THE ACID CATALYZED HYDROLYSIS OF METHYL ISOCYANIDE

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ABSTRACT

The acid catalyzed hydrolysis of methyl isocyanide was studied as a function of temperature, pH, general acid concentration and buffer acid. The rate of disappearance of methyl isocyanide was followed by vapour phase chromatographic analysis.

In the weakly acidic, buffered solutions (pH 4 to 6), the hydrolysis of methyl isocyanide to N-methylformamide is a reaction pseudo-first order in methyl isocyanide showing a small negative salt effect. The reaction shows a linear rate dependence on concentration of the general acid (un-ionized acid) at fixed pH and the rate of disappearance of methyl isocyanide increases with temperature. The activation energy is 16.19 ± 0.87 Kcal $mole^{-1}$.

The observation of general acid catalysis supports a reaction mechanism with an initial formation of a hydrogen-bonded complex between the carbon atom of the isocyano group and the general acid, that is:

1. $CH_3NC + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3NC\cdots\cdots HA$

2. $CH_3NC\cdots\cdots HA + H_2O \underset{(\longleftarrow)}{\overset{k_2}{\longrightarrow}} CH_3-N=C\begin{matrix}H\\ {}^{+}OH\\ H\end{matrix} + A^-$

3. $CH_3-N=C\begin{matrix}H\\ {}^{+}OH\\ H\end{matrix} + H_2O \text{ (or } A^-) \xrightarrow{k_3} CH_3-N=C\begin{matrix}H\\ OH\end{matrix} + H_3O^+ \text{(or HA)}$

4. $CH_3-N=C\begin{matrix}H\\ OH\end{matrix} \underset{}{\overset{K}{\rightleftharpoons}} CH_3-NH-C\begin{matrix}H\\ =O\end{matrix}$

Since water is the solvent (i.e. present in great excess), the rate expression is,

$$\text{Rate} = (k_2k_1/k_{-1})(CH_3NC)(HA).$$

INTRODUCTION

Isocyanides along with carbon monoxide, are the only stable group of compounds with a divalent carbon (1). They are isoelectronic and both can be thought of as a hybrid of the divalent and dipolar structure:

$$R-\ddot{N}=C: \longleftrightarrow R-\overset{+}{N}\equiv\overset{-}{C}:$$

$$:\ddot{O}=C: \longleftrightarrow :\overset{+}{O}\equiv C:^{-}$$

This unusual structure of the isocyanide explains the complicated reactions observed.

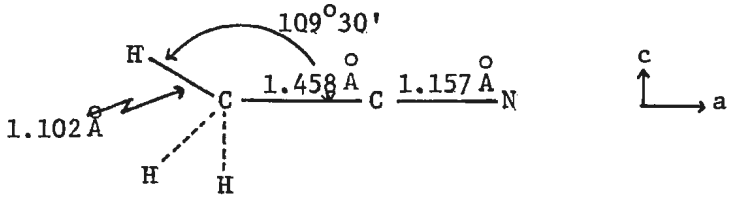
In 1859, Lieke (2) reacted allyl iodide and silver cyanide and obtained a compound with a "penetrating" odor, he erroneously believed to be allyl cyanide. Several years later, Meyer (3) also obtained isocyanides from alkylations of silver cyanide. Both workers unknowingly synthesized isocyanides. Eight years after Lieke's discovery, the isocyanides were recognized and intentionally synthesized by Gautier (4-12) and Hofmann (13-16). Although isocyanides have been known for more than a hundred years, relatively few studies of their chemistry had been done until about a dozen years ago when Ugi et al (17) found a convenient method to prepare them. The repulsive odor of isocyanides also plays a part in the scarcity of the studies.

The structure of isocyanide plays an important role in any discussion of their reaction mechanisms and will be briefly discussed.

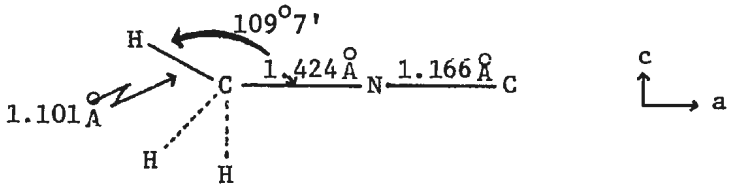
Three types of structure (Structure I to III) have been proposed (18-21), (I) R-N≡C, (II) $R-\ddot{N}=C:$ and (III) $R-\overset{+}{N}\equiv\overset{-}{C}:$ or $R-N\equiv C:$.

Structure I which has a pentavalent nitrogen has been long discarded (22,23). Structure II which has a divalent carbon (carbene) was mainly supported by Nef (24,25) but the large number of α -additions to the isocyanide terminal carbon show its divalent carbene character (24). However, no significant physical evidence for the double bonded structure (Structure II) is found from parachor (26,27) or other studies. Structure III which is a charge separated formula (i.e. one third of the triple bond of isocyanide is a co-ordinate covalent bond) was suggested by Langmuir (28) and later accepted by G.N. Lewis (29), Lowrey Sugden (30) and others (31-33). Most reactions of isocyanides can be explained in terms of this dipolar structure and, in addition there is much physical evidence, especially in the field of microwave studies, supporting the triple bond character (31-34). The strength of the C≡N bond in isocyanides and cyanides is approximately equal, the $\lambda_{N\equiv C}$ at ca. 2150 cm^{-1} and $\lambda_{C\equiv N}$ at ca. 2250 cm^{-1} are in the triple bond region. Dipole moment measurement studies (35) also support the dipolar structure and the linearity of the C-N-C linkage has been established (36). In raman studies, the band between 1960 and 2400 cm^{-1} in isocyanide spectra was pointed out by Dadieu (37) as evidence for the presence of a triple bond. Conclusively, the triple bond character and the linearity of the C-N-C bond system (i.e. dipolar structure) is established (38). Thus in comparative studies of the structure of cyano and isocyano groups, very similar physical properties have been found (39-44), i.e. $K_{N\equiv C}$ = 16.7 mdyne/A^{o}; $K_{C\equiv N}$ = 18.1 mdyne/A^{o} (45) and heats of formation are 88-89 Kcal $mole^{-1}$ for both (46). The absolute values of the molecular dipole moments given by S.N. Ghosh, R. Trambarulo and W. Gordy (47) and the molecular dimensions given by C.C. Costain (36) are also similar as shown below for methyl

cyanide and isocyanide.

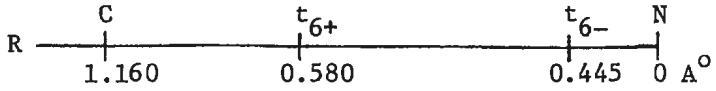


CH_3CN: $|\mu| = (3.92 \pm 0.06) \times 10^{-18}$ esu.cm



CH_3NC: $|\mu| = (3.83 \pm 0.06) \times 10^{-18}$ esu.cm

Bak and co-workers (48) calculated the electron densities of cyano and isocyano groups and found the centers of negative charge (t_{6-}) and positive charge (t_{6+}) were at quite similar positions as below.



Also almost identical molecular quadrupole moments and electric dipole moments for these isomeric species were found by J.M. Pochan et al (44). But the molar bond refraction of the isocyano group is greater than that of the cyano group attached to the same residue (49,50). Since the bonding electron distributions are about the same for isocyano and cyano group, Gillis (49) suggested that the greater molar bond refraction of the isocyano group is due to the looser bonding of the pair electrons on carbon, presumably because of the low electronegativity of carbon atom compared to nitrogen.

Carbon monoxide can also exist in carbene ($\ddot{C}=O:$) and polar structures ($\overset{+}{O}\equiv\overset{-}{C}:$ or $:O\overset{+}{\equiv}\overset{-}{C}$), but is more stable in the carbene structure since it has a very low dipole moment (0.12 D) (51), unlike isocyanides.

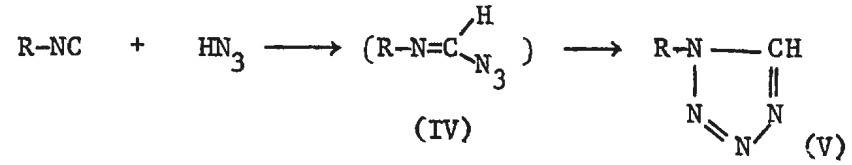
It has been suggested that a resonance hybrid exists between the two canonical structures (Structure II & III), even though no physical evidence is available for the carbene structure (52).

$$\underset{\text{(II)}}{R-\ddot{N}=C:} \longleftrightarrow \underset{\text{(III)}}{R-\overset{+}{N}\equiv\overset{-}{C}:}$$

However, in a study of the infrared spectra of isocyanides, Horrocks and Mann (53) have found that the $-N\equiv C$ stretch frequency increases with increasing solvent polarity. This is in sharp contrast to other multiple bond systems. They concluded that this abnormal solvent shift is due to polar solvent enhancing the contribution of the polar structure (Structure III) and thus increasing the absorption frequency. In other words, the doubly bonded carbene structure must be a significant contributory structure. Considering the mass of physical evidence for triple bond character, the dipolar structure must contribute most to the hybrid or actual structure. Thus, the dipolar structure would be the best single representation of the isocyanide group, or at least that of methyl isocyanide. According to Pauling (54), the dipolar canonical form ($CH_3-\overset{+}{N}\equiv C^{-}$) contributes 74% to the resonance hybrid of methyl isocyanide.

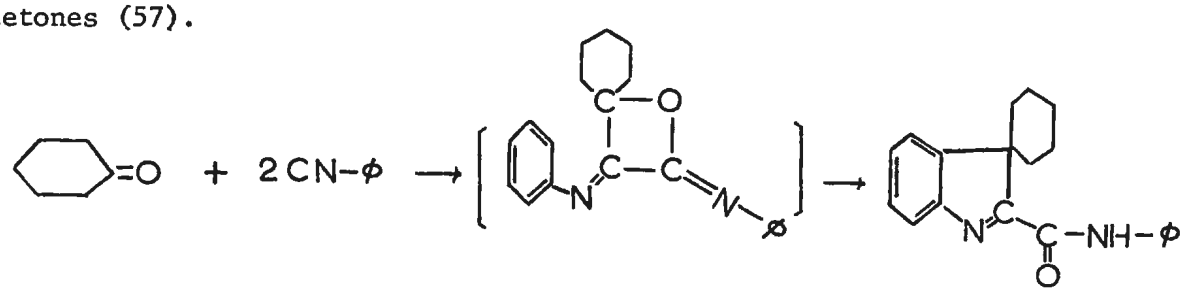
Most studies of the isocyanides are of their more complex synthetic reactions, such as the novel synthetic methods for heterocyclic

compounds, peptides and derivatives of α -amino acid. For example, reaction of an isocyanide and hydrazoic acid gives a general synthetic route to 1-substituted tetrazoles (V) (55,56).



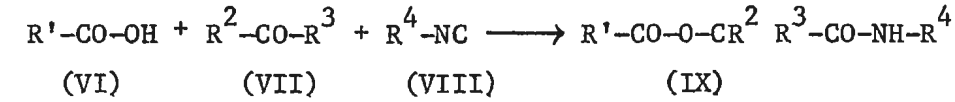
(IV) (V)

The α -adduct of hydrazoic acid (IV) is an unstable intermediate. More complicated heterocyclic compounds such as the indolenins, were found to be readily synthesized by the cyclization of aromatic isocyanides with ketones (57).



These novel synthesis methods are making a great contribution to heterocyclic chemistry.

In 1921, Passerini (58-60) reported the first triple additions of isocyanides, that is, the combination of carboxylic acids (VI), "carbonyl" compounds (VII) (aldehydes, ketones* or acyl cyanides) and isocyanide (VIII) to form α -acyloxycarbonamides (IX).



(VI) (VII) (VIII) (IX)

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* Some α - βunsaturated or sterically hindered ketones, i.e. camphor, do not undergo the Passerini reaction (1).

This reaction called the Passerini reaction, is potentially useful for the synthesis of depsipeptides (61). A wide variety of α -acyloxycarbonamides have been prepared by the Passerini reaction, but the reaction mechanism is still not really understand, Passerini postulated a hemiacetallic adduct like (X) as an intermediate.

$$\text{VI} + \text{VII} \longrightarrow \underset{\text{(X)}}{\text{R'-CO-O-CR}^2\text{R}^3\text{OH}} \xrightarrow{\text{VIII}} \text{IX}$$

However, the dipolar species ($R^2-\overset{R^3}{\overset{|}{\underset{O^-}{\overset{|}{C}}}}-\overset{+}{C}=N-R^4$) (VII + VIII) (62,63), N-protonated isocyanides ($R^4-\overset{+}{\underset{H}{N}}=C$) (64), iminoeirane intermediates ($R^2-R^3\overset{O}{\diagdown\diagup}C=N-R^4$ $R^2-R^3\overset{C}{\underset{O}{\diagdown\diagup}}N-R^4$) (65) and $R'-C\overset{O\cdots\cdots H-O}{\underset{O}{\diagdown\diagup}}\overset{R^2}{\underset{R^3}{C}}C\underset{N-R^4}{=}$ (66) might be intermediates of the Passerini reaction. There is not yet enough information to choose the proper intermediate or intermediates from these alternatives.

It is quite clear that most isocyanide studies have concentrated on the synthetic and more complex reactions and that few systematic studies of simpler reactions with the exception of the isomerision of isocyanides to the cyanide have been carried out (67). The rearrangement of isocyanides to cyanides,

$$R-\overset{+}{N}\equiv C^- \longrightarrow R-C\equiv N$$

has been known for half a century (67), but only in recent years has this thermal rearrangement (68–73) been quantitatively studied, mainly through gas phase kinetics. From studies in solution, Kohlmaier and Rabinovitch (68) did report some studies on the activation energy of rearrangement and

Casanova and co-workers (74) correlated the rate of rearrangement of three para-substituted aryl isocyanide in diglyme through the application of the Hammett Equation,

$$\log (K/K_o) = \sigma\rho$$

where σ is the substituent constant, independent of the nature of the reaction and ρ is the proportionality constant. Casanova (74) et al found that variation in σ and the polarity of the solvent have no effect on the rate of rearrangement. They consequently concluded that there is no separation of molecular fragments and little charge separation during the course of the reaction, and propose a cyclic model for the transition state;

This rearrangement is an example of a Wagner-Meenwein 1-2 shift (72-76). At ordinary temperatures, the rearrangement is a nucleophilic substitution with isomerization. This cyclic model for the transition state was adopted by Schneider (72,76), Maloney (77), Rabinovitch (72, 76,77) and other workers (78,79), both for solution and vapour phase systems.

Other than these thermal rearrangement studies, few careful mechanistic studies have been undertaken. Before the more complex and synthetically useful reactions can really be understood, however, the simpler reactions of the isocyanides, the solvolysis mechanisms for example, must be elucidated.

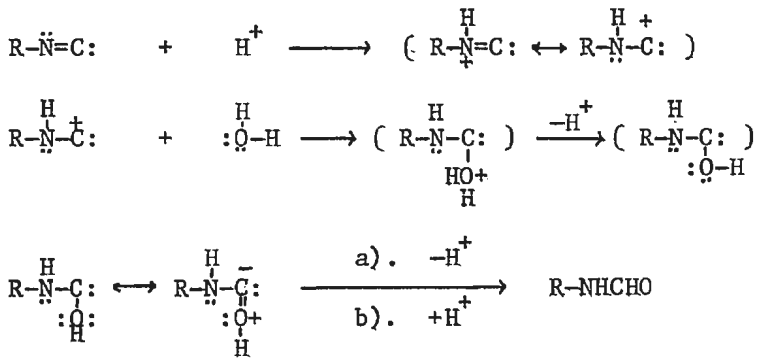
The hydrolysis of methyl isocyanide is known to be an acid catalyzed reaction through the formamide intermediate to the protonated amine and formic acid. Under strongly acidic conditions, the formamide inter-

mediate will be hydrolyzed, but under weakly acidic conditions, good yields of formamide can be obtained. The reaction mechanism of amides in general is well known but the hydrolysis of isocyanides to formamide has not been studied previously. Whether protonation is on the carbon atom (Reaction 1) or the nitrogen atom (Reaction 2) of the isocyano group is unknown.

(1). $R\text{-}NC + H^+ \rightleftharpoons R\text{-}N\equiv CH \xrightarrow{H_2O} R\text{-}NHCHO$

(2). $R\text{-}NC + H^+ \rightleftharpoons R\text{-}N\equiv C^+(H) \xrightarrow{H_2O} R\text{-}NHCHO$

In 1965, M. Khalifa (80) suggested a mechanism for the reaction of carbon monoxide with sodium hydroxide based on the carbene structure of carbon monoxide (:C=Ö:). Likewise, based on the carbene structure of isocyanide (R-N̈=C:), he elaborated a mechanism of hydrolysis of isocyanide as follow:



$R\text{-}\ddot{N}=C: + H^+ \longrightarrow (\ R\text{-}\overset{H}{\overset{|}{\overset{+}{N}}}=C: \longleftrightarrow R\text{-}\overset{H}{\overset{|}{\ddot{N}}}\text{-}\overset{+}{C}: \ )$

$R\text{-}\overset{H}{\overset{|}{\ddot{N}}}\text{-}\overset{+}{C}: + :\overset{H}{\overset{|}{\ddot{O}}}\text{-}H \longrightarrow (\ R\text{-}\overset{H}{\overset{|}{\ddot{N}}}\text{-}\underset{HO^+H}{\underset{|}{C}}: \ ) \xrightarrow{-H^+} (\ R\text{-}\overset{H}{\overset{|}{\ddot{N}}}\text{-}\underset{:\ddot{O}\text{-}H}{\underset{|}{C}}: \ )$

$R\text{-}\overset{H}{\overset{|}{\ddot{N}}}\text{-}\underset{:\ddot{O}:H}{\underset{|}{C}}: \longleftrightarrow R\text{-}\overset{H}{\overset{|}{\ddot{N}}}\text{-}\underset{:\ddot{O}^+H}{\underset{|}{C}}: \xrightarrow[b).\ +H^+]{a).\ -H^+} R\text{-}NHCHO$

The proposed reaction mechanism is through initial protonation on the nitrogen atom rather than the carbon atom. However, in 1962, a study of carbon-hydrogen-carbon bonding by Louis L. Ferstandig (81,82) showed that

there was strong hydrogen bond formation between alcohols and isocyanides. Using experimental evidence, electronic and steric arguments, he argued that the hydrogen bonding is with the carbon atom of the isocyano group. Work by Adam Allerhand and Paul Von Raque Schleyer (83), also suggests that strong hydrogen bonding is to the carbon atom rather than the nitrogen atom of the isocyano group. Their studies of hydrogen bonding between the proton donors and nitriles or isocyanides were made by correlating the infrared spectral shift and Taft's constant.

Besides, isocyanides form organometallic compounds. Stable complexes were formed favourably with softer metal cations (51)(Reaction 1 to 3, Table 10). Isocyanides also give simple addition reactions with halogens, halogen acids, alcohols etc. (9)(Reaction 4 to 8, Table 10).

In the previous discussion on the structure of isocyanides, it was concluded that the isocyanides are best represented by the dipolar structure, $R-\overset{+}{N}\equiv C^{-}$ or $R-N\rightleftarrows C$. If there is hydrogen bond formation with or protonation by an acid, it is no doubt at the negative carbon rather than the positive nitrogen of the isocyano group. Contrary to the mechanism proposed by M. Khalifa (80) then, it is very likely that the site of protonation is the carbon atom of the isocyano group.

Hopefully, with the study of acid catalyzedreaction, we would be able to predict the reaction mechanism.

There are two general kinds of acid catalyzed reactions, those showing specific and those showing general acid catalysis (95,96). Specific acid catalysis is present in deduce that are catalyzed only by the protonated solvent or lyonium ion. Mechanistically, these can be written as,

$$S + H^+ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} SH^+$$

$$SH^+ + R \xrightarrow[k_2]{\text{slow}} \text{products}$$

where S is the substrate, R the other reactant and H^+ the lyonium ion. The rate of this reaction sequence is given by,

$$\text{rate} = k_2 \, [SH^+] \, [R]$$

Since the first step is an equilibrium,

$$\text{rate} = (k_2 k_1 / k_{-1}) \, [S] \, [R] \, [H^+].$$

For general acid catalysis, the rate depends not only upon the concentration of the lyonium ion (H_3O^+ in water), but also upon the concentration of any un-ionized acids present. There are several general mechanistic schemes for general acid catalysis, but there are only two that are likely mechanisms for the acid catalyzed hydrolysis of isocyanides. The first scheme is very similar to that above but with a slow rather than equilibrium protonation of the substrate by the acid.

$$S + HA \xrightarrow[k]{\text{slow}} SH^+ + A^- \text{ (or product)}$$

$$SH^+ + R \xrightarrow{\text{fast}} \text{products.}$$

If more than one acid ispresent, each acid will have its respective rate constant and:

$$\text{rate} = k_a \, [S] \, [HA_a] + k_b \, [S] \, [HA_b] + \cdots\cdots\cdots$$

$$= [S] \sum_{1-a} k_a [HA].$$

The second mechanism is a reaction series involving the formation of a hydrogen-bonded complex between the acid and the substrate, followed by, as the rate determining step, reaction of the complex:

$$S + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S\cdot HA$$

$$S\cdot HA + R \xrightarrow[k_2]{\text{slow}} \text{products.}$$

The rate expression is,

$$\text{rate} = (k_2 k_1 / k_{-1})(S)(HA)(R)$$

In the acid catalysed hydrolysis of methyl isocyanide, slow irreversible protonation or hydrogen-bonding-proton transfer should show general acid catalysis since any acidic species present would contribute. Protonation on the nitrogen atom should show specific acid catalysis since protonation on the nitrogen atom is relatively difficult, a relatively strong acid— the strongest acid present, H_3O^+— is required. Such a protonation should be reversible and the equilibrium should lie well to the left as written. Thus hydrolysis through protonation on the nitrogen atom of cyanimide and cyanide proved to be a specific acid catalyses reaction (for details see the Discussion section). If specific acid catalysis, that is catalysis by H_3O^+, is observed for the hydrolysis of isocyanides, the N-protonation mechanism is not ruled out. However, if general acid catalysis is found, the initial protonation can not be at nitrogen and must be at carbon. It

was to provide more information about the mechanism of the hydrolysis of isocyanides, that the kinetic study of this acid catalyzed reaction as described in this dissertation was undertaken.

EXPERIMENTAL

1. General Considerations

The study of the acid hydrolysis of methyl isocyanide to N-methylformamide is difficult by employing nuclear magnetic resonance or infrared spectroscopy. NMR spectroscopy was found inapplicable because of the low intensity of the signals even at 10% aqueous solutions of methyl isocyanide, where the complication of micro-droplet formation may also arise. The intensity of the peaks of the aldehydic-proton (broad singlet, τ=1.3) and methyl-protons (doublet, τ=6.7) of N-methylformamide and methyl-protons (triplet, τ=6.25) of methyl isocyanide were very low in comparison to the proton peak of water so that determining the rate of hydrolysis through three peaks would give a very low precision.

In infrared spectroscopy, overtones of the water absorption peaks extended into the region of isocyanide N≡C absorption (2170 cm^{-1}) so that the N≡C peak intensity could not be determined. Besides, it was rather difficult to maintain a constant temperature in an infrared cell, so this method was also not used.

Since desirable results could be obtained for the kinetic studies of the acid catalysis hydrolysis of methyl isocyanide to N-methylformamide by using gas chromatography, in the present study, this method was adopted. The procedure used is discussed in detail in part 3 below.

2. Materials

i. Preparation of Methyl Isocyanide

Methyl isocyanide was prepared by dehydration of N-methylformamide

with acylhalides in the presence of base. The large difference in boiling points between the reactants and product made the separation possible and very pure methyl isocyanide can be obtained. A modified produre of E.J. Corey (97) and I. Ugi et al (17) was used.

The N-methylformamide used was Aldrich fine grade which was vacuum distilled (b.p. = 103°C; 23 mm). The colorless liquid was used without further purification. The tributylamine and benzene sulfonyl chloride were Matheson, Coleman and Bell practical grade and were used without purification.

The preparation was carried out with 41 grams (0.685 mole) of N-methylformamide and 350 ml (.62 grams; 1.46 moles) of tributylamine (M.W. = 185.35; ρ = 0.7782) which were placed in a one liter three-necked flask on a steam bath. The flask was equipped with a 100-ml dropping funnel, a high-speed vacuum tight stirrer (Stirovac) and a dry ice condenser filled with dry ice and acetone ($\sim$-20°C) to the top of which two liquid nitrogen traps were connected in series (Figure 12). The system was kept at 20 mm Hg pressure by a vacuum pump connected to the second trap. The reaction was carried out in the hood**. The mixture of N-methylformamide and tributylamine was vigorously stirred and kept at about 65°C by gentle heating on the steam bath. Through the dropping funnel, 90 ml (124 grams; 0.702 mole) of benzene sulfonyl chloride (M.W. = 176.6; ρ = 1.378) was dropped slowly into the warm mixture. Thus the dehydration was carried out smoothly at reflux and the methyl isocyanide (the product) was distilled into the liquid nitrogen traps and frozen as it formed (Reaction 3).

** Methyl isocyanide is toxic and has a very unpleasant odor.

(3) $CH_3NHCHO + C_6H_5SO_2Cl + 2\ nBU_3N \xrightarrow[20\ mm\ Hg]{60\text{-}70^oC} CH_3N{\equiv}C + Cl^- + C_6H_5SO_3^- + 2\ nBU_3\overset{+}{N}H$

The addition of benzene sulfonyl chloride was complete in one half hour. The mixture was then maintained at 65-70°C and pumped at 10 mm Hg pressure for another hour. When the reaction was complete , the two nitrogen traps were removed from the system and the crude methyl isocyanide from the traps was combined. The crude methyl isocyanide was transferred to a pear-shape-flask and distilled through a six inch Vigreaux column behind a safety shield***. The fraction distilling from 58 to 59°C was collected and the rest discarded. This gave a yield of about 74% of methyl isocyanide (21.006 grams; 0.513 mole). After redistillation, gas-liquid chromatography of this product indicated a purity of greater than 99%.

ii. Preparation of Buffer Solution

Two buffer pairs were used in this experiment; potassium biphthalate (1-KOOC-C_6H_4-2-COOH, M.W.=204.23) with added potassium hydroxide and citric acid ($H_3C_6H_5O_7 \cdot H_2O$, M.W.=210.4) with added potassium hydroxide. Potassium chloride was added to the buffer solutions to keep the total ionic strength constant. In order to estimate the effects of specific or general acid catalyst, all the solutions were prepared by keeping the total acid concentration constant, and varying the volume of base to obtain

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*** Explosions of ethyl isocyanide have been reported (98,99) and an explosion occured on distillation of methyl isocyanide during the present study. However, further attemps to induce such an explosion by heating, dropping methyl isocyanide onto hot plates etc., were not successful (100).

the desired pH (pH 4 to 6) (96), except for those used to determine the effect of buffer concentration. In order to keep the pH constant throughout the reaction, the concentration of the buffer solution was kept about five to six times higher than that of methyl isocyanide. The details of the buffer solution preparation are shown in Table 1.

The pH of the solutions was determined with a Radiometer pH Meter 4d using a glass electrode which was standardized with standard pH 4 buffer solution (potassium phthalate-tartaric acid). The standard buffer solution was prepared from the Canadian Laboratory Supplies Ltd. (Harleco) product. All chemicals used were of reagent grade and used without further purification.

3. Gas Chromatography

Isocyanides form complexes with metals (51). In 1963, A. Lifshitz, H.F. Carroll and S.H. Bauer (101) failed to analyse methyl isocyanide with a Perkin-Elmer 154 vapor fractometer by using a six foot R column at 70°C and a column pressure of 50 p.s.i.g.. Similar observation were made in this laboratory (18). In 1965, A.G. Kelso and A.B. Lacey (102) observed that analysis of aliphatic isocyanide with glass tubing was satisfactory but unsatisfactory with the metal. However, on "Chromosorb W-HMDS" (a hexamethyldisilazane-treated support), they found that upon injection of 0.5 µl samples, the peak height was not constant but increased with each injection, unless a total of approximately 4 µl (introduced in several small or one large injection) was injected before the sample injection. Then normal peaks were obtained with 0.5 µl injections.

The study of hydrolysis of methyl isocyanide in this experiment

was based on the peak area of methyl isocyanide. This was satisfactorily analyzed with a dual/differential electrometer on an Aerograph 1520B model gas chromatograph, equipped with a Honeywell recorder with a Disc integrater, under the conditions stated below. Reversible adsorption and tailing effects did not occur, making the present analysis possible.

A five foot glass column was treated with 5% of trimethylchlorosilane in toluene solution, oven dried and packed with Corning pure, inert glass bead support (mesh 100/120) which had been treated with dimethyldichlorosilane and then coated with 0.2% of OV-17. The glass column extended into the flame-ionization detector and out to the injector septum. The sample was injected directly into the glass column. The operating temperature was 70°C, the carrier gas, helium, had a flow rate of about 25-30 and the hydrogen gas, 20-25 ml/min. The dual/differential electrometer was operated at a range setting of one and an attenuator setting of 64 for both the sample and reference columns.

Reversible adsorption was not observed with a 2 µl injection of methyl isocyanide-water solution which was only 0.03601 M. Agreement was within 1.5% (Figure 1). Methyl isocyanide had a retention time of 9.6 seconds and was not interfered with by the buffer solutions or the N-methylformamide (i.e. operating temperature was 70°C which was too low for higher boiling point 103°C, N-methylformamide), the retention time for N-methylformamide varied from 36 to 72 seconds with the various columns.

Due to the high concentration of salt being used (part 2, ii), it was necessary to mechanically clear the salt in the column quite often and the glass column only lasted for about one thousand injections before clogging.

4. Sample Preparation and Analysis

Methyl isocyanide was stored in the refrigerator ($0^{\circ}C$) in the dark and distilled once every ten days. It is a colorless liquid with a strong pyridine-like odor.

Five millilitres of buffer solution was withdrawn with a 5 ml-pipette and transferred to a dry clean reaction vessel, a 10-ml long-necked thin walled flask. After addition of the 5 ml of buffer solution, the reaction vessel was sealed by means of a serum cap. It was then placed in the Sargent Thermonitor S84810 model SW controlled water bath which had an accuracy of better than $\pm$ $0.01^{\circ}C$.

When the temperature of the buffer solution in the reaction vessel was equilibrated in the water bath (about 20 minutes), 10 µl of methyl isocyanide was injected into the buffer solution with a 50 µl-syringe and the solution shaken. The electric timer was started. Every 200 seconds, a Hamilton 10 µl-syringe was inserted through the serum cap into the reaction solution and a 2 µl-sample was withdrawn. The sample was injected onto the column of the gas chromatograph and the chromatogram thus obtained. It took 15-20 seconds from withdrawing the sample to the injection. The aliquots were analyzed until the reaction was 90% complete. If the reaction was slow (i.e. a half life greater than 2 hours), three to six reactions were carried out at the same time and analyzed. Each reaction solution had a separate syringe. The syringe was not washed after each injection but pumped a few times with the solution immediately before withdrawing the 2 µl-sample for analysis. This gave better results than cleaning the syringes after each injection (i.e. minute traces of acetone or other wash solvent left in the syringe often interfered with the methyl

isocyanide peak).

The hydrolysis rate depended on temperature and pH. The fastest reaction measured was the one that took about 4200 seconds to complete and the slowest one was the one that took about eight hours to complete.

After the reaction was complete, the pH of the solution was checked to make certain it was unchanged by the reaction.

5. Analysis of The Chromatogram

Since the rate of reaction was determined from the area of the methyl isocyanide peak, the conditions of gas chromatography were set to favor the analysis for methyl isocyanide. The relative concentration of methyl isocyanide was interpreted by the area under its peak as recorded by the Disc integrater on the chart recorder. The speed of the chart was set at 2 minutes per chart inch, such that the peak width of methyl isocyanide was 0.1 inch (i.e. one division of the chart or 0.2 minute). This is shown in Figure 2. The 0.1 inch width of the peak was projected to the corresponding Disc integrater trace and the "area" measured.

RESULTS

1. The Order of the Acid Catalyzed Hydrolysis of Methyl Isocyanide

To determine the order of the reaction, six runs were carried out with the same initial methyl isocyanide concentration (0.03601 M), pH and temperature. One of the chromatograms is shown in the Figure 2. In Table 2a and 2b, the relative concentration of methyl isocyanide at time t as determined from the area of the methyl isocyanide peaks on the gas chromatograph, is recorded. Plots of the logarithm of the relative concentrations of methyl isocyanide versus time t, are shown in Figure 3a and 3b. The plots give a set of straight lines with slopes of:

(1). $-(0.969 \pm 0.033) \times 10^{-4}\ sec^{-1}$
(2). $-(0.990 \pm 0.032) \times 10^{-4}\ sec^{-1}$
(3). $-(0.993 \pm 0.028) \times 10^{-4}\ sec^{-1}$
(4). $-(1.020 \pm 0.040) \times 10^{-4}\ sec^{-1}$
(5). $-(1.060 \pm 0.040) \times 10^{-4}\ sec^{-1}$
(6). $-(0.969 \pm 0.019) \times 10^{-4} sec^{-1}$

These values were calculated by the least squares method using Olivetti Underwood Programma 101. The standard deviation is ± 4.7%, well within the experimental reproducibility. Since plot of logarithm of relative concentrations of methyl isocyanide versus time give a straight line, therefore, it is concluded that in the acid catalyzed hydrolysis of the methyl isocyanide, the reaction is first order with respect to the methyl isocyanide since water is present in large excess and the pH is constant.

2. The Effect of pH and Buffer Concentration* on the Rate Constant

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* Buffer Concentration = (Acid) + (Acid Anion(s)) in moles $liter^{-1}$.

The results for the dependence of the reaction rate constant on the pH at constant ionic strengths are shown in Tables 3 and 4.

Figures 4 and 5, corresponding to Tables 3 and 4, show the effect of various buffer solutions and temperatures upon the relationship between rate constant and pH. Plots of the observed rate constant against hydrogen ion activity, equating activity and concentration, from Tables 3 and 4 are shown in Figures 10 and 11. In all cases curves result. The ionic strength is kept constant in each set of buffer solutions at the various pH values, so the salt effects can be neglected.

The observed non-linear relationship of reaction rate constant and proton activity shows that the hydrolysis is certainly not a specific acid catalyzed reaction. If it is a general acid catalyzed reaction, the rate constant would not only be dependent on the hydronium ion concentration but also on the concentration of un-ionized acids. Another set of experiments were carried out at pH 4.18 with various buffer concentrations. These results are shown in Table 5 and are presented graphically in Figure 6. They show that the reaction rate constant is directly proportional to the buffer concentration at constant pH, such that a factor of two in buffer concentration gives a doubling of the rate constant. These results confirm that the acid hydrolysis of methyl isocyanide is a general acid catalyzed reaction.

Since the study of the rate constant versus pH was done with fixed total buffer concentration, that is a constant initial amount of citric acid or biphthalate was used and potassium hydroxide solution was added to give the desired pH, the concentration of citric acid or biphthalate is not constant at the different pH values. Hence the contribution to the observed rate from the general acid catalysis by citric acid or biphthalate would

decrease as the activity of the hydronium ion decreased. At "zero" hydronium ion activity, the activities of the various acids would also be "zero". Therefore, extrapolation of the $a_{H_3O^+}$ versus k_{obs} curve to intersect at zero hydronium activity, gives the rate constant for the only remaining acid, the solvent, water. From Figures 10 and 11, the rate constant for water (i.e, non-catalyzed hydrolysis), is near zero for temperatures between 25 and 45°C, that is, water catalysis makes a very small contribution to the overall reaction.

3. The Dependence of the Rate Constant on Temperature.

The rate of the acid catalyzed hydrolysis of methyl isocyanide at temperatures between 25 and 45°C was studied. This was carried out in either phthalate-biphthalate or citrate-citric acid buffer solution. The results are shown in Tables 6a and 6b and are plotted in Figure 7.

In Figure 7, the logarithm of the rate constant is plotted as a function of 1/T, and straight lines are obtained. The slopes of the lines were calculated by the least squares method using a Olivetti Underwood Programma 101. The results are given in Table 7.

Table 7. The Calculated Slopes and Activation Energies for the Phthalate-Biphthalate and Citrate-Citric Acid Buffer Solutions.

Buffer Solution	pH	Slopes ($\times 10^3$)	Activation Energies (Kcalmole^{-1})	
A (phthalate-biphthalate buffer solution)	4.75	3.61 ± 0.14	16.51 ± 0.62	Average 16.56 ± 0.78
	4.95	3.62 ± 0.16	16.57 ± 0.72	
	5.18	3.58 ± 0.20	16.58 ± 0.90	
B (citrate-citric acid buffer solution)	4.68	3.46 ± 0.22	15.81 ± 0.96	

In Buffer Solution A (phthalate-biphthalate buffer solution), at pH 4.75 to 5.18, the calculated activation energies are all roughly the same, that is pH does not affect the activation energy. Apparently, the reaction mechanism is not changed by the pH. Comparison of the activation energy using Buffer Solution A (as above) and Buffer Solution B (citrate-citric acid buffer solution), shows that the activation energies are the same within the limits of experimental error. It is very difficult to find another buffer solution having a higher acid strength than citric acid or potassium biphthalate within the desired pH range, which also has suitable solubility to give the necessary concentration and that is sufficiently non-volatile for gas chromatographic analysis. The acetate-acetic acid, formate-formic acid and the phosphate buffer solutions failed to provide satisfactory analysis by gas chromatography. After several injections a sudden drop of the peak height was observed, probably because of the accumulation of a liquid acid phase in the column. Since no hydrolysis was carried out with a buffer solution made with a stronger acid, we can only assume that the reaction path (mechanism) is not changed by the different weak acid buffer solutions.

4. Ionic Strength Effects

It is difficult to estimate the ionic strength effect. This is partly because of the ionic strength effect is small and not much greater than experimental error, and partly because of the difficulty of obtaining buffer solutions at various ionic strengths but with unchanged pH. Also while farther hydrolysis of the formamide was much slower than its formation from methyl isocyanide, a limited amount of hydrolysis would always occur.

In the acidic media used, formic acid and protonated methyl amine would be the products. To prevent pH changes, especially in the later stages of runs where the formamide concentration is high and hence its hydrolysis would be greatest, moderately high buffer concentration and consequently ionic strength, is required. No studies were possible at very low ionic strengths.

In Figure 5, the reaction rates of the citrate-citric acid buffer solution at the three ionic strengths are shown. No simple correlation between ionic strength and reaction rate was apparent. Other experiments were carried out at each of pH 4.16, 4.23 and 4.29 with ionic strengths of 2.00, 1.00 and 0.7 and the reaction rate constants determined. The curves a, b and c in Figure 5 were used to compute the reaction rate constants at various pH values and ionic strengths. These results are given in Table 8 and plots of the reaction rate constant as a function of ionic strength shown in Figure 8. In Figure 8, the points calculated from curve a (ionic strength = 2.00) do not fall upon the straight line and are tentatively assumed to be in error. The plots indicate an inverse relationship between ionic strength and reaction rate, a factor of two change in the former resulting in about a 7% change in the reaction rate constant.

5. The Dependence of the Rate Constant Upon the Acid Strength of the Buffer Solution.

The results shown in Table 4 for the citric acid buffer solution are derived from reactions which do not have the same buffer concentration (before reaction with the base) as the biphthalate buffer solution. Using the ionic strength and acid concentration relationship (see Figures 6 and

8), these results were corrected to the same acid concentration and ionic strength as those used for the biphthalate buffer solution (ionic strength =0.69; buffer concentration = 0.312 M). These corrected results are shown on the Table 9 and presented graphically on Figure 9.

DISCUSSION

1. Reaction Mechanism

The hydrolysis of isocyanide by aqueous acid through a substituted formamide intermediate to formic acid and a primary amine is well known (103) (Reaction 4). Isocyanide is stable to base but will hydrolyze in water at high temperature (180°C)(80,103).

(4). $$CH_3NC + H_2O \xrightarrow[(1)]{H^+} RNHCOH \xrightarrow[(2)]{H^+} RNH_3^+ + HCOOH$$

In weakly acidic buffer solutions (pH 4 to 6), the rate of hydrolysis of N-methylformamide (Step 2) was found to be very much lower than the rate of hydrolysis of methyl isocyanide (Step 1). Hence in studying the rate of disappearance of methyl isocyanide, only step 1 of the reaction need be considered.

The hydrolysis of methyl isocyanide has been found in this study to show general acid catalysis and to be a first order reaction with respect to the concentration of methyl isocyanide (Details, see **Results**, section 1 & 2). Equating activity and concentration, the experimental rate of disappearance of methyl isocyanide will be expressed by the following equation:

$$-\frac{d(CH_3NC)}{dt} = \{ k_{H_3O^+}(H_3O^+) + k_{H_2O}(H_2O) + k_{HA}(HA) + k_{HA'}(HA') + k_{HA''}(HA'') + \cdots\cdots\cdots \} (CH_3NC)$$

where $k_{H_3O^+}$ is the catalytic constant for H_3O^+, k_{HA} for the general acid HA and so on.

Brônsted (32) showed that there is a simple relationship between the catalytic constant and the ionization constant,

$$k_a = G_a K_a^{\alpha}$$

where k_a is the catalytic constant and K_a is the ionization constant for the acid. G_a and α are constant characteristic of solvent, the reaction and the temperature. Applying the Brônsted Catalysis Relationship, a comparison of citric acid (K_1=1.45 x 10^{-4}, K_2=1.73 x 10^{-5} and K_3=4.02 x10^{-7}) to the biphthalate (K_2=3.90 x 10^{-6}) buffer solutions under the same condition gives

$$k_{H_3O^+} >> k_{\text{citrate I}} > k_{\text{citrate II}} > k_{\text{biphthalate}} > k_{\text{citrate III}} > k_{H_2O}$$

Therefore, at the same temperature and pH, the rate of the hydrolysis should be greater in citric acid than biphthalate buffer solution. The results shown in the Figure 9, are consistent with the Brônsted Catalysis Relationship, especially when it is noted that to achieve the same pH at the same "buffer concentration" with the stronger acid (citric acid) requires that the stronger acid be at a lower concentration than the weaker acid (biphthalate). These results comfirm that the hydrolysis of methyl isocyanide is without doubt, a general acid catalyzed process.

2. Site of Protonation.

The hydrolysis of methyl isocyanide to N-methyl formamide may

proceed through protonation on(or hydrogen-bonded complexation to)either the carbon atom or the nitrogen atom of the isocyano group followed by the nucleophilic attack of water (Reactions 1 and 2).

(1). $CH_3NC + H^+ \longrightarrow R\text{-}N\overset{+}{\equiv}CH \xrightarrow{+H_2O} \longrightarrow RNHCHO$

(2). $CH_3NC + H^+ \longrightarrow R\text{-}\underset{H}{N}\overset{+}{\equiv}C \xrightarrow{+H_2O} \longrightarrow RNHCHO$

In the study of acid catalyzed hydrolysis of cyanamide (104-108), Grube (106,107) showed that the hydrolysis is specific acid catalyzed reaction with a large linear salt effect. This was accepted by Hammett and Paul (105) and conforms to the relationship:

$$H_o + \log_{10} k_{obs} = \text{constant}$$

where H_o is the acidity function of Hammett and k_{obs} is the observed reaction rate constant. The following reaction mechanism was proposed by Mary Kilpatrick (108). The protonation on the N-atom of the cyanamide is the first step in the reaction pathway,

$$NH_2CN + A \longrightarrow B + \underset{(XI)}{\left(NH_2C\overset{+}{\equiv}NH \leftrightarrow NH_2\text{-}\overset{+}{C}\text{=}NH \leftrightarrow NH_2\text{=}\overset{+}{C}\text{=}NH \right)}$$

where A is an acid and B is its conjugate base. Some protonated material may have the structure $\overset{+}{NH_3}CN$ rather than structure XI. Besides this, hydrolysis of cyanide with protonation on the N-atom will take place only

in the presence of strong acid (109-111), that is the hydrolysis is a specific acid catalyzed one. By analogy, acid catalyzed hydrolysis via protonation on the nitrogen atom of isocyanide should also show specific acid catalysis. On the contrary, the experimental results prove that hydrolysis of methyl isocyanide shows general acid catalysis. Hence, it is very unlikely that protonation is on the nitrogen atom. The studies of carbon-hydrogen-carbon bonding by L. Ferstandig, A. Allerhand and Paul Von Raque Schleyer (81-83) prove that the hydrogen bonding between the proton donor and the isocyanide is at the carbon atom of the isocyano-group. In the addition reactions and metal complexes (Table 10), the addition or coordination is through the carbon atom of the isocyano-group (51,18). In the discussion of the structure of isocyanide, the conclusion was reached that the dipolar structure ($R-\overset{+}{N}\equiv\overset{-}{C}:$ or $R-N\overset{+}{\equiv}C:$) is the best single structural representation of isocyanides (for details see the Introduction). Therefore, if there is any hydrogen-bond complex formation to or protonation of isocyanide by the proton donor, it is no doubt at the negative carbon atom of the isocyano group of isocyanide. Should a hydrogen-bonded complex be formed with the nitrogen atom of the isocyanide, the complex (XII) would be much less stable than complex (XIII).

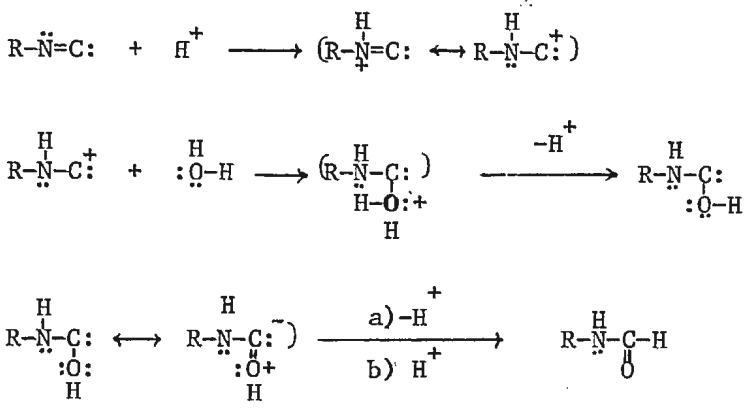
$$CH_3-\overset{+}{\underset{\underset{C:}{\|}}{N}}-HA^- \longleftrightarrow CH_3-\ddot{\underset{:\dot{C}+}{N}}-HA^- \qquad \text{(XII)}$$

$$CH_3-\overset{+}{N}\equiv CHA^- \longleftrightarrow CH_3-\ddot{N}=\overset{+}{C}-H\cdots A^- \qquad \text{(XIII)}$$

This is because the carbon-bonded complex much more closely resembles the unbonded resonance hybrid isocyanide (81,82). In conclusion, it is safe to assume that in hydrolysis of methyl isocyanide the initial protonation

or hydrogen-bonding is at the carbon atom, not the nitrogen atom.

In 1965, M. Khalifa (80) suggested a mechanism for the reaction of carbon monoxide with sodium hydroxide based on the carbene structure of carbon monoxide (:C=O:). Likewise, based on the carbene structure of isocyanide (R-N̈=C:), he elaborated a mechanism of hydrolysis of isocyanides as follows:



If this mechanism is correct, the protonation on the nitrogen atom would be expected to result in specific acid catalysis. In the present study, the experimental results prove that the hydrolysis of isocyanide shows general acid catalysis. Therefore, it is very unlikely that the reaction mechanism proposed by M. Khalifa is correct. Additionally, isocyanide, especially in ionizing solvents like water (53), is more stable in the dipolar structure (R-N≡C or R-$\overset{+}{N}\equiv\overset{-}{C}$) than the carbene structure (R-N=C:), opposite to carbon monoxide which is more stable as :C=O: (51). Thus, it is not very reasonable to elaborate the reaction mechanism of the acid catalyzed hydrolysis of isocyanide through the carbene structure of isocyanide.

3. Mechanistic Conclusions

Two possible mechanistic schemes involving initial carbon protonation for the acid catalyzed hydrolysis of methyl isocyanide (Schedule 1 and 2) can be proposed. Structures XIV, XV, XVI and XVII are probable intermediates.

Schedule 1:

1). $CH_3NC + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3\overset{+}{N}{\equiv}CH + A^-$ (XIV)

2). $CH_3-\overset{+}{N}{\equiv}CH + H_2O \overset{k_2}{\rightleftharpoons} CH_3-N=C(H)(\overset{+}{O}H_2)$ (XV)

3). $CH_3-N=C(H)(\overset{+}{O}H_2) + H_2O \text{ (or } A^-) \xrightarrow{k_3} CH_3-N=C(H)(OH) + H_3\overset{+}{O} \text{ (or HA)}$ (XVI)

4). $CH_3-N=C(H)(OH) \underset{}{\overset{K}{\rightleftharpoons}} CH_3-NH-C(H)=O$

Schedule 2:

1). $CH_3NC + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3NC\cdots\cdots HA$ (XVII)

2). $CH_3NC\cdots\cdots HA + H_2O \underset{(\rightleftharpoons)}{\overset{k_2}{\longrightarrow}} CH_3-N=C(H)(OH^+H) + A^-$

(XV)

3). $CH_3-N=C(H)(OH^+H) + H_2O\ (\text{or } A^-) \xrightarrow{k_3} CH_3-N=C(H)(OH) + H_3O^+ (\text{or HA})$

(XVI)

4). $CH_3-N=C(H)(OH) \underset{}{\overset{K}{\rightleftharpoons}} CH_3-NH-C(H)=O$

The main difference between these two mechanisms is protonation (Schedule 1) and the formation of hydrogen-bonded complex (Schedule 2). The step in which hydrated cation (Intermediate XV) yields a proton to an approaching water (or base) (Step 3 of each schedule) can be rejected as the rate-determining step. If this step were rate-determining, general base catalysis would be observed.

In Schedule 1, step 1 is rejected as rate-determining because protonation on the carbon to form a carbonium ion generally is a fast and reversible reaction (96). Thus the assumption is made that the equilibrium is immediately established between isocyanide and its cation. Then, the only possibility as the rate-determining step is step 2, that is the attack of molecule of water on the isocyanide cation. If so, the rate of this step will depend directly upon the concentration of the isocyanide cation (Intermediate XIV), which in turn is governed by the hydrogen-ion concentration, so that specific acid catalysis should be shown. This is contra-

dictary to the experimental result that the hydrolysis shows general acid catalysis. In order to have hydrolysis via schedule 1 show general acid catalysis, step 1 must be the rate-determining step, that is be slow and non-reversible. Protonation on the carbon atom is known to be a fast and reversible reaction, reaction via schedule 1 can therefore be ruled out since it would show specific acid catalysis.

In the reaction mechanism of Schedule 2, by argumentsanalogous to those above, the rate-determining step would be the reaction of hydrogen bonded complex with a molecule of water. The rate expression is:

$$\text{rate} = k_2 \left(S \cdot HA \right) \left(H_2O \right)$$

Since the formation of the hydrogen bonded complex is reversible,

$$\left(S \cdot HA \right) = \left(k_1/k_{-1} \right)(S)\ (HA)$$

so that,

$$\text{rate} = \left(k_2 k_1/k_{-1} \right)(S)\ (HA)\ (H_2O)$$

Since water is the solvent, it is present in a very large excess, and its concentration is effectively constant so that,

$$\text{rate} = (k_2' k_1/k_{-1})(S)\ (HA) \quad \text{where } k_2' = k_2\ (H_2O).$$

The concentration of the acid can also be treated as a constant under the

high buffer concentrations used (i.e. five to ten times higher than the concentration of isocyanide), so that a pseudo-first order reaction with respect to the methyl isocyanide is observed. The higher the concentration of acid, the faster the rate. If the acid strength is higher, k_1 will be higher and the reaction rate greater.

In this reaction schedule, the reaction of the hydrogen-bonded complex is expected to be the slow step. The kinetic data do not permit a decision as to whether there is a concerted process of attack of the water and the transfer of the hydrogen-bonding proton or whether the hydrogen-bonded complex first forms an ion-pair followed by water attack. The small negative linear salt effect suggests that there is a decrease or a spreading of charge at the transition state. If proton transfer preceded water attack, a rate acceleration with increasing ionic strength would be expected. Consequently, a concerted nucleophilic attack-proton transfer is favoured for the transition state.

In conclusion, the acid catalyzed hydrolysis of methyl isocyanide is most likely through the reaction mechanism given in Schedule 2. The possible mechanism involving protonation on the nitrogen atom, while not completely ruled out, is rendered very unlikely by the present study.

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Table 1. The Preparation and Composition of the various sets of Buffer Solution.

Buffer Solution Set	Composition of Buffer Solution	Ionic Strength (moles K^+/ liter)	Buffer Concentration*
Solution A	100 ml of 0.5 M potassium phathalate, A ml of 1 M potassium hydroxide and (60-A) ml of 1 M potassium chloride	0.6875	0.312
Solution B	100 ml of 0.5 M citric acid, B ml of 1 M potassium hydroxide, (200-B) ml of 1 M potassium chloride and 0.1675 g of potassium chloride	0.6875	0.167
Solution C	same as solution B, except 14.9117 g instead of 0.1675 g of potassium chloride	1.3333	0.167
Solution D	same as solution B, except 22.3728 g instead of 0.1675 g of potassium chloride	2.0000	0.167
Solution E	100 ml of 1 M citric acid, 79 ml of 2M potassium hydroxide and 121 ml of 2 M of potassium chloride buffer solution was made up. Diluted this solution to the desirable buffer concentration	1.3333	varying, but pH (=4.18)was constant

* Buffer concentration ={(Acid) +(Acid Anion(s)) } in moles/liter.

Table 2a. Relative Concentration of Methyl Isocyanide versus Time for Buffer Solution A (Phthalate-Biphthalate Buffer Solution) at 40° C and pH of 5.18.

Run No. 1		Run No. 2		Run No. 3	
Time ($\times 10^2$ sec.)	Relative Concentration*	Time ($\times 10^2$ sec.)	Relative Concentration*	Time ($\times 10^2$ sec.)	Relative Concentration*
6.00	0.70	6.00	0.72	6.00	0.73
12.00	0.60	12.30	0.67	12.15	0.64
18.00	0.52	18.15	0.60	20.10	0.53
26.00	0.45	26.00	0.46	26.00	0.48
32.00	0.39	32.00	0.40	35.40	0.38
41.30	0.33	40.50	0.36	40.20	0.36
46.85	0.29	46.50	0.30	46.00	0.32
52.00	0.23	52.00	0.27	52.00	0.28
58.05	0.23	58.00	0.24	58.00	0.23
64.00	0.19	64.00	0.22	64.00	0.21
70.00	0.16	70.00	0.19	70.00	0.17
76.00	0.12	76.00	0.13	76.00	0.15

* The relative concentration of CH_3NC is based upon the area of its peak on the gas chromatograph so that the concentration units are the areas of the peak as traced by the Disc Integrator.

Table 2b. Relative Concentration of Methyl Isocyanide versus Time for Buffer Solution A (Phthalate-Biphthalate Buffer Solution) at 40° C and pH of 5.18.

Run No. 4		Run No. 5		Run No. 6	
Time ($\times 10^2$ sec.)	Relative Concentration*	Time ($\times 10^2$ sec.)	Relative Concentration*	Time ($\times 10^2$ sec.)	Relative Concentration*
6.00	0.61	6.00	0.80	6.00	0.73
12.00	0.56	12.00	0.63	12.00	0.64
18.10	0.53	18.10	0.57	18.00	0.57
24.00	0.44	24.00	0.46	24.20	0.48
30.00	0.42	30.00	0.41	30.00	0.46
38.00	0.34	38.00	0.38	38.00	0.37
44.20	0.27	44.25	0.31	44.00	0.31
50.10	0.24	50.05	0.29	50.15	0.26
56.00	0.22	56.15	0.23	56.00	0.24
62.00	0.19	62.00	0.21	62.00	0.22
68.00	0.16	68.05	0.18	68.00	0.17

* The relative concentration of CH_3NC is based upon the area of its peak on the gas chromatograph so that the concentration units are the areas of the peak as traced by the Disc Integrator.

Table 3. The Rate Constant as a Function of pH for Buffer Solution A (Phthalate-Biphthalate Buffer Solution; Ionic Strength = 0.6875; Buffer Concentration = 0.312 M) at Temperatures between 25 and 45°C and at various pH Values.

Temperature (°C)	pH	$a_{H_3O^+}$ (x 10^4)	Number of Runs.	Average Rate Constant (x 10^4 sec)
25	3.86	1.73	8	3.84 ± 0.18
	3.97	1.07	6	3.29 ± 0.12
	4.16	0.69	6	2.33 ± 0.11
	4.33	0.47	5	2.23 ± 0.08
	4.55	0.28	6	1.63 ± 0.07
	4.75	0.18	6	1.14 ± 0.05
	4.95	0.11	6	0.913 ± 0.034
	5.18	0.066	6	0.609 ± 0.024
30	3.97	1.07	5	4.71 ± 0.24
	4.16	0.69	5	3.78 ± 0.20
	4.33	0.47	5	3.08 ± 0.12
	4.55	0.28	6	2.77 ± 0.22
	4.75	0.18	6	1.92 ± 0.11
	4.95	0.11	6	1.36 ± 0.06
	5.18	0.066	6	0.922 ± 0.069
	5.37	0.043	6	0.695 ± 0.050
35	4.33	0.47	7	5.03 ± 0.29
	4.55	0.28	4	3.75 ± 0.19
	4.75	0.18	6	2.70 ± 0.13
	4.95	0.11	7	2.45 ± 0.12
	5.18	0.066	3	1.70 ± 0.09
	5.37	0.043	6	1.11 ± 0.08
	5.63	0.023	6	0.599 ± 0.030

cont'n of Table 3.

Temperature (°C)	pH	$a_{H_3O^+}$ (x 10^4)	Number pf Runs	Average Rate Constant (x 10^4 Sec)
40	4.55	0.28	6	5.69 ± 0.25
	4.75	0.18	6	4.60 ± 0.17
	4.95	0.11	6	3.45 ± 0.13
	5.18	0.066	6	2.30 ± 0.07
	5.37	0.043	6	1.64 ± 0.05
	5.63	0.023	6	0.992 ± 0.040
	5.81	0.016	6	0.653 ± 0.024
	6.09	0.0081	6	0.351 ± 0.021
45	4.75	0.18	6	6.55 ± 0.32
	4.95	0.11	6	5.16 ± 0.32
	5.18	0.066	6	3.38 ± 0.12
	5.37	0.043	6	2.37 ± 0.13
	5.63	0.023	6	1.36 ± 0.07
	5.81	0.016	5	0.860 ± 0.048
	6.09	0.0081	6	0.496 ± 0.021

Table 4. The Rate Constant as a Function of pH for Citrate-Citric Acid Buffer Solution (Buffer Concentration ≒ 0.167 M) with Different Ionic Strengths at 30°C and various pH Values.

Ionic Strength	pH	$a_{H_3O^+}$ (x 10^4)	Number of Runs	Average Rate Constant (x 10^4 sec)
0.6875 (Buffer Solution B)	3.67	2.14	6	4.53 ± 0.14
	3.88	1.32	6	3.31 ± 0.14
	4.09	0.813	6	2.57 ± 0.09
	4.29	0.513	6	1.95 ± 0.07
	4.48	0.331	6	1.64 ± 0.05
	4.68	0.209	6	1.34 ± 0.08
	4.88	0.132	6	0.851 ± 0.030
	5.08	0.083	6	0.663 ± 0.017
1.3333 (Buffer Solution C)	3.57	2.70	5	4.65 ± 0.18
	3.78	1.66	3	3.53 ± 0.15
	3.99	1.02	6	2.62 ± 0.12
	4.18	0.66	6	1.96 ± 0.12
	4.37	0.43	6	1.64 ± 0.09
	4.59	0.26	6	1.18 ± 0.10
	4.77	0.17	6	0.859 ± 0.042
	4.97	0.11	6	0.656 ± 0.025
2.0000 (Buffer Solution D)	4.04	0.91	6	2.59 ± 0.08
	4.41	0.39	6	1.60 ± 0.06
	4.77	0.17	6	0.847 ± 0.027

Table 5. Effect of Buffer Concentration on Reaction Rate Constant: Citrate-Citric Buffer, pH = 4.18, Ionic Strength = 1.3333 and 30°C.

Buffer Concentration (mole liter^{-1})	Number of Runs	Average Rate Constant (x 10^4 sec)
0.033	6	0.523 ± 0.019
0.067	6	0.816 ± 0.044
0.117	6	1.44 ± 0.05
0.167	6	1.93 ± 0.09
0.200	6	2.37 ± 0.07
0.267	6	3.23 ± 0.11

Table 6a. The Calculated Values of the Logarithm of the Rate Constants and 1/T for Buffer Solution A (Phthalate-Biphthalate Buffer Solution; Ionic Strength = 0.6875; Buffer Concentration = 0.312 M).

pH	Temperature (^{o}C)	T^{o} K	Average Rate Constant (x 10^{4} sec.)	1/T (x 10^{3} ^{o}K)	-Log_{10} Rate Constant
	25	298.1	1.14 ± 0.05	3.36	3.94
	30	303.1	1.92 ± 0.11	3.30	3.72
4.75	35	308.1	2.70 ± 0.13	3.25	3.57
	40	313.1	4.60 ± 0.17	3.19	3.34
	45	318.1	6.55 ± 0.32	3.14	3.18
	25	298.1	0.913 ± 0.034	3.36	4.04
	30	303.1	1.36 ± 0.06	3.30	3.87
4.95	35	308.1	2.45 ± 0.12	3.25	3.61
	40	313.1	3.45 ± 0.13	3.19	3.46
	45	318.1	3.38 ± 0.12	3.14	3.47
	25	298.1	0.609 ± 0.024	3.36	4.22
	30	303.1	0.922 ± 0.069	3.30	4.04
5.18	35	308.1	1.69 ± 0.09	3.25	3.77
	40	313.1	2.30 ± 0.07	3.19	3.64
	45	318.1	3.38 ± 0.12	3.14	3.47

Table 6b. The Calculated Values of the Logarithm of the Rate Constants and 1/T for Buffer Solution B (Citrate-Citric Acid Buffer Solution; Ionic Strength = 0.6875; Buffer Concentration = 0.167 M).

pH	Temperature (^{o}C)	T ^{o}K	Average Rate Constant (x 10^{4} sec)	1/T (x 10^{3} ^{o}K)	-Log_{10}Rate Constant
	25	298.1	0.723 ± 0.022	3.36	4.14
	30	303.1	1.34 ± 0.08	3.30	3.87
4.68	35	308.1	1.85 ± 0.06	3.25	3.73
	40	313.1	2.94 ± 0.10	3.19	3.53
	45	318.1	3.97 ± 0.11	3.14	3.40

Table 8. The Effect of Ionic Strength on the Reaction Rate Constant at $30^{o}C$ and pH 4.16, 4.23 and 4.29.

	Rate Constant ($\times 10^{4}$ sec) at Ionic Strength equal to:				
pH	2.0000	1.3333	1.0000	0.7000	0.6875
4.16	2.28 (1) 1.99	2.13 (2)	--	--	2.41 (3)
4.23	2.05 (1)	1.93 (2)	2.01	--	2.19 (3)
4.29	1.90 (1)	1.78 (2)	--	2.06	2.03 (3)

(1), (2) and (3) represented the values which were computed from curve a, b and c in Figure 5 respectively.

Table 9. Comparison of Rate Constants for Citrate-Citric Acid* and Phthalate-Biphthalate Buffer Solution.

pH	Rate Constant of Buffer Solution B ($\times 10^4$ sec)	pH	Rate Constant of Buffer Solution C ($\times 10^4$ sec)
3.67	8.57	3.57	9.84
3.88	6.26	3.78	7.47
4.09	4.86	3.99	5.54
4.29	3.70	4.18	4.15
4.48	3.10	4.37	3.47
4.68	2.54	4.59	2.50
4.88	1.61	4.77	1.82
5.08	1.26	4.97	1.39

* Concentration and ionic strength corrected to those used with the phthalate-biphthalate buffer solution.

Table 10. Simple α-Additions and Organometallic Reactions of Isocyanides.

Number	Reactions	References
(1).	$Ni(CO)_4 + 4\ RNC \longrightarrow Ni(CNR)_4 + 4\ CO$	84-87
(2).	$(Co(NO)(CO)_3) + 2\ RNC \longrightarrow (Co(NO)(CO)(CNR)_2) + 2CO$	88
(3).	$(Fe(CO)_4)_3 + 3\ RNC \longrightarrow 3\ (Fe(CO)_4(CNR))$	87,89
(4).	$RNC + X_2 \xrightarrow[CHCl_3]{-15^\circ C} R\text{-}N{=}CX_2$ (X = halogen)	22,90
(5).	$RNC + R'SH \rightarrow R\text{-}N{=}CHSR'$ and $R\text{-}N{=}C{=}S + R'H$	91,92
(6).	$\phi\text{-}NC + NH_2OH \longrightarrow \phi\text{-}N{=}CHNHOH$	93
(7).	$RNC + 2\ R'\text{-}COOH \longrightarrow R\text{-}NHCOH + (R'CO)_2O$	22,90
(8).	$RNC + R'\text{-}OH \longrightarrow R\text{-}N{=}CH\text{-}OR'$	90,94

Figure 1

The Reproducibility of the Chromatogram: Injection of 2 µl-samples of 0.03601 M Methyl Isocyanide-Water Solution at 200 seconds Intervals.

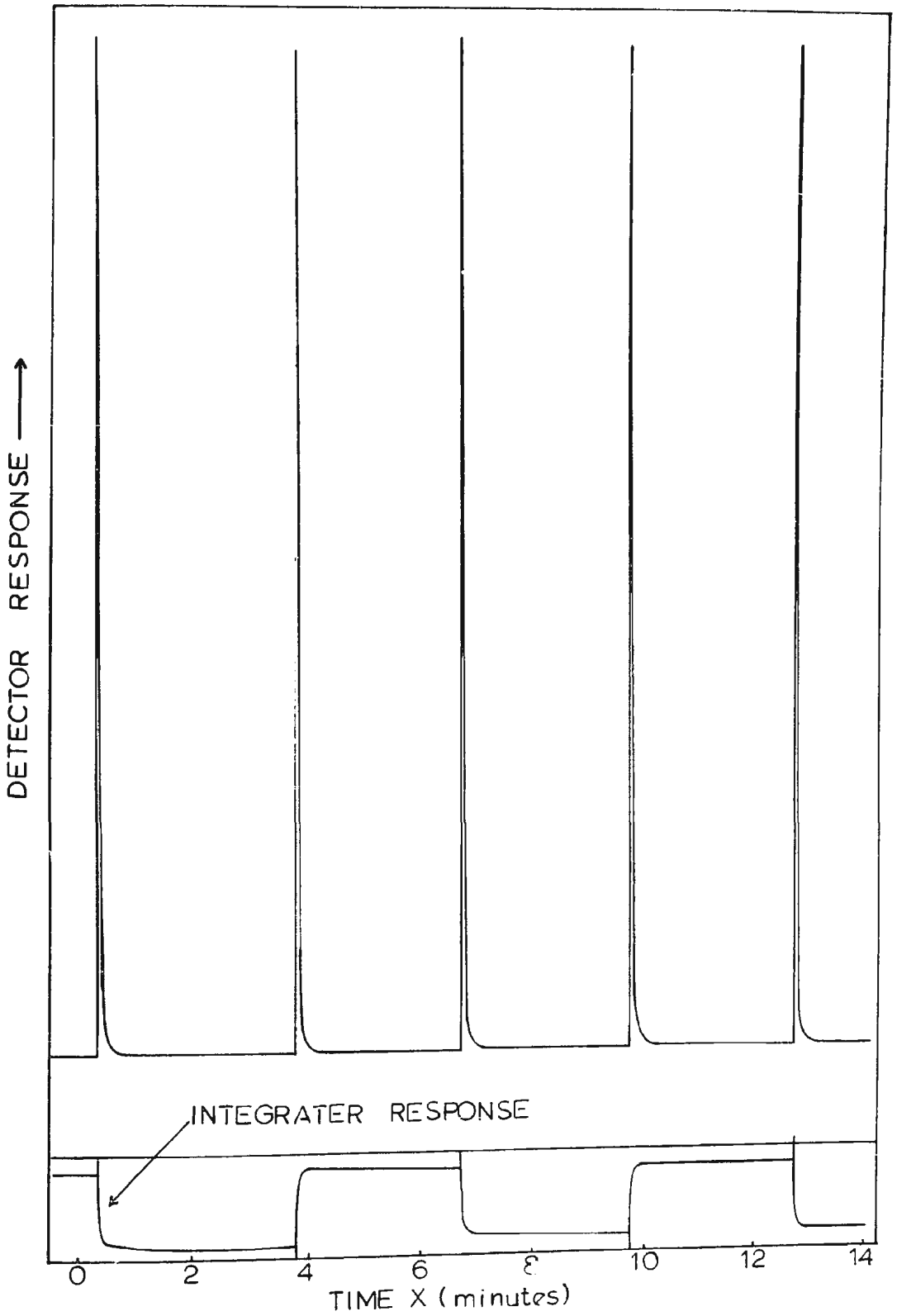

DETECTOR RESPONSE ⟶
INTEGRATER RESPONSE
0
2
4
6
8
10
12
14
TIME X (minutes)

Figure 2

The Chromatogram of the Acid Catalyzed Hydrolysis of Methyl Isocyanide.

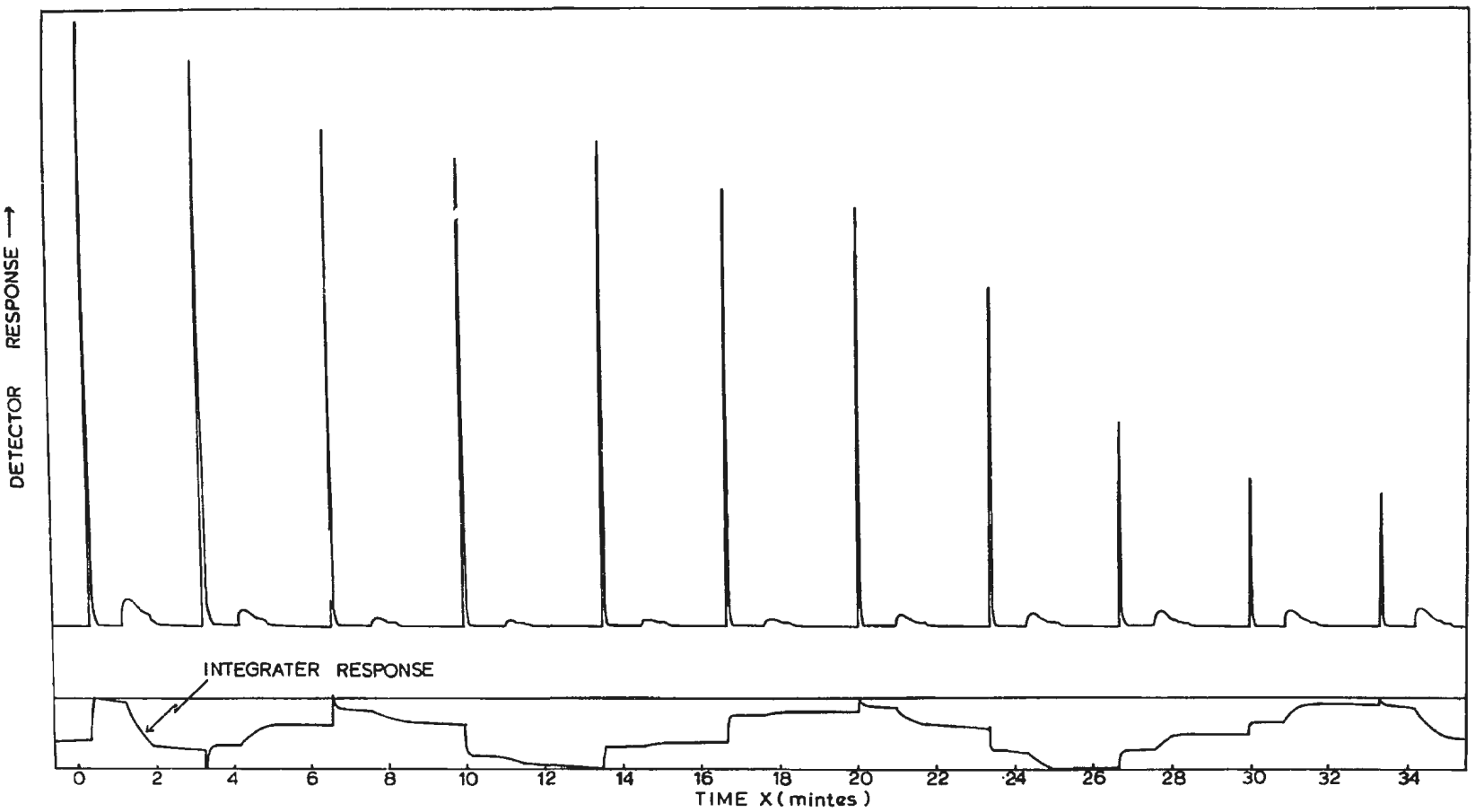

DETECTOR RESPONSE ⟶
INTEGRATER RESPONSE
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
TIME X (mintes)

Figure 3a

The Logarithm of Relative Methyl Isocyanide Concentration versus Time for Buffer Solution A (Phthalate-Biphthalate) at 40°C and pH of 5.18.

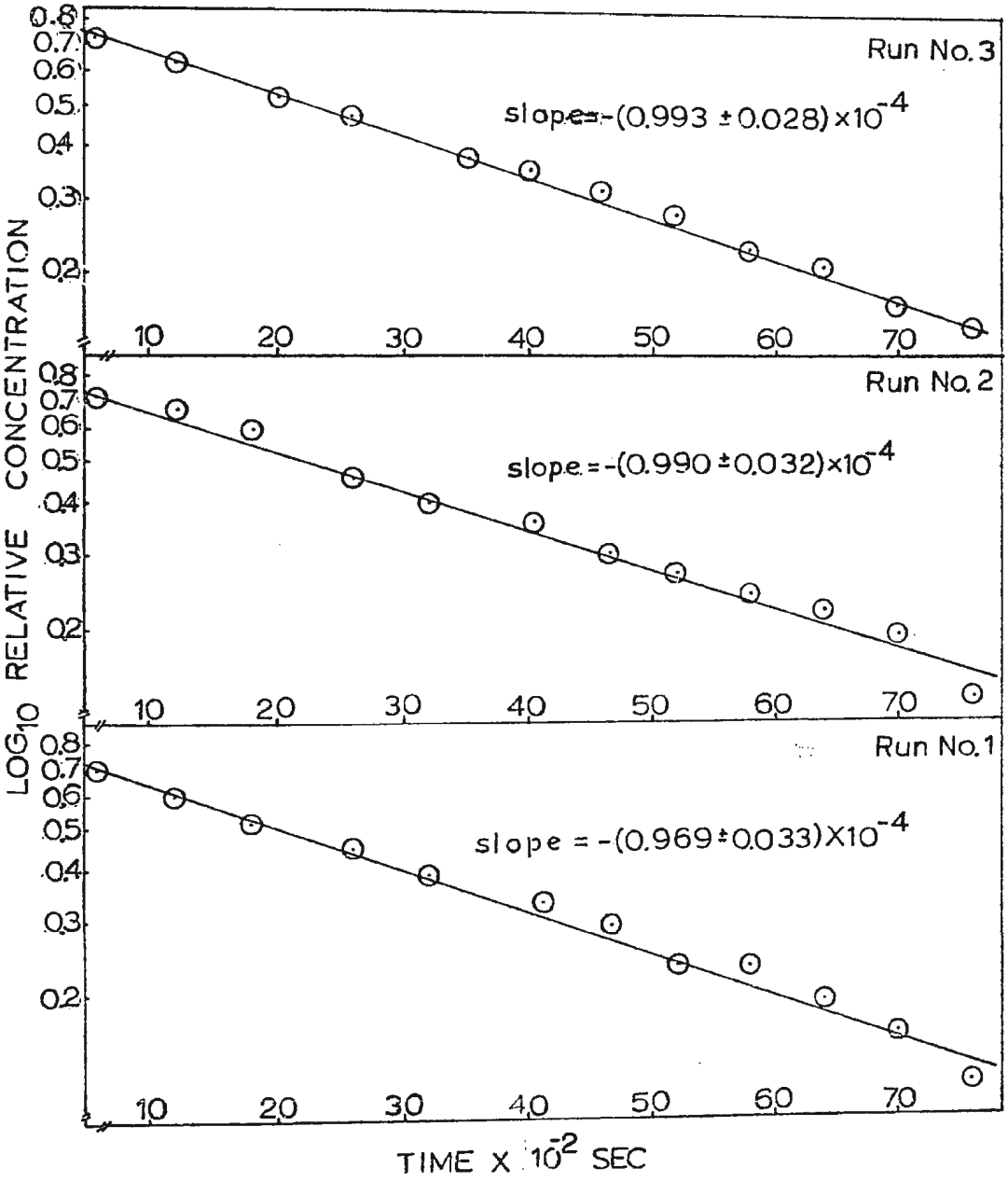

Run No. 3
slope = -(0.993 ± 0.028) × 10^-4
Run No. 2
slope = -(0.990 ± 0.032) × 10^-4
Run No. 1
slope = -(0.969 ± 0.033) X 10^-4
LOG10 RELATIVE CONCENTRATION
TIME X 10^-2 SEC
0.8
0.7
0.6
0.5
0.4
0.3
0.2
10
20
30
40
50
60
70

Figure 3b

The Logarithm of Relative Methyl Isocyanide Concentration versus Time for Buffer Solution A (Phthalate-Biphthalate) at 40°C and pH of 5.18.

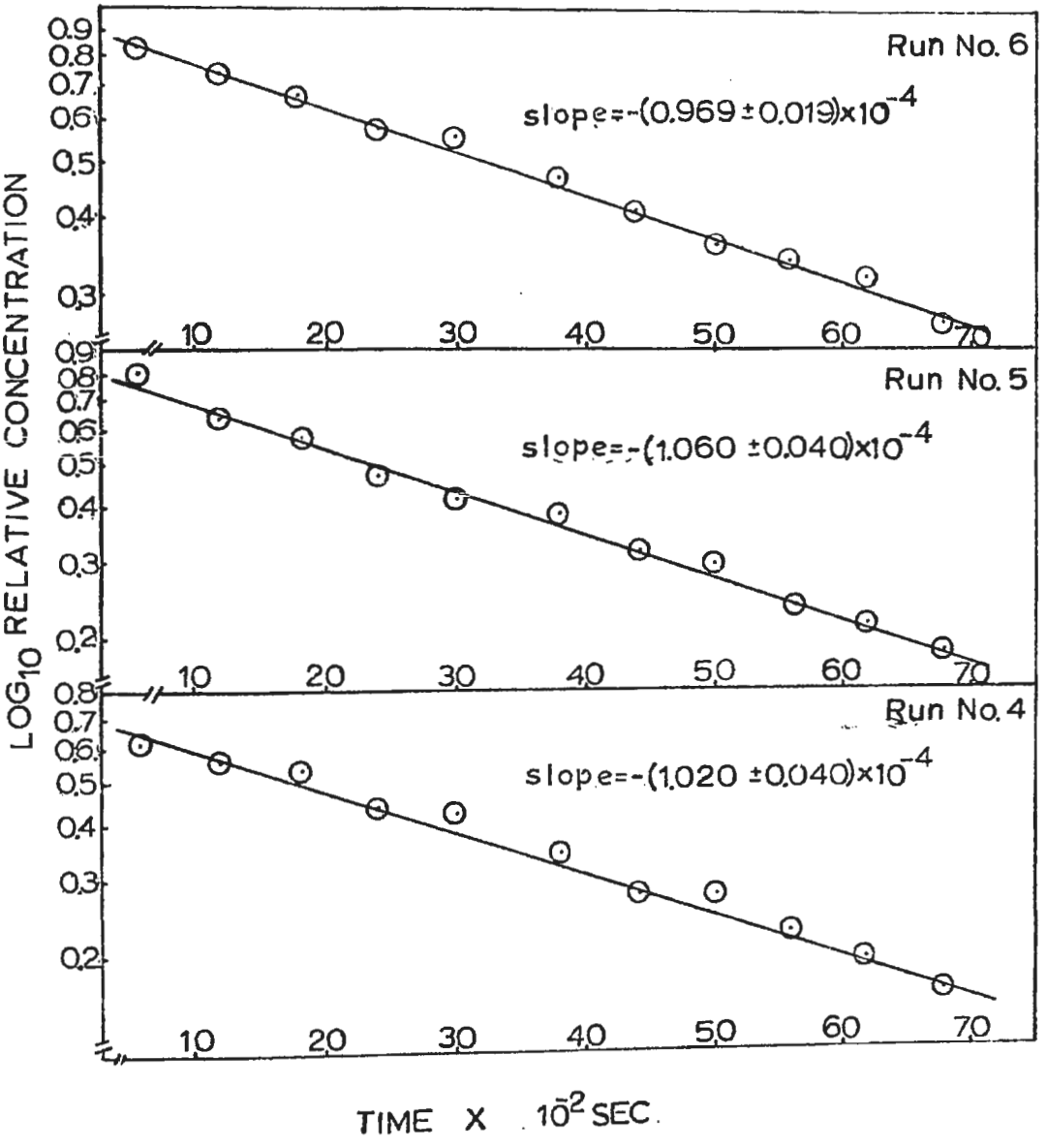
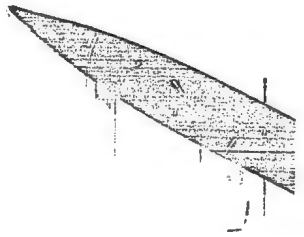

Run No. 6
slope=-(0.969 ±0.019)x10^{-4}
Run No. 5
slope=-(1.060 ±0.040)x10^{-4}
Run No. 4
slope=-(1.020 ±0.040)x10^{-4}
LOG$_{10}$ RELATIVE CONCENTRATION
TIME X 10^{2} SEC

Figure 4

The Rate Constant versus pH for the Buffer Solution A (Phthalate-Biphthalate Buffer Solution; Ionic Strength of 0.6875; Buffer Concentration of 0.312 M) at Temperatures of 25° to 45°C.



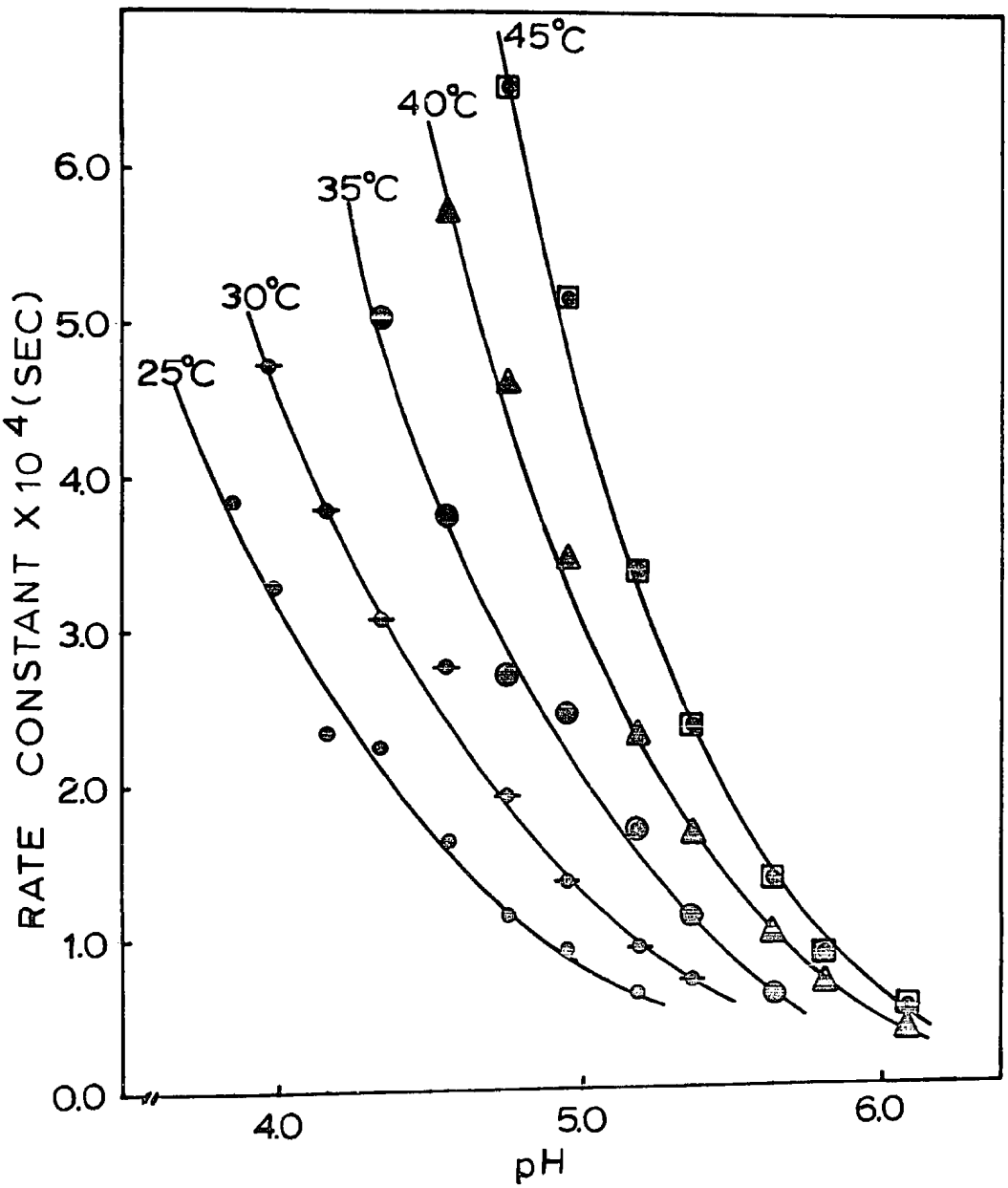

45°C
40°C
35°C
30°C
25°C
6.0
5.0
4.0
3.0
2.0
1.0
0.0
RATE CONSTANT X 10 4 (SEC)
4.0
5.0
6.0
pH

Figure 5

The Rate Constant versus pH for the Citrate-Citric Acid Buffer Solutions (Buffer Concentration of 0.167 M) at Different Ionic Strengths at 30°C.

Curve a: Buffer Solution D (ionic strength = 2.0000)
Curve b: Buffer Solution C (ionic strength = 1.3333)
Curve c: Buffer Solution B (ionic strength = 0.6875)

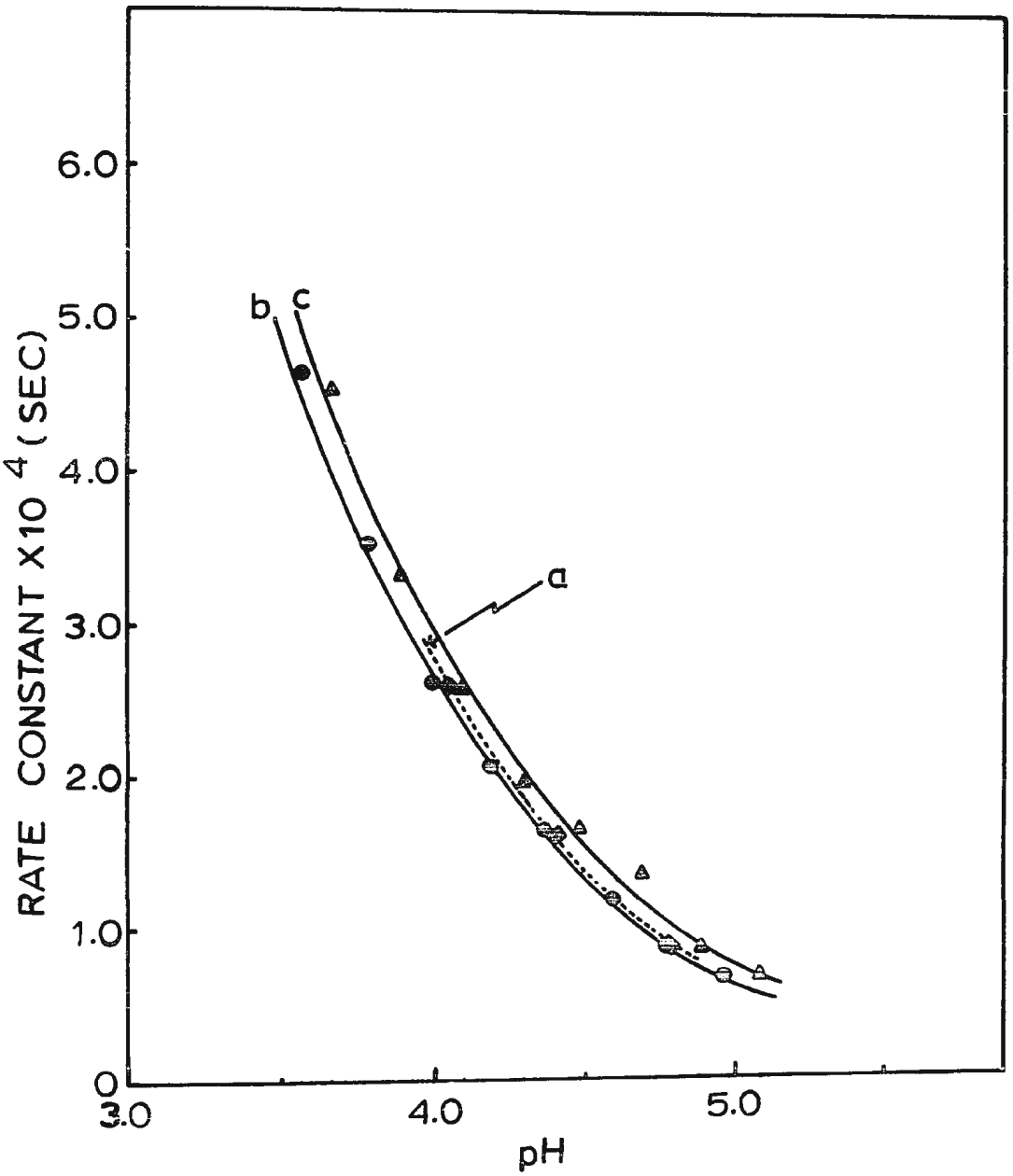

RATE CONSTANT X10 4 (SEC)
6.0
5.0
4.0
3.0
2.0
1.0
0
3.0
4.0
5.0
pH
a
b
c

Figure 6

Rate Constant versus Buffer Concentration for Buffer Solution E (Citrate-Citric Acid Buffer Solution; Ionic Strength of 1.3333; pH of 4.18) at $30^{\circ}C$.

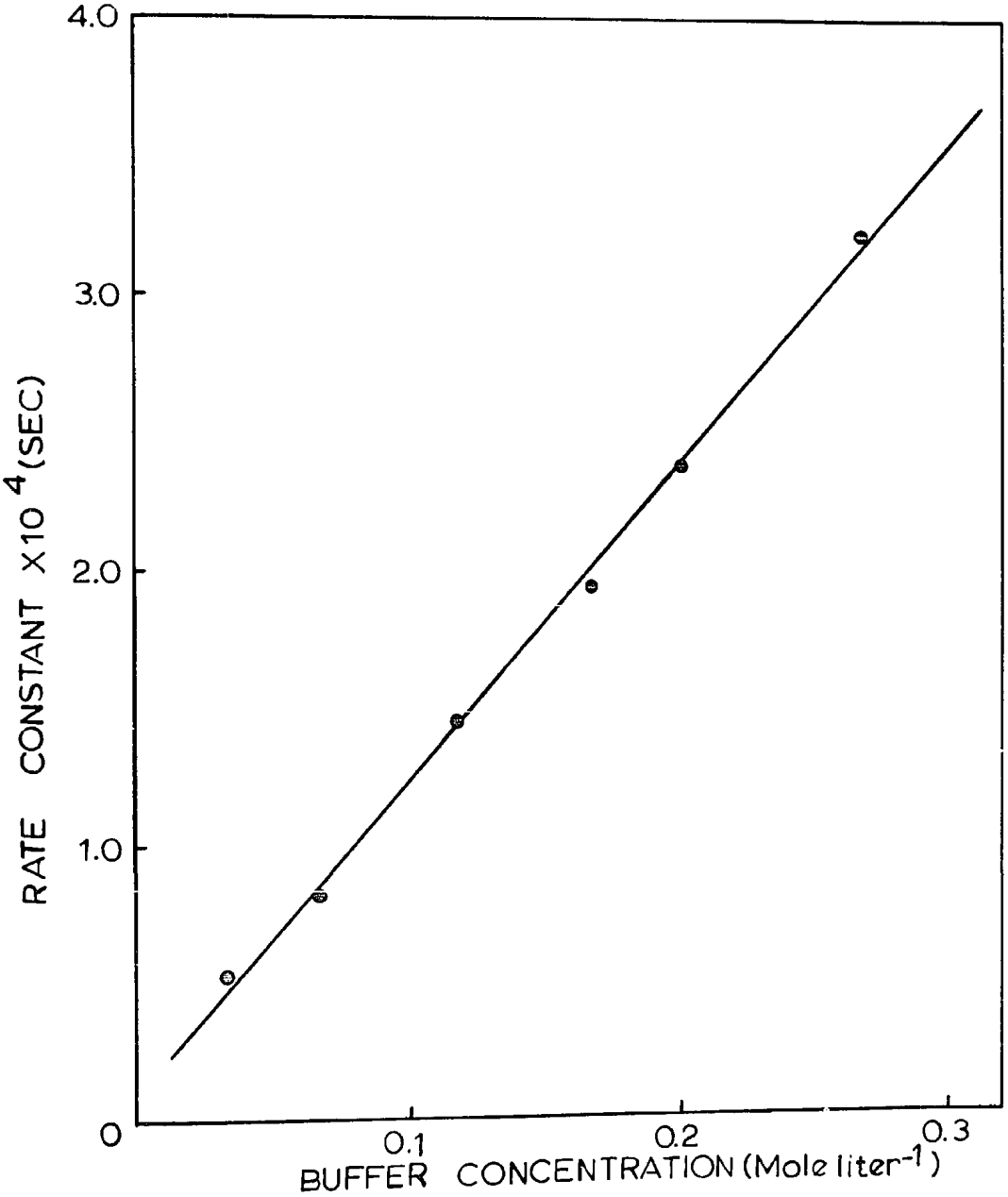

4.0
3.0
2.0
1.0
0
RATE CONSTANT X10 4 (SEC)
0.1
0.2
0.3
BUFFER CONCENTRATION (Mole liter-1)

Figure 7

Logarithmic of Rate Constant versus 1/T for the Phthalate-Biphthalate (Buffer Solution A) and Citrate-Citric Acid (Buffer Solution B) Buffer Solution.

 denotes for phthalate-biphthalate buffer solution at pH 5.18, 4.95 and 4.75 respectively.

 denotes for citrate-citric acid buffer solution at pH 4.68.

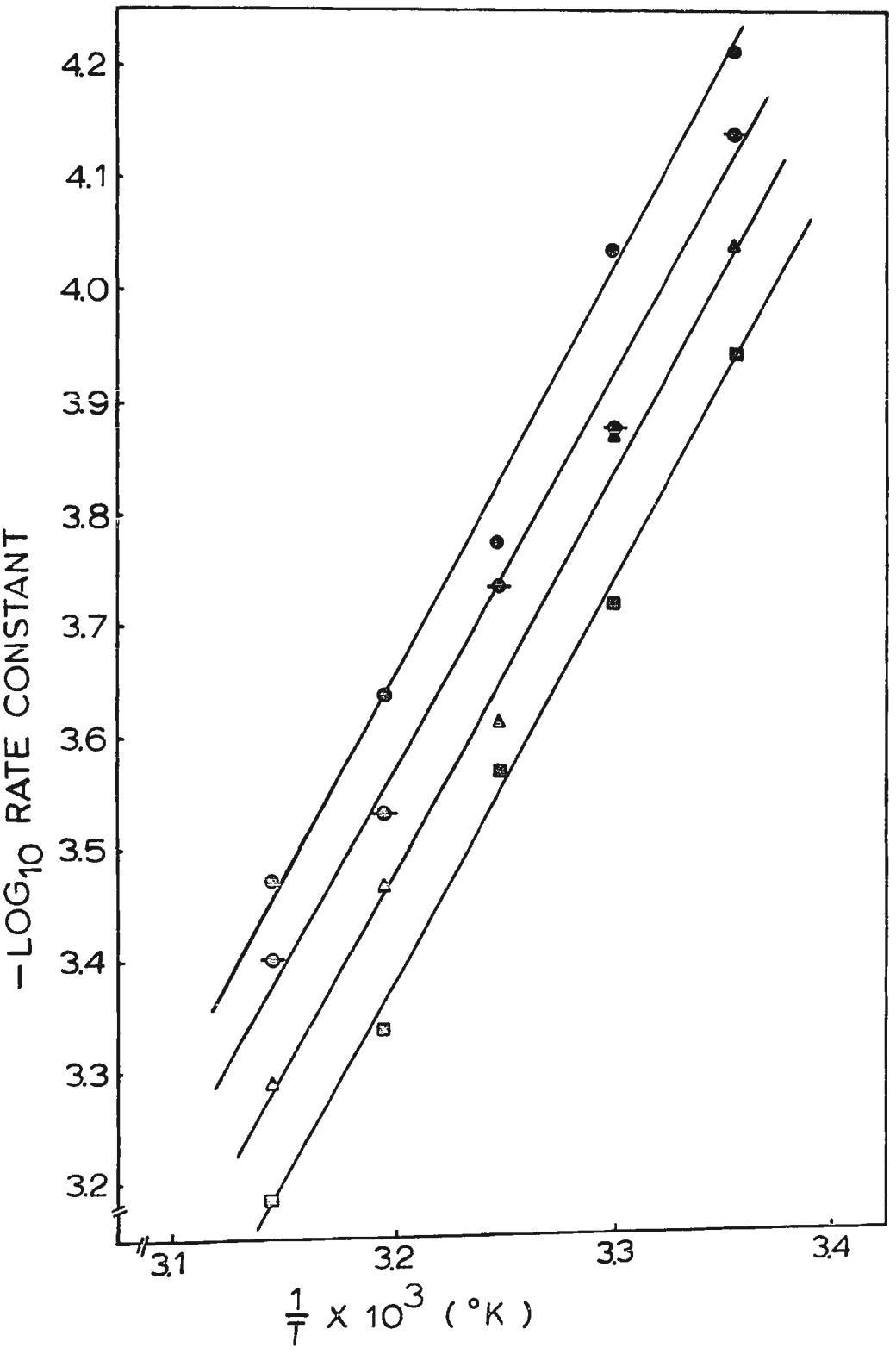

4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
$-LOG_{10}$ RATE CONSTANT
3.1
3.2
3.3
3.4
$\frac{1}{T} \times 10^3$ (°K)

Figure 8

The Rate Constant versus Ionic Strength for the Citrate-Citric Acid Buffer Solution at 30°C and pH 4.16 (⊖), 4.23(▲) and 4.29 (■).

○,△ & □ denotes the value which was computed from Curve a in Figure 5 at pH 4.16, 4.23 and 4.29 respectively.

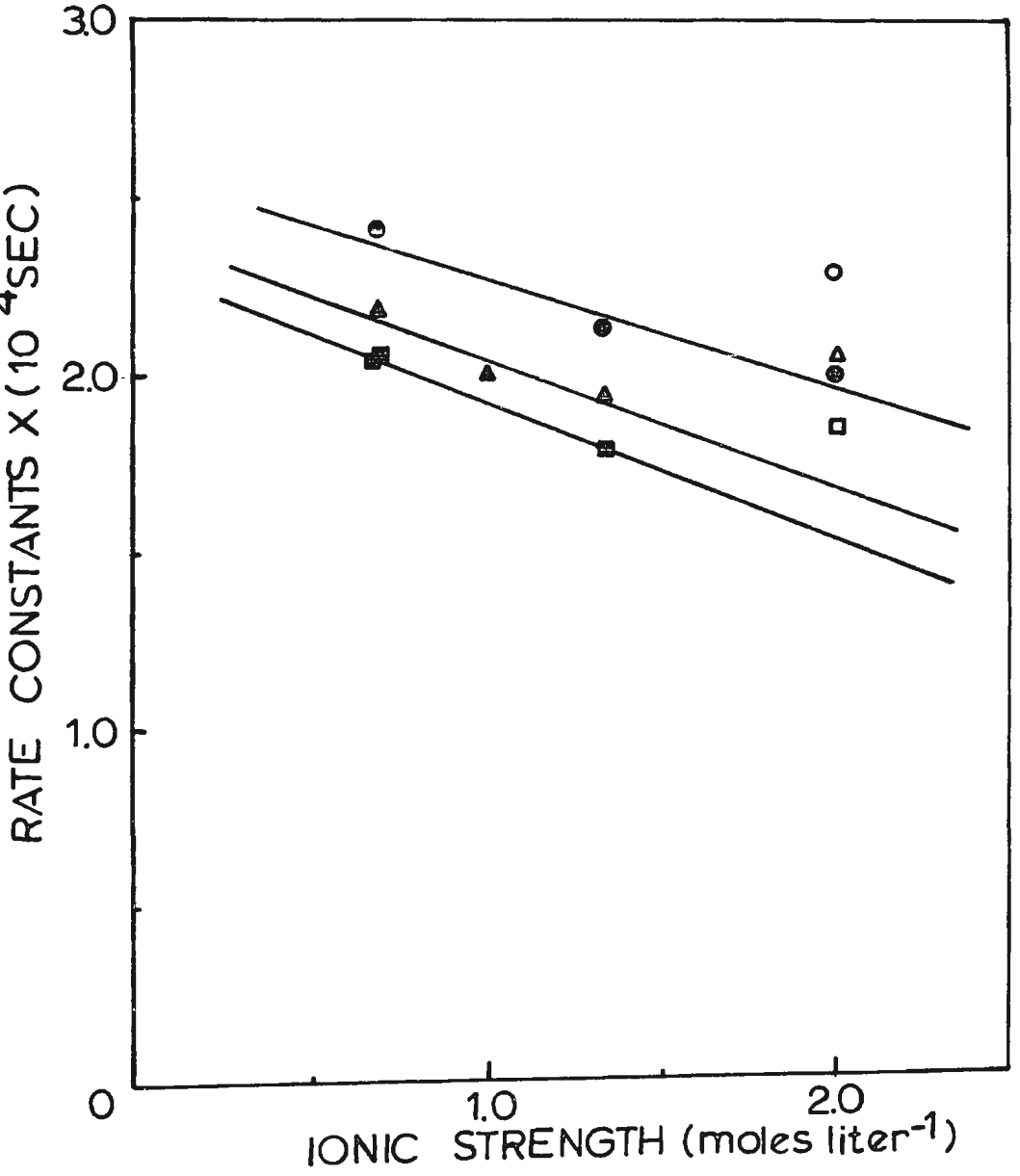

3.0
2.0
1.0
0
RATE CONSTANTS X (10 4SEC)
1.0
2.0
IONIC STRENGTH (moles liter-1)

Figure 9

Reaction Rate Constant versus pH for the Phthalate-Biphthalate and Citrate-Citric Acid Buffer Solution at the Same Buffer Concentration (0.312 M), Ionic Strength (0.6875) and Reaction Temperature ($30^{o}C$).

- The phthalate-biphthalate buffer solution (Buffer Solution A).
- The citrate-citric acid buffer solution (Buffer Solution B)*.
- The citrate-citric acid buffer solution (Buffer Solution C)*.

* corrected to the same buffer concentration and ionic strength as Buffer Solution A.

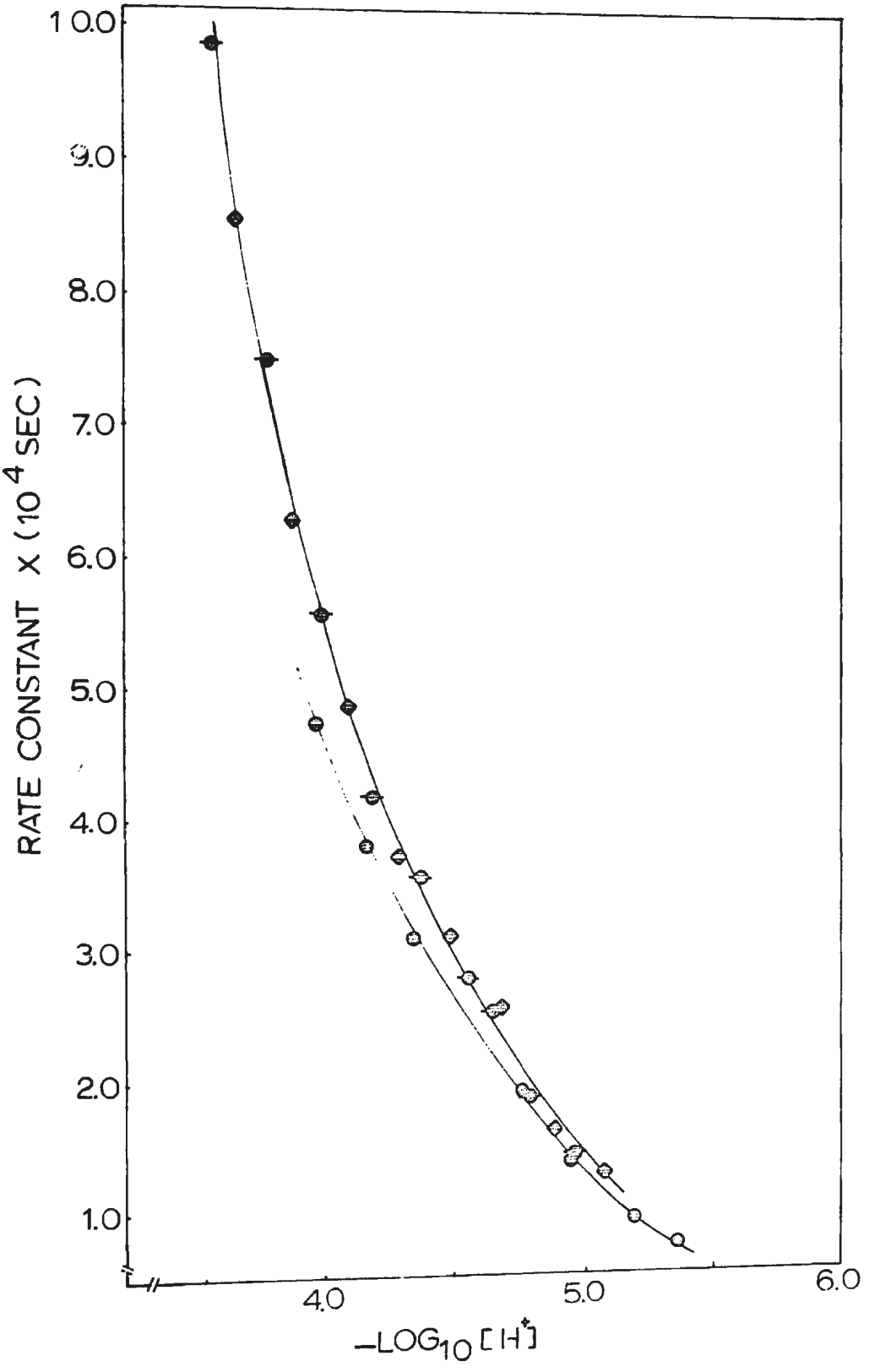

10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
RATE CONSTANT X (10^4 SEC)
4.0
5.0
6.0
$-LOG_{10}[H^+]$

Figure 10

The Rate Constant versus Activity of the Hydronium Ion for the Buffer Solution A (Phthalate-Biphthalate Buffer Solution; Ionic Strength of 0.6875; Buffer Concentration 0.312 M) at Temperature 25^{o} to $45^{o}C$.

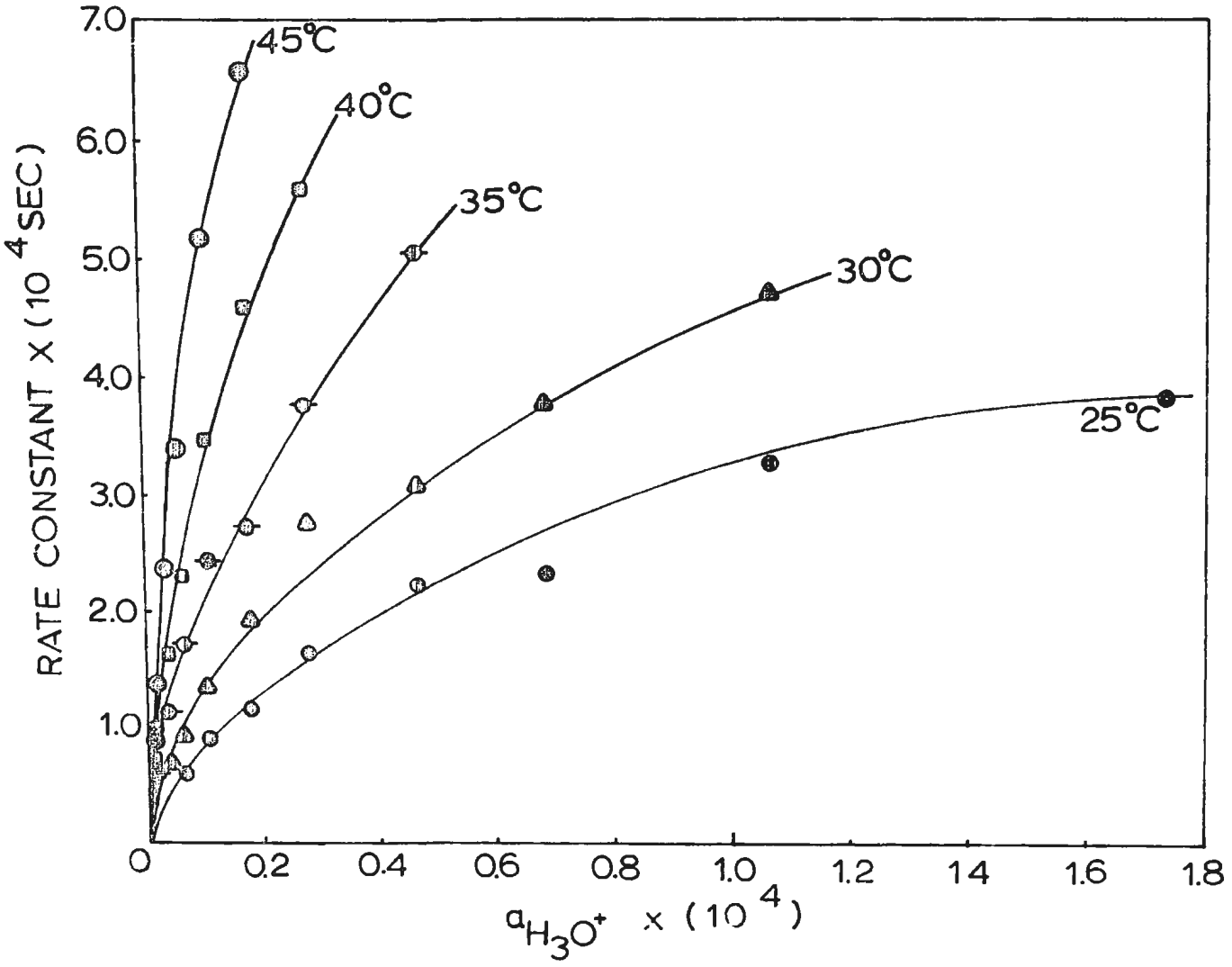

7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
RATE CONSTANT X (10 4 SEC)
45°C
40°C
35°C
30°C
25°C
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
a H3O+ x (10 4)

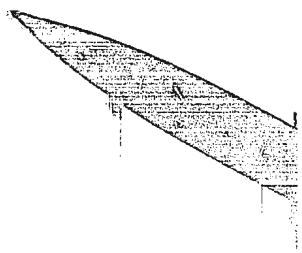
Figure 11

The Rate Constant versus Activity of Hydronium Ion for the Citrate-Citric Acid Buffer Solution (Buffer Concentration of 0.167 M) with Different Ionic Strength at Temperature 30°C.

⊖ Buffer Solution B (ionic strength = 0.6875).

⊡ Buffer Solution C (ionic strength = 1.3333).

⊕ Buffer Solution D (ionic strength = 2.0000).



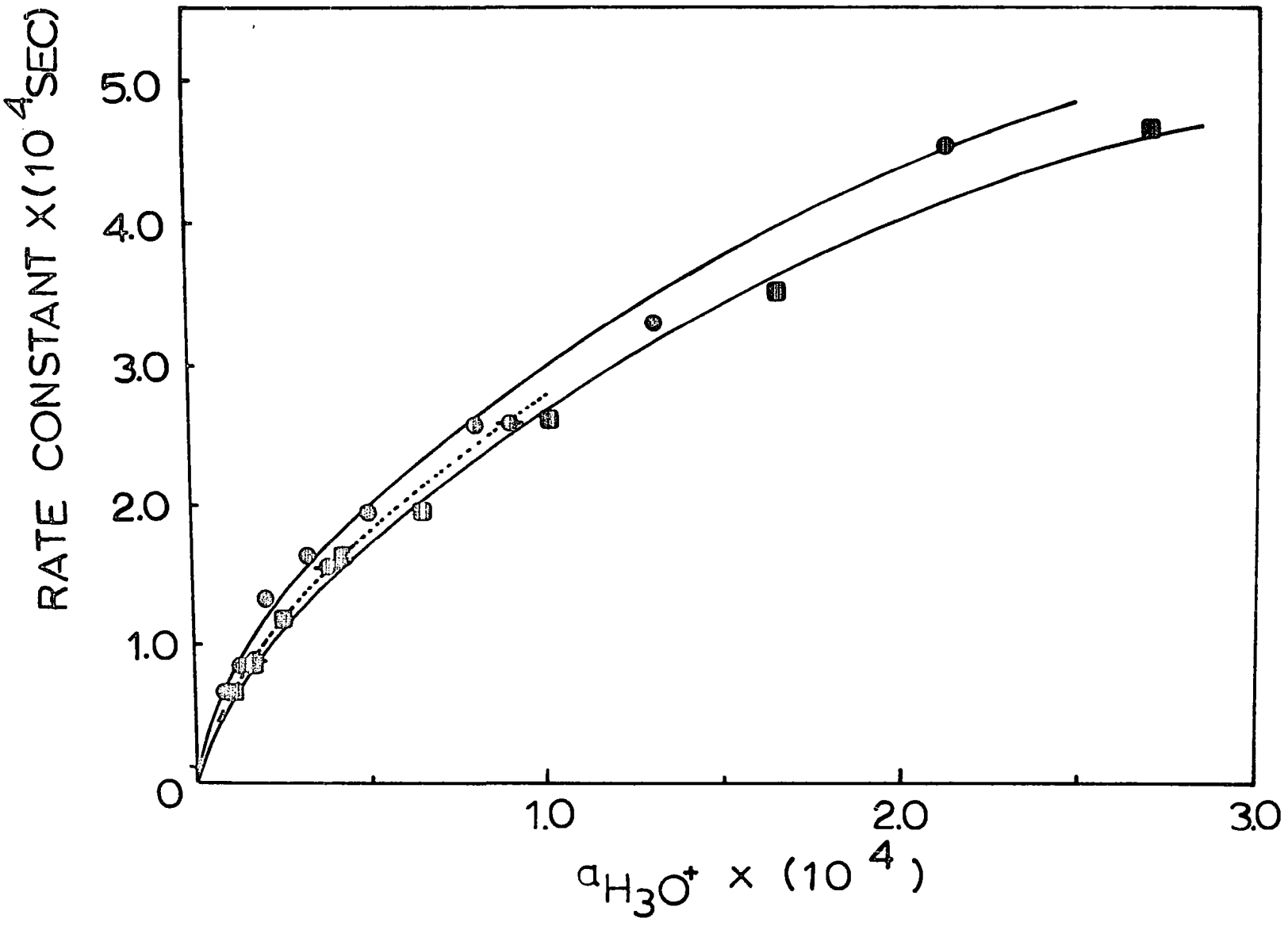
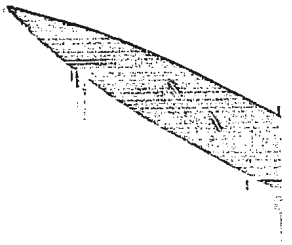
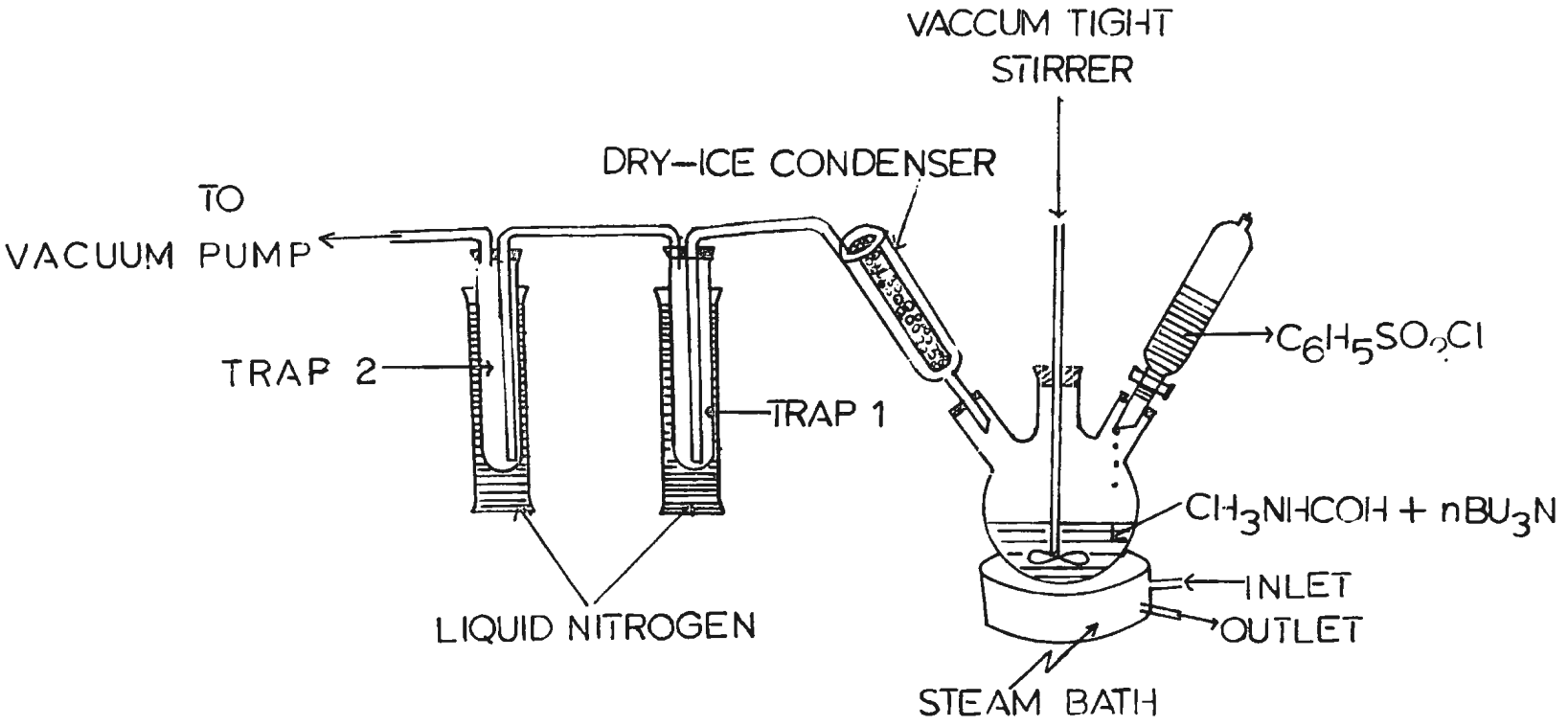

RATE CONSTANT X(10 4 SEC)
5.0
4.0
3.0
2.0
1.0
0
1.0
2.0
3.0
aH3O+ x (10 4)

Figure 12

The Apparatus Set-Up for the Preparation of Methyl Isocyanide.




VACCUM TIGHT
STIRRER
DRY–ICE CONDENSER
TO
VACUUM PUMP
TRAP 2
TRAP 1
$C_6H_5SO_2Cl$
$CH_3NHCOH + nBU_3N$
INLET
OUTLET
LIQUID NITROGEN
STEAM BATH