The Effects of Substituents on the Hydrolysis of Substituted Cyanamides in Sulfuric acid Solution

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Introduction

Mono- and di-substituted cyanamides are hydrolysed in a sulfuric acid solution to give the corresponding ureas. Several works have already been given on the hydrolysis of cyanamide in aqueous acid solutions. In these earlier communications,[2,3,4], it was shown that the reaction is of the first order with respect to the concentration of cyanamide, and the rate increases steadily with increase in acid concentration. The reaction was also shown as an example of hydrogen-ion catalysis which was accepted by Hammett and Paul as an illustration of specific hydrogen ion catalysis.[5]

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[1] Laboratory of Organic Chemistry, Tokyo Institute of Technology.

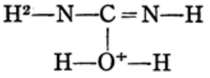
[2] H. C. Hetherington and J. M. Braham, *J. Am. Chem. Soc.* **45**, 824 (1923).

[3] G. Grube and Motz, *Z. phys. Chem.*, **118**, 145 (1925).

[4] G. Grube and G. Schmid, ibid., **119**, 19 (1926).

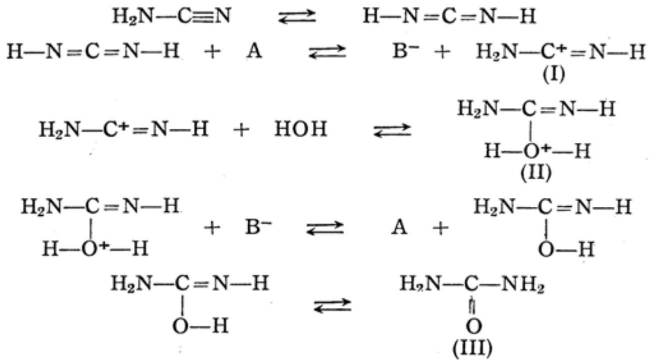
[5] L. P. Hammett and M. A. Paul, *J. Am. Chem. Soc.*, **56**, 830 (1934).

Sullivan and Kilpatrick⁶⁾ studied the rate of hydrolysis of cyanamide in solutions of nitric, hydrochloric, hydrobromic and trichloroacetic acids, and they explained the results by assuming a two-stage protolysis, the rate-determining step being the reaction between the hydrated cation of cyanamide,



$$\begin{array}{c} H^2{-}N{-}C{=}N{-}H \\ | \\ H{-}O^+{-}H \end{array}$$

and any base present. Kilpatrick⁷⁾ also presented the following paths for the hydrolysis of cyanamide in acid solution,



$$H_2N{-}C{\equiv}N \rightleftarrows H{-}N{=}C{=}N{-}H \qquad (1)$$

$$H{-}N{=}C{=}N{-}H + A \rightleftarrows B^- + \underset{\text{(I)}}{H_2N{-}C^+{=}N{-}H} \qquad (2)$$

$$H_2N{-}C^+{=}N{-}H + HOH \rightleftarrows \begin{array}{c} H_2N{-}C{=}N{-}H \\ | \\ H{-}O^+{-}H \\ \text{(II)} \end{array} \qquad (3)$$

$$\begin{array}{c} H_2N{-}C{=}N{-}H \\ | \\ H{-}O^+{-}H \end{array} + B^- \rightleftarrows A + \begin{array}{c} H_2N{-}C{=}N{-}H \\ | \\ O{-}H \end{array} \qquad (4)$$

$$\begin{array}{c} H_2N{-}C{=}N{-}H \\ | \\ O{-}H \end{array} \rightleftarrows \begin{array}{c} H_2N{-}C{-}NH_2 \\ \| \\ O \\ \text{(III)} \end{array} \qquad (5)$$

where A is an acid and B is its conjugate base. Step (4) was shown as the rate-determining step.

In the present work, the rate constants of the hydrolysis of mono- and di-substituted cyanamides in 20% sulfuric acid solution were measured. Based on the energies of activation and the entropies of activation obtained, the effect of substituents on the reaction was discussed.

Experimental Part

The hydrolysis of cyanamide to urea is accompanied by a contraction in volume which we made use of to follow the reactions dilatometrically. The experiments were performed in a dilatometer like that described by Broensted, Kilpatrick and Kilpatrick.⁸⁾ The dilatometer was a bulb of 10 cc.capacity, from the top of which extended a capillary tube 0.3 mm. in diameter and 15 cm. long. The readings were taken by using a cathetometer.

In order to avoid the formation of air bubbles during the reaction, prior to each run, the solvent was degassed under reduced pressure. The temperature control of the reaction thermostat was accurate to ±0.05° within the temperature range 5∼85°C.

As an aqueous sulfuric acid is not suitable for kinetic studies owing to the low solubility of cyanamides, dioxane was used as a diluent. Sulfuric acid concentration was 20% by weight in dioxane-water (3:1) solution. In these experiments the initial cyanamide concentration was 0.1 mol.

Mono-substituted Cyanamides.—Ethyl, *n*-butyl, isopropyl, *t*-butyl, allyl and phenyl cyanamides were used. They were synthesized by adding gradually a solution of an amine (1 mol.) in anhydrous ether to cyanogen bromide⁹⁾ (1.5 mol.) in anhydrous ether. The temperature of the reaction mixture was kept below 0°C. (except in the case of phenylcyanamide which was prepared at room temperature). After the reaction was completed, the precipitate (amine hydrobromide) was filtered and then ether and unreacted cyanogen bromide were distilled under reduced pressure. The residual cyanamide was then carefully distilled in vacuo. Methylcyanamide and heptylcyanamide synthesized by the above method could not be distilled.

The attempted distillation resulted in the formation of the corresponding melamines in the claisen distilling flask. They were therefore used without further purification. The boiling points and melting point for the amines and the cyanamides are shown in Table III.

TABLE III

Amine	b.p.(C°.)	reference	Cyanamide	b.p.(C°.)	m.p.(C°.)
ethyl-	16.6		ethyl-	94∼95/4 mm.	
n-butyl-	77		*n*-butyl-	117/14 mm.	
n-heptyl-	152	(10)	*n*-heptyl-		
isopropyl-	62	(11)	isopropyl-	108/10 mm.	
t-butyl-	44	(12)	*t*-butyl-	109∼110/11 mm.	
allyl-	55	(13)	allyl-	92/3 mm.	
phenyl-			phenyl-		42

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6) M. J. Sullivan and M. L. Kilpatrick, *J. Am. Chem. Soc*,. **67**, 1815 (1945).

7) M. L. Kilpatrick, *J. Am. Chem. Soc.*, **69**. 40 (1947).

8) J. N. Broensted, M. Kilpatrick and M. Kilpatrick, *J. Am. Chem. Soc.*, **51**. 428 (1929).

9) Organic Syntheses, **11**, 30.

10) Organic Syntheses, **11**, 58.

11) R. Paul, Bull. soc. chem., (5), **4**, 1121 (1937).

12) Organic Syntheses, **29**, 18.

13) Organic Syntheses, **2**, 732.

Di-substituted Cyanamides.—Di-ethyl, di-*n*-butyl, di-isopropyl, di-allyl and di-benzylcyanamides were used. Diethylcyanamide was synthesized from diethylamine and cyanogen bromide. Di-*n*-butylcyanamide,[14] di-allylcyanamide[14] di-isopropylcyanamide[15] were synthesized from the corresponding bromide or chloride by the action of sodium cyanamide. The boiling points and meltting point for these cyanamides are shown in Table IV.

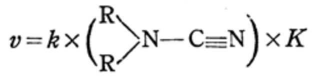
TABLE IV

Cyanamide	b.p.(C°.)	m.p.(C°.)
di-ethyl-	78/16 mm.	
di-n-butyl-	120–121/16 mm.	
di-isopropyl-	93–94/25 mm.	
di-allyl-	107–108/18 mm.	
di-benzyl-		53.5

Dioxane used as the diluent was purified by distillation from sodium metal. The reation products, ureas, were identified by their melting points. Diallylurea, which is not recorded in the literature, melted at 64°C. after recrystallization from petroleum ether (Found: N, 19.6. Calcd. for $C_7H_{12}N_2O$: N, 20.0%)

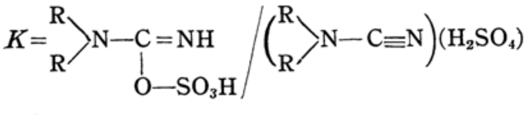
Results and Disscussion

Under the condition of the experiments, as the concentration of (H^+) and (H_2O) can be considered to be constant during the reaction, the reaction velocity can be expressed as follows:



$$v=k\times\left(\begin{matrix}R\\R\end{matrix}\!\!>N-C\equiv N\right)\times K$$

where



$$K=\begin{matrix}R\\R\end{matrix}\!\!>N-\underset{\displaystyle O-SO_3H}{\underset{|}{C}}=NH\bigg/\left(\begin{matrix}R\\R\end{matrix}\!\!>N-C\equiv N\right)(H_2SO_4)$$

On plotting against time t the logarithm of the contraction in volume, ΔY, which had taken place in a constant period of time beginning at time t, we have obtained a straight line. This indicates a first order reaction rate with respect to cyanamide. The rate constant is given[16] by the gradient of such a plot, as shown in Fig. I. The results are shown in Table I.

The rate data were further analyzed by means of the Arrehenius equation

$$\ln k=\ln A-E/RT,$$

and by the absolute rate equation

$$\ln(k/T)=\ln(R\kappa/Nh)+\Delta S^{\ast}/R-\Delta H^{\ast}/RT$$

The transmission coefficient, κ, was set equal to unity. The calculated kinetic functions are collected in Table II.

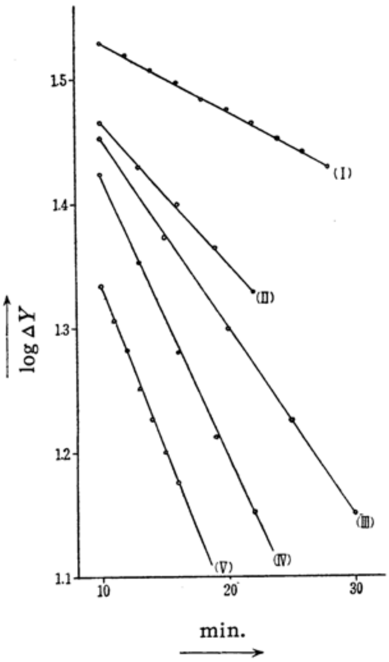


Fig. 1. Hydrolysis of di-ethylcyanamide in 20% sulfuric acid solution: the plot of log ΔY against t.
(I) 26.14° (II) 33.56° (III) 38.50°
(IV) 44.19° (V) 48.15°

TABLE I

THE RATE CONSTANTS OF THE HYDROLYSIS OF SUBSTITUTED CYANAMIDES IN 20% SULFURIC ACID SOLUTION

Cyanamide	t (C°.)	$k\times10^{-5}$ (sec.$^{-1}$)
methyl-	2.55	5.10
	3.62	6.0
	4.50	6.57
	5.57	7.02
	6.50	7.90
	7.65	8.63
ethyl-	5.55	3.46
	8.25	4.56
	9.21	5.06
	11.25	6.02
	12.15	6.48
	13.10	6.82
n-butyl-	10.0	5.56
	11.13	6.29
	12.15	6.78
	13.20	7.40
	14.18	8.05
	16.78	9.54
n-heptyl-	5.92	5.00
isopropyl	16.52	5.12
	17.32	5.37
	18.06	6.06
	19.08	6.30
	20.10	6.78
	21.20	8.06
	22.50	9.26

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[14] Organic Syntheses., **1**, 197.

[15] W. Traube and A. Engelhardt, *Ber.*, **44**, 3151 (1911).

[16] E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

t-butyl-	34.10	1.47
	35.07	1.81
	37.47	2.09
	39.0	2.55
	40.83	2.92
allyl-	12.98	6.70
	14.10	7·83
	15.05	8.24
	16.00	9.22
	17.85	11.90
	18.91	14.10
	19.83	14.60
phenyl-	42.75	2.54
cyanamide-	27.07	2.75
diethyl-	26.14	0.394
	33.56	0.613
	38.50	1.06
	41.05	1.25
	44.19	1.72
	48.15	2.06
di-n-butyl-	32.45	0.505
	42.55	1.10
	45.92	1.43
	48.60	1.53
	52.10	2.64
	55.20	3.20
di-allyl-	31.10	0.407
	35.16	0.576
	40.03	0.885
	42.88	1.28
	46.80	1.62
	52.50	2.99
di-benzyl-	60.90	0.274
	65.05	0.335
	66.81	0.357
	69.12	0.485
	70.56	0.502
	74.09	0.730
di-isopropyl-	60.90	0.464
	66.04	0.715
	70.74	0.760
	76.22	1.55
	79.81	1.89
	85.04	3.20

TABLE II

THE ACTIVATION ENERGY AND THE ENTROPY OF ACTIVATION FOR THE HYDROLYSIS OF CYANAMIDES IN SULFURIC ACID SOLUTION

Cyanamide	Activation Energy (kcal. mol.$^{-1}$)	Entropy of Activation (cal. mol.$^{-1}$ deg.$^{-1}$)
methyl-	14.8	−26.4
ethyl-	14.4	−29.2
n-butyl-	13.1	−33.6
isopropyl-	17.1	−21.6
t-butyl-	16.6	−28.6
allyl-	19.0	−13.1
di-ethyl-	15.7	−31.4
di-n-butyl-	15.9	−30.4
di-allyl-	18.9	−21.6
di-benzyl-	19.5	−21.8
di-isopropyl-	20.2	−23.4

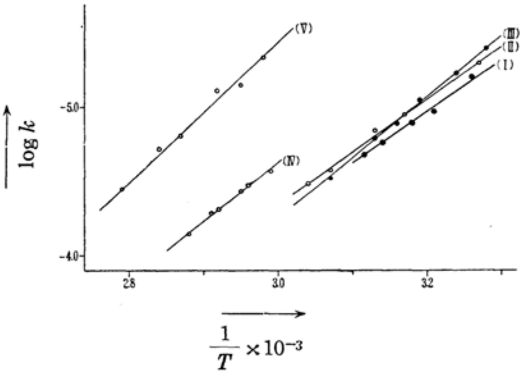


Fig. 2. Hydrolysis of di-substituted cyanamides in 20% sulfuric acid solution: the plot of log k against $1/T$.
(I) di-ethylcyanamide. (II) di-n-butylcyanamide. (III) di-allylcyanamide. (IV) di-benzylcyanamide. (V) di-isoprophylcyanamide.

Cyanamide is hydrolysed to give urea in sulfuric acid solution and the rate of reaction increases as the acid concentration increases. In 10% sulfuric adid solution, the reaction proceeds very slowly.

The effects of substituents on the hydrolysis of the cyanamides in 20% sulfuric acid solution reported in this paper may be summarized as follows:

According to the values of the energies of activation observed for the reaction, the substituents are classified in three groups, (1) normal alkyl groups (13.1–15.9 Kcal.), (2) branched alkyl groups (16.6–20.2 Kcal.) and (3) unsaturated groups (19.0–20.5 Kcal.). The first group contains methyl, ethyl, di-ethyl, n-butyl and di-n-butylcyanamides, the second isopropyl di-isopropyl and t-butyl cyanamides and the third allyl, di-allyl and di-benzyl cyanamides.

As shown in Table I, the rate of reaction for the following eight cyanamides increases in the series:

di-isopropyl- < di-ethyl- < phenyl- < t-butyl- < cyanamide < isopropyl- < ethyl- < heptyl-.

The results described above allow the following conclusions to be drawn.

(a) The cyanamide with branched alkyl group requires more energy of activation than the cyanamides with n-alkyl group.

(b) The energy required for the hydrolysis of the cyanamides with unsaturated group is nearly equal to those of the cyanamides with branched alkyl group.

(c) In comparing the mono-substituted cyanamide and the di-substituted cyanamide, the latter requires several kilocalories more than the former.

(d) Mono-alkyl cyanamides and mono-isopropyl cyanamide are hydrolysed more easily than the unsubstituted cyanamide.

(e) Phenylcyanamide is hydrolysed more slowly than that which is unsubstituted.

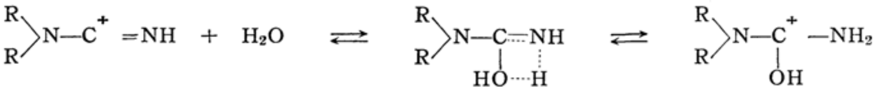
According to the mechanism of hydrolysis of cyanamide in nitric acid solution proposed by Kilpatrick,7) as mentioned before, the rate-determining step is step (4), which means that (II), the hydrated cation, splits off a molecule of water much more frequently than it yields a proton to an approaching base. In view of experimental results obtained (a)∼(e) in this work, however, step (4) is not suitable as the rate-determining step.

On the basis of the electronic effects, supposing that step (4) is the rate-determining step, cyanamides with unsaturated groups would be hydrolysed more readily than the cyanamides with *n*-alkyl groups, because the former cyanamides might be considered to yield a proton to the base more easily than the latter, on account of the negativities of substituents, which make the hydrated cation more acidic. Also, if step (4) limits the reaction, the rates for the hydrolysis of ethylcyanamide, cyanamide and phenylcyanamide should fall into the series,

phenylcyanamide > cyanamide
> ethylcyanamide.

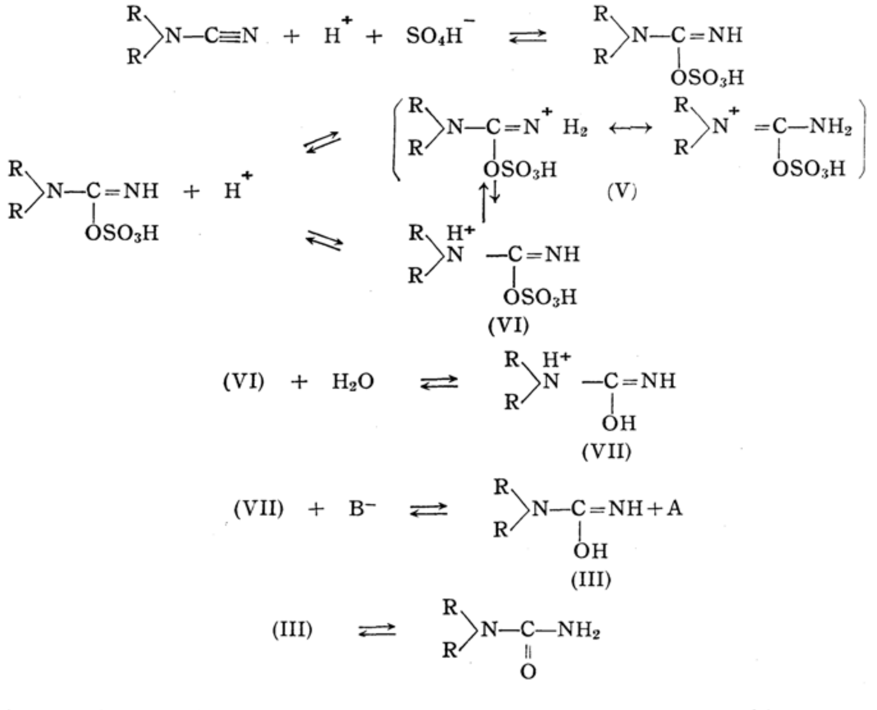
However, the experiments show the reversed order. The result shows that the cyanamides with electron-releasing groups are hydrolysed more easily than the cyanamide with electron-attracting group, like phenylcyanamide.

These experimental results do not support a mechanism which identifies the rate-determining step with the process of attacking by a water molecule of cyanamide cation.



$$\begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{N{-}\overset{+}{C}{=}NH} + \mathrm{H_2O} \rightleftarrows \begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{N{-}\underset{HO\cdots H}{C}{\cdots}NH} \rightleftarrows \begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{N{-}\underset{OH}{\overset{+}{C}}{-}NH_2}$$

The results (a)∼(e) can be rationalized by considering the following paths for the hydrolysis of cyanamide in 20% sulfuric acid solution.



$$\begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{N{-}C{\equiv}N} + \mathrm{H^{+}} + \mathrm{SO_4H^{-}} \rightleftarrows \begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{N{-}\underset{OSO_3H}{C}{=}NH} \qquad (6)$$

$$\begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{N{-}\underset{OSO_3H}{C}{=}NH} + \mathrm{H^{+}} \rightleftarrows \underset{\mathrm{(V)}}{\left(\begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{N{-}\underset{OSO_3H}{C}{=}\overset{+}{N}H_2} \longleftrightarrow \begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{\overset{+}{N}{=}\underset{OSO_3H}{C}{-}NH_2}\right)} \qquad (7)$$

$$\uparrow\!\downarrow$$

$$\rightleftarrows \underset{\mathrm{(VI)}}{\begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{\overset{H^{+}}{N}{-}\underset{OSO_3H}{C}{=}NH}} \qquad (8)$$

$$\mathrm{(VI)} + \mathrm{H_2O} \rightleftarrows \underset{\mathrm{(VII)}}{\begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{\overset{H^{+}}{N}{-}\underset{OH}{C}{=}NH}} \qquad (9)$$

$$\mathrm{(VII)} + \mathrm{B^{-}} \rightleftarrows \underset{\mathrm{(III)}}{\begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{N{-}\underset{OH}{C}{=}NH}} + \mathrm{A} \qquad (10)$$

$$\mathrm{(III)} \rightleftarrows \begin{smallmatrix}\mathrm{R}\\ \mathrm{R}\end{smallmatrix}\!\!>\!\mathrm{N{-}\underset{\overset{\|}{O}}{C}{-}NH_2} \qquad (11)$$

Under the condition of the experiment, cyanamide-sulfate may be formed in the first place, and by the further protonation, formation of disulfate (VI) and (V) may be expected. The less stable tautomer (VI) is hydrolysed very easily to give an isourea cation, which yields a proton to a base to give urea. On the other hand, the stable tautomer

(V) is more difficult to hydrolyse than (VI) and the isourea is formed via process (8) alone.

It is deemed probable that one nitrogen in a mono-substituted cyanamide has a similiar property to a secondary amine and in a di-subtituted cyanamide to a tertiary amine. As explained by the idea of B-strain introduced by C. H. Brown, the tertiary amines are anomalously weak bases even toward protonic acid. The ability of alkyl amine to add a proton at the nitrogen atom by coordination increases along the series:

$$R_3N < H_3N < RNH_2 < R_2NH.$$

This suggests that a second protonation of cyanamide to form disulfate (VI) is more favorable in cyanamides with *n*-alkyl group and mono-substituted ones than in cyanamides with branched alkyl group and di-subtituted ones, respectively.

As shown in Table V, the basic strength of amines are expressed by their pK_b scale.

TABLE V

ethylamine	ammonia	aniline
3.27	4.75	9.4

The order of the rates for mono-substituted cyanamides (ethylcyanamide, cyanamide and phenylcyanamide) have the same order as to the strength of amines.

Therefore, the second protonation of cyanamide, step (8), can be considered as the rate-determining step.

Summary

The energies and the entropies of activation have been determined for the hydrolysis of mono- and di-substituted cyanamides in 20% sulfuric acid solution.

The effect of substituents are distinctly shown in these kinetic data and the substituents are classified in three groups, (1) normal alkyl group substituted, (2) branched alkyl group substituted and (3) unsaturated group substituted cyanamides. The difference in energy of activation required for the hydrolysis of cyanamides may be explained by assuming the intermediate cyanamide-disulfate, the rate-determining step being the second protonation of cyanamide to give cyanamide-disulfate.

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