ALKALINE HYDROLYSIS OF BENZOATES AND ρ-NITROBENZOATES OF SUBSTITUTED 4-HYDROXYPIPERIDINES

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It was found by means of a spectrophotometric method that esters of substituted 4-hydroxypiperidines are hydrolyzed four times faster in water and in 50% aqueous methanol in the presence of alkali than in isosteric carbocyclic ester; this is due to the presence of the inductive effect of the nitrogen atom and the additional polar effect of an as yet unknown nature. Esters with an axial acyloxy group are hydrolyzed more slowly by a factor of two to three than their epimers with an equatorial acyloxy group owing to the steric effect, but this difference vanishes when a charge is introduced into the ring, apparently because of an electrostatic interaction.

In the investigation of the interrelationship of the structure and properties of saturated six-membered heterocyclic compounds, the establishment of the effect of the heteroatom and spatial orientation of the reaction group on their reactivities seems extremely important. Both of these problems have received very little study in the case of functional derivatives of piperidine. In this connection, we began a study of this problem with an investigation of the kinetics of alkaline hydrolysis of some esters of 4-hydroxypiperidines. The kinetics of hydrolysis of the esters of saturated nitrogen heterocyclic alcohols have been previously examined only in a few cases (in particular, see [1-3]). We studied the alkaline hydrolysis of cyclohexyl benzoate (I) and the esters (II-VI) of substituted 4-hydroxypiperidines (Table 1) in water and 50% aqueous methanol. The rate of hydrolysis of the investigated compounds was measured by a spectrophotometric method [4, 5] based on the difference in the UV spectra of starting esters I-VI and of the $RC_6H_4COO^-$ anions formed during their hydrolysis (the 4-hydroxypiperidines formed as a result of the reaction have practically no absorption in the working wavelength region). The working wavelengths, which were selected in accordance with [4], for benzoates I-III were 260 and 274 nm, whereas those for p-nitrobenzoates IV-VI were 264 and 300 nm. The parameters of the UV spectra of I-VI are presented in Table 1. The degree of transformation was calculated from Eq. (1) [4]:

$$X=\frac{(D_1/D_2)\cdot\varepsilon_E{}^2-\varepsilon_E{}^1}{(D_1/D_2)(\varepsilon_E{}^2-\varepsilon_B{}^2)-(\varepsilon_E{}^1-\varepsilon_B{}^1)}, \qquad (1)$$

where D is the observed optical density, ε is the molar-extinction coefficient, the E and B subscripts pertain to the ester and the $RC_6H_4COO^-$ anion, respectively, and the superscripts 1 and 2 refer to the working wavelengths.

Inasmuch as the alkali concentration under the conditions that we adopted either exceeded the initial ester concentration by more than an order of magnitude or was maintained constant by means of a buffer, the hydrolysis of I-VI was first-order in ester and pseudo-zero order in alkali. This is confirmed by the constancy of rate constant k_1, calculated from first-order Eq. (2), during the experiment:

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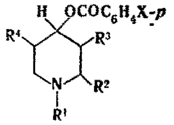
TABLE 1. UV Parameters of the Spectra of Benzoates and p-Nitrobenzoates



Compound	R¹	R²	R³	R⁴	X	Form	Orientation of the C-methyl group	Orientation of the acyloxy group	λ_{max}, nm	ε_{max}	ε^1	ε^2
I*	—	—	—	—	—	—	—	*e*	274	865	865	695
II	CH_3	H	H	H	H	Base	—	*e*	274	1075	1075	890
III	CH_3	CH_3	H	CH_3	H	Base	2*e*5*e*	*e*	274	955	955	690
IV	CH_3	H	H	H	NO_2	Methiodide		*e*	264	13400	13400	3240
						Hydrochloride		*e*	264	12050	12050	2380
V	$C(CH_3)_3$	H	CH_3	H	NO_2	Methiodide	3*e*	*e*	264	12570	12570	3080
								a	264	12860	12960	2690
						Hydrochloride		*e*	264	13560	13560	3290
								a	264	12410	12410	2575
VI	CH_3	H	CH_3	H	NO_2	Methiodide	3*e*	*e*	264	14250	14250	3290
								a	264	13350	13350	3250
						Hydrochloride		*a*	264	12900	12900	3065
								e	264	13150	13150	2820

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*Cyclohexyl benzoate.

$$k_1 = \frac{2.3}{\tau} \lg \frac{1}{1-x}. \tag{2}$$

The observed constant also proved to be independent of the starting ester concentration and the buffer concentration.

Second-order constant k_2 was calculated from Eq. (3):

$$k_2^{obs} = k_1 / c_{OH^-}, \tag{3}$$

in which case c_{OH^-} in aqueous solutions was determined from the measured pH value with allowance for the activity coefficient ($f_{OH^-} = 0.755$ at 25°, and $\mu = 0.15$ [6]), and c_{OH} in aqueous methanol solutions was determined by direct titration with a 0.1 N HCl solution. Inasmuch as II-VI can exist in both protonated and unprotonated forms, depending on the pH value, the kinetic equation in the general case has the form (4)

$$\omega = k_2^{obs} \cdot c_{tot}^E \cdot c_{OH^-} = k_C \cdot c_C \cdot c_{OH^-} + k_B \cdot c_B \cdot c_{OH^-}, \tag{4}$$

where c_C, c_B, and c_{tot}^E are the salt, base, and total concentrations of the ester, respectively, c_{OH^-} is the hydroxide ion concentration, k_2^{obs} is the experimental hydrolysis rate constant, and k_C and k_B are the hydrolysis rate constants of the protonated and unprotonated forms, respectively.

When (pH $- pK_a$) ≥ 2 (which was the case during the hydrolysis of benzoates I-III), k_2^{obs} can be determined as the true hydrolysis rate constant of the unprotonated form (k_B). In other cases, the c_B and c_C values were calculated from the pK_a values of IV-VI. The k_B and k_C values in these cases were calculated by the method of least squares from Eq. (5), obtained by transformation of Eq. (4):

$$\frac{k_2^{obs}}{c_B / c_{tot}^E} = k_B + k_C \cdot \frac{c_C}{c_B}. \tag{5}$$

In the case of the methiodides of IV-VI the $k_2^{obs} = k_N$ value proved to be independent of the pH and characterizes their reactivity directly. The obtained $k_2^{obs} = k_B$ values for I-III are presented in Table 2, and the k_B, k_C, and k_N values obtained for IV-VI are presented in Table 3.

In order to ascertain the effect of the presence of a ring nitrogen atom on the reactivities of the cyclic esters we compared the rate of alkaline hydrolysis of benzoates of cyclohexanol (I), 1-methyl-4-hydroxypiperidine (II), and 1,2,5-trimethyl-4-hydroxypiperidine (III) in 50% aqueous methanol at 25 and 60°. It is seen from Table 2 that the k_B rate constant for ester II is greater by a factor of 3.8-4.1 than the constant

TABLE 2. Hycrolysis of Benzoates of Cyclohexanol and Substituted 4-Hydroxypiperidines (II-III) in 50% Aqueous Methanol ($\mu = 0.1$)

Compound	Temp. °C	mp of the base, °C (from ether)		$k_B \cdot 10^2$, liter/mole sec	Activation energy, E, kcal/mole	lg A (25°)
		$c_{tot}^{ester} \cdot 10^4$	c_{OH^-}			
I	25	5,5—10,8	0,1	0,115±0,01	14,4±0,6	7,6
	40	5,5—7,08	0,097	0,35±0,03		
	60*	5,5—8,30	0,007—0,24	1,5±0,1		
II	25	5,5—6,8	0,045—0,09	0,50±0,03	14,0±0,6	7,9
	40	5,7	0,039	1,60±0,25		
	60	3,45—6,1	0,004—0,01	5,8±0,3		
III	25	4,3—7,5	0,068—0,11	0,23±0,02	12,1	6,2
	60	5,4—7,2	0,01—0,02	2,0±0,2		

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* The dependence of the hydrolysis rate constant on μ was verified in the 0.1-0.5 range; the difference did not exceed the experimental error.

TABLE 3. Hydrolysis of p-Nitrobenzoates of Substituted 4-Hydroxypiperidines in Water (25° C, $\mu = 0.15$)

Compound	Three-dimensional orientation of the	mp of the base, °C (from ether)	pK_a values		Rate constant, liter/mole · sec		
			methanol—water (1 : 1) (found)	water (calc.)	k_B of the base	k_C of the hydrochloride	k_N of the methiodide
IVβ	*e*	83—84	7,90	8,49	0,58±0,02	2,3±0,1	2,05±0,08
Vβ	*e*	104—105	8,67	9,36	0,25±0,02	1,20±0,05	1,74±0,08
Vγ	*a*	94—95	8,99	9,73	0,13±0,03	1,2±0,1	1,2±0,2
VIβ	*e*	59—60	7,72	8,31	0,57±0,01	1,9±0,1	1,55±0,04
VIγ	*a*	72—73	8,07	8,69	0,18±0,01	1,4±0,2	1,52±0,08

for ester I. This ratio considerably exceeds the value found in [2] for the hydrolysis of esters I and II in water and is closer to the value presented in [1] for the analogous esters of azobenzenecarboxylic acid at 25° in 40% aqueous dioxane (6.0). Inasmuch as the cyclohexane and piperidine rings are practically isosteric relative to the reaction center, the observed difference should be ascribed exclusively to the polar effect of the cyclic nitrogen atom. Calculations show, however, that, with allowance for the regularity of transmission of the inductive effect [7], one should have expected an effect that was approximately half the observed value. This indicates either increased effectiveness of transmission of polar effects through the piperidine system as compared with the saturated acyclic hydrocarbon chain [7] or the presence of an additional polar effect of noninductive character. The "field effect" was considered as this sort of effect in [1], whereas interaction between anticoplanar C—H bonds was considered in [8]. The available experimental data do not as yet make it possible to make a choice from the proposed explanations. Insofar as ester III is concerned, it is hydrolyzed more slowly by a factor of approximately two to three than II, most likely because of steric hindrance caused by the CH_3 group adjacent to the reaction center. This is confirmed by the decreased value of the preexponential factor (Table 2).

For a more detailed investigation of the transmission of polar effects through the piperidine ring it seems of interest to compare the reactivities of compounds with ring-nitrogen atoms in different states, i.e., to study, in addition to the amino ester bases, their analogs containing quaternary ($> \overset{+}{N}R_2$) and protonated ($> \overset{+}{N}HR$) ammonium groups. In the latter case, it was necessary to study the reaction rate at low pH values, and we therefore turned to an investigation of the alkaline hydrolysis in water of p-nitrobenzoates IV-VI, which are approximately one order of magnitude more reactive than benzoates II and III (Table 3). From the data in Table 3 it is first of all seen that the hydrolysis rates of all of the charged derivatives (k_C and k_N) are five to 10 times higher than in the case of their electrically neutral uncharged analogs (k_B). This effect is apparently a combination of the inductive and electrostatic effects of the ammonium group.

One's attention is directed to the fact that the k_C and k_N values in all cases are extremely close — the difference between them does not exceed 30%. This differs markedly from the situation observed in a number of aliphatic amino esters, for which the protonated forms are 30 to 50 times more reactive than their quaternary analogs [9, 10]. This is apparently due to the effect of the approach of the $^+NHR_2$ and COO^-

groups in aliphatic compounds; this proves to be impossible in 4-hydroxypiperidines, which have quite rigid geometries. The conformational stability of the molecules of the investigated compounds, particularly in the case of N-tert-butyl derivaties Vβ,γ, enabled us to compare the rates of hydrolysis of the geometrical isomers that are epimeric with respect to C_4 and have different three-dimensional orientations of the acyloxy groups. It is seen from Table 3 that geometrical isomers Vγ and VIγ with axial acyloxy groups are saponified more slowly than their epimers Vβ and VIβ with an equatorial acyloxy group, and $k_B{}^{eq}/k_B{}^{ax} \sim 2$-3,* i.e., a ratio that is extremely close to the values observed in the hydrolysis of esters of 4-tert-butylcyclohexanol ($k^{eq}/k^{ax} = 2.5$-6.7 [11, 12]).

Thus the nitrogen atom does not have any substantial effect in this case, and this confirms the steric character of the observed effect. The absence of a dependence of the hydrolysis rate constant on the spatial orientation of the acyloxy group in the charged derivatives – the hydrochlorides and methiodides of V and VI – is unexpected and interesting. This is most likely associated with the presence of an additional electrostatic effect, which should be somewhat different for the geometrical isomers because of the different distances between the acyloxy groups and the cationic center; this difference apparently compensates the steric effect of the axially oriented reaction center. To verify this hypothesis one must investigate the dependence of the rate of hydrolysis of the charged forms of esters of substituted 4-hydroxypiperidines on the ionic strengths, the results of which will be presented in our next communication.

EXPERIMENTAL

The synthesis of esters II and III was described in [13, 14]. We obtained the geometrical isomers of the esters (IVβ,γ–VIβ,γ) from the appropriate 4-hydroxypiperidines and p-nitrobenzoyl chloride, and the products were purified by crystallization from ether†.

Benzoates I-III were hydrolyzed in 50% aqueous methanol with an ionic strength of 0.1 (chemically pure KCl) at pH values from 10.76 to 13.30 directly in the thermostatted cuvette of an SF-4 spectrophotometer. The hydrolysis of p-nitrobenzoates IV-VI was carried out in a 0.01-0.05 M borate buffer ($Na_2B_4O_7$–HCl, pH = 8.70-9.00; $Na_2B_4O_7$–NaOH, pH = 9.25-11.00) [6] at 25° and an ionic strength of 0.15 (the ionic strength was maintained by means of the addition of chemically pure KCl).

The spectrophotometric measurements were made from aliquot samples or directly in a thermostatted spectrophotometer cuvette.

The basicities of esters IV-VI were determined by potentiometric titration in 50% aqueous methanol at 25°. The pK_a values in water were calculated from the Taft equation (6) with a correction for the ionic strength:

$$pK_{a\omega,I} = pK_{a\omega} - \frac{\rho^*_{\omega}}{\rho^*_s} pK_0{}^s - \frac{\rho^*_{\omega}}{\rho^*_s} pK_0{}^s + 0{,}5\sqrt{I}, \qquad (6)$$

where pK_0 and ρ^*_{ω} are the parameters of the Taft equation for the thermodynamic basicities of tertiary amines in water at 25° ($pK_0\,\omega = 9.61$ and $\rho^*_{\omega} = -3.3$ [15]), $pK_0{}^S$ and ρ^*_S are the same parameters for 50% aqueous methanol ($pK_0{}^S = 9.06$, $\rho^*_S = -2.98$ [16]), $pK_a{}^S$ is the experimental basicity of the amino ester in 50% aqueous methanol at 25°, and 0.5 I is the correction for the ionic strength, according to [17].

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* The somewhat elevated rate of hydrolysis of VIβ is possibly associated with a certain amount of distortion of the geometry of the ring in the transition state.

†The synthesis and investigation of the tree-dimensional structure of esters IV-VI will be described in a separate communication.

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