Effect of Hydroxyl Group Substituents on Pyran Ring on Hydrolysis Rate of Benzoates: 2-Tetrahydropyranyl Benzoate

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Abstract □ The hydrolysis of 2-tetrahydropyranyl benzoate was followed spectrophotometrically at 240 nm and was first order with respect to the compound, independent of pH, and very sensitive to solvent polarity and had an isotope effect (k_{D_2O}/k_{H_2O}) near unity. The pH-independent hydrolysis rate was about 1×10^6 times faster than that of the corresponding glucosyl benzoate. The results suggest that the presence of hydroxyl groups on the pyran ring has tremendous effect on the hydrolysis rate of these compounds.

Keyphrases □ Hydrolysis kinetics—2-tetrahydropyranyl benzoate, effect of pH □ Kinetics, hydrolysis—2-tetrahydropyranyl benzoate, effect of pH □ 2-Tetrahydropyranyl benzoate—hydrolysis kinetics, effect of pH

Various enzyme-catalyzed glycosyl transfer reactions are thought to involve intermediate formation of an acyl linkage (1). Brown and Bruice (2) showed that the hydrolysis of glucosyl benzoate (I) is catalyzed by hydrogen and hydroxide ion and at pH 4 and 25°. The I hydrolysis rate was 4.4×10^{-8} sec^{-1}.

In view of the importance of the acyl linkage in enzymatic reactions and of the possible utility of such linkage as a blocking group for carboxylic acids (3), the hydrolysis kinetics of 2-tetrahydropyranyl benzoate (II) were studied over a wide pH range. The data indicate that the presence of hydroxyl groups on the tetrahydropyran ring has a dramatic effect on the hydrolysis rate of these compounds.

EXPERIMENTAL

Syntheses of II—Compound II was prepared according to the following procedure. To 3.0 g of benzoic acid in 50 ml of freshly distilled
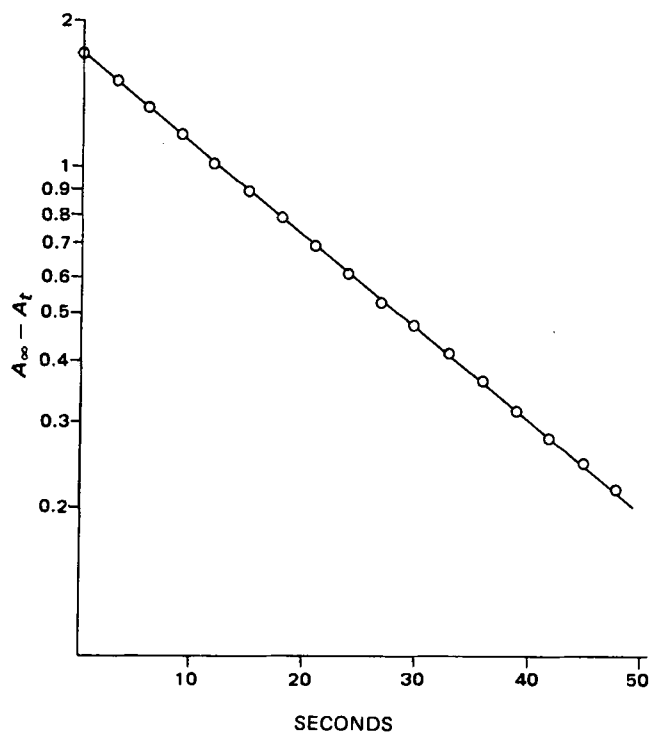

Figure 1—*Semilog plot of* $A_\infty - A_t$ *versus time for the hydrolysis of 2-tetrahydropyranyl benzoate.*
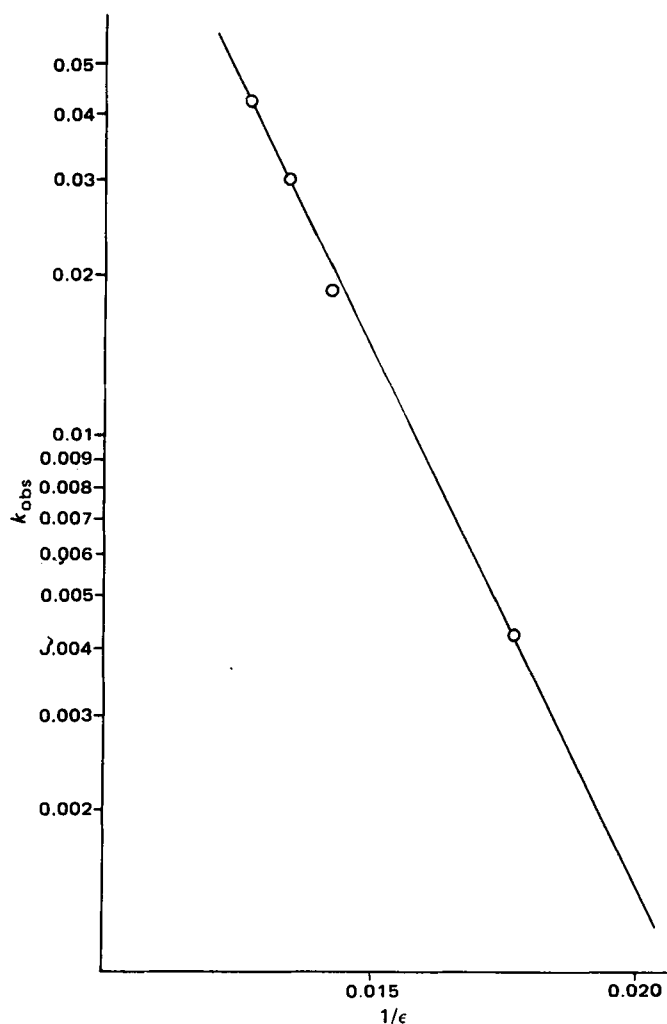

Figure 2—*Plot of* log k_{obs} *for the hydrolysis of 2-tetrahydropyranyl benzoate versus the reciprocal of the dielectric constant of the solution* [log $k_{obs} = -(199.7/\epsilon) + 1.164$].

Table I—Half-Lives for II Hydrolysis at 25° and Ionic Strength of 0.1

pH	$t_{1/2}$, sec[a]
2.04	11.8
3.05	15.5
4.00	16.0
5.23	16.2
6.28	16.0
8.80	16.2
10.25	16.8
12.00	16.8

[a] Each half-life is an average of four determinations.

Table II—Effect of Buffer Concentration on the II Hydrolysis Rate at 25° and Ionic Strength of 0.7

Total Acetate Buffer, pH 4.6, M	$t_{1/2}^a$, sec	Total Phosphate Buffer, M	$t_{1/2}^a$, sec
0.01	15.8	0.01	15.8
0.05	15.8	—	—
0.20	15.9	0.2	16.0

[a] Each half-life is an average of three determinations.

Table III—Dependency of First-Order Constants for II Hydrolysis on the Dielectric Constant of the Solution

Dioxane, %	Dielectric Constant, ϵ
0	78.6
5	74
10	70
25	56.3
50	34.3

dihydropyran[1], 10 ml of 0.4% p-toluenesulfonic acid in benzene and 30 ml of freshly distilled dihydropyran were added. The reaction mixture was stirred at room temperature for 3 hr. At the completion of the reaction, the remaining p-toluenesulfonic acid was neutralized with 1 equivalent of pyridine. The solvents were then removed at 40° with a rotary evaporator, leaving a viscous liquid.

The NMR spectra and the elemental analysis were consistent with the structure of II; NMR (CDCl₃): δ 7.23–8.30 (m, 5H, ArH), 6.30 (m, 1H, 2-CH), 3.10–4.23 (m, 2H, 6-CH₂), and 1.0–2.2 (m, 6H, 3-, 4-, and 5-CH₂).

Anal.—Calc. for $C_{12}H_{14}O_3$: C, 70.20; H, 6.38. Found: C, 72.15; H, 6.30.

The purity of the derivative also was determined spectrophotometrically and was found to be 99% when a known amount of the derivative was hydrolyzed to the parent compound at room temperature with 0.01 N HCl and the concentration in solution was calculated from a standard Beer's law plot.

Kinetic Measurements—A stock solution containing 0.02 M II was prepared freshly in spectral grade dioxane. A 12-μl aliquot of this stock solution was placed in a 5-cm cell, and 12 ml of a buffer at the desired pH and an ionic strength of 0.1 was added. After rapid mixing, the appearance of benzoic acid was followed at 240 nm with a recording spectrophotometer[2]. Buffer species and concentrations to obtain the desired pH were similar to those employed by Garrett and Won (4).

The effect of acetate and phosphate buffers on the II hydrolysis rate was determined at a constant ionic strength of 0.7.

The effect of the dielectric constant on the II hydrolysis rate was determined in pH 6.28, 0.01 M phosphate buffer with an ionic strength of

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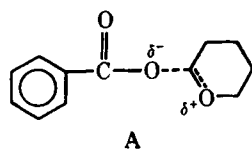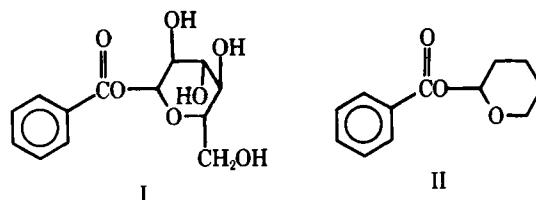
0.1. The dielectric constant of these solutions was varied by the addition of spectral grade dioxane to the aqueous buffer solutions (5).

The hydrolysis rate of II also was determined in deuterium oxide and water containing 1 mg of anhydrous sodium carbonate/ml.

RESULTS

The hydrolysis rate of II to benzoic acid was first order with respect to the concentration of the compound over a wide pH range. Figure 1 shows a typical semilog plot of ($A_\infty - A_t$) *versus* time.

Table I illustrates the dependency of the hydrolysis rate of II on the solution pH. The hydrolysis rates were independent of the hydroxide-ion concentration.

The rate constants for II hydrolysis were determined as a function of acetate and phosphate buffer concentrations (Table II). The hydrolysis rate was independent of the buffer concentration.

The effect of the dielectric constant on the II hydrolysis rate is reported in Table III. Figure 2 shows a typical plot of the logarithms of these rate constants *versus* the reciprocal of the dielectric constant $1/\epsilon$ (6). As is seen in Table III and Fig. 2, the II hydrolysis rates were influenced markedly by the dielectric constant of the medium.

To determine the solvent kinetic isotope effect, the hydrolysis rate of II was determined in deuterium oxide and water containing 1 mg of anhydrous sodium carbonate/ml. The ratio of the two rates of hydrolysis, k_{D_2O}/k_{H_2O}, was 1[3].

DISCUSSION

Compound I hydrolyzes at a much slower rate than II. For example, in the pH 3–5 range and at 25°, I hydrolyzed by a factor of 2×10^{-6} times slower than II. Furthermore, the pH rate profile of I hydrolysis was characterized by three distinct regions: a hydrogen-ion-catalyzed region at low pH, a pH-independent region at pH 3–5, and a hydroxide-ion-catalyzed region at pH > 7, whereas the hydrolysis of II was independent of pH over a wide range (Table I). This result, coupled with the facts that the hydrolysis rate of II was markedly dependent on the dielectric constant of the medium (Table III and Fig. 2) and independent of the buffer concentration (Table II) and that the ratio of k_{D_2O}/k_{H_2O} was unity, strongly suggests that II hydrolysis proceeds by a classical S_N1 mechanism. The rate-limiting step in the hydrolysis reaction is probably the C—O bond cleavage, as shown in Structure A.

The hydrolysis of I in the pH-independent region was postulated (2) to proceed *via* an S_N1 mechanism. In that case, the dramatic difference in the hydrolysis rate of the two compounds apparently is due to the differences in the stability and ease of formation of the carbonium-ion intermediate. This finding indicates that the presence of the hydroxyl group substituent on the pyran ring has a significant effect on the formation of the carbonium ion.

Preliminary studies on the hydrolysis of esters of aspirin[4] strongly suggest that the number, as well as the position, of the hydroxyl group substituents on the pyran ring influences the cleavage rate of these compounds.

REFERENCES

(1) B. Capon, *Chem. Rev.*, **69**, 407 (1969).

(2) A. Brown and J. Bruice, *J. Am. Chem. Soc.*, **95**, 1593 (1977).

(3) A. Hussain, M. Yamuzaki, and J. Truelove, *J. Pharm. Sci.*, **63**, 627 (1974).

(4) E. R. Garrett and C. M. Won, *ibid.*, **60**, 1801 (1971).

(5) C. A. Kraus and R. M. Fuoss, *J. Am. Chem. Soc.*, **55**, 21 (1933).

(6) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed., Wiley, New York, N.Y., 1961, p. 145.

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[1] Aldrich Chemical Co.
[2] Cary 15.

[3] The half-lives in seconds for II hydrolysis in deuterium oxide and water were 17.0, 16.9, and 16.9 and 16.2, 16.3, and 16.2, respectively.
[4] A. Hussain, J. Truelove, and H. Kostenbauder, unpublished work.