The Reaction of 2-(Diethylamino)ethanol with Imides[*]

By Tsuyoshi OGATA

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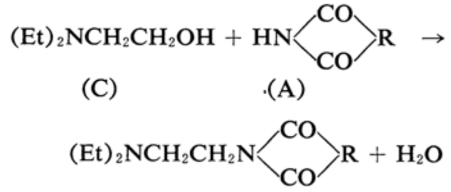
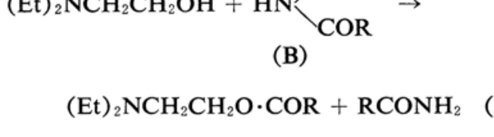
In the previous paper of this series,[1] it was reported that the imides of dibasic acids (A) were condensed with 2-(diethylamino)ethanol (C) with the elimination of water, while the imides of monobasic acids (B) were converted into the corresponding amides and the esters of the aminoalcohol (C) in good yields.



$$\underset{\text{(C)}}{(Et)_2NCH_2CH_2OH} + \underset{\text{(A)}}{HN\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle R} \rightarrow (Et)_2NCH_2CH_2N\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle R + H_2O \qquad (1)$$



$$(Et)_2NCH_2CH_2OH + \underset{\text{(B)}}{HN\left\langle\begin{matrix}COR\\COR\end{matrix}\right.} \rightarrow (Et)_2NCH_2CH_2O\cdot COR + RCONH_2 \qquad (2)$$

The present investigation has been undertaken to clarify the cause of the different in reactivity on the aminoalcohol (C) between the imides of dibasic acids (A) and those of monobasic acids (B).

Experimental Results and Discussion

The Reaction of 2-(Diethylamino)ethanol (C) with Imides or Their Analogues.[1]—The rerults summarized in Table I show that: 1) The presence of two carbonyl groups attached to

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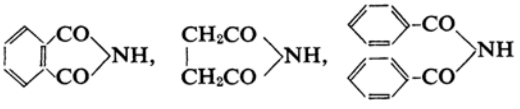
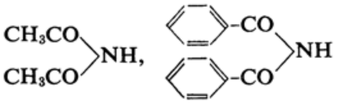
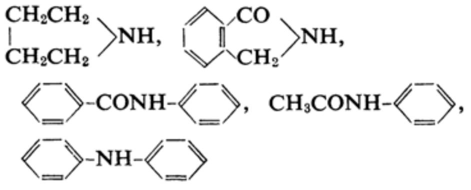
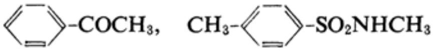
[*] Presented at the Symposium on Organic Reaction Mechanisms, Fukuoka, October, 1963. This is the third paper of the series, "Studies of the Reaction of 2-(Diethylamino)ethanol with Imides."

[1] R. Goto and T. Ogata, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **84**, 653 (1963).

TABLE I. RELATIVE REACTIVITIES OF IMIDES AND THEIR ANALOGUES ON THE AMINOALCOHOL (C)

No.	Imides or their analogues	Type of reaction	Note
(I)		Eq. 1	The aminoalcohol (C) does not react below 180°C. Usual alcohols and amino-*t*-alcohol do not react with imides (A).
(II)		Eq. 2	Usual alcohols react with imides (B).
(III)		No reaction	
(IV)		No reaction	

an imino group is essential to both reactions, 1 and 2.

2) The imides of dibasic acids (cyclic imides)** (A) are condensed with the aminoalcohol (C) with the elimination of water.

3) The imides of monobasic acids (straight-chain imides)** (B) are converted into the corresponding amides and the esters of the aminoalcohol (C).

4) Usual alcohols do not react with the imides of dibasic acids (A). Therefore, a diethylamino group in the aminoalcohol (C) is necessary for reaction 1.

5) The imides of monobasic acids (B) react with alcohols in the same manner as with the aminoalcohol (C). Thus, an attack of the alcohol or the aminoalcohol (C) on acyl groups seems to be easier than that on an imino group of imide (B).

Reaction of 2-(Diethylamino)ethanol (C) with Unsymmetrical Imides of Monobasic Acids (B).[2] —In these experiments the reactivities of the two acyl groups in imide were compared. The experimental data are shown in Table II.

The data in Table II lead to the following conclusions:

1) In the cases of I, II, IV, and V, unsymmetrical imides predominantly yield the esters of the stronger acids. In the cases of VI and VII, however, unsymmetrical imides yield the esters of the weaker acids exclusively. Therefore, it seems that the steric influence predominates over the acidity of the acyl group.

2) I and II, where the parent acids are of approximately the same strength, gave the esters in a different molar ratios. These results may be explained by the greater steric hindrance of the isobutyryl group over that of the propionyl group.

3) In the case of III, the ester of the weaker acid forms predominantly.

As Fig. 1 shows, the resonance in the benzoyl group would disperse the postive charge of the carbonyl carbon atom into a benzene ring, making the benzoyl group less susceptible to a nucleophilic attack than the acetyl group, which would be polarized by the inductive effect of the methyl group.[3]

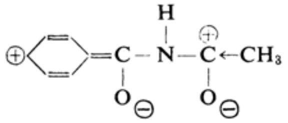


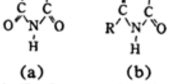
Fig. 1.

Reaction Mechanism

1) In discussing the reaction mechanism, it is first necessary to consider the role of a diethylamino group in 2-(diethylamino)ethanol (C).

Recently, Komori and his co-workers[4]

** From the measurement of the dipole moments of imides, only a cis-cis conformation (a) is possible in cyclic imides (A), while a cis-trans conformation (b) is likely in straight-chain imides (B). W. D. Kumler and C. M. Lee, *J. Am. Chem. Soc.*, **83**, 4586 (1961); **84**, 571 (1962).



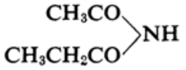
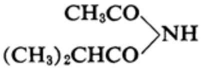
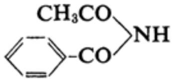
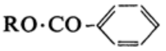
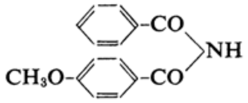
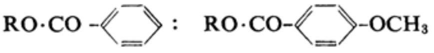
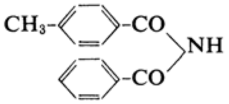
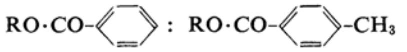
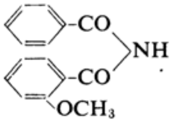
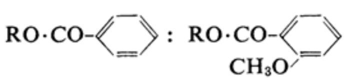
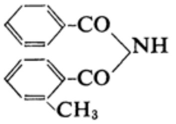
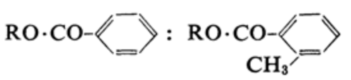
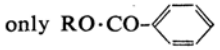
(a) (b)

[2] R. Goto and T. Ogata, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **84**, 849 (1963).

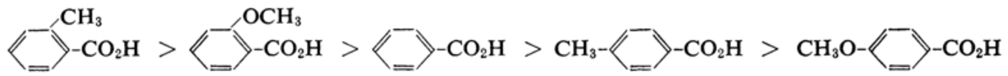
[3] P. S. Baily and Y.-G. Chang, *J. Org. Chem.*, **27**, 1193 (1962).

[4] S. Komori, M. Ochiai and Y. Ōki, *J. Chem. Soc. Japan, Ind. Chem. Sec.* (*Kogyo Kagaku Zasshi*), **64**, 1588 (1961); **65**, 1830 (1962).

TABLE II. RELATIVE REACTIVITIES OF UNSYMMETRICAL IMIDES OF MONOBASIC ACIDS ON THE AMINOALCOHOL (C)

No.	Unsymmetrical imides*	Esters formed**	Molar ratio of esters fromed
(I)	 $\mathrm{(CH_3CO)(CH_3CH_2CO)NH}$	$\mathrm{RO{\cdot}COCH_3}$: $\mathrm{RO{\cdot}COCH_2CH_3}$	1 : 0.93
(II)	 $\mathrm{(CH_3CO)((CH_3)_2CHCO)NH}$	$\mathrm{RO{\cdot}COCH_3}$: $\mathrm{RO{\cdot}COCH(CH_3)_2}$	1 : 0.51
(III)		$\mathrm{RO{\cdot}COCH_3}$: 	1 : 0.51
(IV)			1 : 0.25
(V)			1 : 0.29
(VI)			1 : 0.08
(VII)			

* The order of acidities (pK_a^{25}) of monobasic acids, of which unsymmetrical imides are constituted, is as follows.



pK_a^{25} (3.91) (4.09) (4.20) (4.34) (4.47)

$> \mathrm{CH_3CO_2H} > \mathrm{(CH_3)_2CHCO_2H} > \mathrm{CH_3CH_2CO_2H}$
(4.76) (4.85) (4.88)

"Series of Comprehensive Organic Chemistry (Dai Yuki-kagaku)," Additional Vol. 2, Asakura Publishing Co., Tokyo (1963), p. 638.

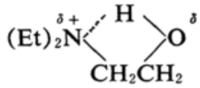
** $\mathrm{R=(Et)_2NCH_2CH_2-}$

reported that, in the preparation of polyhydroxyethylene alkyl ether from alcohol and ethylene oxide in the presence of tertiary amine serving as a catalyst, the reaction rate increased in proportion to the basicity of the amine and considerably decreased as *N*-substituents of the amine became bulky. In this reaction, therefore, it seems that a hydroxyl group in alcohol is activated by tertiary amine, as is shown in Eq. 3.

$$\mathrm{ROH + R'_3N \rightarrow R-\overset{\delta-}{O}-H\cdots\overset{\delta+}{N}R'_3} \qquad (3)$$

Douheret and Pariaud[5] suggested the presence of an intramolecular hydrogen bond in dialkylaminoethanol on the basis of their measurement of its infrared sepctrum in carbon tetrachloride. Therefore, a hydroxyl group in 2-(diethylamino)ethanol seems to be activated by a diethylamino group, as is shown in Eq. 4.

$$\mathrm{(Et)_2NCH_2CH_2OH} \rightleftharpoons$$

 (4)

$$\mathrm{(Et)_2\overset{\delta+}{N}\cdots H-\overset{\delta-}{O}(CH_2CH_2)} \qquad (4)$$

Furthermore, in the reaction of benzyl alcohol on dibenzamide, benzamide and benzyl benzoate were produced in good yields.[1] In the case of lauryl alcohol, however, in spite of a longer reaction time, benzamide

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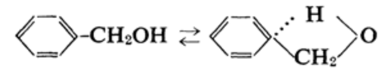
[5] G. Douheret and J. C. Pariaud, *J. Chim. Phys.*, 59, 1021 (1962).

and lauryl benzoate were produced in lower yields than in benzyl alcohol.

Ōki and Iwamura⁽⁶⁾ concluded that in benzyl alcohol there is an interaction between an aromatic nucleus and a hydroxyl group, as is shown in Eq. 5. Therefore, it seems that a hydroxyl group is activated by an aromatic nucleus and that, toward dibenzamide, benzyl alcohol is more reactive than lauryl alcohol.



(5)

2) Lamberton and Standage⁽⁷⁾ investigated the alkaline and acid hydrolysis of some *N*-acylbenzamides ($x\,C_6H_4CONRCOR'$) and found that in the alkaline medium the ortho-substituent x almost completely prevented the attack of hydroxyl ions on the nearer carbonyl group, while meta- and para-substituent did not have such a steric effect. Thus, *N*-acyl ortho-substituted benzamides gave ortho-substituted benzamide ($x\,C_6H_4CONHR$) and acid ($R'COOH$) upon alkaline hydrolysis, while meta- and para-substituted benzamides gave the stronger acid preferentially.

In the acid hydrolysis, on the other hand, the ortho-substituent showed no sign of the steric effect. In meta- and para-substituted benzamides, the weaker acid was liberated preferentially.

From these facts, it may be generally concluded that in the alkaline hydrolysis, the S_N2-type mechanism is operative, as is shown in Fig. 2-A, while in the acid hydrolysis, the results are explicable by the formation of acylium ions, as is shown in Fig. 2-B.

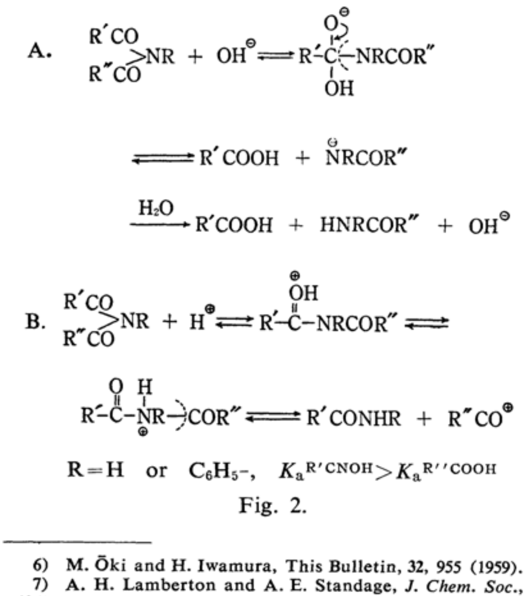


Fig. 2.

Tedder⁽⁸⁾ summarized the reactions of unsymmetrical carboxylic anhydrides on amines or ethanol and showed that these reactions proceeded in the same fashion as the alkaline hydrolysis of diacylamines mentioned above. Furthermore, he showed that Friedel-Crafts acylation by unsymmetrical carboxylic anhydrides in the presence of aluminum chloride proceeded in the same fashion as the acid hydrolysis of diacylamine, and that the ketones derived from the weaker acids were produced preferentially.

On the basis of these data, reasonable conclusions may be deduced as follows:

i) In the case of the imides of monbasic acids (B), a nucleophilic attack of the aminoalcohol (C) will occur preferentially at the more positive carbonyl group and, when the position is sterically hindered, at another, less hindered carbonyl group.

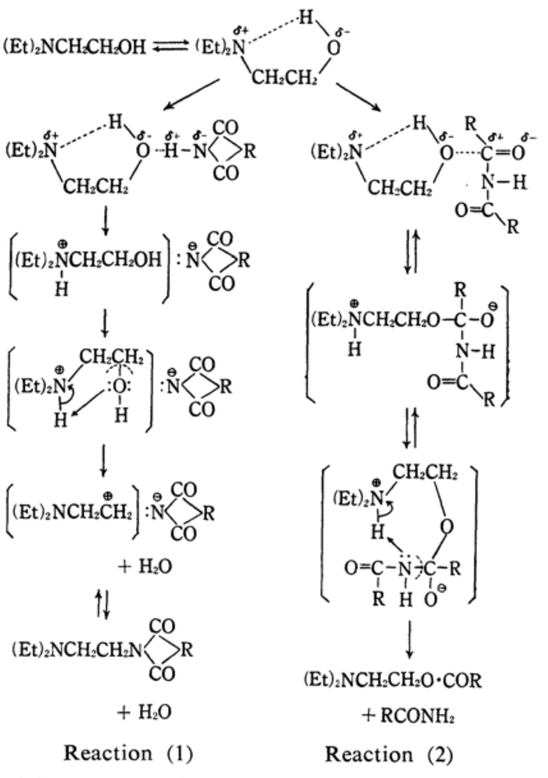


Fig. 3. Reaction mechanism of 2-(diethylamino)ethanol with imides

ii) In the case of the imides of dibasic acids (A), it seems that, on account of the steric hindrance of the carbonyl group of the imide, a nucleophilic attack of the aminoalcohol (C) is almost completely prevented and that an attack of the aminoalcohol (C) will

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6) M. Ōki and H. Iwamura, This Bulletin, 32, 955 (1959).

7) A. H. Lamberton and A. E. Standage, *J. Chem. Soc.*, **1960**, 2957.

8) J. M. Tedder, *Chem. Revs.*, 55, 805 (1955).

occur at the imino group.

These conclusions are schematically summarized in Fig. 3.

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Department of Chemistry
Faculty of Science
Kyoto University
Sakyo-ku, Kyoto