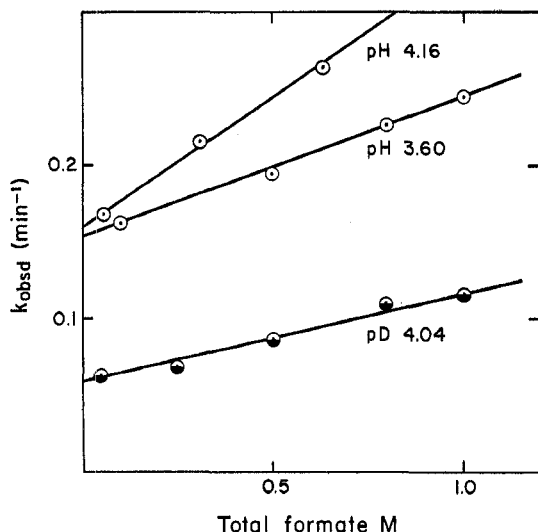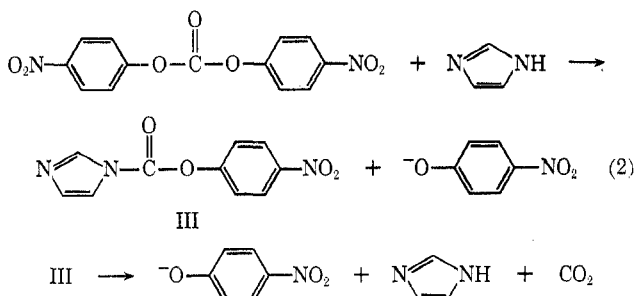
Figure 1.—Plot of k_{obsd} for hydrolysis of bis(4-nitrophenyl) carbonate at 50° and $\mu = 0.5$ vs. total formate concentration (HCOO$^-$ + HCOOH) in H_2O ○ and D_2O ◐.

substrate was rapidly released. This reaction was then followed by a much slower release of p-nitrophenoxide ion. The observed rate constants for both steps were pseudo-first-order. Thus, the reaction scheme being followed is that of eq 2. Identical first-order rate

$$O_2N-\text{—}-O-\overset{\overset{O}{\|}}{C}-O-\text{—}-NO_2 + N\text{—}NH \longrightarrow$$

$$N\text{—}N-\overset{\overset{O}{\|}}{C}-O-\text{—}-NO_2 + {}^-O-\text{—}-NO_2 \quad (2)$$

$$\text{III}$$

$$\text{III} \longrightarrow {}^-O-\text{—}-NO_2 + N\text{—}NH + CO_2$$

constants were obtained in the presence of 1.04×10^{-4} M p-nitrophenol showing that there is little reversibility under the conditions of the experiments. Plots of k_{obsd} for formation of the intermediate III vs. imidazole concentration at two pH values in H_2O and one pD value in D_2O were linear. The ratio $k_{Im}{}^{H_2O}/k_{Im}{}^{D_2O}$ is 0.97.

Plots of k_{obsd} for hydrolysis of the intermediate vs. imidazole concentration at 2 pH values show a definite upward curvature. A plot of $(k_{obsd} - k_0)/Im_B$ vs. Im_B in Figure 2 is linear following eq 3, where Im_B is the

$$k_{obsd} = k_0 + k'_{Im}(Im_B) + k''_{Im}(Im_B)^2 \quad (3)$$

concentration of imidazole in the free base form. An intercept is observed. Thus, hydrolysis of the intermediate acyl imidazole displays both a first-order and a second-order dependence on imidazole concentration. The value of k'_{Im} is 12 l. mol^{-1} min^{-1}, and k''_{Im} has the value 1610 l.^{2} mol^{-2} min^{-1}. It will be noted in Table I that the rate constants in imidazole buffers for hydrolysis of the intermediate from II and for p-nitrophenyl chloroformate are nearly identical, as would be expected if the same intermediate is being formed in the two reactions. This was supported by synthesis of III and the study of its hydrolysis in imidazole buffers. As seen in Table I, the rate constants obtained are nearly
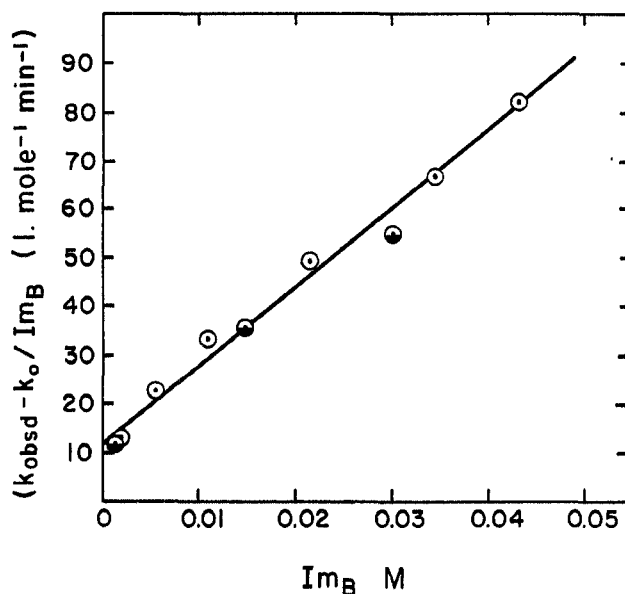

Figure 2.—Plot of $(k_{obsd} - k_0)/Im_B$ for hydrolysis of the intermediate formed in the hydrolysis of bis(4-nitrophenyl) carbonate at 30° vs. Im_B, the concentration of imidazole in the free base form at pH 7.17 ○ and pH 6.74 ◐.

identical with those for hydrolysis of the intermediate from II and p-nitrophenyl chloroformate.

The values of k_{obsd} for hydrolysis of o-(4-nitrophenylene) carbonate at 30° and at various HCl concentrations are presented in Table III. Also given in Table III are

TABLE III
RATE CONSTANTS FOR HYDROLYSIS OF
o-(4-NITROPHENYLENE) CARBONATE IN
VARIOUS AQUEOUS SOLUTIONS AT 30°

HCl, M	pH	$k_{obsd} \times 10^2$ min^{-1}
5.29		5.24
3.53		11.69
2.03		25.26
1.36		39.48
1.01		44.28
0.10		66.0
0.10[a]		63.22
0.10[b] (D_2O)		28.1
0.01		66.31
0.01[a]		60.69
0.001	3.02	70.9
0.001[a]	3.02	66.20
	3.60[c]	62.3[d]
	4.62[e]	58.5[d]
	5.34[f]	66.8[d]
	6.74[g]	77.0[d]
	6.74[h]	75.2[d]
	7.17[g]	93.0[d]
	7.64[g]	135.0[d]

[a] $\mu = 0.5$ with KCl. [b] DCl in D_2O. [c] Formate buffer, $\mu = 0.5$ with KCl. [d] Rate constants were obtained by extrapolation to zero buffer concentration. [e] Acetate buffer, $\mu = 0.5$ with KCl. [f] Pyridine buffer, $\mu = 0.5$ with KCl. [g] Imidazole buffer, $\mu = 0.5$ with KCl. [h] Phosphate buffer, $\mu = 0.5$ with KCl.

values of k_{obsd} for spontaneous hydrolysis at various pH values. When buffer solutions ($\mu = 0.5$) were employed these rate constants were obtained by extrapolation to zero buffer concentration. The rate constants decrease significantly as HCl concentration is increased
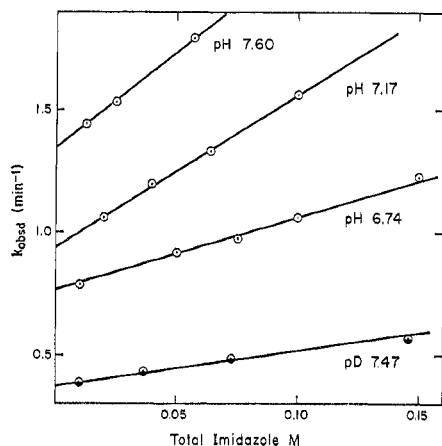
Figure 3.—Plot of k_{obsd} for hydrolysis of o-(4-nitrophenylene) carbonate at 30° vs. total imidazole concentration (Im + ImH$^+$) in H_2O ⊙ or D_2O ◐.

Figure 4.—Plot of log k_B for catalysis of the hydrolysis of o-(4-nitrophenylene) carbonate by various bases at 30° vs. the pK_a of the catalyzing base.

from 1.0 M to 5.29 M. When ionic molarity was held constant at 4.80 M with LiCl however, the decrease in k_{obsd} was smaller as HCl concentration was increased, k_{obsd} being 0.101 min^{-1} at 1.08 M HCl and 0.066 min^{-1} at 3.82 M HCl. At pH values from 1–7 spontaneous hydrolysis is independent of pH. Hydroxide ion catalysis occurs at pH values greater than 7. Increasing the ionic strength with KCl has a small rate retarding effect on the spontaneous reaction. For example, k_{obsd} is 0.663 min^{-1} in 0.01 M HCl and 0.607 min^{-1} in 0.01 M HCl with 0.5 M KCl added. Addition of 0.5 M NaClO$_4$ produced only a slightly larger effect, k_{obsd} being 0.523 min^{-1}. The pH-independent reaction is much slower in D_2O than H_2O, the ratio k_{H_2O}/k_{D_2O} being 2.35 for hydrolysis in 0.1 M HCl and 0.1 M DCl in D_2O.

A pronounced buffer catalysis is observed in the hydrolysis of o-(4-nitrophenylene) carbonate. In Figure 3 a plot is shown of k_{obsd} vs. total imidazole concentration at 3 pH values in H_2O and 1 pD value in D_2O. The plots are linear, and the slope increases as pH increases showing the base form of imidazole to be catalytically active. There is a large D_2O solvent isotope effect for both the imidazole-catalyzed reaction and the spontaneous reaction. The ratio $k_{Im}^{H_2O}/k_{Im}^{D_2O}$ is 3.49. The second-order rate constants for general base catalysis are given in Table IV. A plot of log k_B vs. pK_a of the acid of the catalyzing base is shown in Figure 4. The plot is linear with all bases, including water, fitting well on a line with a slope of 0.30 (r = 0.989). Statistical corrections had essentially no effect on the slope. With statistical corrections[7] the slope was 0.32 and the correlation coefficient was 0.983.

Discussion

The lack of acid catalysis in the hydrolysis of o-(4-nitrophenylene) carbonate is similar to what was observed previously for bis(4-nitrophenyl) carbonate and esters of dichloracetic acid[5] and can be explained in the same manner. Strong electron withdrawal from the carbonyl group will greatly reduce the equilibrium concentration of protonated ester so that acid catalysis cannot compete with the rapid pH-independent reaction. Thus, kinetically significant protonation is not taking place. The large rate decreases produced by

(7) R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A.,* **291**, 297 (1966).
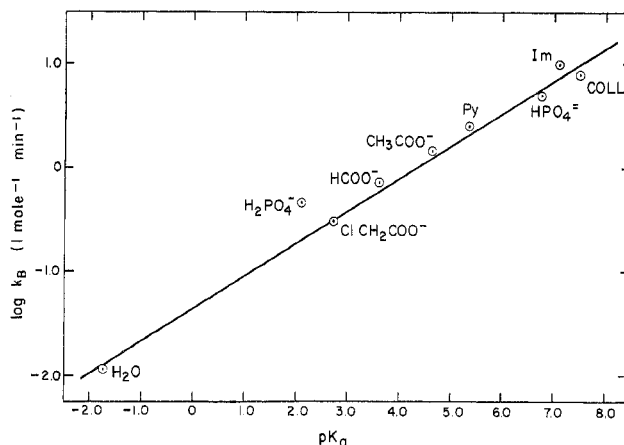
TABLE IV
SECOND-ORDER RATE CONSTANTS FOR GENERAL
BASE CATALYZED HYDROLYSIS OF o-(4-NITROPHENYLENE)
CARBONATE AT 30°, μ = 0.5 WITH KCl

Catalyst	pK_a	k_B, l. mol^{-1} min^{-1}
H_2O	-1.74	0.012[a]
$H_2PO_4^-$	2.10	0.468[b]
$ClCH_2COO^-$	2.70	0.305
$HCOO^-$	3.60	0.736
CH_3COO^-	4.62	1.48
Pyridine	5.34	2.55
HPO_4^{2-}	6.74	5.02[c]
Imidazole (pH 6.74)		9.55
Imidazole (pH 7.17		10.92
Imidazole (pH 7.64)		9.73
Imidazole (average)	7.10	10.06
Imidazole (D_2O)	7.54	2.88
sym-Collidine	7.50	8.04

[a] $k_0/55.5$. [b] Determined in H_3PO_4–$H_2PO_4^-$ buffers. [c] Corrected for catalysis by $H_2PO_4^-$.

increasing acid concentration with these compounds are similar to those observed in reactions where acid has no further catalytic effect because protonation of the substrate is complete.[4c,8-10] This behavior occurs when water is involved in the critical transition state. The observed rate decreases in those cases have been explained by the decrease in water activity as acid concentration is increased,[11] or by a change in rate-determining step.[10] Fedor and Bruice[12] have observed a similar dependence on acidity of the rate constants for spontaneous hydrolysis of ethyl trifluoro-thiolacetate. A plot of log k_{obsd} for o-(4-nitrophenylene)carbonate vs. the logarithms of the activity of water in the acid solutions had distinct curvature, but when ionic molarity and the activity of H_2O was maintained constant with LiCl the decrease in k_{obsd} with increasing acidity was relatively small. This was also observed in the case of p-nitrophenyl dichloroacetate.[5]

The pH-independent hydrolysis of both bis(4-nitrophenyl) carbonate[5] and o-(4-nitrophenylene) carbonate

(8) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.,* 2000, 2009 (1957); J. A. Leisten, *ibid.,* 765 (1959).
(9) S. Marburg and W. P. Jencks, *J. Amer. Chem. Soc.,* **84**, 232 (1962).
(10) E. H. Cordes and W. P. Jencks, *ibid.,* **84**, 832 (1962).
(11) J. F. Bunnett, *ibid.,* **83**, 4956, 4968, 4973 (1961).
(12) L. R. Fedor and T. C. Bruice, *ibid.,* **87**, 4138 (1965).

undoubtedly involves a water-catalyzed reaction. Proton transfer is taking place in the transition state as in IV or a kinetic equivalent as indicated by the much slower reactions in D_2O than in H_2O.
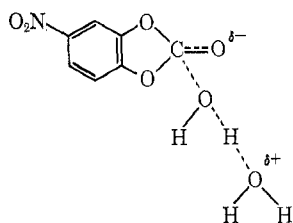
Imidazole-catalyzed hydrolysis of bis(4-nitrophenyl) carbonate proceeds with imidazole functioning as a nucleophile. Detection of an intermediate in the reaction shows this conclusively. Accordingly, the second-order rate constant for intermediate formation is approximately the same in D_2O as in H_2O ($k_{Im}^{H_2O}/k_{Im}^{D_2O} = 0.97$). Nucleophilic catalysis does not lead to a D_2O solvent isotope effect appreciably greater than unity,[13] whereas general base catalysis of ester hydrolysis by imidazole, involving proton transfer in the transition state, generally gives rise to a D_2O solvent isotope effect of 2–3.

The second-order rate constant for imidazole catalysis of the hydrolysis of II (intermediate formation) is much greater than might be expected on the basis of its pK_a in comparison with the other bases studied. As seen in Table II, the rate constant for imidazole catalysis at 30° is 128 times as large as that for HPO_4^{2-} at 50°, even though these bases have closely similar pK_a values, in accord with the fact that imidazole is participating as a nucleophile in this reaction. Water is very likely acting as a general base since $k_{H_2O}/k_{D_2O} = 2.88$.[5] It is probable that the formate ion catalysis is also, to a large extent, general base catalysis in view of the low pK_a of formate in comparison to the leaving group, and the D_2O solvent isotope effect significantly greater than unity (1.63). Acetate ion catalyzed hydrolysis of *p*-nitrophenyl acetate has been found previously to be largely general base.[14] A line with a slope of 0.3 can be drawn through the points for water, formate, and acetate in a plot of log k_B *vs.* pK_a, but, with the exception of *sym*-collidine, there is marked positive deviation of the points for the other bases. A change in mechanism to nucleophilic as the pK_a of the catalyst base becomes comparable to that for the leaving group (7.1) should result in a positive deviation from the Brønsted plot. It has previously been observed that, in nucleophile-catalyzed hydrolysis of *p*-nitrophenyl acetate, bases of different type lie on different lines in a Brønsted plot,[15] whereas, in the general base catalyzed hydrolysis of ethyl dichloroacetate,[16] bases of divergent type fit a single plot ($\beta = 0.47$).
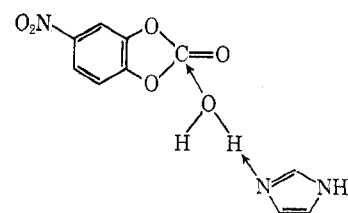
In the case of the cyclic carbonate ester *o*-(4-nitrophenylene) carbonate, the evidence strongly indicates that a mechanism change has taken place, with imidazole catalysis most likely proceeding by a general base mechanism. Thus, the ratio $k_{Im}^{H_2O}/k_{Im}^{D_2O}$ is 3.49. A linear plot of log k_B *vs.* pK_a is now obtained (Figure 4)

with all points, including those for H_2O and imidazole, fitting well on a line with a slope of 0.30. It will be noted that now imidazole and HPO_4^{2-} have approximately the same rate constant, as might be expected for catalysts with nearly the same pK_a in a general base catalyzed reaction.[16] The kinetically equivalent general-acid, specific-base catalysis can also be considered as a possibility.

An alternative possibility is the mechanism shown in eq 4. Such a reaction, although involving nucleophilic

$$(4)$$
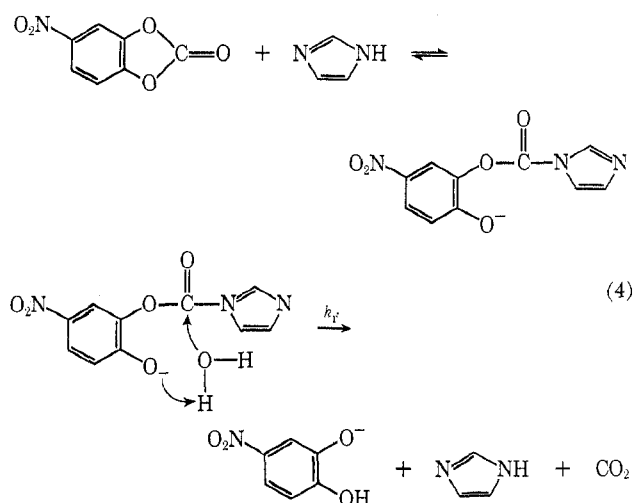
attack by imidazole, would still give rise to a large solvent isotope effect since proton transfer takes place in the rate-determining step. In ester hydrolysis reactions general base catalysis by a neighboring phenoxy anion has been suggested for hydrolysis of *p*-nitrophenyl 5-nitrosalicylate.[17] However, the mechanism of eq 4 is very unlikely for imidazole-catalyzed hydrolysis of the cyclic carbonate since imidazole lies on the same line in the plot of log k_B *vs.* pK_a with all of the other catalysts, including H_2O, chloroacetate, and formate which certainly are not acting solely as nucleophiles in view of their low pK_a. The point for imidazole should deviate from the plot if a different mechanism was occurring. The point for *sym*-collidine (2,4,6-trimethylpyridine) also fits well on the same line with imidazole and the other bases. *sym*-Collidine cannot effectively participate as a nucleophile because of the methyl groups at the 2 and 6 positions of the pyridine ring which sterically inhibit nucleophilic attack by nitrogen at carbon.[18] In general base catalyzed reactions the effects of the 2,6-methyl group substitution are small compared with those in nucleophilic reactions.[19] Thus, all of the compounds in the series, including imidazole, are most likely catalyzing ring opening by a general base mechanism.

(13) M. L. Bender, E. J. Pollock, and M. C. Neveu, *J. Amer. Chem. Soc.*, **84**, 595 (1962).

(14) A. R. Butler and V. Gold, *J. Chem. Soc.*, 1334 (1962).

(15) T. C. Bruice and R. Lapinski, *J. Amer. Chem. Soc.*, **80**, 2265 (1958).

(16) W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961).

(17) M. L. Bender, F. J. Kezdy, and B. Zerner, *ibid.*, **85**, 3017 (1963).

(18) J. G. Pritchard and F. A. Long, *ibid.*, **79**, 2365 (1957).

(19) F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963).

There would appear to be no reason why imidazole could not attack the cyclic ester as a nucleophile. The reason for a general base or kinetic equivalent mechanism must then be that the reaction cannot readily go forward to products when imidazole attacks as a nucleophile. This could be due to a rapid reclosure of the ring as in eq 5 to regenerate starting material.

$$\tag{5}$$
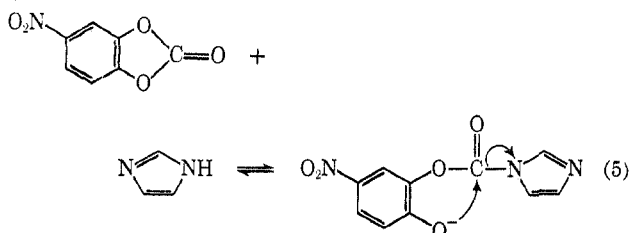
The mechanism might therefore change to the normally less favorable general base pathway since the reaction would then go directly to products. This argument assumes that there is no great energy barrier for ring formation. Reversibility was not detected in the imidazole reaction with II at low concentrations of p-nitrophenol, but in an intramolecular reaction the effective concentration of the attacking group is greatly increased.[20]

The second-order rate constant for attack of imidazole on bis(4-nitrophenyl) carbonate at 30° is 144 times as large as k_{Im} for the cyclic carbonate at 30°, whereas the rate constant for water catalysis is 4 times as large

at 30° for the cyclic ester as that for the noncyclic ester at 50°. Thus, the cyclic compound, while more reactive in the water-catalyzed reaction is much less susceptible to imidazole catalysis, in accord with the fact that a normally less favorable mechanism is involved.

Five- and six-membered ring lactones having a cis configuration are hydrolyzed with hydroxide ion catalysis much more rapidly than are lactones having a trans configuration or noncyclic esters.[21,22] Facile imidazole catalysis was observed in the hydrolysis of the cis lactones, γ-butyrolactone and δ-valerolactone,[23] but imidazole catalysis of the hydrolysis of aliphatic esters without acyl group activation can be detected as occurring at only an extremely slow rate.[24] Thus, the reactive cis configuration is enhancing imidazole catalysis of lactone hydrolysis. In the case of carbonate ester hydrolysis, however, as indicated in the present study, when reversibility of ring opening is likely on steric grounds imidazole catalysis will be less effective for esters in the cis configuration than for analogous noncyclic esters.

(20) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 10–13.

(21) R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).
(22) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, p 22.
(23) T. C. Bruice and J. J. Bruno, *J. Amer. Chem. Soc.*, **83**, 3493 (1961).
(24) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 833, 837 (1964).

Acid-Catalyzed Reactions of Certain δ-Hydroxyamides Having γ Hydrogen. Mechanisms[1a]

CHUNG-LING MAO AND CHARLES R. HAUSER[1b]

Department of Chemistry, Duke University, Durham, North Carolina 27706

Received October 14, 1969

Certain δ hydroxyamides having γ hydrogen undergo three types of acid-catalyzed reactions; these involve cyclodeamination, linear dehydration, and cyclodehydration to form a δ lactone, an olefin–amide, and a δ lactam, respectively. The predominant course of reaction is dependent on the acidic medium, the temperature, and the structure of the hydroxyamide. The olefin–amide is evidently an intermediate in the conversion of certain hydroxyamides into lactams, but not in that of certain others. Mechanisms are suggested and the usefulness of the methods in synthesis are indicated.

Recently,[2] δ-hydroxyamides such as **1a** were shown to undergo cyclodehydration with cold concentrated sulfuric acid to furnish a useful method of synthesis of corresponding δ lactams, which are substituted 3,4-dihydroisocarbostyrils. Thus, **1a** afforded lactam **2a**. The hydroxyamides **1a** and **1b** are readily prepared by
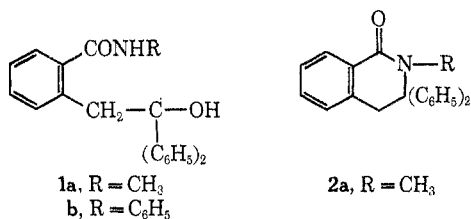
dilithiation of the appropriate N-substituted o-toluamide with n-butyllithium followed by condensation of the resulting dilithioamide with benzophenone.[3]

In the present investigation, a study was made of the reactions and mechanisms of hydroxyamides such as **1a** with various acidic reagents. This study promised to be of interest because of the possibility of effecting two new types of acid-catalyzed reactions and of determining the mechanisms of all three types of reactions. Both new types of reaction were realized. Thus, hydroxyamides **1a** and **1b** underwent linear dehydration and cyclodeamination with appropriate acidic reagents to give olefin–amides **3a** and **3b** and lactone **4**, respectively. Also, olefin–amide **3a** under-

1a, R = CH₃
b, R = C₆H₅

2a, R = CH₃

(1) (a) Supported by the National Science Foundation. (b) Deceased.
(2) C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6**, 83 (1969).

(3) R. L. Vaulx, W. H. Puterbaugh, and C. R. Hauser, *J. Org. Chem.*, **29**, 3514 (1964).