BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 3215—3216 (1972)

The Effect of Intramolecular Hydrogen Bonding on Benzoylation of 2-(*N*,*N*-Dialkylamino)ethanols

Kunihiro Ichimura and Junko Yoshida*
Research Institute for Polymers and Textiles, Sawatari 4, Kanagawa-ku, Yokohama
** Department of Chemistry, Faculty of Science, Toho University, Narashino, Chiba*

(Received December 4, 1971)

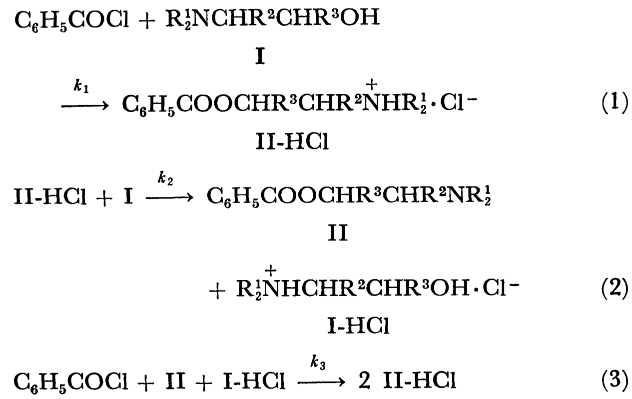
We have synthesized some *O*-acylated 2-(*N*,*N*-dialkylamino)ethanols by the action of acyl chloride on aminoalcohols. When an equimolar amount of acyl chloride was used, the yields of the hydrochloride of *O*-acylated aminoalcohol were found to be relatively low, the hydrochloride of aminoalcohol also being formed. Although various *O*-acylated 2-(*N*,*N*-dialkylamino)ethanols have been synthesized, the mechanism does not seem to be fully understood. We have examined the reaction mechanism of some 2-(*N*,*N*-dialkylamino)ethanols with benzoyl chloride by means of IR-spectrometry. It was found that the reaction rate is affected by the intramolecular hydrogen bonding of the aminoalcohols.

Results and Discussion

It was observed that the reaction of acyl chloride with equimolar 2-(*N*,*N*-dialkylamino)ethanol at room temperature gives a mixture of the hydrochloride of *O*-acylated aminoalcohol and of the parent aminoalcohol. The yields of acylated amines were thus reduced, although the reaction was expected to proceed smoothly through the intramolecular base-catalysed mechanism. Because of the good solubility of the hydrochloride of products in dichloromethane, benzoylation of aminoalcohols was followed by means of infrared spectrometry.

As soon as an equimolar amount of *N*,*N*-diethylaminoethanol (Ia) was mixed with benzoyl chloride (3.30×10^{-2} M) in dichloromethane at room temperature, the ester C=O band of diethylaminoethyl benzoate (IIa) at 1717 cm^{-1} and OH stretching vibration of diethylaminoethanol hydrochloride (Ia-HCl) at 3280 cm^{-1} began to develop. After 24 hr, the C=O ester band was found to shift to 1727 cm^{-1} due to formation of the hydrochloride of diethylaminoethyl benzoate (IIa-HCl), as the OH band at 3280 cm^{-1} weakened. About 42% benzoyl chloride remained. The products were identified with the authentic samples.

However, the IR-spectrum of a reaction mixture of benzoyl chloride and twofold molecular amount of aminoalcohol differs from the above result. The ester carbonyl band of IIa-HCl at 1727 cm^{-1} and OH band of Ia-HCl at 3280 cm^{-1} increase monotonously and isoabsorptive points at 3400 cm^{-1} are observed. This indicates that a twofold molecular amount of aminoalcohol is neccessary to complete the reaction to afford diethylaminoethyl benzoate and hydrochloride of diethylaminoethanol. The spectral change during the course of the reaction of equimolar amount of aminoalcohol is then interpreted by the following scheme (scheme 1). Aminoalcohol (Ia) is at first benzoylated to give ester hydrochloride (IIa-HCl) according to reaction (1), which, in turn, is readily deprotonated by aminoalcohol (Ia) to form Ia-HCl and free ester (IIa)(reaction (2)). Reaction (2) was confirmed by the fact that the infrared spectrum of an equimolar mixture of IIa-HCl and Ia is essentially the same as that of IIa and Ia-HCl.[1] Twofold molar aminoalcohol is thus consumed according to reactions (1) and (2). Remaining benzoyl chloride reacts then more slowly with the hydrochloride of aminoalcohol (Ia-HCl), free ester (IIa) acting as the scavenger of hydrogen chloride formed (reaction (3)). From observation of the infrared spectral change we assume that the rate constants are qualitatively in the order; $k_2 \gg k_1 > k_3$, where k_1, k_2, and k_3 are the rate constants of reactions (1), (2), and (3), respectively.



$$\mathrm{C_6H_5COCl} + \underset{\mathrm{I}}{\mathrm{R^1_2NCHR^2CHR^3OH}} \xrightarrow{k_1} \underset{\mathrm{II\text{-}HCl}}{\mathrm{C_6H_5COOCHR^3CHR^2\overset{+}{N}HR^1_2\cdot Cl^-}} \tag{1}$$

$$\mathrm{II\text{-}HCl} + \mathrm{I} \xrightarrow{k_2} \underset{\mathrm{II}}{\mathrm{C_6H_5COOCHR^3CHR^2NR^1_2}} + \underset{\mathrm{I\text{-}HCl}}{\mathrm{R^1_2\overset{+}{N}HCHR^2CHR^3OH\cdot Cl^-}} \tag{2}$$

$$\mathrm{C_6H_5COCl} + \mathrm{II} + \mathrm{I\text{-}HCl} \xrightarrow{k_3} 2\ \mathrm{II\text{-}HCl} \tag{3}$$

Scheme 1. Benzoylation of 2-(*N*,*N*-dialkylamino)ethanols (Ia: $\mathrm{R^1=CH_3CH_2}$, $\mathrm{R^2=R^3=H}$; Ib (*threo*), Ic (*erythro*): $\mathrm{R^1=R^2=CH_3}$, $\mathrm{R^3=C_6H_5}$).

Using the stationary state approximation, we obtain the kinetic equation

$$\mathrm{d}x/\mathrm{d}t = k_1(a-x)(b-2x) \tag{4}$$

$$\text{if } a=b,\ k_1t = 2.303\log((a-x)/(a-2x)) \tag{5}$$

$$\text{if } 2a=b,\ k_1t = x/(2a(a-x)) \tag{6}$$

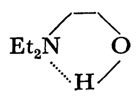
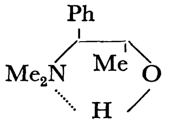
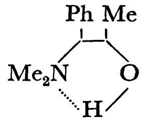
where a and b are the initial concentrations of benzoyl chloride and aminoalcohol, respectively, and x is the concentration of the product or benzoyl chloride consumed at time t. The rate at 24°C was thus calculated by estimating the disappearance of carbonyl band of benzoyl chloride at 1775 cm^{-1}. The second order kinetic plots according to Eq. (6) gave a straight line

---

[1] It is reported that aminoethanol (pK_a=9.50) is more basic than the *O*-acetylated derivative (9.10).[2]

[2] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, (1965).

Table 1. Physical properties of 2-(N,N-dialkylamino)ethanols

				Cinchonidine
rate const. (k_1)a) (l mol^{-1} sec^{-1})	2.64×10^{-2}	3.94×10^{-3}	1.01	too rapidly
pK_a (26°C)2)	9.74b)	10.00	9.26	8.40c)
ν_{OH} (cm^{-1})d)	3420	3300	3400	3280
ν_{OH} of HCl saltd)	3280	3280	3240	3280

a) Although the rate constants may be lacking accuracy with respect to constancy and homogeneity of temperature of the reaction mixture during the kinetic measurement, the present method (see Experimental) is sufficient for a discussion of the difference in rate under the same conditions. b) Corrected to 26°C.5) c) In 80% Methyl Cellosolve at 15°C.4) d) The wave numbers did not change in the range 0.12—0.024 M in dichloromethane.

when twofold molecular amount of aminoalcohol was used. In the case of equimolar aminoalcohol a straight line was also obtained only up to 40% consumption of benzoyl chloride according to Eq. (5). The second order rate constants in both cases are identical within experimental error. It is therefore noteworthy that the concerted push-pull mechanism is excluded, in contrast to the alcoholysis of some acyl chloride which have been found to be second order in alcohol.3) In order to obtain further information with regard to the acylation, benzoylation of *threo*-1-phenyl-2-dimethylaminopropanol-1 (Ib) and the diastereomeric *erythro* compound (Ic) was carried out in the same manner. A remarkable difference in reaction rate between these diastereomers was observed (Table 1). If the rate determining step of reaction (1) is the attack of benzoyl chloride upon hydroxy group of aminoalcohol, then the stronger the intramolecular hydrogen bonding, the faster the reaction. Although the hydrogen bonding of *threo* compound (Ib) is stronger than that of *erythro* isomer (Ic) as a result of the steric requirement (see ν_{OH} in Table 1), the benzoylation of *erythro* isomer (Ic) is about 250 times faster than that of *threo* isomer (Ib). The effects of molecular structure of these diastereomers on the rate should predominantly arise from the intramolecular hydrogen bonding. We can thus conclude that the intramolecular hydrogen bonding reduces the nucleophilicity of nitrogen atom to form N-acylammonium cation (III). In view of failure to detect the intermediate and from observation of isoabsorptive points during the course of reaction by means of IR-spectroscopy, we propose that the intermediate (III) undergoes immediately the N–O acyl rearrangement to yield hydrochloride of O-acylated aminoalcohol.

The rate of benzoylation (k_1) increases apparently with decrease in pK_a of aminoalcohol. Cinchonidine whose pK_a is 8.40 was in fact found to be benzoylated so rapidly that measurement of the rate by the present method failed. The correlation could be caused by the effect of intramolecular hydrogen bonding which gives rise to depression of the nucleophilicity of nitrogen atom as mentioned above and contrariwise to enlargement of pK_a value. It is seen that the geometrical isomer of β-aminoalcohol with a stronger intramolecular hydrogen bonding is more basic than that with a weaker one.4)

Such acyl chlorides as phenylacetyl- or phthaloylaminoacyl chloride also react too rapidly with 2-(N,N-dialkylamino)ethanols to make observation of the infrared spectral change of the reaction mixture possible. This suggests another mechanism where hydrogen at the α-position of acyl chloride could readily be eliminated to give ketene as Pracejus has proposed from the results of the asymmetric esterification of acyl chloride in the presence of alkaloids.5)

Experimental

Materials: Benzoyl chloride was distilled before use. Diethylaminoethanol was fractionally distilled and used immediately. *erythro*- and *threo*-1-Phenyl-2-dimethylaminopropanol-1 were obtained by the Leuckardt reaction of ephedrine and ψ-ephedrine and purified by distillation or sublimation. Cinchonidine was recrystallized from aqueous propanol-2 and dried *in vacuo*. 2-N,N-Diethylaminoethyl benzoate (bp$_7$ 140—141°C), hydrochloride of the ester (mp 124—125°C) and 2-(N,N-diethylamino)ethanol hydrochloride (mp 134—135°C) were synthesized in the usual way. Dichloromethane was purified and dried.

Kinetic Measurement: The absorbance of benzoyl chloride at 1775 cm^{-1} in dichloromethane was found to be proportional to concentration in the range 0.8×10^{-2}—3.5×10^{-2} M. A solution of benzoyl chloride of 3.30×10^{-2} M(1 ml) in dichloromethane was mixed rapidly with shaking with equi- or twofold molecular amount of aminoalcohol solution (1 ml) in a test tube immersed in a water bath, the temperature of which was equilibriated with room temperature controlled at 24°C. This instant was taken as the origin of time. The KBr cell (0.5 mm thick) was then filled with the combined solution. These operations required at least 30 sec. The IR-spectrum was recorded at intervals with a JASCO DC-402 Type IR-Spectrometer. We could observe no other band than that due to aromatic ring system within the range 2400—1800 cm^{-1}. The concentration of benzoyl chloride in the reaction mixture was calculated by the estimation of absorbance of carbonyl band at 1775 cm^{-1}. The second order kinetic plots of Ia, Ib, and Ic according to Eq. (5) or (6) deviated from a straight line within 4%, 10%, and 5% error, respectively.

---

3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, (1959), p. 332.

4) V. Prelog and O. Häfliger, *Helv. Chim. Acta*, **33**, 2021 (1950).

5) G. Pracejus, *Liebigs Ann. Chem.*, **622**, 10 (1959).

6) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen (1962).