## On the Thermal Dissociation of Organic Compounds. XII. The Effects of the Substituents on the Thermal Dissociation of Substituted Phenylureas

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#### Introduction

The kinetics of the thermal dissociation of urea, di- and tri-substituted ureas in fatty acids have been studied<sup>1-4</sup>). In the

present work, more than ten new ureas of the types, 1, 1-diethyl-3-phenylureas (I), 1-pentyl-3-phenylureas (II) and 1,3-diphenylureas (III), substituted for methoxy, methyl, chloro and nitro in ortho, meta and para positions, respectively have been synthesized, and the kinetics of the thermal dissociation of these ureas in fatty acids have been studied. The effects of the substituents on the thermal dissociation of these ureas are discussed.

T. Hoshino, T. Mukaiyama and H. Hoshino, J. Am. Chem. Soc., 74, 3097 (1952).
 T. Mukaiyama and T. Matsunaga, ibid., 75, 6209

<sup>(1953).</sup> 3) T. Mukaiyama, S. Ozaki and T. Hoshino, This Bulletin, 27, 578 (1954).

<sup>4)</sup> T. Mukaiyama, S. Ozaki and Y. Kobayashi, ibid., 29, 51 (1956).

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The dissociation of substituted ureas, e.g., 1,1-diethyl-3-(p-chlorophenyl) ureas in chloroacetic acid, takes place according to the following equations:

$$(C_{2}H_{5})_{2}N - C - N \not \subset C \qquad \longleftrightarrow$$

$$(C_{2}H_{5})_{2}NH + OCN \not \subset C \qquad (1)$$

$$\begin{array}{cccc} & O & O \\ CICH_2C & -O & -CNH & \searrow CI & \longrightarrow \\ & & & & O \\ CICH_2CNH & & \searrow CI + CO_2 \end{array}$$
(3)

The reaction in fatty acids can be followed by measuring the rate of evolution of carbon dioxide (eq. 3), as the reaction (1) is the rate-determining step.

1, 1-Diethyl-3-arylureas (I)<sup>5)</sup> were prepared from diethylcarbamyl chloride, corresponding amines and triethylamine. 1-Pentyl-3-arylureas (II) could be obtained from pentyl isocyanate and amines. 1,3-Diarylureas (III) were obtained in the course of the syntheses of ureas (I) and (II) as mentioned below. Reactivity of aromatic amines towards isocyanate and diethylcarbamyl chloride is of a similar order to those observed by Van Opstall<sup>6</sup>) and Linke<sup>7</sup>) in the reaction between 1chloro-2,4-dinitrobenzene and aromatic amines, and by C. Naegeli<sup>8)</sup> et al. in the reaction of the amines with phenyl isocyanate. Methoxy-, methyl- and chloro- anilines react easily with pentyl isocyanate, but nitroanilines do not react at room temperature. m-Nitroaniline reacts at 80°C., and p-nitroaniline does to an extent of only 1% in 5 hours at the same temperature. The reactivity of diethylcarbamyl chloride towards amines is smaller than that of isocyanate. In the reaction of unreactive amines, such as nitro- and chloro- anilines, towards diethylcarbamyl chloride, the yields were poor, and by raising the temperature, 1,3-diarylureas were produced as byproducts. As 1,1,3trisubstituted ureas dissociate much more easily by Eq. (4) than 1,3-diarylureas as

shown in Table II and in a previous report<sup>4</sup>), 1,3-diarylureas were obtained probably through the following mechanism.

$$X \xrightarrow{H_0}_{N-C} \stackrel{R_1}{\underset{R_2}{\times}} \rightleftharpoons X$$

$$X \xrightarrow{X} \xrightarrow{NCO + HNR_1R_2} (4)$$

$$X \xrightarrow{X} \xrightarrow{X} \xrightarrow{NCO +} \swarrow NH_2 \rightleftharpoons X$$

$$X \xrightarrow{X} \xrightarrow{H_0} \stackrel{H_0}{\underset{N-C-N}{\times}} \bigwedge (5)$$

1, 3-Bis-(p-nitrophenyl) urea was produced also in the reaction of p-nitroaniline with pentyl isocyanate at 150°C.

Aniline derivatives having more than two substituents such as 2,4,5-trichloroand 2,6-dichloro- aniline have small reactivity, and 2, 4, 5-trichloro- is less reactive than 2,6-dichloro-aniline.

#### Experimental

Ureas.-The various constants of the ureas synthesized and the experimental conditions of syntheses are summarized in Table I. As an example, the synthetic procedure for 1,1-diethyl-3-(o-methoxyphenyl)urea is given: A mixture of 4.1 g. (4/100 mole) of diethylcarbamyl chloride, 4.8 g. (4/100 mole) of o-anisidine and 5 g (5/100 mole) of triethylamine are heated under a reflux condenser with a calcium chloride tube for 2hours at 80-90°C. The triethylamine hydrochloride precipitated is filtered off, and the salt is washed with benzene. The combined filtrate and benzene washing are washed with 2 N hydrochloric acid, and then with water. After dried over anhydrous sodium sulfate, benzene was evaporated and 5.3 g. (59%) of 1, 1-diethyl-3-(omethoxyphenyl)urea was obtained by distillation, colourless liquid boiling at 143-145°C/0.40-0.45mm.

Solvents.-The solvents were purified by the same method as described<sup>3)</sup> previously. The boiling point of caproic acid was 104-106°C/16-17 mm. and that of chloroacetic acid was 184-185°C.

Rate measurement.—The procedure for measuring the rate of dissociation of ureas in fatty acids has been described previously<sup>1,3)</sup>. On plotting against time the logarithm of the volume of carbon dioxide,  $\Delta Y$ , evolved at regular intervals of time, a straight line was obtained. This indicates a first order reaction rate. The rate constant is given by the gradient of such a plot. The molar ratio of ureas to solvents was 1:100in each case.

The rate constants of the thermal dissociation of these ureas in fatty acids are summarized in Table II and in part are shown in Fig. 1 and 2.

The activation energy (Ea) of the dissociation reaction of 1,1-diethyl-3-phenylurea in chloroacetic

<sup>5)</sup> Some of ureas (I) are reported to be useful as herbicides named C. M. U. (Chlorophenyl Methyl Urea). U. S. P. 2655444, 2655445, 2655446 and 2655447. Kagaku to Kogyo (Chemistry and Chemical industry) 9, 63 (1956).

Van Opstall, Rec. trav. Chim., 52, 901 (1933).
 Linke, Ber., 56, 848 (1923).

<sup>8)</sup> C. Naegeli, A. Tyabji and C. Conrad, Helv. Chim. Acta, 21, 1127 (1938).

						Shoi	chi	ro O	ZAKI	an	d Ts	sut	omu NAG	GOY	A					[Vol	. 3	0,	No. 5
	lysis ogen	Found						11.47			11.89		9.97							18.44			
	Ana Nitr	Calcd.						11.66			11.66		9.95							18.54			
	Yield	(%)	16					18	8		25		30			2				17	14		
	M.P.	(.°°)	235					241-242	221.5		265		225-226			247				244.5-245			
	Byproduct		1,3-diphenyl- urea					1,3-di-(o- tolyl)urea	1,3-di-(m-tolyl) urea		1,3-di-( <i>p</i> -tolyl)urea		1,3-di-( <i>o</i> - chlorophe- nyl)-urea			1,3-di-(o- chlorophe- nvl) urea				1,3-di-(m- nitrophe- nyl)urea	*		
	Analysis Nitrogen	Calcd. Found				12.60 12.46	12.60 12.58	13.58 13.49		13.58 13.52		13.58 13.60	Carbon 58.30 58.01 Hydrogen 6.65 6.87		12.36 12.57								
SODS	rield	(%)	0	30	62	59	33.4	40	0	27.1	0	32	8	42	17	0	17	0	0	0	12	0	0
HETIC METH	M.P.	(.C.)		84.5-85	*	B.P.143-145/ 0.45	61.5 - 62	78-79		101 - 102		67.5 - 68	B.P.124-126/ 0.4	*	89-89.5		118 - 118.5				88-89		
EIR SYN'	Reaction time.	(hours)	0.5	24	з	2	24	П	-	24	0.5	24	2	200	24	2	1	9	2	2	8	120	150
EAS AND TH	1 Reaction temp.	(°C.)	60	room temp. $(5\sim 20)$	40	80	room temp.	80-100	80-100	room temp.	80	room temp.	100	room temp.	*	80	50	100	80	100	80	80	100-120
ŬR	Triethy amine	(c.c.)	0	1	2	4.8	1.5	4.8	0	2.5	0	0.5	4.8	2	1.5	0	1.5	0.5	0	pyridine 5	ŝ	2	1.5
	Solvent	(c.c.) benzene	4	0	0	0	4	0	0	0	4	0	0	0	0	8	0	0	30	0	80	100	0
	Diethyl- carbamyl chloride	(c.c.)	7	1	4.8	4.12	1.5	4.1	1	1	1	1	4.1	2	1	1	1	0.5	1.5	1.5	3	2	1.6
	X X NH <sub>s</sub>	(g)	1	1	3.7	4.8	1.4	4.27	Ţ	1.5	1	1.5	5 2	2	1	1	1	0.5	2	2	°	2	1.35
	$\stackrel{\mathrm{Ureas}}{\times} \stackrel{\mathrm{Ureas}}{\searrow} \stackrel{\mathrm{N-C-N}(C_{2}H_{5})_{2}}{\overset{\mathrm{Ureas}}{\longrightarrow}}$	Ì	X= H	*	4	<i>o</i> 0CH <sub>8</sub>	$p-0$ CH $_3$	<i>o</i> CH <sub>3</sub>	mCH <sub>8</sub>	4	$p-CH_3$	"	0C15)	4	m-C15)	pCl <sup>5)</sup>	4	0NO2	$m-\mathrm{NO}_2$		*	$p-NO_2$	2,4,5-trichloro

TABLE I

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#### TABLE II

# The rate constants of the thermal dissociation of phenylureas in fatty acids $k\!\times\!10^2(min^{-1})$

U	reas		$-N(C_2H_5)_2$	$X \xrightarrow{H} O H O H N - C - NC_5 H_{11}$					
Fa	tty acids	chloroacetic	caproic acid	chloroacetic acid	chloroacetic acid				
х	σ	at 95°C.	at 150°C	at $139.5^{\circ}C$	at 139.5°C				
<b><i>p</i></b> -OCH <sub>3</sub>	-0.268	3.55	0.81	$3.83 \\ 4.69 \\ 5.13$					
<b>p</b> —CH <sub>3</sub>	-0.170	3.37	0.56	$4.87 \\ 5.06 \\ 5.77$	9.67 9.20				
m—CH <sub>3</sub>	-0.069	2.92	1.37	$4.77 \\ 4.99$					
Н	0	2.82	1.61	5.46	$10.82 \\ 10.58 \\ 10.30$				
<i>p</i> —C1	0.227	$\substack{2.77\\2.70}$	2.92	5.47 5.75	$\begin{array}{c} 6.72 \\ 5.61 \end{array}$				
<i>m</i> —C1	0.373	2.60							
m-NO <sub>2</sub>	0.710	2.21	2.39	$7.36 \\ 6.96$	$5.45 \\ 4.80$				
	$\rho$	$-0.196 \pm 0.028$		$0.1778 \pm 0.0025$					
o-OCH <sub>3</sub>		1.16							
o-CH <sub>3</sub>		3.3			2.1				
oC1		2.10			4.69				

TUDER III	TABLE	II	I
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Products	Benzyl N-phenyl- carbamate	1,3-diphenyl urea	Benzyl N-pentyl- carbamate	Dissociation ratio
(g)	(g)	(g)	(g)	(A) : (B)
4	2.2	0.1	0.1	1.59:1
1.5	0.5	0.28	trace	1.57:1

\*\*

$$\begin{array}{c} H \stackrel{O}{\longrightarrow} H \\ C_5H_{11}N - C - NC_6H_5 \rightarrow C_5H_{11}NH_2 + C_6H_5NCO \quad (A) \\ \swarrow C_5H_{11}NCO + C_6H_5NH_2 \quad (B) \end{array}$$

but it is impossible to determine which path is followed in the course of dissociation of the ureas in fatty acids. Therefore the dissociation ratio was determined in benzyl alcohol instead of fatty acid used in the other experiments. On heating 1-pentyl-3-phenylurea in benzyl alcohol for 4 hours at 170°C, the products shown in Table III were obtained.

From this table the ratio A/B is equal to 1.6 for 1-pentyl-3-phenylurea at 170°C. This ratio will differ in other 1-pentyl-3arylureas. Therefore, rate constants and  $\rho$  value (0.1778±0.025) may be insignificant in these ureas. The correlation coefficient r was low (0.895).

The dissociation mechanism of ureas in fatty acids is as follows<sup>3</sup>:

$$X \xrightarrow{H} O H \xrightarrow{k_2} H$$

From Eqs. (6) and (7)

$$\frac{d(R-NCO)}{dt} = \frac{Kk_2(Ureas)(H^+)}{1+\frac{k_2}{k_{-1}}}$$
(8)

where  $K = \frac{k_1}{k_{-1}}$ 

We can consider two cases as follows: a) When  $k_{-1}$  is greater than  $k_2$  or of comparable magnitude, then July, 1957]

$$\frac{d(R-NCO)}{dt} = CKk_2(Ureas)(H)$$
 (9)

where C = constant

In Eq. (9), K and  $k_2$  will fit the Hammett equation, therefore  $Kk_2$  also will agree with it. The product  $\rho\sigma$  for the reaction is given by:

$$\log \frac{Kk_2}{K_0 k_{2 \cdot 0}} = \rho \sigma \tag{10}$$
$$\log \frac{K}{K_0} = \rho_1 \sigma$$

where  $\log \frac{k_2}{k_{2.0}} = \rho_2 \sigma$ 

 $\rho = \rho_1 + \rho$ 

Substituents having a positive  $\sigma$ -value decrease K (or  $k_1$ ), since such substituents decrease the basicity of 1 nitrogen; and they also increase  $k_2$ , since such substituents make the deprotonation at 3 nitrogen easier. On the other hand, substituents having a negative  $\sigma$ -value increase K (or  $k_1$ ) and decrease  $k_2$ , that is,  $\rho_1$  will have a negative value and  $\rho_2$  will be positive. Therefore the sign of  $\rho$  will be determined by the magnitude of  $\rho_1$  and  $\rho_2$ , and if  $|\rho_1|$  is greater than  $|\rho_2|$ ,  $\rho$  will have a negative value, and vice versa.

The value of  $\rho$  obtained in this experiment was  $-0.198\pm0.028$  indicating that  $|\rho_1|$  is greater than  $|\rho_2|$ . This seems improbable, since in reaction (6), the reaction center is 1-nitrogen, while in reaction (7), it is 3-nitrogen which is nearer the substituent<sup>9</sup>). Therefore the hypothesis (a) does not appear likely.

b) When  $k_2$  is much greater than  $k_{-1}$ , then

$$\frac{d(R-NCO)}{dt} = k_1(Ureas)(H^+)$$
(11)

In this case,  $\rho$  will have a negative value from the reason just mentioned, and the experimental data are in accord with this hypothesis.

From the above, hypothesis (b) is probable rather than hypothesis (a), that is, the rate-determining step seems to be a protonation process (Eq. 6) and not a deprotonation process (Eq. 7). This contrasts with the fact<sup>10</sup>, that in the dissociation reaction of benzyl N-arylcarbamate in a basic medium such as an amine, the dissociation rate was proportional to the rate of the deprotonation, as indicated by the positive value of  $\rho$  which was obtained.

The discussion concerning the positive  $\rho$  value in the dissociation reaction of 1-pentyl-3-arylureas (II) will not be given here for the reason mentioned in the earlier part of this result and discussion.

As to the effect of ortho substituents in 1,1-diethyl-3-arylureas, 1,1-diethyl-3-(omethoxyphenyl)urea dissociates one third as fast as p-methoxy-, o-chloro- slightly slower than p-chloro-, and o-methyl- at a nearly equal rate to p-methyl-. With 1,3-diarylureas, o-methyl- dissociates a quarter as fast as p-methyl-, and o-chloroat a nearly equal rate to p-chloro-.

The activation energy of the dissociation reaction of 1,1-diethyl-3-phenylurea in chloroacetic acid was 22.4 Kcal.; this is smaller than the value obtained with 5, 6, 7 and 11 membered polymethylene ring ureas in the same solvent (24–27 Kcal.)<sup>11)</sup>, or those of 1,3-diphenylurea in propionic acid (27.9 Kcal.) and butyric acid (28.0 Kcal.)<sup>1)</sup>. The smaller value is due to the more facile protonation on tri-substituted ureas than on 1,3-di-substituted ureas.

### Summary

Eleven new ureas of the type, 1,1-diethyl-3-arylureas and 1-pentyl-3-arylureas were synthesized. The rate constants and  $\rho$ values of thermal dissociation of these ureas in fatty acids were determined. In 1,1-diethyl-3-arylureas, the  $\rho$  value of the dissociation reaction at 95°C. in chloroacetic acid was -0.196, and it may be concluded that the protonation process seems to be the rate-determining step in the dissociation reaction of ureas in fatty acid. The activation energy was compared with those of other ureas.

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<sup>9)</sup> T heargument is rather weak, because  $\rho_1$  and  $\rho_2$  are reaction constants for reactions of different types,  $\rho_1$  referring to equilibrium (6) and  $\rho_2$  to reaction (7).

<sup>10)</sup> T. Mukaiyama and M. Iwanami, J. Am. Chem. Soc., 79, 75 (1957).

<sup>11)</sup> Unpublished data.