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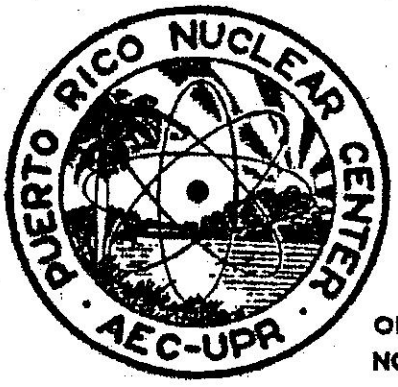
BASE CATALYZED FORMATION OF IMIDATES



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BASE CATALYZED FORMATION OF IMIDATES

by

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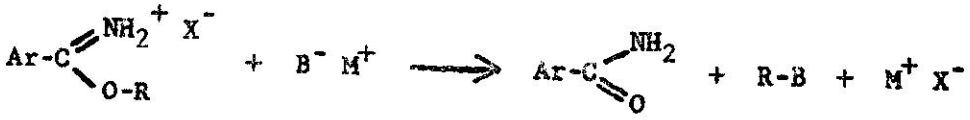
INTRODUCTION

The ultimate aim of this research is the preparation of potential antimetabolites by the selective replacement of a hydroxyl group in a polyfunctional alcohol and carbohydrate.

The reaction chosen for this purpose is the nucleophilic substitution of imidates



where X^- is a poor nucleophile, and B^- is a good nucleophile

In order to augment the driving force of the substitution reaction, the imidates were derived from negatively substituted nitriles such as the cyanopyridines, and in order to minimize undesired and complex side reactions in the case of the polyfunctional alcohols, the formation of imidates was chosen to be catalyzed by bases rather than acids.

In the first phase of this work there were investigated the factors which affect the base-catalyzed formation of the imidates, and this report deals exclusively with this aspect of the problem.

RESULTS

The formation of the imidates was followed using the method described recently by Schaeffer and Peters (1). Using an excess of the alcohol, the reaction kinetics obeyed the pseudo-unimolecular rate law, and the specific reaction rate gave linear dependence on the concentration of the nitrile. However, in order to achieve better comparisons of the reaction rates of different alcohols and of systems containing inert diluents, the rates were calculated on the basis of the pseudo-bimolecular rate law by taking into account the variations in the initial concentrations of the different alcohols. The expression

$\frac{dx}{dt} = k\,(a-x)\,(b-x)\,(\text{base})$, where x = concentration of imidate at time t
a = initial concentration of nitrile
b = initial concentration of alcohol

gives, upon integration, the expression

$\frac{2.3}{a-b} \log \frac{b(a-x)}{a(b-x)} = k\,(\text{base})\,t$, and from the slope of the linear plots

of $\log \frac{a-x}{b-x}$ vs. t there can be calculated the rate constants k.

Tables I and II list the results obtained at 27°C with several alcohols and the isomeric cyanopyridines. Since the rate of imidate formation of t-butyl alcohol is very low and the use of t-BuOK in place of the corresponding alkoxide introduced relatively insignificant changes in the rate constants (vide infra), it was convenient to employ t-BuOK catalyst in these experiments.

TABLE I

Base Dependence in the Reaction of Methanol[a/] and 3-Cyanopyridine[b/] at 27.0°C

$(t\text{-BuOK}) \times 10^3$ mole $\times l^{-1}$	$k\ (t\text{-BuOK}) \times 10^5$ $l \times mole^{-1}\ sec^{-1}$	$k \times 10^3$ $l^2\ mole^{-2}\ sec^{-1}$
6.0	0.618	1.03
8.8	0.80	0.91
18.9	1.84	0.97
23.2	2.14	0.92

a/ Concentration 20 mole $\times l^{-1}$. b/ Concentration 1.0 mole $\times l^{-1}$.

The results listed in Table I agree with the work of Schaeffer and Peters (1) and demonstrate that the rates are directly dependent on the concentration of the base catalyst.

TABLE II

Reactions of Alcohols with Cyanopyridines[a] at 27.0°C

Alcohol (mole x l^{-1})	(t-BuOK) x 10^3 mole x l^{-1}	k x 10^3 $l^2 mole^{-2} sec^{-1}$	% Imidate (equilibrium)	K_{Im} x 10^2
3-Cyanopyridine				
Methyl (20)	2.8 - 23.2	0.96 ± 0.06	72.0 (71)[b]	13 (11.4)[b]
Ethyl (15)	11.4	1.82 0.40	68.3	22
i-Propyl (12)	6.0 - 20.0	0.15 0.04	35.7	4.8
t-Butyl (11)	8.2	max. 0.016	2.4	0.23
Ethylene glycol (16)	8.2 - 31.2	0.037 ± 0.007	36.9	3.75
1,3-Propanediol (12.5)	4.2 - 15.2	0.11 0.01	51.0	8.7
2-Cyanopyridine				
Methyl (20)	6.0	0.53 ± 0.13[c]	98.9 (97)[b]	473 (150)[b]
Ethyl (15)	17.0	0.69 0.12	76.3	23
i-Propyl (12)	13.4 - 26.0	1.82 0.15	81.0	38
4-Cyanopyridine				
Methyl (20)	6.4 - 12.8	5.8 ± 0.2	-	-
Ethyl (15)	6.4 - 9.8	13.3 0.3	95.0	99.7
i-Propyl (12)	10.6 - 13.2	7.3 0.2	35.7	4.8

[a] Concentration 1.0 mole x l^{-1}. [b] Values reported in Ref. (1). [c] At 30°C.

In view of the appreciable variation in the rate constants with changes in the structure of both the alcohol and the cyanopyridine, it was of interest to examine the effect of temperature on the rates of reactions and on the equilibrium concentrations of the imidates.

TABLE III

Reactions of Alcohols with Cyanopyridines[a] at Different Temperatures

Alcohol (mole x l^{-1})	Temp. (±0.3°C)	k x 10^3 l^2 $mole^{-2}sec^{-1}$	% Imidate (equilibrium)	K_{Im} x 10^2
		2-Cyanopyridine		
Methyl (20)	7.0	0.063	88	38
	30.0	0.57	98.9 (97)[c]	473 (150)[c]
	42.5	1.54	96	
Ethyl (15)	11.0	0.14		
	27.0	0.69	76.3	23
	42.5	3.16	98.0	350
i-Propyl (12)	11.0	0.21		
	27.0	1.82	90	76
	42.5	4.72	67.5	18
		3-Cyanopyridine		
Methyl (20)	7.0	0.11		
	27.0	0.96	72.0 (71)[c]	13 (11.4)[c]
	42.5	7.9		
Ethyl (15)	9.0	0.29	78.0	25
	27.0	1.82	68.3	22
	42.5	2.9		
i-Propyl (12)	10.0	0.021		
	27.0	0.15	35.7	4.8
	42.5	0.53		
Ethylene glycol (9.2)[b]	30.0	0.30	39.5	7.4
	42.0	0.79	29.0	4.6
	55.0	1.70	19.5	2.7
1,3-Propanediol (7.0)[b]	30.0	0.96	46.4	12.4
	42.0	2.32	38.4	9.4
	55.0	5.3	28.7	6.0
1,4-Butanediol (5.6)[b]	30.0	0.53	46.0	15.2
	42.0	1.77	32.3	9.0
	55.0	4.15	28.7	7.6
		4-Cyanopyridine		
Methyl (20)	14.0	1.5		
	27.0	5.7	95.0	99.7
	42.5	14.9		
Ethyl (15)	14.0	2.6		
	27.0	13.3	95.0	99.7
	42.5	42.2		
i-Propyl (12)	10.0	1.5		
	27.0	7.3	35.7	4.8
	42.5	21.0		

[a] Concentration 1.0 mole x l^{-1}. t-BuOK catalyst employed in all runs except where noted.

[b] In the presence of 4.55 mole x l^{-1} of dioxane and using the K salt of the glycolate as catalyst.

[c] Values at 25°C from Ref. (1).

The data presented in Table III gave linear plots of log k vs. 1/T. The enthalpies and entropies of activation were calculated by means of the Eyring equation

$$k = \frac{kT}{h} e^{-\frac{\Delta H^{\ddagger}}{RT}} e^{-\frac{\Delta S^{\ddagger}}{R}}$$

(where k and H are the Boltzmann and Planck constants, respectively) and are listed in Table IV.

TABLE IV

The Enthalpies and Entropies of Activation for the Reaction of Alcohols with Cyanopyridines

Pyridine	Alcohol	$\Delta H^{\ddagger}$ kcal x mole^{-1}	$\Delta S^{\ddagger}$ (e.u.)
2-Cyano	Methyl (2)	6.6	- 8.0
	Ethyl (15)	6.7	- 9.2
	i-Propyl (12)	6.8	- 8.4
3-Cyano	Methyl (20)	8.5	- 2.95
	Ethyl (15)	7.5	- 6.1
	i-Propyl (12)	7.3	- 8.9
	Ethylene glycol (9.2)a/	12.7	-32.4
	1,3-Propanediol (7.8)a/	12.5	-30.9
	1,4-Butanediol (5.6)a/	15.4	-21.8
4-Cyano	Methyl (20)	5.0	-13.2
	Ethyl (15)	5.5	-11.6
	i-Propyl (12)	4.7	-16.1

a/ In the presence of 4.55 mole x l^{-1} of dioxane.

The results listed in Table IV indicate that the entropy of activation is the principal responsible factor for the differences in the reaction rates of the isomeric cyanopyridines with the simple alcohols. There is noted a trend toward more negative entropies of activation for the reaction of 2- and 4-cyanopyridines, and especially so with the latter compound. The large negative entropies of activations for the reaction of the glycols also account to a large degree for the lower reaction rates as compared to those of the simple alcohols.

Table II and III include information concerned with the equilibrium value of the formation of imidates. Wherever comparisons are possible, the results of this work agree well with those reported previously (1). There is noted a remarkable difference between the 2- and 4-cyanopyridines, on one hand, and the 3-cyano isomer on the other, with the latter compound being less favorable for the formation of the imidates. It is also confirmed that higher temperatures tend to repress the formation of the imidates.

Table V summarizes the experiments performed to test the effect of using potassium t-butoxide as base catalyst in place of the appropriate sodium alkoxide, and there is noted a consistent decrease in the reaction velocity when the sodium alkoxide is employed.

TABLE V

Effect of Different Base Catalyst on the Reaction Rates of Methanol[a] and Cyanopyridines[b]

Pyridine	$k \times 10^3$ (l^2 mole^{-2} sec^{-1})	
	t-BuOK	MeONa
2-Cyano	0.90	0.57
3-Cyano	0.96	0.51
4-Cyano	5.7	4.8

a/ Concentration 20 mole x l^{-1} at 27°C. b/ Concentration 1.0 mole x l^{-1}.

In view of the interest to employ polyfunctional and possibly solid alcohols in this research there was investigated the formation of imidates in the presence of different solvents rather than excessive amounts of the reacting alcohol. It was discovered that the equilibrium concentration of imidate was greatly affected by the nature of the solvent, as shown by the results reported in Table VI and summarized in Fig. 1.

TABLE VI

Effect of Solvents on the Equilibrium Concentration of Imidates Derived from Methanol and 3-Cyanopyridine[a/] at 27°C with varying Methanol/ Nitrile Concentrations.

Solvent	Methanol Mole x l^{-1}	% Imidate (equilibrium)
Dimethyl sulfoxide	5	12
	7.5	18
	10	25
Dimethyl formamide	5	19
	7.5	26
	10	36
	15	52.5
Dioxane	1	11
	2.5	19.5
	5	30.0
	10	53.0
	17.5	65.0
t-Butyl alcohol	1	14
	4	30
	9	61
	12	80
Toluene	1	27.5
	2	38.2
	4	47.5
	6.5	54
	9	61
	12	67

a/ Concentration 1.0 mole x l^{-1}. Variable amounts of t-BuOK did not affect the equilibrium values.

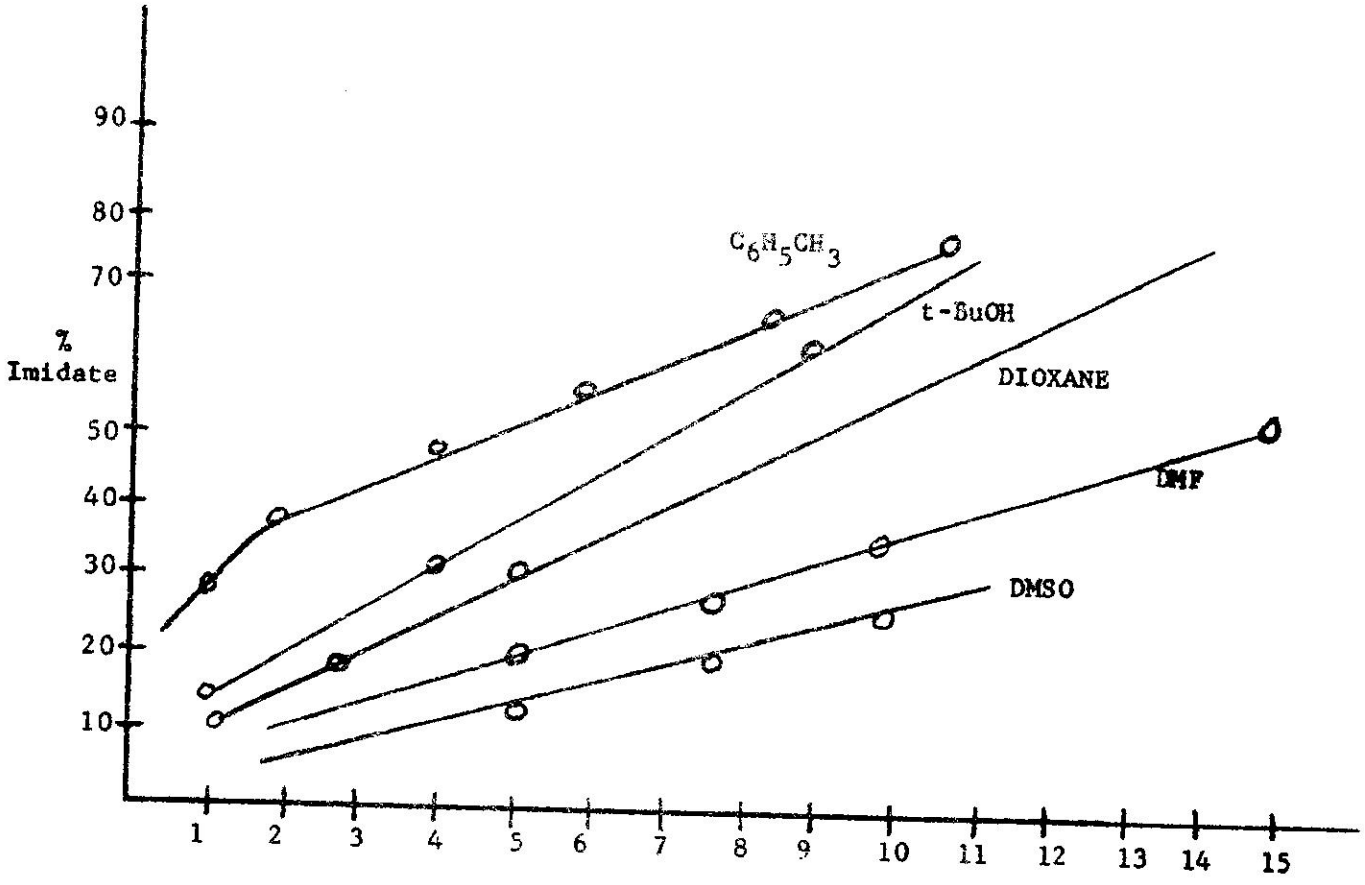


Fig. 1

Equilibrium of Imidate Formation as Function of (MeOH)/(ArCN) in Different Solvents (Table VI).

The observed effect of solvents on the position of the equilibrium during the formation of imidates is believed to be of great potential value as a means to promote better yields in the synthesis of imidates.

It was mentioned in the Introduction that the proposed study of the nucleophilic substitution reactions of imidates presumes the availability of imidate salts derived from acids containing an anion of low nucleophilicity, and the picrate ion is an example of such an anion. Also, the imidates tend to be liquids that are normally isolated by rather tedious procedures (1). For both these reasons there was investigated the possibility of isolating the imidates as crystalline, and relatively insoluble picrates, and the success of this procedure is shown by the analytical data reported in Table VII.

TABLE VII

Picrates of Imidates Derived from 3-Cyanopyridine[a/]

Alcohol	M.p. (°C)	Formula		% C	% H	% N
Methyl	137-138	$C_{13}H_{15}N_5O_7$	Calcd.	42.75	3.04	19.17
			Found	42.87	2.98	15.28
i-Propyl	139-140	$C_{15}H_{15}N_5O_7$	Calcd.	45.83	3.81	17.83
			Found	45.63	3.57	14.09
Ethylene glycol	134-135	$C_{14}H_{13}N_5O_8$	Calcd.	42.54	3.31	17.72
			Found	42.11	3.19	14.23
1,3-Propanediol	122-123	$C_{15}H_{15}N_5O_8$	Calcd.	44.02	3.70	17.12
			Found	44.62	3.45	15.75

a/ Microanalyses by Dr. Alfred Bernhardt, Mülheim, Germany.

The low nitrogen analyses indicate partial hydrolysis of the imidate to the ester during the repeated crystallizations of the picrates from acetone. Since the change of the NH group for an oxygen produces practically no change in the molecular weight, and the picrate can still be formed by virtue of the pyridine ring, the C and H analyses suffer no alterations as a consequence of the hydrolysis.

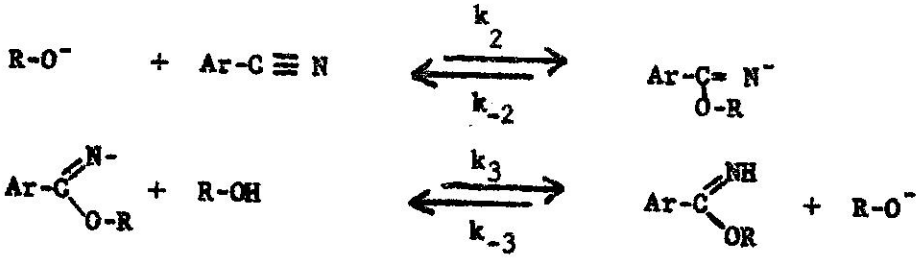
Discussion

A mechanism of the imidate formation consistent with the results described above involves a rapid equilibration of the reacting alcohol with potassium t-butoxide,

$$R\text{-}OH + t\text{-}BuO^- K^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\text{-}O^- K^+ + t\text{-}Bu\text{-}OH$$

The fact that the reactions of methanol catalyzed by t-BuOK are consistently more rapid than those catalyzed by sodium methoxide (Table V) indicates that the nature of the metal is of greater significance than that of the alkoxide introduced as the base catalyst, and this result is in agreement (2) with the recognized difference in the degree of dissociation of the alkali metal alkoxides.

The reaction of the alkoxide with the nitrile is more likely to be the rate-determining step than the subsequent reaction of the anion with another molecule of alcohol, since the latter is a relatively simple proton transfer process involving an anion expected to by highly solvated by an alcohol, in the first place.



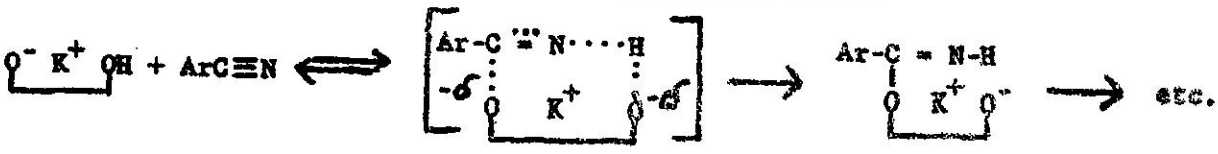
If $k_3 > k_2$

$$\frac{d\,(\text{imidate})}{dt} = k_2\,(\text{ArCN})\,(\text{RO}^-), \text{ and since } (\text{RO}^-) \propto k_1\,(\text{ROH})\,(\text{tBuOK}),$$

$$\therefore \quad \frac{d\,(\text{imidate})}{dt} = k_2 k_1\,(\text{ArCN})\,(\text{R-OH})\,(\text{t-BuO}^-\text{K}^+)$$

While it is true that k_1 must vary from one alcohol to another, because of the fact that the proton transfer in alcohols is many magnitudes greater (3) than the rate of imidate formation, one can assume that the rate of the latter reaction is affected very little by the relatively small differences in acidity of different alcohols (4).

It would seem from the data reported in Table II for 3- and 4-cyanopyridines, that in the series methyl, ethyl, and isopropyl alcohols, the reaction rates increase at first because of the greater nucleophilicity of the alkoxide ion, but that this trend is more than offset by steric impediments. However, it is difficult to arrive at clear-cut conclusions along these lines because of differences in the degree of solvation that undoubtedly affect the reaction rates and which manifest themselves primarily as the variations in the entropies of activation reported in Table IV. In the case of imidate formation by 3-cyanopyridine, the progressive increase in the negative entropy of activation (as one proceeds from methyl to isopropyl alcohol) can be interpreted to mean a progressively greater loss of freedom of the system (comparing the initial and transition states) when we go from a more highly organized alcohol, such as methanol, to an alcohol in which the intermolecular forces of attractions are relatively small. The notable increase in the enthalpy of activation for the reaction of the glycols is most likely due to chelation that renders the alkoxide $O^- K^+ OH$ less reactive, and the large negative entropy of activation could mean that initially formed species in the rate determining step requires a rigid, intramolecularly coordinated transition state:



The equilibrium constants for the imidate formation were shown (1) to obey the Hammett equation and to be favored by negative substituents (positive rho value). In line with the greatest positive sigma constant for the 4-pyridyl group (5), it is expected that the 4-cyano compound is the most favorable reagent among the isomeric cyanopyridines for the formation of imidates. The incomplete data listed in Table II bear out this expectation, but there is an indication that 2-cyanopyridine may be of special use in the formation of imidates derived from secondary alcohols (note the high equilibrium value for isopropyl alcohol). Should this result be confirmed by additional work, it will be an example of an ortho-acceleration effect (6).

The results shown in Table VI and Figure 1 indicate the profound effect on the imidate equilibrium exerted by different solvents. The equilibrium constants for imidate formation (K_{Im}) listed in Tables II and III were estimated in a manner analagous to that described previously (1), but the data of Tables VI and Figure 1 are suitable for the calculation of imidate equilibrium constants in the presence of different solvents in the following fashion.

For a given equilibrium concentration of imidate (a) and known initial concentrations of the alcohol (b) and nitrile (c), the equilibrium constant is given by

$$K_{Im} = \frac{(\text{Imidate})}{(\text{ROH})\ (\text{ArCN})} = \frac{a}{(b-a-x)\ (c-a)}$$

, where x represents the concentration of the alcohol which is "inactive" in the equilibrium due to strong involvement with the solvent molecules. As a first approximation one can ignore the quantity x and estimate K_{Im} values for different (ROH)/(ArCN) ratios. Then we can plot the apparent K_{Im} values against the mole fraction of the given solvent and extrapolate to zero concentration of ROH to obtain an improved K_{Im} value. This operation is justified on the basis that with decreasing amounts of alcohol the value of x becomes less significant. Figure 2 shows this application of this procedure to several solvents, and Table VIII lists the K_{Im} values obtained for the imidate formation from methanol and 3-cyanopyridine in different solvents at 27°C. It is noteworthy that strong interactions between solvent molecules and the alcohol have an adverse effect on the equilibrium constant, and that, on the other hand, the use of "inert" solvents produces favorable displacements of the equilibrium even in the absence of excessive amounts of the alcohol.

TABLE VIII

Equilibrium Constants for Imidate Formation from Methanol and 3-Cyanopyridine at 27°C in Different Solvents.

Solvent	$K_{Im} \times 10^2$
Dimethyl sulfoxide	3
Dimethel formamide	8
Methyl alcohol[a]	13
Dioxane	18
t-Butyl alcohol	30
Toluene	ca. 66

a/ From Table II.

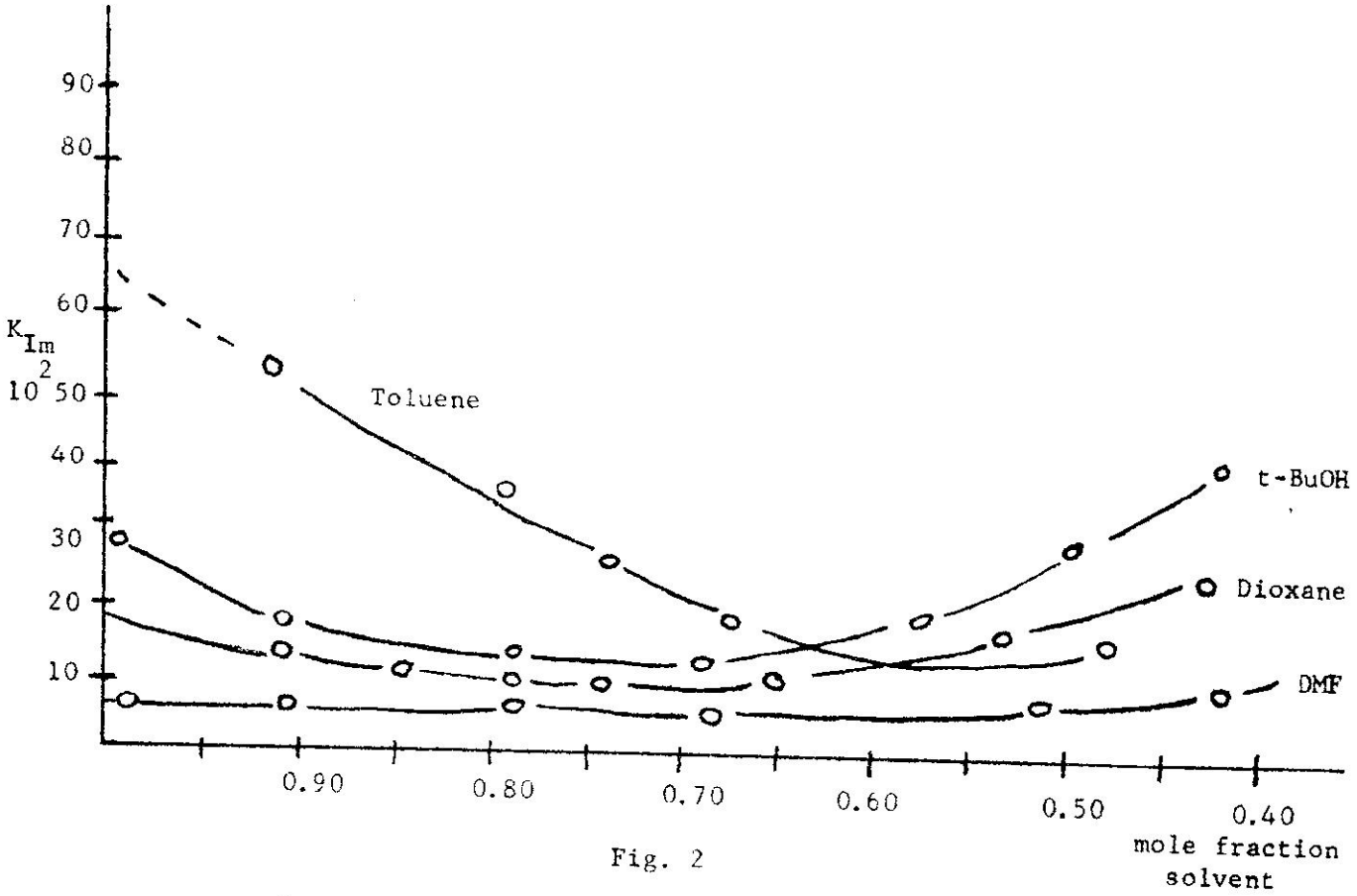


Fig. 2

Estimate of K_{Im} for the Reaction of Methanol and 3-Cyanopyridine at 27°C in Different Solvents

REFERENCES

(1) F. C. Schaefer and G. A. Peters, J. Org. Chem. 26, 412 (1961)

(2) J. D. Reinheimer, J. T. Gerig and J. C. Cochran, J. Am. Chem. Soc., 83, 2873 (1961)

(3) E. Grunwald, C. F. Jumper and S. Meiboom, ibid., 84, 4664 (1962)

(4) P. Ballinger and F. A. Long, ibid., 82, 795 (1960)

(5) H. H. Jaffé, Chem. Revs., 53, 191 (1953)

(6) (a) R. O. C. Norman and G. K. Radda, J. Chem. Soc., 1961, 3030

(b) R. G. Sheperd, W. E. Tafl and H. M. Krazinski, J. Org. Chem., 26, 2764 (1961)