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KINETICS OF THE FORMATION OF ACETOGUANAMINES FROM DICYANDIAMIDE AND ACETONITRILES[1]

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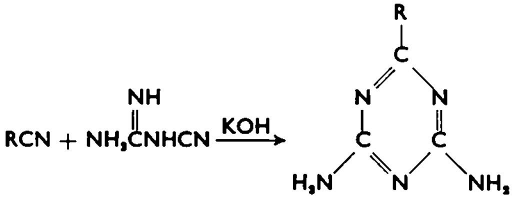
Abstract—The rate of the alkali-catalysed formation of acetoguanamine from dicyandiamide and acetonitrile in 2-methoxyethanol and dimethyl sulfoxide and other solvents has been measured by means of UV spectrophotometry. The rate is expressed as $v = k_2K_1[\mathrm{KOH}][\text{dicyandiamide}][\mathrm{CH_3CN}]/(1 + K_1[\mathrm{KOH}])$ in 2-methoxyethanol. An equilibrium exists between acetonitrile and the complex of the base and acetonitrile. The application of the rate data with methyl-, dimethyl-, phenyl- and methoxyacetonitrile in solvent 2-methoxyethanol to the Taft's equation gives a ρ^*-value of $+2{\cdot}7$. The rate in 2-methoxyethanol–dimethyl sulfoxide mixtures of various composition follows approximately first-order equation with nitrile, and increases with increasing molar fraction of dimethyl sulfoxide in the mixture solvents. A probable mechanism involving an addition of base to acetonitrile and a nucleophilic attack of the resulting addition complex on the cyano carbon of dicyandiamide is suggested and the solvent effect on the rate is discussed. The former step is rate-determining in dimethyl sulfoxide, while the latter step determines the rate in pure 2-methoxyethanol.

THE rate of the formation of benzoguanamine from dicyandiamide and benzonitrile in 2-methoxyethanol has been reported to follow the kinetic equation: $v = k[\text{dicyandiamide}][\text{benzonitrile}][\text{base}]$. The reaction does not go by way of cyanamide produced from dicyandiamide.[2] The analogous reaction is possible by using aliphatic nitriles, which leads to acetoguanamine with acetonitrile and in general to 2,4-diamino-6-alkyl-s-triazines.[3,4]



The present paper summarizes the further kinetic studies on the formation of acetoguanamine and 2,4-diamino-6-alkyl-s-triazines from dicyandiamine and aliphatic nitriles in 2-methoxyethanol by means of spectrophotometry and the effect of various solvents on the rate.

RESULTS AND DISCUSSION

Rate Law. The rate of the formation of acetoguanamine in 2-methoxyethanol is first-order with dicyandiamide and also with acetonitrile as shown in Table 1.

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[1] Contribution No. 80.

[2] Y. Ogata, A. Kawasaki and K. Nakagawa, *Tetrahedron* **20**, 2755 (1964).

[3] E. M. Smolin and L. Rapoport, *s-Triazines and Derivatives* p. 240. Interscience, New York (1959).

[4] W. Zerweck and W. Brunner, U.S. Patent 2,302,162 (1942).

TABLE 1. THE INITIAL RATE CONSTANTS FOR THE FORMATION OF ACETOGUANAMINE IN 2-METHOXYETHANOL AT 105° [KOH] = 0·13M

Initial conc. Dicyandiamide M	Initial conc. Acetonitrile M	$k'' \times 10^4$ M^{-1} sec^{-1}	Rate constant $k'(DD)^a \times 10^5$ sec^{-1}	Rate constant $k'(RCN)^b \times 10^5$ sec^{-1}
0·400	0·201	1·61	3·98	8·10
0·400	0·301	1·32	4·41	5·90
0·401	0·400	1·26	5·42	5·42
0·400	0·601	1·25	7·77	5·08
0·200	0·400	1·64	7·61	3·74
0·600	0·401	1·07	4·01	6·29

[a] First-order rate constants with dicyandiamide.
[b] First-order rate constants with acetonitrile.

However, the rate tends to decrease with increasing initial concentration of dicyandiamide, which is explicable by the retarding effect of cyanamide existing in equilibrium with dicyandiamide[2] and by assuming that the rate is not strictly second-order, as reported previously.[3] The plot of the second-order rate constant vs. the reciprocal of the concentration of potassium hydroxide gives a straight line not passing through the origin, which satisfies the expression:

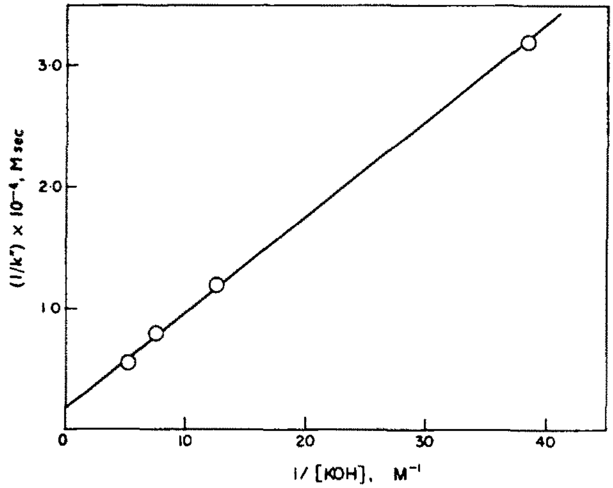

FIG. 1. The relationship between second-order rate constant and the concentration of potassium hydroxide for the formation of acetoguanamine in 2-methoxyethanol at 105°.

$$k'' = \frac{[\mathrm{KOH}]}{a + b[\mathrm{KOH}]} \; (a, b\text{:constant})$$

i.e., the equation implies the existence of an addition compound of acetonitrile with the base in a mobile equilibrium with original acetonitrile as will be shown later. The kinetics of the reaction were studied in other solvents, especially in dimethyl sulfoxide. Since potassium hydroxide does not dissolve in dimethyl sulfoxide, a solvent which contains an appropriate amount of 2-methoxyethanol in dimethyl sulfoxide was employed. The kinetic data in a mixture of dimethyl sulfoxide and 2-methoxyethanol in 70:30 vol% are shown in Table 2. Rather surprisingly, the rate equation was found from the data in Table 2 to satisfy approximately $v = k$[acetonitrile] rather than $v = k$[acetonitrile][dicyandiamide]. Similar results were also obtained in 80 vol% dimethyl sulfoxide. The first-order rate coefficient holds better constancy than a second-order one in each run as well as in various initial concentrations. As shown in Fig. 2, the rate increases with increasing molar fraction of dimethyl sulfoxide in the mixture solvents, but the acceleration is not so remarkable as observed for the S_N2 reaction.[5] The relationship between the first-order rate constant, k', and the concentration of potassium hydroxide in 70 vol% dimethyl sulfoxide solution is shown in Fig. 3. The Fig. shows that the rate is proportional to the concentration of catalyst or alkoxide ion.

TABLE 2. THE INITIAL RATE CONSTANTS FOR THE FORMATION OF ACETOGUANAMINE IN A MIXTURE OF DIMETHYL SULFOXIDE AND 2-METHOXY-ETHANOL (70:30 vol) AT 105° [KOH] = 0·13M

Initial conc.			Initial rate constant	
Dicyandiamide M	Acetonitrile M	$k'' \times 10^4$ M^{-1} sec^{-1}	k'(DD) $\times 10^4$ sec^{-1}	k'(RCN) $\times 10^4$ sec^{-1}
0·400	0·200	3·20	0·601	1·25
0·400	0·400	3·27	1·24	1·24
0·200	0·400	5·76	2·18	1·03

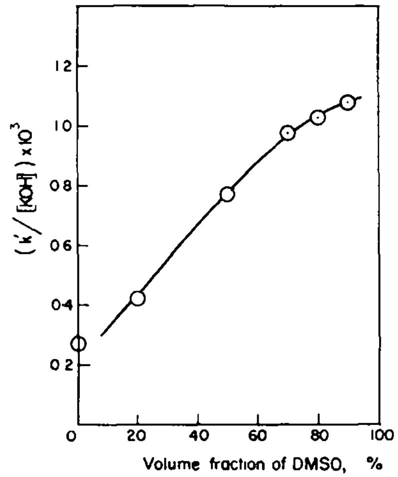

FIG. 2. The relationship between the rate and the volume fraction of dimethyl sulfoxide in dimethyl sulfoxide-2-methoxyethanol for the formation of acetoguanamine at 105°.

The application of the second-order rate constant, k'', in 2-methoxy-ethanol to the Taft's equation gives a ρ^*-value of +2·7, which means that the electron-releasing group in nitrile retards the rate and hence the reaction involves a nucleophilic attack on nitriles.

Reaction mechanism. The rate of the formation of acetoguanamine is $v = k'$

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[5] A. J. Parker, *Quart. Revs.* **16**, 163 (1962).

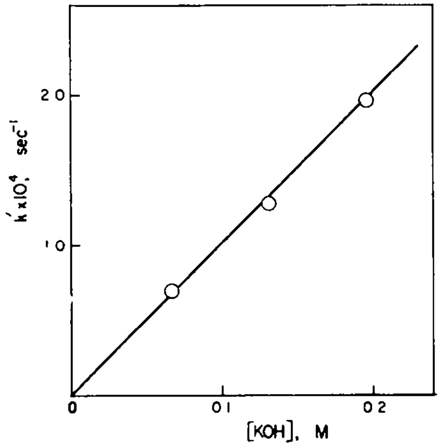


FIG. 3. Plot of the apparent first-order rate constant vs. concentration of potassium hydroxide for the formation of acetoguanamine in dimethyl sulfoxide-2-methoxyethanol (70:30 vol) at 105°.

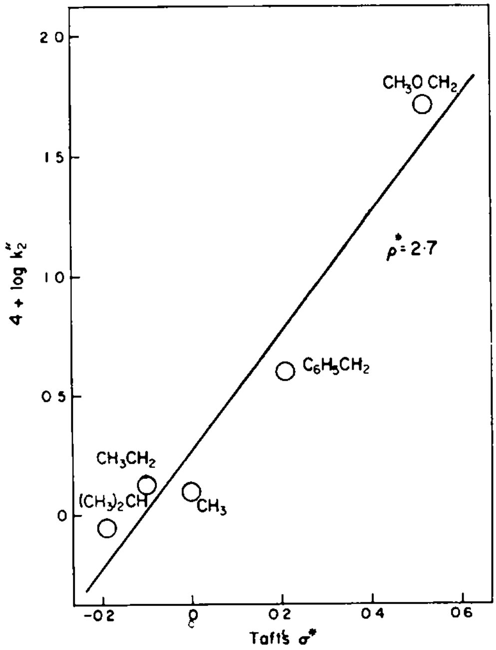
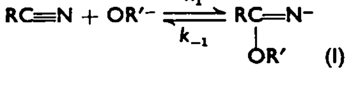
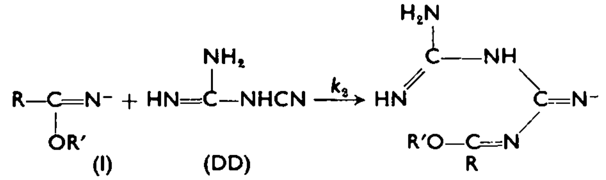


FIG. 4. Plot of the logarithm of the second-order rate constant vs. Taft's sigma constant for the formation of 2,4-diamino-6-alkyl-s-triazines in 2-methoxyethanol at 105°.

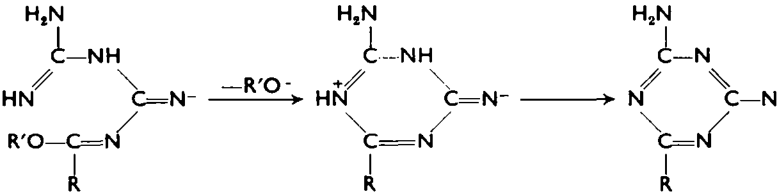
[dicyandiamide][nitrile] in the solvent of 2-methoxyethanol and $v = k$[nitrile] in dimethyl sulfoxide. Hence the previously suggested mechanism[2] involving a rate-determining attack of the conjugate base of dicyandiamide on nitrile cannot explain the latter rate. Therefore, the following mechanism is suggested.



$$RC\equiv N + OR'^{-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\displaystyle OR' \quad (I)}{RC{=}N^{-}} \qquad (1)$$

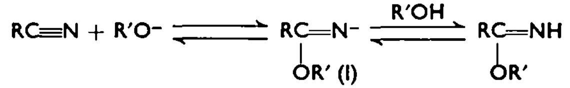


(2)



(3)

Nitriles are in an equilibrium with iminoether in the presence of alkoxide catalyst.[6]



$$RC{\equiv}N + R'O^- \rightleftharpoons \underset{OR'\ (I)}{RC{=}N^-} \underset{}{\overset{R'OH}{\rightleftharpoons}} \underset{OR'}{RC{=}NH} \tag{4}$$

This intermediate, iminoether anion I, may attack on the carbon atom of the cyano group in dicyandiamide and cyclize to form aceto- or benzoguanamine. The application of the steady-state approximation method leads to the following rate expression, k's representing the rate constants for the subscripted steps.

$$v = \frac{k_1k_2[\mathrm{DD}][\mathrm{RCN}][\mathrm{R'O^-}]}{k_{-1} + k_2[\mathrm{DD}]} \tag{5}$$

If $k_{-1} \gg k_2[\mathrm{DD}]$, i.e., if step 1 is a mobile equilibrium with equilibrium constant K_1, the overall rate should be

$$v = K_1k_2[\mathrm{DD}][\mathrm{RCN}][\mathrm{R'O^-}]$$

In this case, the stoichiometric concentration of nitrile $[\mathrm{RCN}]_S$ is expressed as:

$$\begin{aligned}[\mathrm{RCN}]_S &= [\mathrm{RCN}](1 + K_1[\mathrm{R'O^-}]) \\ &= [\mathrm{I}]\left(1 + \frac{1}{K_1[\mathrm{R'O^-}]}\right)\end{aligned}$$

Thence the rate may also be represented as:

$$v = k_2[\mathrm{I}][\mathrm{DD}] = \frac{k_1k_2[\mathrm{DD}][\mathrm{RCN}]_S[\mathrm{R'O^-}]}{k_{-1} + k_1[\mathrm{R'O^-}]} \tag{6}$$

As described in the section of rate law, the effect of the concentration of potassium hydroxide in pure 2-methoxyethanol satisfies the above Eq. (6). It is necessary from Eq. 6 that the observed second-order rate constant, k'', should have the relationship:

$$\frac{1}{k''} = \frac{1}{k_2} + \frac{1}{k_2K_1[\mathrm{R'O^-}]} \tag{7}$$

The values of k_2 and K_1 can be obtained from the intersection and slope of the line of the plot for $1/k''$ vs. $1/[\mathrm{R'O^-}]$ in Fig. 1. The values of K_1 at 105° and 115° are 2·6 and 1·5M^{-1}, respectively, which leads to the heat of reaction of ca. −15 kcal/mole.

On the other hand, if $k_{-1} \ll k_2[\mathrm{DD}]$, i.e., if the reverse step of 1 is much slower

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[6] F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

than step 2, the overall rate is determined by the addition step 1 and is expressed as:

$$v = k_1[\mathrm{RCN}][\mathrm{R'O^-}] = k_1[\mathrm{RCN}]_8[\mathrm{R'O^-}] \tag{8}$$

This is the case for the solvent of dimethyl sulfoxide mixed with a small amount of 2-methoxyethanol, which shows the first-order dependence on $[\mathrm{RCN}]_8$ and $[\mathrm{R'O^-}]$ and the independence of the concentration of dicyandiamide (Table 2 and Fig. 3). It is known that in dipolar aprotic solvents such as dimethyl sulfoxide a smaller anion is poorly solvated, while a large polarizable activated complex is effectively solvated and thus the reaction is accelerated.[7] It has been also reported that dimethyl sulfoxide in comparison with protic solvents like methanol, tends to increase the rate of S_N2 reaction involving an anionic polar transition state.[5,8] Although the present reaction is not S_N2 but a nucleophilic addition, the similar speculation may be applied.

The observed facts that first-order constant in dimethyl sulfoxide increases with increasing initial concentration of dicyandiamide and that it decreases as the reaction proceeds are explicable by Eq. 5, since

$$k' = \frac{k_1 k_2[\mathrm{DD}]}{k_{-1} + k_2[\mathrm{DD}]}$$

On the other hand, as expected from Eq. 5, the second-order coefficient in dimethyl sulfoxide expressed as:

$$k'' = \frac{k_1 k_2}{k_{-1} + k_2[\mathrm{DD}]}$$

decreases with increasing initial concentration of dicyandiamide and increases as the reaction proceeds. The similar phenomenon was observed in pure 2-methoxyethanol. If the acetoiminoether anion is an intermediate, acetoimino-ether synthesized from acetonitrile should also form acetoguanamine under the same conditions, which is the case. The rate of formation of acetoguanamine from acetoiminoether was measured, which followed the second-order kinetics in 2-methoxyethanol ($k_2 = 8{\cdot}1 \times 10^{-5}$ $\mathrm{M^{-1}sec^{-1}}$) and showed nearly first-order kinetics in 70% dimethyl sulfoxide as shown in Table 3. Acetoguanamine is not formed from acetonitrile, while it is formed from acetoiminoether in the presence of triethylamine in a mixture of 30% 2-methoxyethanol and 70% dimethyl sulfoxide. This fact supports the intermediary formation of acetoiminoether anion, although the rate is slow with this weaker base.

TABLE 3. THE INITIAL RATE CONSTANTS FOR THE FORMATION OF ACETOGUANAMINE FROM ACETOIMINOETHYLETHER AND DICYANDIAMIDE IN A MIXTURE OF DIMETHYL SULFOXIDE AND 2-METHOXYETHANOL (70:30 vol) AT 105° [KOH] = 0·13M

Initial conc.		Initial rate constant		
Acetoiminoethylether M	Dicyandiamide M	$k'' \times 10^4$ $\mathrm{M^{-1}\,sec^{-1}}$	$k'(\mathrm{DD}) \times 10^5$ $\mathrm{sec^{-1}}$	$k'(\mathrm{AIE})^a \times 10^5$ $\mathrm{sec^{-1}}$
0·200	0·400	2·76	6·45	10·8
0·400	0·400	2·72	10·3	10·3
0·400	0·200	5·11	19·7	9·4

[a] First-order rate constants with acetoiminoether.

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[7] J. Miller and A. J. Parker, *J. Amer. Chem. Soc.* **83**, 117 (1961); A. J. Parker, *J. Chem. Soc.* **1328** (1961).

[8] D. J. Cram, B. Rickborn, C. A. Kingsbury and P. Haberfield, *J. Amer. Chem. Soc.* **83**, 3678, 3688 (1961).

TABLE 4. SOLVENT EFFECT ON THE FORMATION OF ACETOGUANAMINE AT 105°. $[DD]_0 = 0{\cdot}400M$, $[CH_3CN]_0 = 0{\cdot}400M$, $[KOH]_0 = 0{\cdot}13M$

		Rate const.			
Solvent	Dielectric const. (temp)	$k'' \times 10^4$ M^{-1} sec^{-1}	$k' \times 10^4$ sec^{-1}	ΔH‡ kcal $mole^{-1}$	ΔS‡ e.u.
ME[a]	16·0 (30°)	0·993	—	19·1	−23
Triethylene glycol	23·7 (20°)	0·817	—	24·8	−8
n-BuOH: ME (50:50 vol)	17·1[c] (25°)	1·76	—	—	—
Cyclohexanol: ME (50:50 vol)	15·0[c] (25°)	2·86	—	—	—
DMSO[b]:ME (20:80 vol)	46·7[c] (25°)	—	0·554	18·9	−24
DMSO:ME (70:30 vol)			1·24	17·0	−28

[a] ME = 2-Methoxyethanol.

[b] DMSO = Dimethyl sulfoxide.

[c] Dielectric constant of pure solvent.

Solvent effect. The rate data are summarized in Table 4. The rate increases by changing solvents from 2-methoxyethanol (dielectric constant ε, 16·0) to dimethyl sulfoxide (ε, 46·7), and the reaction order varies from second to first, while the change of solvent from 2-methoxyethanol to ethylene glycol having similar dielectric constant (ε, 37·7) causes a marked reduction in the rate. Further, the reaction in ethylene glycol is accompanied by side reactions. In triethylene glycol having higher dielectric constant (ε, 23·7) the rate follows second-order kinetics and the reaction is somewhat slower than in 2-methoxyethanol. The rate in a mixture of n-butanol or cyclohexanol and 2-methoxyethanol is faster than in pure 2-methoxyethanol. These results indicate that almost no relationship exists between the rate and the dielectric constant of solvent. In other dipolar aprotic solvents, dimethyl-formamide and cyclohexanone, the rate could not be measured because of the side reactions.

Energies of activation were obtained from the Arrhenius plot, the enthalpies and entropies of activation being calculated (Fig. 5). As shown in Table 4, the rate is controlled mainly by the enthalpy change. Both enthalpy and entropy of activation are larger in triethylene glycol than in 2-methoxyethanol, whereas an increase in content of dimethyl sulfoxide in a dimethyl sulfoxide-2-methoxyethanol mixture results in a decrease in the enthalpy and entropy of activation. These facts correspond to the similar observation in the hydrolysis of ethyl benzoate.[9]

In general the enthalpy of activation for a reaction between ions and neutral molecules seems to be influenced by the solvation of original ions and the enthalpy becomes higher as the solvent is more associated with original ion which needs the desolvation for the reaction. In contrast, the entropy of activation for the same type of reaction seems to be elevated by using the solvent more solvated with original reactants, which increases the difference of the solvations between original and transition states, and hence leveling the degrees of freedom of both states.

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[9] D. D. Roberts, *J. Org. Chem.* **29**, 2039 (1964).

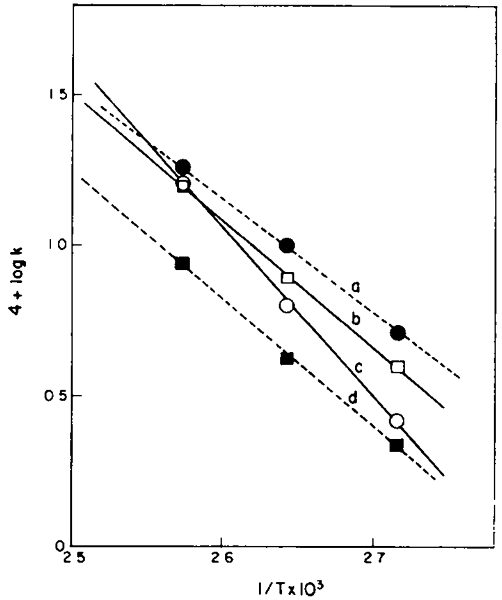

FIG. 5. The Arrhenius plot of the rate data for the formation of acetoguanamine in various solvents. a, in dimethyl sulfoxide-2-methoxyethanol (70:30 vol); b, in 2-methoxyethanol; c, in triethylene glycol; d, in dimethyl sulfoxide-2-methoxyethanol (20:80 vol).

The enthalpy of activation in triethylene glycol is so large that the rate of formation of acetoguanamine is lower in spite of its higher ΔS‡. The enthalpy of activation in ethylene glycol is probably much higher and the rate is much lower. The change of solvent from 2-methoxyethanol to the glycols leads to an increase in the solvation of alkoxide ion or iminoether anion by hydrogen bonding, whereas change to dimethyl sulfoxide leads to a marked decrease in solvation of alkoxide and an increase in that of a larger polarizable transition state with concomitant decrease in enthalpy of activation, which eventually results in the rate enhancement. Further, the alcoholic hydrogen in 2-methoxyethanol is more acidic than that in n-butanol and cyclohexanol because of their electron-withdrawing β-methoxy group and solvates smaller alkoxide anions more strongly by the hydrogen bonding, hence the rate diminishes.

On the contrary, the complex formation of cyano group with dimethyl sulfoxide solvent[10] diminishes the reactivity of cyano groups and hence the rate of reaction. This may explain the fact that the rate enhancement in dimethyl sulfoxide is not so remarkable.

These observations suggest that the rate is controlled by the solvation of alkoxide ion rather than by dielectric constant of solvent in these addition reactions.

EXPERIMENTAL

Materials. Dicyandiamide, m.p. 210°, with purity over 99·4% purchased from Nippon Carbide Co. was used without further purification. Commercial acetonitrile was rectified after drying over P_2O_5, b.p. 81·5°. 2-Methoxyethanol, b.p. 122–123°, and MeOH, b.p. 63·5°, were purified by rectification and had no appreciable absorption over 220 mμ. Propionitrile was prepared from diethyl

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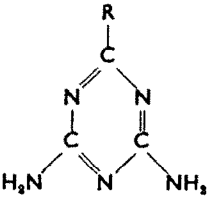
[10] C. D. Ritchie and A. L. Pratt, *J. Amer. Chem. Soc.* **86**, 1571 (1964).

sulfate and KCN,[11] b.p. 96·0–98·0°, isobutyronitrile from isobutyric acid,[12] b.p. 98·0–100°, methoxyacetonitrile from glycolonitrile and dimethyl sulfate,[13] b.p. 120–122°, and benzyl cyanide from benzyl chloride and NaCN,[14] b.p. 67–70°/2·5 mmHg. Acetoiminoether was prepared from its hydrochloride,[15] b.p. 89·0–90·0°. Dimethyl sulfoxide, triethylene glycol, cyclohexanol and n-butanol were distilled after drying over $MgSO_4$ or Na_2SO_4.

Products. Acetoguanamine and substituted acetoguanamines were prepared from dicyandiamide and the corresponding nitriles in 60–90% yield. Substituent (R), m.p., absorption maximum (λ_{max}) and logarithm of extinction (log ε) are as follows:



CH_3, 274–276°, 255 mμ (3·49); CH_2CH_3, 292–294°, 255 mμ (3·47); $(CH_3)_2CH$, 264–266°, 255 mμ (3·55); CH_2OCH_3, 257–259°, 257 mμ (3·53); $C_6H_5CH_2$, 244–245°, 258 mμ (3·55).

Analysis of products. A methanolic solution of 6×10^{-4} M acetoguanamine has an absorption maximum at 255 mμ, where there is no appreciable absorption for dicyandiamide and acetonitriles. The plot of absorbance at absorption maximum vs. concentration gave a straight line, from which acetoguanamine could be determined in 98·2 ± 0·8 percent accuracy. Other acetoguanamines are estimated analogously.

Typical procedure for rate measurements. A solution of 0·8M acetonitrile and 0·8M dicyandiamide in 2-methoxyethanol (10 ml) and a solution of 0·23M KOH in 2-methoxyethanol (10 ml) which had been previously maintained at 105 ± 0·3°, were mixed in a 100 ml flask. An aliquot (1 ml) was pipetted out, the absorption at 254 mμ being measured by Shimadzu spectrophotometer type SV 50A.

Acknowledgment—The authors are grateful to Nippon Carbide Co. and Nissan Chemical Co. for their gift of materials.

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[11] G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.* 679 (1948).

[12] R. E. Kent and S. M. McElvain, *Organic Syntheses* Coll. Vol. III; pp. 490 and 493. J. Wiley New York (1955).

[13] J. A. Scarrow and C. F. H. Allen, *Organic Syntheses* Coll. Vol. II; p. 387 (1955).

[14] R. Adams and A. F. Thal, *Ibid.* Coll. Vol. I, p. 107 (1950).

[15] S. A. Glickman and A. C. Cope, *J. Amer. Chem. Soc.* **67**, 1017 (1945).