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THE KINETICS AND MECHANISM OF NUCLEOPHILIC SUBSTITUTION ON 9-SUBSTITUTED-6-CHLOROPURINES

A THESIS

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GLOSSARY OF ABBREVIATIONS

UV	Ultraviolet
n.m.r.	Nuclear magnetic resonance
DMSO	Dimethyl sulfoxide
DABCO	Diaza [2.2.2.]bicyclooctane
DNCB	2,4-Dinitrochlorobenzene
DNFB	2,4-Dinitrofluorobenzene
Pip	Piperidine

SUMMARY

The research described herein is a mechanistic study of the effects of additives on the reaction of piperidine with 6-chloro-9-ethylpurine in isooctane. The investigation was accomplished by means of kinetic and product analysis.

Piperidine as well as certain additives were found to catalyze the reaction. A plot of the second order rate coefficient (k_{obs}) obtained from pseudo first order kinetic data against the concentration of piperidine was found to increase linearly with increasing piperidine concentration; however, at higher concentrations of amine the increase was not linear and a smooth curve was obtained. This phenomena is characteristic of the multi-step, addition-elimination mechanism originally proposed by Bunnett and co-workers for the reactions of amines with 2,4-dinitrohalobenzenes in protic media.

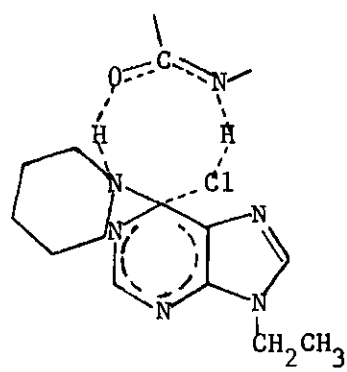
An isotopic study involving piperidine (-N-h and -N-d) was undertaken. It was demonstrated that piperidine-N-d reacted slightly faster than piperidine-N-h with the purine in isooctane at 29.75 °C; however, at 49.5 °C an unusual effect was observed. Initially, the deuterium-labeled compound reacted faster, but at higher concentrations of amine the lines crossed and a $k_H/k_D > 1$ was obtained.

Vapor pressure studies of piperidine in isooctane indicated that piperidine was not appreciably associated in the concentration range under investigation.

Other compounds were added to the reaction solution at 29.75° C

while maintaining the piperidine concentration constant. All catalytic coefficients (k_4') were obtained from the slope of the plot of k_{obs} against the concentration of additive. Triethylamine and 2,6-dimethylpiperidine did not catalyze the reaction, nor did tetrahydrofuran, tetrahydropyran or acetone. Steric hindrance could prevent the amines from accelerating the piperidine-purine reaction; however, failure of a catalytic effect by the ethers and ketone seemed to indicate that simple base catalysis was not operating. Pyridine produced a weak catalytic effect, but 1-aminobutane and 1,2-ethanediamine gave a catalytic constant (k_4') comparable to that obtained from the piperidine studies at that temperature.

The addition of the lactam 2-azacyclononanone to the reaction solution produced a very large rate enhancement. This was attributed to the possibility that the amide could act as a bifunctional catalyst without high accumulation of charge in the transition state.



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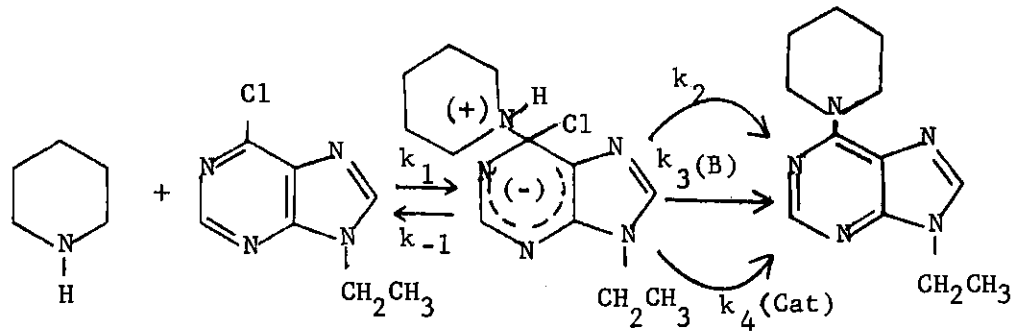
Alcohols such as methanol, 1-butanol, and 2-methyl-2-propanol were also effective as catalysts in these reactions; however, it was observed

that a different catalytic coefficient was obtained with a change in the "constant" piperidine concentration. This effect was attributed to hydrogen bonding of the alcohol and amine components. The data was treated by assuming that the alcohol existed as a dimer which then associated with monomeric amine molecules to produce a trimeric species with $K_{eq} = 5$. Using the data corrected for association, the plot of k_{obs} versus the catalyst concentration was then linear. A few points at higher concentrations of amine and alcohol deviated from the linear plot. This was attributed to either more extensive association of the components or a situation where k_{-1} was approximating $k_2 + k_3$ (B) in the multi-step reaction.

Finally, a linear Hammett plot was constructed from the catalytic coefficients of a series of meta and para substituted benzyl alcohols in an attempt to determine the relative importance of basic, acidic or bifunctional catalysis on the reaction. The catalysis coefficients were determined by first assuming no association of the components, and then by assuming alcohol dimer interacting with monomeric amine to produce the trimer ($K_{eq} = 5$). The rho values obtained were + 0.22 (assuming no association) and + 0.26 (assuming association of the components). The low values for rho appeared to indicate that the acidic portion of the alcohol was only of slightly more importance than the basic portion in these reactions.

Thus, based on the information determined herein, the reaction of piperidine with 6-chloro-9-ethylpurine in isooctane appears to go through a multi-step, addition-elimination mechanism such as the following:



The uncatalyzed step may be rationalized using a 4-center transition state, while the catalyzed steps appear to involve a bifunctional interaction of the catalyst with the intermediate complex.

A summary of the catalytic data is listed in Table 1 in which k_3', k_4', and k_2' are defined as:

$$k_3' = \frac{k_1 k_3}{k-1}, k_4' = \frac{k_1 k_4}{k-1}, \text{and } k_2' = \frac{k_1 k_2}{k-1} .$$

Table 1. Summary of the Catalytic Rate Coefficients Obtained from the Reaction of Piperidine with 6-Chloro-9-ethylpurine in Isooctane

Additive	Concentration of Piperidine (moles liter^{-1})	Catalytic Coefficient (k_3' or k_4') (M^{-2} sec.$^{-1}$)	Catalytic Ratio (k_4'/k_3')
Piperidine-H		1.29×10^{-2}	
Piperidine-D		1.43×10^{-2}	
Triethylamine	0.0960	non-catalytic	
Tetrahydrofuran	0.1906	non-catalytic	
Tetrahydropyran	0.1881	non-catalytic	
Acetone	0.2042	non-catalytic	
Pyridine	0.1261	9.16×10^{-4}	0.07
1-Aminobutane	0.1881	1.16×10^{-2}	0.90
1,2-Ethanediamine[1]	0.2429-0.2448	1.17×10^{-2}	0.91
2-Azacyclononanone	0.1852-0.1861	27.6×10^{-2}	21.40
Methanol-O-h	0.0537	9.61×10^{-2}	7.45
Methanol-O-h	0.1055	8.54×10^{-2}	6.62
Methanol-O-h	0.2290	5.23×10^{-2}	4.05
1-Butanol	0.0282	12.80×10^{-2}	9.92
1-Butanol	0.0537	11.63×10^{-2}	9.02
1-Butanol	0.0972	9.44×10^{-2}	7.32
1-Butanol	0.1906	6.47×10^{-2}	5.02
2-Methyl-2-propanol	0.0972	5.18×10^{-2}	4.02
2-Methyl-2-propanol	0.1982	3.96×10^{-2}	3.07
Methanol-O-d_2	0.2271	5.53×10^{-2}	4.29
Methanol-O-h[2]		27.35×10^{-2}	21.20
1-Butanol[2]		30.22×10^{-2}	23.43
2-Methyl-2-propanol[2]		18.84×10^{-2}	14.60
Methanol-O-d[2]		25.69×10^{-2}	19.91
Benzyl Alcohol	0.1852-0.1857	6.75×10^{-2}	5.23
p-Chlorobenzyl Alcohol	0.1867-0.1877	8.04×10^{-2}	6.23
p-Methylbenzyl Alcohol	0.1868-0.1876	6.58×10^{-2}	5.10
m-Chlorobenzyl Alcohol	0.1867-0.1876	8.49×10^{-2}	6.58
Benzyl Alcohol[2]		31.07×10^{-2}	24.08
p-Chlorobenzyl Alcohol[2]		36.42×10^{-2}	28.23
p-Methylbenzyl Alcohol[2]		27.74×10^{-2}	21.50
m-Chlorobenzyl Alcohol[2]		37.89×10^{-2}	29.37

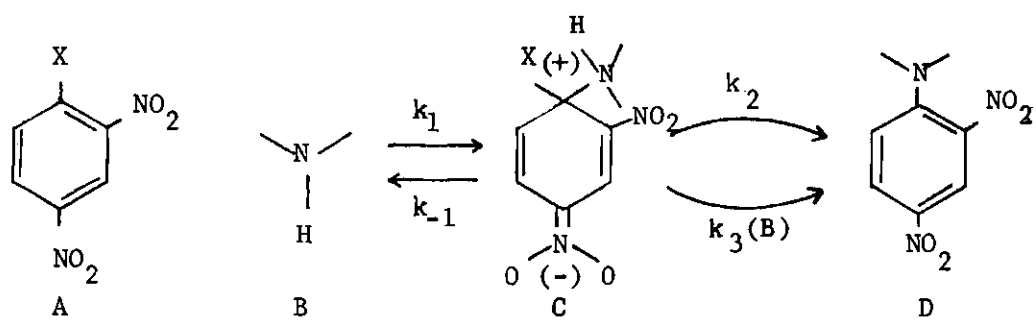
[1] Corrected for statistical factor.
[2] Corrected for association.

CHAPTER I

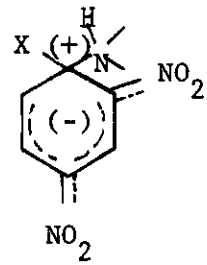
HISTORICAL BACKGROUND

The subject of nucleophilic aromatic substitution in polar, protic solvents has been widely investigated by many workers (1-40). However, studies of such reactions in aprotic, non-polar solvents are somewhat limited. It is in this latter media that catalysis by acids, bases or "bifunctional" species can be examined without complications by polar effects or hydrogen bonding with the solvent. The purpose of this chapter is to present the investigations of nucleophilic aromatic substitution which have been reported in non-polar, aprotic media.

Studies by Bunnett and co-workers in polar, protic solvents led to the theory that nucleophilic aromatic substitution on certain systems may take place in a multi-step, addition-elimination process such as the following:



Initial attack by the nucleophile on the substrate (A) produces the intermediate (C) (a Meisenheimer complex) which is adequately represented in the following manner (35):



Decomposition of the intermediate can occur either through an uncatalyzed process involving spontaneous loss of a proton and ejection of the leaving group, X, or by a catalyzed route incorporating the nucleophile or another additive (B). The latter pathway has been found to be enhanced by various acids, bases, salts, and "bifunctional" species, the effect being dependent on the nature of the nucleophile, the substrate, and the solvent. A kinetic treatment of this theory is easily developed:

$$\frac{-d(B)}{dt} = \frac{d(D)}{dt} = k_1(A)(B) - k_{-1}(C).$$

Using the steady-state approximation,

$$\frac{d(C)}{dt} = 0 = k_1(A)(B) - k_{-1}(C) - k_2(C) - k_3(B)(C),$$

thus,

$$(C) = \frac{k_1(A)(B)}{k_{-1} + k_2 + k_3(B)},$$

and,

$$\frac{d(D)}{dt} = k_1(A)(B) - \frac{k_{-1}k_1(A)(B)}{k_{-1} + k_2 + k_3(B)} .$$

Upon rearranging terms,

$$\frac{d(D)}{dt} = \frac{k_1[k_{-1} + k_2 + k_3(B)](A)(B) - k_{-1}k_1(A)(B)}{k_{-1} + k_2 + k_3(B)}$$

$$= \frac{[k_1k_2 + k_1k_3(B)](A)(B)}{k_{-1} + k_2 + k_3(B)} .$$

Then, the observed second order rate coefficient

$$(k_{obs}) = \frac{k_1k_2 + k_1k_3(B)}{k_{-1} + k_2 + k_3(B)},$$

or,

$$k_{obs} = \frac{k_1k_2}{k_{-1} + k_2 + k_3(B)} + \frac{k_1k_3(B)}{k_{-1} + k_2 + k_3(B)}$$

Now, if $k_{-1} \gg k_2 + k_3(B)$, that is, initial formation of the intermediate is fast and the decomposition of (C) is slow then, $k_{obs} = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3(B)}{k_{-1}}$. A plot of k_{obs} against the concentration of (B) is linear with a slope = $\frac{k_1k_3}{k_{-1}}$ and the intercept = $\frac{k_1k_2}{k_{-1}}$, i.e. the catalyzed and uncatalyzed processes, respectively. At low concentrations of the catalyst (or nucleophile) this linear relationship of the second order rate coefficient and the catalyst concentration has been observed. If $k_{-1} \ll k_2 + k_3(B)$, then initial formation of the intermediate is rate-determining and the relationship reduces to: $k_{obs} = k_1$. This has been found to be the case at high concentrations of the catalyst where catalysis is a maximum and the plot of k_{obs} against the catalyst concentration becomes parallel to the abscissa. At intermediate concentrations k_{-1} and $k_2 + k_3(B)$ are of comparable magnitudes and curvature of the plot occurs.

If both additive and nucleophile catalyze the reaction, then the observed second order rate constant may also be written in the following manner:

$$k_{obs} = \frac{k_1k_2 + k_1k_3(\text{nucleophile}) + k_1k_4(\text{additive})}{k_{-1} + k_2 + k_3(\text{nucleophile}) + k_4(\text{additive})};$$

again, if $k_{-1} \gg k_2 + k_3(\text{nucleophile}) + k_4(\text{additive})$, then the equation becomes:

$$k_{obs} = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3(\text{nucleophile})}{k_{-1}} + \frac{k_1k_4(\text{additive})}{k_{-1}} .$$

Therefore, if the concentration of the nucleophile is maintained constant, the plot of k_{obs} against the concentration of additive is linear with a slope $= \frac{k_1k_4}{k_{-1}}$ and an intercept $= [\frac{k_1k_2}{k_{-1}} + \frac{k_1k_3(\text{nucleophile})}{k_{-1}}]$.

Although certain catalysis studies are interpretable in protic media, the reactions are complicated by the interactions of the solvent. Thus, studies carried out in non-polar, aprotic solvents can be especially important in the investigation of reactions which proceed by this multistep mechanism.

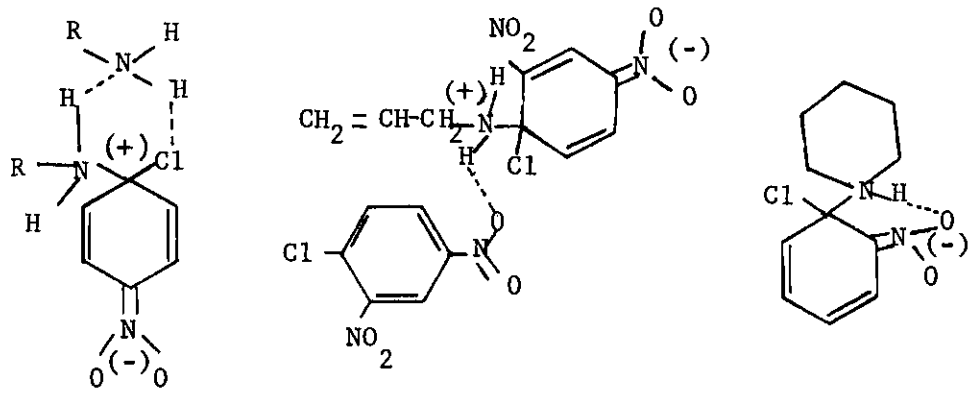
Ross and co-workers have studied reactions of amines such as n-butylamine, 2-phenylethylamine and di-n-butylamine with 2,4-dinitrochlorobenzene in chloroform (41,42). At a constant 2,4-dinitrochlorobenzene concentration, the second-order rate coefficients were found to increase with increasing amine concentration and plots of the observed second order rate coefficients versus the initial amine concentrations were linear in all cases. Similar results were obtained for the reaction of n-butylamine with 2,4-dinitrobromobenzene and 2,4-dinitroiodobenzene in

chloroform (43). Mild catalysis by triethylamine in which the ratio of catalyzed to uncatalyzed rates $\cong$ 1 was also discovered in the reaction studies of n-butylamine with 2,4-dinitrochlorobenzene in this solvent (44). Table 2 summarizes the catalyzed and uncatalyzed rate coefficients for the reaction of this particular amine with the 2,4-dinitrohalobenzenes as calculated using the multi-step, addition-elimination (Bunnett) mechanism.

Table 2. Rates of Reaction of 1-Halo-2,4-dinitrobenzenes with n-Butylamine in Chloroform at 24.8 $\pm$ 0.1 C

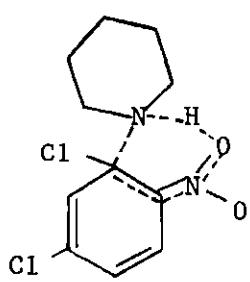
Halogen	$k_{(uncat.)} \times 10^4 (\underline{M}^{-1}sec^{-1})$	$k_{(cat)} \times 10^4 (\underline{M}^{-2}sec^{-1})$
Chlorine	2.2	5.4
Bromine	3.0	7.0
Iodine	0.94	1.7

The reaction of allylamine with 2,4-dinitrochlorobenzene in chloroform was observed to be catalyzed by the aromatic nitro groups as well as by the amine (45). A deuterium isotope effect was absent in this latter reaction which suggests the possibility that the rate-determining step is a concerted process including breaking of the N-H bond together with breaking of the C-Cl bond. Thus, the energy of the process is essentially that required to break the C-Cl bond which would cause a "masking" of the isotope effect; therefore, catalysis steps such as (I), (II) and (III) are certainly plausible in view of the information thus far (41, 45, 46).



I II III

Brieux and Greizerstein (47) found a thirty-fold increase in the k_o/k_p ratio in going from methanol to benzene in the reaction of 2,4-dichloronitrobenzene-4-Cl^{36} with piperidine. These results also support the intramolecular step (III) since such a process would minimize charge accumulation in the non-polar medium.



An interesting study conducted by Brieux and co-workers (48) demonstrates the varied reactivity of the ortho- and para-chloronitrobenzenes in benzene and ethanol with piperidine as the nucleophile. The results show that the catalyzed to uncatalyzed ratio (k_3/k_2) decreases for the p-nitrochlorobenzene in going from benzene to ethanol solvent, but increases for the reaction of o-nitrochlorobenzene with piperidine.

The effect appears to indicate that solvation and catalysis by ethanol on the intermediate is probably occurring in both cases. This analysis is also justified based on the large increase in k_{obs} for the p-nitrochlorobenzene reaction in going from the non-polar, aprotic to the polar, protic medium; however, it is interesting that the k_3/k_2 ratio is smaller than unity for the o-nitrochlorobenzene case in both solvents. This seems to demonstrate that hydrogen bonding (46) and built in solvation (4) by the o-nitro group stabilizes the intermediate and makes the abstraction of a proton by a base of less relative importance kinetically.

Table 3. Rate Data for the Reactions of p-Nitrochlorobenzene and o-Nitrochlorobenzene with Piperidine in Two Solvents (Temp. = 100°C)

Compound*	Solvent	10^5k_2	10^6k_3	k_3/k_2	Piperidine (moles l^{-1})	10^6k_{obs}
p-Nitrochlorobenzene	Benzene	0.05	1.2	2.4	0.75	1.39
p-Nitrochlorobenzene	Ethanol	1.6	3.7	0.23	0.77	18.2
o-Nitrochlorobenzene	Benzene	8.3	8.1	0.10	0.72	90.0
o-Nitrochlorobenzene	Ethanol	4.0	12.0	0.30	0.77	48.5

*Substrate concentration was 0.07 M.

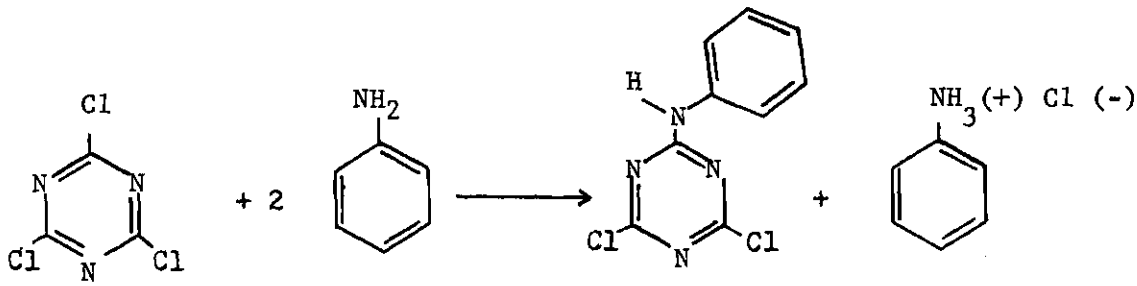
The effect by the ortho-nitro group has also been reported for the 2- and 4-fluoronitrobenzene systems in benzene (49). It is obvious from the following table that while the reaction of 4-fluoronitrobenzene with piperidine is catalyzed by increasing concentrations of amine resulting in third order overall kinetics, the reaction of 2-fluoronitrobenzene is only weakly catalyzed by excess piperidine. Therefore, the intramolecular interaction of the ortho-nitro group appears to be very important in

these systems (it has been proposed that the tetrahedral nature of the transition state is retained in certain nucleophilic aromatic substitution reactions in which an ortho-nitro group is present; in such a model the ortho-nitro group can adapt itself between the entering and leaving groups, thus attaining coplanarity and resonance with the benzene ring) (50,51).

Table 4. Reaction Rates of Piperidine with Fluoronitrobenzenes in Benzene

(a) Fluoro-4-nitrobenzene (2.52×10^{-5} M) (85°C)						
10 [Piperidine] (M)	1.76	2.56	3.60	4.37	5.22	6.00
10^6 x Rate/[ArF] [Piperidine] (mole^{-1} liter sec^{-1})	8.73	12.5	17.7	20.8	25.1	29.2
10^5 x Rate/[ArF] [Piperidine]^2 (mole^{-2} liter sec^{-1})	4.96	4.88	4.92	4.76	4.81	4.87
(b) Fluoro-2-nitrobenzene (3.21×10^{-4} M) (25°C)						
10 [Piperidine] (M)	0.326	0.652	1.34	1.96	2.67	3.26
10^4 x Rate/[ArF] [Piperidine] (mole^{-1} liter sec^{-1})	5.61	5.68	5.97	6.12	6.43	6.58

In 1961, Bitter and Zollinger reported the kinetics of the reactions of several triazines with aniline and monomethylaniline in benzene (52). These workers found the reaction of cyanuric chloride (IV) and aniline to be first order with respect to cyanuric chloride and approximately first order with respect to aniline. Also, the reaction was catalyzed by the product (V) (Table 5) and, to a much lesser extent, by the nucleophile (Table 6).



IV V

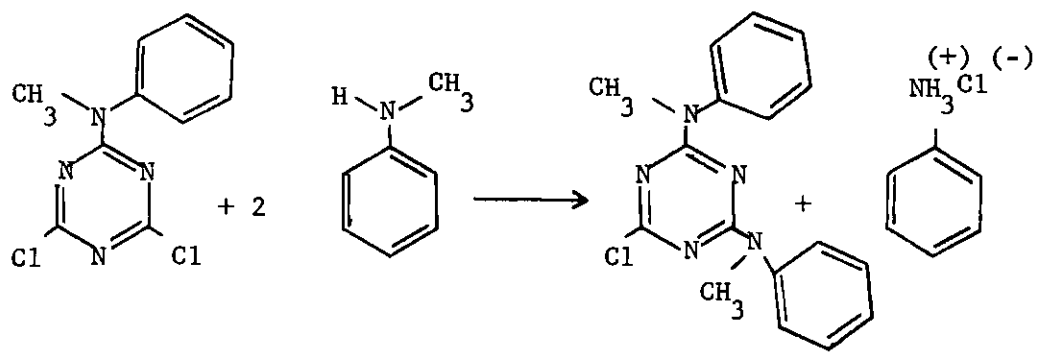
Table 5. Variation of k_{obs} with Added 1-Anilino-3,5-dichloro-2,4,6-triazine (V) at 25 °C
[Cyanuric Chloride] = 0.0025M, [Aniline] = 0.005 M

Molarity of Additive	Time (min)	k_{obs} (M^{-1} min^{-1})
0.0025	5	20.6
0.0025	10	18.0
0.0050	5	27.1
0.0050	10	23.5
0.0100	5	35.6
0.0100	10	36.2
0.0200	5	60.0
0.0200	10	57.2
0.0400	5	127.0
0.0400	10	123.0

Table 6. Variation of k_{obs} with Added Aniline at 25°C
[Cyanuric Chloride] = 0.00125 M

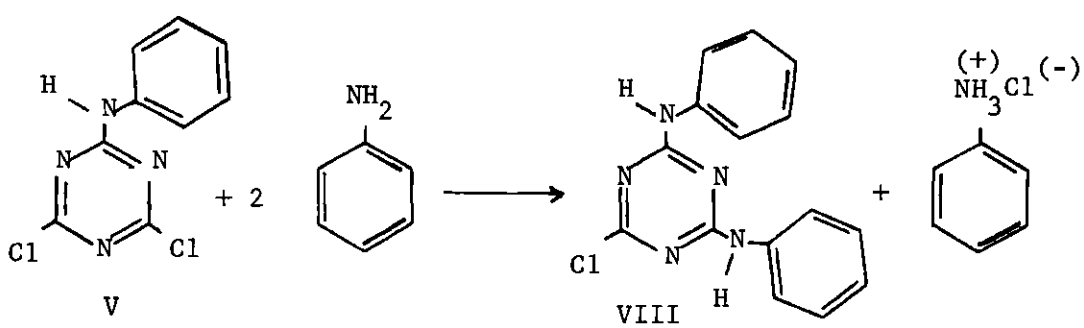
Molarity of Aniline	Time (min)	k_{obs} (M^{-1} min^{-1})
0.005	4	19.8
0.005	5	20.6
0.005	6	21.2
0.005	10	19.7
0.010	4	22.5
0.010	5	21.6
0.010	6	22.2

Both the product (V) and the nucleophile contain acidic hydrogens which could interact along the reaction pathway to produce a catalytic effect. To test further the idea that the amino hydrogen was responsible for the auto-catalysis, N-methylaniline-3,5-dichlorotriazine (VI) was reacted with N-methylaniline at 50° and the reaction was discovered to be strictly second order overall. No autocatalysis by the product was observed. Furthermore, the reaction of 1-anilino-3,5-dichlorotriazine (V) and aniline was found to be second order in the triazine and approximately



VI VII

first order in aniline. It is also catalyzed by the product (VIII).



V VIII

Additional information regarding the nature of the catalysis was obtained by adding acetic acid, chlorinated acetic acids, and phenols to

the reaction of cyanuric chloride with aniline. All of the carboxylic acids employed were found to catalyze the reaction, but the order of reactivity ($CH_3COOH > CH_2ClCOOH > CCl_3COOH$) was opposite to that which was expected. Addition of the phenols seemingly did not accelerate the reaction at all; however, large variations in the rate constants were obvious. Unfortunately, the workers assumed there was no interaction of the nucleophile with the acids in the concentration range studied. This is contrary to what other workers have found regarding reactions of amines with acids in benzene solutions (53). Phenols have been observed to catalyze the reaction of piperidine with 2,4-dinitrofluorobenzene in benzene while the corresponding reaction with 2,4-dinitrochlorobenzene was not accelerated by these additives in this solvent. However, extensive association of the phenol with piperidine complicated the analysis of the data (54).

Apparently, these discrepancies in the order of catalysis by carboxylic acids and the non-catalytic effect of the phenols reported by Bernasconi and Zollinger are primarily due to association of the amine with the acid catalyst, thus removing a substantial amount of the nucleophile from participation in the reaction. This appears to be the problem in many reactions studied in non-polar solvents in which a rather polar or acidic catalyst is employed.

To test the effects of non-protic bases, triethylamine and pyridine were added to the reaction mixture of cyanuric chloride and aniline (52). Both of these additives were found to catalyze the reaction.

In addition to the carboxylic acids already mentioned, the authors studied the effects of α-pyridone and γ-pyridone on the reaction of cyanuric chloride and aniline in an attempt to explore the possibility

Table 7. Effect of Carboxylic Acids and Phenols on the Reaction of Cyanuric Chloride with Aniline
[Cyanuric Chloride] = 0.0025 M, [Aniline] = 0.005 M

Additive	Molarity	Time (min)	k_{obs} ($\underline{M}^{-1}$ min^{-1})
CH_3COOH	0.002	10	38.0
	0.004	10	56.8
	0.005	10	64.6
	0.010	10	82.1
	0.0109	10	80.0
	0.016	10	114.0
$CH_2ClCOOH$	0.002	10	38.9
	0.020	10	150.0
CCl_3COOH	0.002	10	30.0
	0.004	10	30.0
	0.010	10	22.7
	0.020	10	22.7
Phenol	0.002	10	12.2
	0.01	10	11.6
	0.02	10	10.5
o-Nitrophenol	0.002	10	15.7
	0.01	10	15.4
	0.02	10	12.4
p-Nitrophenol	0.01	10	13.5
	0.02	10	21.0
	0.002	10	15.2

Table 8. Effect of Triethylamine and Pyridine on the Reaction of of Cyanuric Chloride with Aniline
Cyanuric Chloride = 0.00125 M, [Aniline] = 0.00250 M

Additive	Molarity (moles $liter^{-1}$)	Time (min)	k_{obs} ($\underline{M}^{-1}$ min^{-1})
Triethylamine	0.00025	20	21.0
Triethylamine	0.0005	21	36.1
Triethylamine	0.001	18	67.1
Pyridine	0.00005	8	67.8
Pyridine	0.0001	5	152.8

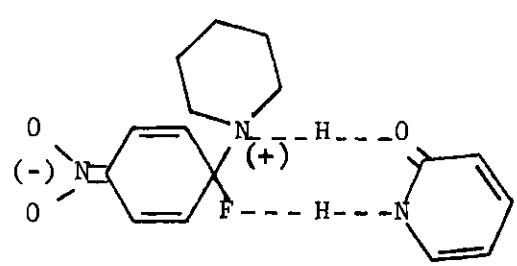
of "bifunctional" catalysis (55,56) in which the catalyst can act as both an acid and a base. The α- pyridone was found to catalyze the reaction while γ-pyridone was apparently ineffective as a catalyst.

Table 9. Effect of α-Pyridone and γ-Pyridone on the Reaction of Cyanuric Chloride and Aniline. [Cyanuric Chloride] = 0.0025 M, [Aniline] = 0.005 M.

Additive	Molarity	Time (min)	k_{obs} (M^{-1} sec^{-1})
α-Pyridone	0.001	10	48.5
α-Pyridone	0.002	10	71.0
α-Pyridone	0.0025	10	76.3
α-Pyridone	0.0100	10	75.2
γ-Pyridone	0.0025	10	14.7
γ-Pyridone	0.0025	20	13.2

Bitter and Zollinger thus concluded that the reaction of aniline and cyanuric chloride is accelerated by bifunctional and basic catalysts, but the bifunctional catalyst must possess a basic center in these reactions in addition to an acidic hydrogen atom (52).

Experiments conducted by Pietra and Vitali (53) show that α-pyridone substantially enhances the rate of the reaction of piperidine with 2,4-dinitrofluorobenzene in benzene while N-methyl-α-pyridone does not affect the rate at all. A reasonable explanation for these observations lies in the bifunctional nature of α-pyridone which can assist in the more or less concerted separation of both ammonium proton and fluoride ion from the intermediate:



This interpretation is substantiated by the finding that N-methyl-α-pyridone which, compared to α-pyridone lacks the acidic hydrogen, is devoid of any catalytic activity.

Further studies of aromatic substitution reactions in aprotic, non-polar solvents indicate the effect of additives on these reactions. The reactions of 2,4-dinitrofluorobenzene and 4-nitrofluorobenzene with piperidine in benzene solution were found to be catalyzed by excess piperidine, but not by triethylamine (57). Furthermore, experiments with piperidine-N-d disclosed no measurable isotope effect in the experimental concentration range. Addition of methanol to the reaction solution accelerated the reaction rate for the lower amine concentrations and decreased the rate at higher piperidine concentrations. These effects were explained by electrophilic catalysis in which the amine or alcohol is involved in the rate-determining abstraction of the fluoride ion through hydrogen bonding.

Electrophilic catalysis indicates that the breaking of the carbon-fluorine bond is important in the rate-determining transition state while the lack of base catalysis and isotopic effects indicates that the breaking of the nitrogen-hydrogen bond may not be important. The reaction of 2,4-dinitrochlorobenzene and 4-nitrochlorobenzene with piperidine was found not to be catalyzed by the addition of excess amine.

Similar results on these same systems have been reported by other workers (58,59), again using piperidine as the nucleophile and benzene as the solvent. In the case of the 2,4-dinitrofluorobenzene-piperidine reaction a plot of the observed second order rate coefficient against piperidine was found to increase linearly with increasing concentration

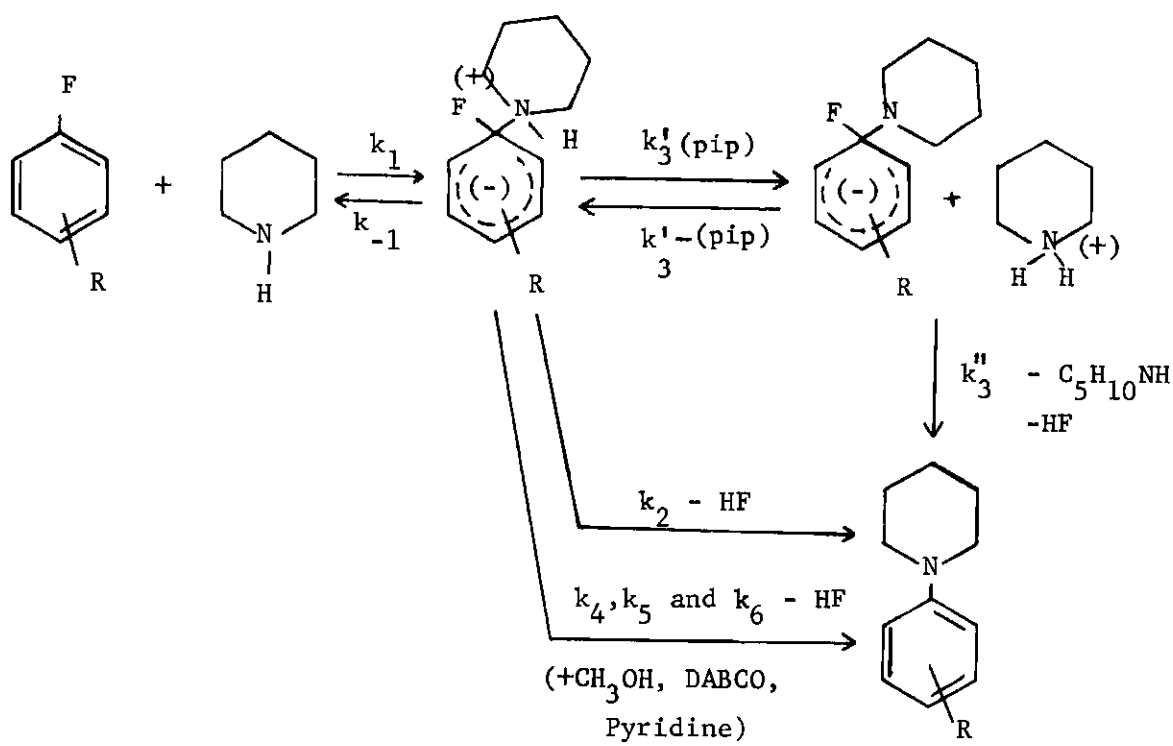
of the amine. When the reaction was run in 0.1 M methanol the second order rate constant again increased, but in a curvilinear fashion. At higher concentrations of alcohol (0.15 M) the rate constant was found to decrease with increasing piperidine concentration. The decrease in the reaction rate at higher alcohol-amine concentrations was attributed to hydrogen-bonding of piperidine with methanol, thus removing a portion of the nucleophile from the reaction. This theory was verified by adding increasing amounts of methanol to the 2,4-dinitrochlorobenzene-piperidine reaction which does not appear to be catalyzed by additives. The rate constant in this case was found to decrease with increasing concentrations of the alcohol.

The addition of p-dioxane to the reaction of piperidine with 2,4-dinitrofluorobenzene in benzene provides important information concerning the electrophilic nature of the catalysis steps in these reactions. Although the dielectric constant of p-dioxane corresponds almost exactly to that of benzene (60), the ether possesses a bonding dipole between the carbon and oxygen atoms and should be in some degree comparable to methanol in these studies if it acts as a basic catalyst or if the C-O bonding dipole interacts with the transition state of the reaction. The results by Bernasconi and Zollinger (60) clearly indicate that p-dioxane exerts no detectable influence on the reaction rate. Therefore, the authors concluded that the acidic proton of methanol is responsible for its catalytic effect and by the loosening of the leaving group plays the role of an electrophilic (acidic) or bifunctional catalyst.

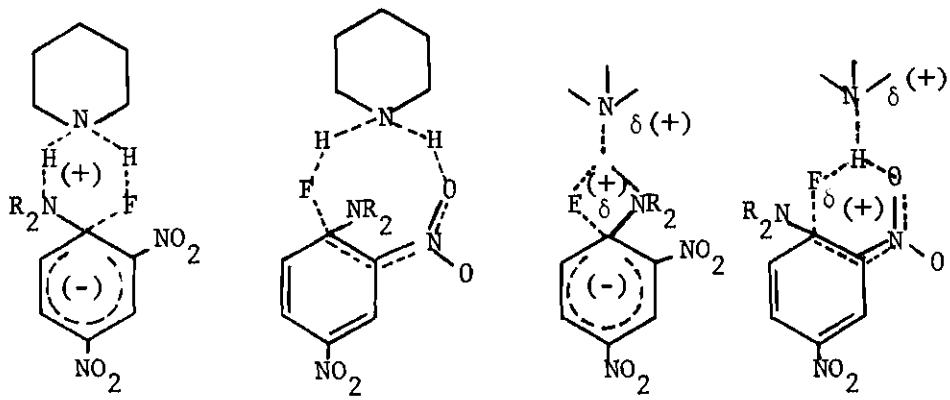
Other additives such as diaza[2.2.2.]bicyclooctane (DABCO) and pyridine were also found to catalyze these reactions (59). The catalytic

effect by DABCO is particularly significant since it is a relatively unhindered tertiary amine; however, it has been observed in these laboratories that commercially prepared diaza[2.2.2.]bicyclooctane is very impure and apparently contains water of hydration (61). Sublimation or recrystallization from isooctane does not improve the melting point, which is 50 degrees below the literature value of 159°C. The authors report that the DABCO used in their reactions was commercially purchased and not further purified. Therefore, their results with this particular reagent are suspect.

The catalysis by pyridine was very small compared to the other additives; this may be interpreted to be due to a small increase in the dielectric constant of the medium (59). The mechanism proposed by these workers is a multi-step, addition-elimination process:



Several catalyzed steps are possible for these reactions:



IX X XI XII

It is interesting that all of the catalyzed reactions discussed here can be viewed as a type of bifunctional catalysis. The kinetic results of these experiments are listed in Table 10.

Dimethylsulfoxide (DMSO) has a pronounced effect on the reaction of piperidine with 2,4-dinitrofluorobenzene or 2,4-dinitrochlorobenzene in benzene. Suhr (62) found that the reaction of piperidine with 4-nitrofluorobenzene proceeds quite rapidly if one uses DMSO as a solvent, the difference in the reaction rate in benzene versus DMSO being on the order of 5×10^3 (in pure DMSO clean second order kinetics are observed for these reactions (51,63). Bernasconi and Zollinger (60) found that an addition of only 11 percent dimethylsulfoxide to the reaction of piperidine with 2,4-dinitrofluorobenzene in benzene increased the rate by a factor of about 400. These workers reasoned that since pure solvents which exhibit a dielectric constant comparable to this mixture yield substantially smaller rate constants, the action of DMSO is indicative of a catalytic effect (others (64) have shown the reaction of allylamine with

Table 10. Second Order Rate Constants for the Reaction of Piperidine With 2,4-Dinitrofluoro- and 2,4-Dinitrochlorobenzene at 25° in Benzene

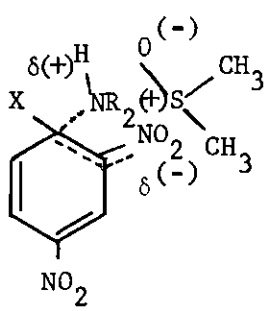
(a) Dinitrofluorobenzene (DNFB) (2.75×10^{-5} M)						
$10^3 \times$ [Piperidine] (moles liter^{-1})	0.3	0.5	1.0	1.5	2.0	3.0
k (liter mole^{-1} sec^{-1})	0.67	0.80	1.10	1.42	1.73	2.34
(b) (DNFB) (2.75×10^{-5} M) + 10^{-3} M Piperidine						
[Methanol] (moles liter^{-1})	0	0.03	0.06	0.10	0.15	
k (liter mole^{-1} sec^{-1})	1.05	1.68	2.38	3.22	4.06	
(c) (DNFB) (2.75×10^{-5} M) + 10^{-3} M Piperidine						
[DABCO] (moles liter^{-1})	0	0.025	0.05			
k (liter mole^{-1} sec^{-1})	1.05	2.64	4.42			
(d) (DNFB) (2.75×10^{-5} M) + 10^{-3} M Piperidine						
[Pyridine] (moles liter^{-1})	0	0.1	0.2	0.3	0.5	
k (liter mole^{-1} sec^{-1})	1.05	1.24	1.46	1.67	2.13	
(e) (DNFB) (2.75×10^{-5} M) + CH_3OH (0.1 M)						
10^3 [Piperidine] (mole liter^{-1})	0.3	0.5	1.0	1.5	2.0	2.5
k (liter mole^{-1} sec^{-1})	2.82	2.92	3.19	3.42	3.52	3.68
(f) (DNFB) (2.75×10^{-5} M) + CH_3OH (0.15 M)						
10^3 [Piperidine] (mole liter^{-1})	0.5	1.0	1.5	2.0	2.5	
k (liter mole^{-1} sec^{-1})	4.02	4.04	3.92	3.97	3.91	
(g) Dinitrochlorobenzene (2.54×10^{-5} M) + Piperidine (10^{-3} M)						
[Methanol] (mole liter^{-1})	0	0.05	0.1	0.2	0.5	
10^3 k (liter mole^{-1} sec^{-1})	9.31	6.95	6.01	4.39	2.41	

dinitrochlorobenzene in 2-phenylethanol to be easily accelerated by the addition of DMSO). Although dimethylsulfoxide is a much weaker base than pyridine in benzene solution (60), the catalytic effect by this reagent is much greater than that of pyridine (actually, on the order of the effect by DABCO (59)). Therefore, base catalysis cannot be the main reason for the catalytic effect of DMSO. Since the addition of dimethylsulfoxide to the reaction of piperidine with 2,4-dinitrochlorobenzene (which is not found to be appreciably catalyzed by additives) increases the values of the second order rate coefficients as indicated in Table 11, the rate enhancement by this additive was attributed to a medium effect.

Table 11. Second Order Rate Coefficients for the Reaction of Piperidine with 2,4-Dinitrochlorobenzene with the Addition of Dimethylsulfoxide in Benzene at 25°C

DNCB (2.75×10^{-5} M), Piperidine (1×10^{-3} M)					
[DMSO] (moles liter^{-1})	0	0.05	0.10	0.15	0.20
k (liter mole^{-1} sec^{-1})	0.086	0.11	0.134	0.157	0.18

The nature of the medium effect may be a solvation process which can be represented in the following possible transition states:



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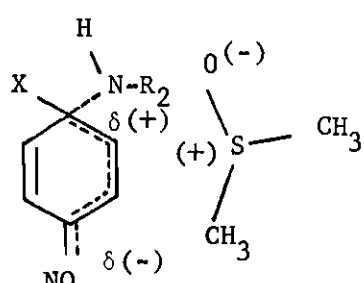


XIV

It has been observed that the second order rate coefficients for the reaction of 2,4-dinitrofluorobenzene with 2-methylpiperidine or 2,6-dimethylpiperidine in benzene increase slightly with increasing amine concentrations. However, the rate constants for the reaction of 2,4-dinitrochlorobenzene with these same amines remained essentially unchanged as indicated in the following table (65,66).

Table 12. Reaction Rates of 2-Methylpiperidine and trans-2,6-Dimethylpiperidine with Fluoro-2,4-dinitrobenzene (FDNB) or Chloro-2,4-dinitrobenzene (CDNB) in Benzene [FDNB] = 0.025 M, [CDNB] = 0.050 M

(a) FDNB, 2-Methylpiperidine (25°C)							
10^2 x [Amine] (moles liter^{-1})	0.209	0.406	0.674	1.30	1.90	3.95	7.77
10^3 x k (mole^{-1} liter sec^{-1})	2.66	2.83	2.76	3.36	3.85	5.52	9.14
(b) FDNB, trans-2,6-dimethylpiperidine (100.4°C)							
[Amine] (moles liter^{-1})	0.0504	0.125	0.252				
10^5 x k (mole^{-1} liter sec^{-1})	18.1	19.0	23.0				
(c) FDNB, trans-2,6-dimethylpiperidine (60.0°C)							
[Amine] (moles liter^{-1})	0.0504	0.184					
10^5 x k (mole^{-1} liter sec^{-1})	4.74	7.15					
(d) CDNB, 2-Methylpiperidine (25°C)							
10 x [Amine] (moles liter^{-1})	1.12	2.01	3.16				
10^4 x k (liter mole^{-1} sec^{-1})	0.643	0.623	0.672				
(e) CDNB, trans-2,6-dimethylpiperidine (100.4°C)							
[Amine] (moles liter^{-1})	0.109	0.650					
10^6 x k (mole^{-1} liter sec^{-1})	40.0	40.7					

Apparently, steric hindrance does not completely restrict the catalytic effect of the amine possessing an acidic hydrogen.

The effect of temperature on amine catalyzed aromatic nucleophilic substitution reactions in non-polar, aprotic solvents is not extensively discussed in the literature although Brieux and co-workers have studied the reaction of piperidine with o-chloronitrobenzene in benzene at two different temperatures (75°C and 100°C) (67). Their results, as shown in Table 13 and Figure 1 indicate a linear catalysis effect at 75° while at the higher temperature of 100°C a curvilinear relationship is demonstrated. These effects were explained by assuming that in the multi-step,

Table 13. k_{obs} Values for the Reaction of o-Chloronitrobenzene with Piperidine in Benzene at 75°C and 100°C

Temp = 75°C			Temp = 100°C		
ArCl (mole liter^{-1})	Piperidine (mole liter^{-1})	k_{obs} x 10^6 (l mole^{-1} sec^{-1})	ArCl (mole liter^{-1})	Piperidine (mole liter^{-1})	k_{obs} x 10^6 (l mole^{-1} sec^{-1})
0.1103	0.2662	26.1	0.0732	0.160	80.9
0.1099	0.9824	27.7	0.0756	0.393	85.0
0.1099	2.0347	31.3	0.0750	0.720	90.3
0.1101	3.0349	34.1	0.0751	1.610	96.0
0.1099	5.8841	40.9	0.0698	2.540	104.1
0.1101	8.9975	48.6	0.0728	4.890	105.0
			0.767	10.000	108.0

addition-elimination mechanism proposed for this reaction $k_{-1} \gg k_2 + k_3$ (B) for the reaction at the lower temperature, but $k_{-1} \approx k_2 + k_3$ (B) at the higher temperature. Therefore, the rate-determining step in the mechanism appears to be temperature dependent.

Caution must be exercised in accepting these results since; (a) the reactions were run at high concentrations of the substrate where the

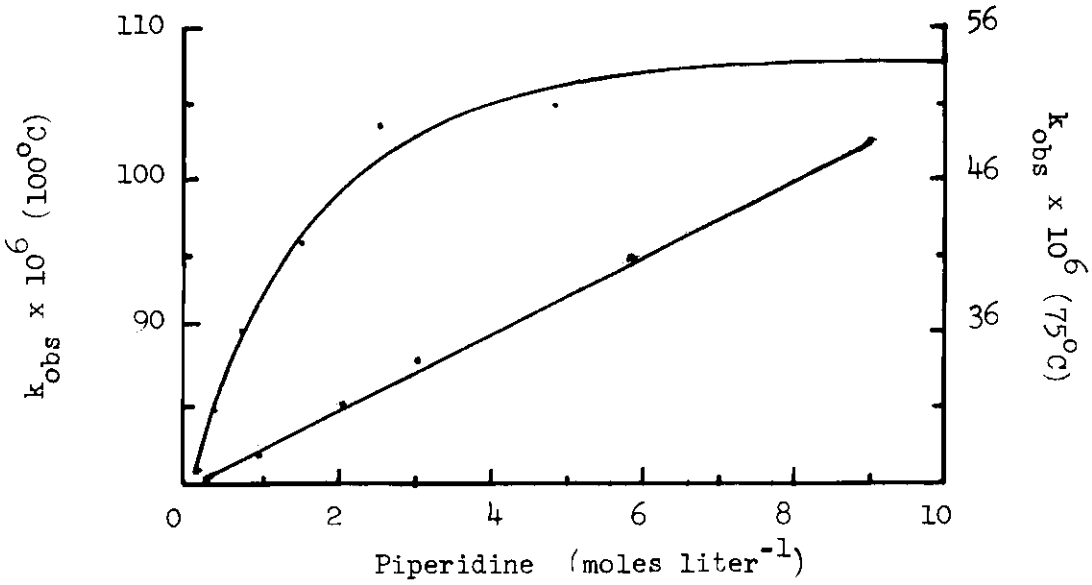


Figure 1 Plots of Table 13 Data

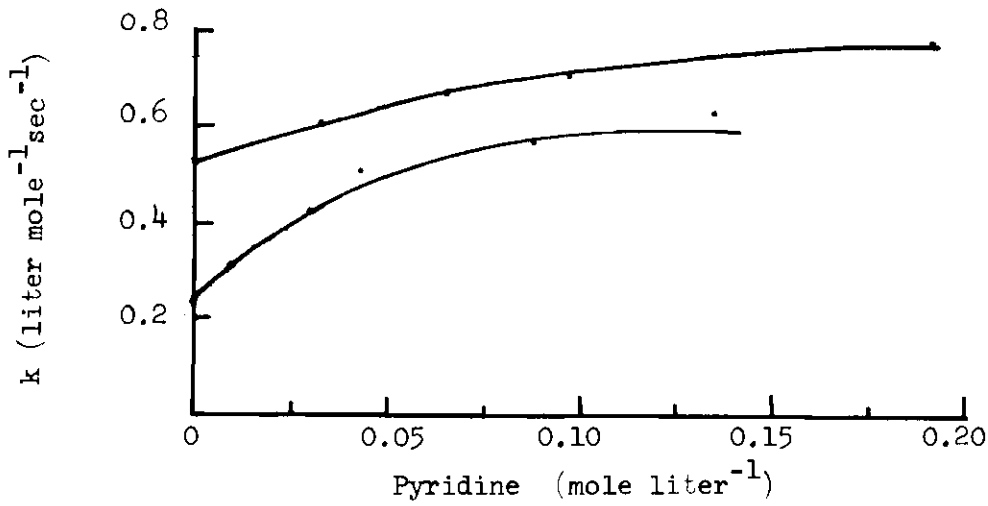
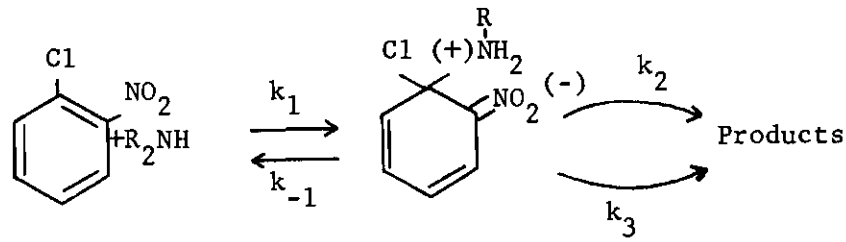


Figure 2 Plots of Table 14 Data (n-Butylamine)



influence of the nitro group has been found to be rate-accelerating (49); (b) the anchimeric assistance by ortho-nitro groups has been shown to be of importance in the removal of an ammonium proton from the intermediate complex; and (c) the concentrations of the piperidine are so high that one might question the nature of the solvent (at these concentrations extensive associations of the components might possibly complicate the interpretation of the data).

Simonetta and co-workers studied the effect of temperature on the reaction of piperidine with 1-chloro-4,7-dinitronaphthalene in benzene (68). Pseudo second order rate constants (k_{obs}) of the reactions with piperidine were found to be linearly related to the amine concentration according to the equation $k_{obs} = k_2 + k_3(pip)$. The catalyzed to uncatalyzed ratios (k_3/k_2) for this reaction were found to be 27 and 17 M^{-1} at 30° and 50°C, respectively. However, Pietra (74) conducted a similar study with these same reagents and reported a value for $k_3/k_2 = 17\ M^{-1}$ at 25°C. The lack of agreement in these independent investigations is indeed confusing.

Other amine nucleophiles reacting with 2,4-dinitrofluorobenzene and 2,4-dinitrochlorobenzene in benzene were found to behave in a fashion similar to that exhibited by piperidine in its reactions with these same

substrates. 1-Butylamine, sec-butylamine and t-butylamine were found to catalyze the reaction of the respective amine with DNFB (69). When the observed second order rate coefficient was plotted against the amine concentrations an increasing linear relationship which curved at high amine concentrations was obtained in all three cases. The reactions of 2,4-dinitrochlorobenzene with these amines in benzene were strictly of first order with respect to the nucleophile. Pyridine was also observed to catalyze the reaction of n-butyl or t-butylamine with 2,4-dinitrofluorobenzene. Furthermore, it was discovered that pyridine was a better catalyst at low than at high n-butylamine concentrations as demonstrated in Table 14 and Figure 2.

Table 14. Effect of Pyridine on the Reactions of 2,4-dinitrofluorobenzene with n-Butyl or t-Butylamine in Benzene at 25 °C

(a) n-Butylamine (0.00438 M)							
10^3 x [Pyridine] M	0	9.01	14.5	29.5	44.1	88.2	133
10k (1 $mole^{-1}$ sec^{-1})	2.09	3.15	3.53	4.29	5.07	5.85	6.33
(b) n-Butylamine (0.0604 M)							
10^3 x [Pyridine] M			0	32.0	64.1	96.0	190
10 k (1 $mole^{-1}$ sec^{-1})			5.35	6.09	6.69	7.10	7.80
(c) t-Butylamine (0.0505 M)							
10^3 x [Pyridine] M	0	0.55	0.92	1.67	2.71	3.61	5.42
10 k (1 $mole^{-1}$ sec^{-1})	2.05	2.70	3.06	3.80	4.40	4.70	5.28

Due to the low nucleophilicity of p-anisidine the reactions of this amine with 2,4-dinitrochlorobenzene and 2,4-dinitrofluorobenzene were

run at higher concentrations of the nucleophile (70). Under these conditions it was observed that the second order rate coefficients in both reactions increased with increasing amine concentration. These results are illustrated in Table 15 and Figures 3 and 4.

Table 15. Rate Data for the Reaction of p-Anisidine with 2,4-Dinitrofluorobenzene and 2,4-Dinitrochlorobenzene in Benzene at 25°C

(a) Dinitrochlorobenzene (2×10^{-3} M)						
p-Anisidine		0.1	0.2	0.4		
10^6 k (1 mole^{-1} sec^{-1})		1.36	1.92	3.10		
(b) Dinitrofluorobenzene						
p-Anisidine	0.05	0.10	0.155	0.20	0.26	0.30
10^5 k (1 mole^{-1} sec^{-1})	2.20	5.70	10.6	19.0	24.7	37.5

From the linear relationship in Figure 3 it is difficult to decide if the weak catalysis is due only to a medium effect or some other catalytic influence. It is obvious from Figure 4 that the reaction is more than second order with respect to p-anisidine. The conclusion by the authors is that p-anisidine has an influence on the reaction rate with 2,4-dinitrofluorobenzene first, as a basic catalyst and second, through a solvation or association effect. Addition of even a small amount of pyridine or diaza [2.2.2.]bicyclooctane (DABCO) to the reaction of p-anisidine with either substrate increases the second order rate coefficient significantly (the DABCO was reported to be "purified" by sublimation).

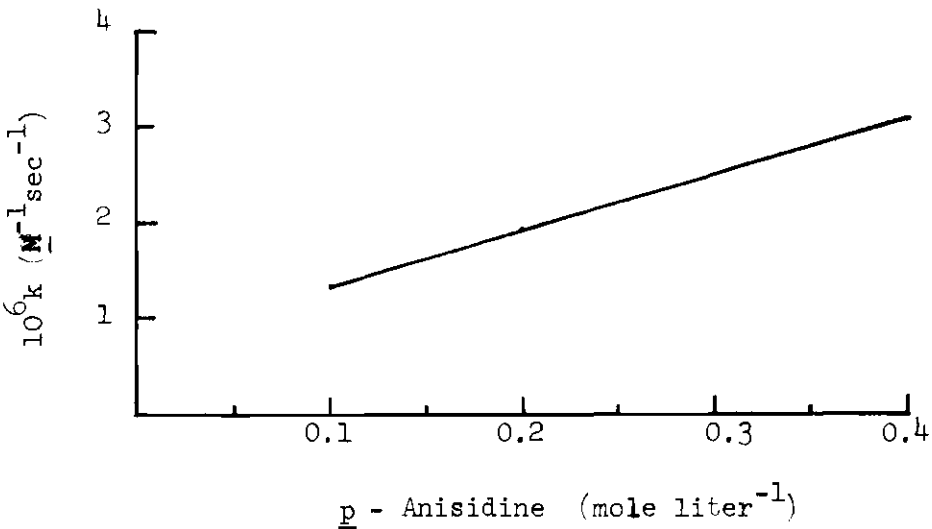


Figure 3 Reaction of p - Anisidine with 2,4-Ditrochlorobenzene in Benzene at 25°C

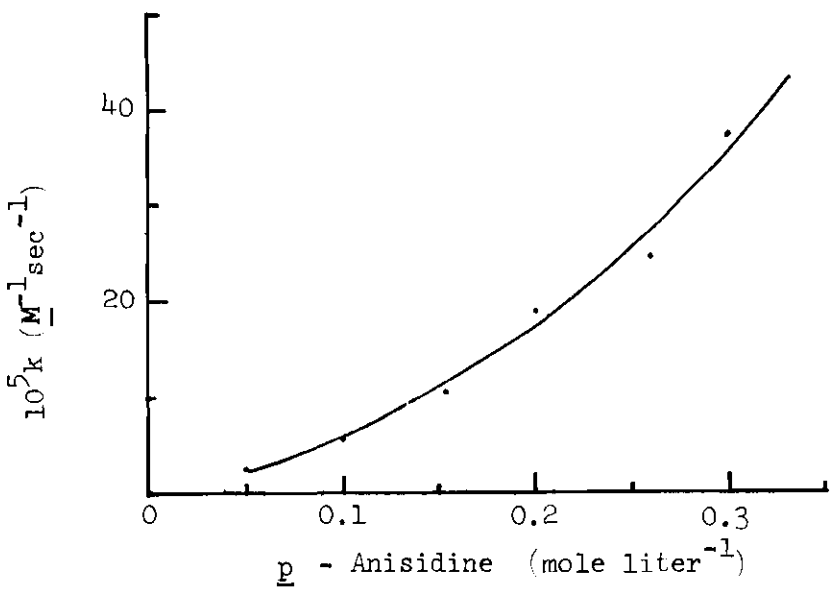


Figure 4 Reaction of p -Anisidine with 2,4-Dinitrofluorobenzene in Benzene at 25°C

Table 16. Rate Data for the Reaction of p-Anisidine with 2,4-Dinitrochlorobenzene and 2,4-Dinitrofluorobenzene in Benzene at 25°C (With Additives)

(a) Dinitrochlorobenzene (2×10^{-3} M), p-Anisidine (0.2 M)					
[Pyridine] (M)	0	0.01	0.03	0.05	
10^6 k (1 mole^{-1} sec^{-1})	1.92	2.24	2.83	3.52	
(b) Dinitrochlorobenzene (4.44×10^{-5} M), p-Anisidine (0.21 M)					
10^2 [DABCO] (M)	0	0.52	2.01	3.10	5.00
10^6 k (1 mole^{-1} sec^{-1})	1.92	2.74	5.20	6.59	10.02
(c) Dinitrofluorobenzene (2×10^{-3} M), p-Anisidine (0.05 M)					
[Pyridine] (M)	0.0	0.005	0.01	0.02	
10^5 k (1 mole^{-1} sec^{-1})	2.20	5.57	9.21	17.2	
(d) Dinitrofluorobenzene (2×10^{-3} M), p-Anisidine (0.2 M)					
[Pyridine] (M)	0.0	0.005	0.01	0.02	
10^5 k (1 mole^{-1} sec^{-1})	19.0	23.1	28.7	38.3	
(e) Dinitrofluorobenzene (3.72×10^{-5} M), p-Anisidine (9.47×10^{-2} M)					
10^2 [DABCO] (M)	0.52	1.03	1.55	2.06	4.09
10^4 k (1 mole^{-1} sec^{-1})	6.10	11.42	17.0	22.1	46.0

From the slope of the plot of the second order rate coefficient against catalyst concentration, the rate coefficient due to the catalysis of the additive is obtained. The plot of the second order rate coefficient in the absence of additives versus amine concentration is the uncatalyzed rate constant. Thus, Bernasconi and Zollinger found the ratio of the rate coefficients for the catalyzed to uncatalyzed steps in the reaction of p-anisidine with dinitrofluorobenzene to be approximately 5500 and 750-975 for the DABCO and pyridine catalysis, respectively (for pyridine a small variation in the slopes was observed in going from 0.05 to 0.2 M p-anisidine). Further, a comparison of these values with those obtained in the reaction of the stronger base piperidine with this substrate is interesting; the quotients in this case are much smaller, k(DABCO)/ $k_{o(uncat)}$ = 64.5 and k(pyridine)/$k_{o(uncat)}$ = 4.3. The authors thus attribute the bulk of the influence by DABCO and pyridine in these p-anisidine-halobenzene reactions to base catalysis and perhaps to a lesser extent, a "medium" effect of some sort. Furthermore, they draw the conclusion that the sensitivity to base catalysis, for which the catalyzed to uncatalyzed ratio is a measure, appears to increase with increasing basicity of the leaving group (F^- being a stronger base than Cl^-) and decreasing basicity of the entering amine.

Base-catalyzed substitution, in which proton transfer takes place in a rate-determining step, should exhibit a rather large hydrogen isotope effect (about 7-9) (71,72). Investigations into the reactions of 2- and 4-nitrochlorobenzenes with piperidine in xylene (73), of 2,4-dinitrochlorobenzene with n-butylamine in chloroform (45) and of 2,4-dinitrofluorobenzene with piperidine in benzene (57) show no change in the reaction rate with the use of N-deuterated amines. In the reactions

of piperidine with certain substituted naphthalenes and nitrobenzenes only small to absent isotope effects were observed as shown in Table 17 (74, 75 and 76).

Table 17. Isotope Effects in the Reaction of Piperidine with Several Substrates in Benzene at 25 °C

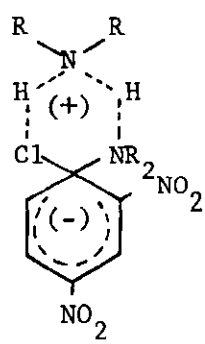
Substrate	k_H/k_D	Reaction Order with Respect to Piperidine
1-Chloro-4,7-dinitronaphthalene	1.02	First
2,4-Dinitrophenyl cyclohexyl ether	1.50	Second
1-Fluoro-4-nitrobenzene	1.05	Second
1-Fluoro-4,7-dinitronaphthalene	1.03	Second
2,4-Dinitrophenyl phenyl ether	1.27	Second

Brieux (77) reported an isotope effect of $k_H/k_D = 2.1$ for the catalyzed step of the reaction of 4-chloro-3-nitrobenzotrifluoride with piperidine in benzene at 35 °C; however, Pietra and co-workers (78) repeated Brieux's experiments and found no deuterium isotope effect in this reaction. Bernasconi and Zollinger (70), likewise, found only small isotope effects in the reaction of p-anisidine with 2,4-dinitrochloro- and 2,4-dinitrofluorobenzene in benzene. The results of their studies are listed in Table 18. Therefore, it seems that large primary isotope effects are not observed in these reactions. Bernasconi and Zollinger interpreted the observation that $k_H/k_D < 1$ in the 2,4-dinitrochlorobenzene reaction with p-anisidine as a secondary effect due to enhanced nucleophilicity of the deuterated amine. This interpretation does not, however, explain the k_H/k_D values in the dinitrofluorobenzene reaction with

Table 18. Isotope Studies in the Reaction of 2,4-Dinitrochlorobenzene (DNCB) and 2,4-Dinitrofluorobenzene (DNFB) with p-Anisidine-N-h or -N-d in Benzene

Substrate	Isotope	Anisidine (moles liter^{-1})	Temp (°C)	k_H/k_D
DNCB	H or D	0.1	60	0.88
DNCB	H or D	0.4	25	0.80
DNFB	H or D	0.05	25	1.06
DNFB	H or D	0.10	25	0.95
DNFB	H or D	0.05	60	1.05

this same amine. Rather, it appears most likely that these are small primary isotope effects evolving from a bifunctionally catalyzed transition state in which proton and leaving group are more or less concerted:



XV

Benzylamine and N-methylbenzylamine were found to catalyze the reaction of 2,4-dinitrofluorobenzene with the respective amine in benzene (79). While the benzylamine catalysis is a curvilinear relationship, that by N-methylbenzylamine is quite linear as evidenced from the following table and graphs.

Table 19. Rate Data for the Reaction of Benzylamine and N-Methylbenzylamine with 2,4-Dinitrofluorobenzene in Benzene at 25°C

(a) Dinitrofluorobenzene (5.20×10^{-5} M)							
[Benzylamine] (moles liter^{-1})	0.001	0.002	0.003	0.005	0.010	0.015	0.020
10^2 k (liter mole^{-1} sec^{-1})	0.83	1.10	1.29	1.70	2.43	3.19	3.64
(b) Dinitrofluorobenzene (5.15×10^{-5} M)							
[Methylbenzylamine] (moles liter^{-1})	0.001	0.002	0.003	0.004	0.005	0.008	0.010	0.015	0.020
10^2 k (liter mole^{-1}sec^{-1})	0.72	0.99	1.23	1.53	1.79	2.67	3.22	4.73	6.14

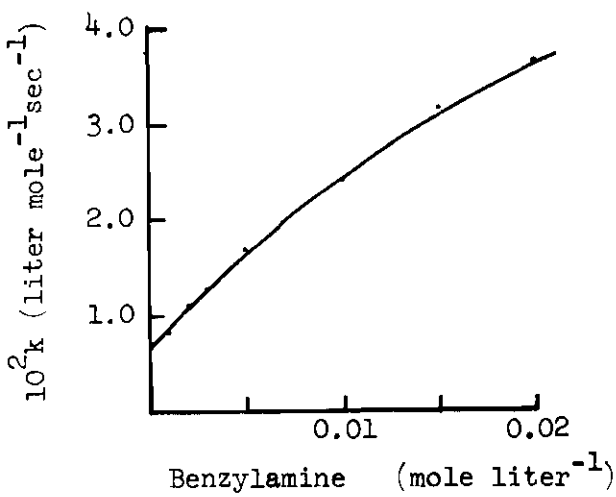


Figure 5 Reaction of Benzylamine with DNFB in Benzene at 25°C

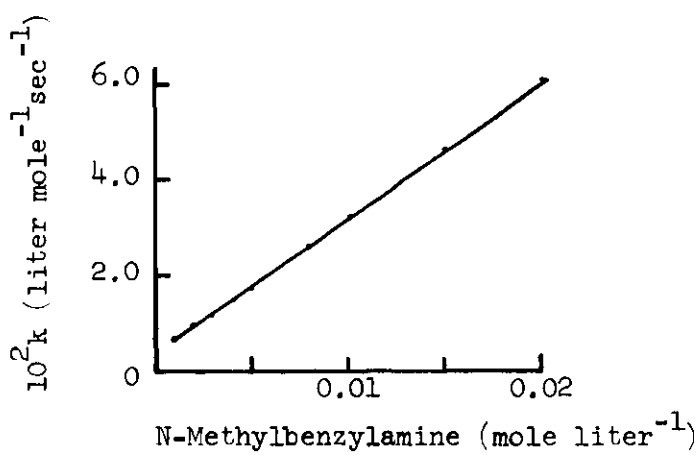


Figure 6 Reaction of N-Methylbenzylamine with DNFB in Benzene at 25°C

Thus, there is an indication that a change in the rate-determining step of the multi-step, addition-elimination mechanism is occurring,[i.e. k_{-1} is approximating $k_2 + k_3$ (B)] for the benzylamine reaction; for the reaction of the N-methylamine it appears that the decomposition of the intermediate complex is still rate determining [i.e. $k_{-1} > k_2 + k_3$ (B)].

The effect of the addition of pyridine and diaza [2.2.2.]bicyclo-octane (DABCO) to these reactions is similar to the catalysis exhibited by the amine in the absence of additives. These results are recorded in Table 20 and Figures 7, 8, 9 and 10 (79).

Table 20. Rate Data for the Reaction of Benzylamine and N-Methylbenzylamine with 2,4-Dinitrofluorobenzene in Benzene at 25°C in the Presence of Additives

(a) Dinitrofluorobenzene (5.20×10^{-5} M), Benzylamine (0.003 M)							
Pyridine (moles liter^{-1})	0.000	0.005	0.010	0.015	0.020	0.025	
10^2 k (liter mole^{-1} sec^{-1})	1.29	2.00	2.68	3.31	3.86	4.40	
(b) Dinitrofluorobenzene (5.20×10^{-5} M), Benzylamine (0.003 M)							
DABCO (moles liter^{-1})	0.000	0.001	0.002	0.003	0.005	0.010	0.015
10^2 k (liter mole^{-1} sec^{-1})	1.29	1.60	1.86	2.03	2.39	3.19	3.85
(c) Dinitrofluorobenzene (5.15×10^{-5} M), N-Methylbenzylamine (0.003 M)							
Pyridine (moles liter^{-1})	0.00	0.05	0.10	0.15	0.20		
10^2 k (liter mole^{-1} sec^{-1})	1.23	1.51	1.87	2.20	2.63		
(d) Dinitrofluorobenzene (5.15×10^{-5} M), N-Methylbenzylamine (0.003 M)							
DABCO (moles liter^{-1})	0.00	0.002	0.005	0.010	0.015	0.020	
10^2 k (liter mole^{-1} sec^{-1})	1.23	2.38	4.20	6.80	9.82	12.60	

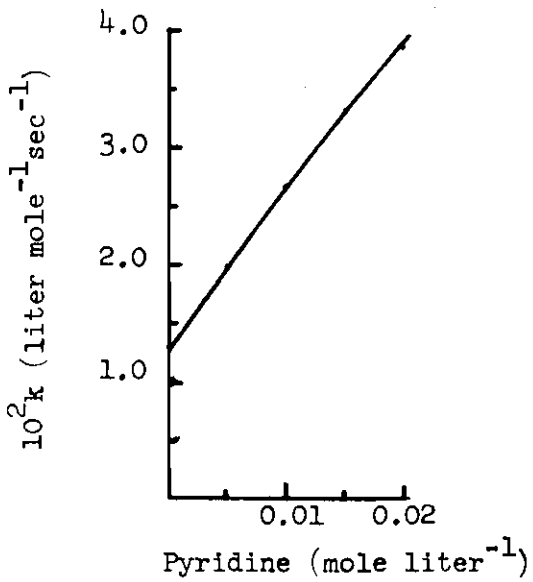


Figure 7 Reaction of Benzylamine with DNFB in Benzene at 25°C (Addition of Pyridine)

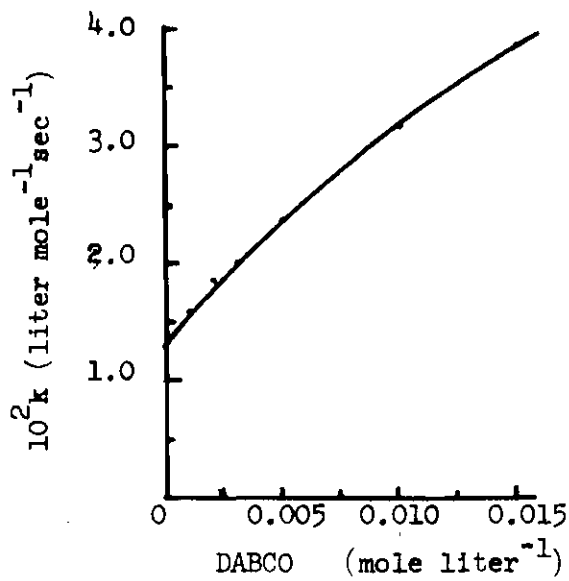


Figure 8 Reaction of Benzylamine with DNFB in Benzene at 25°C (Addition of DABCO)

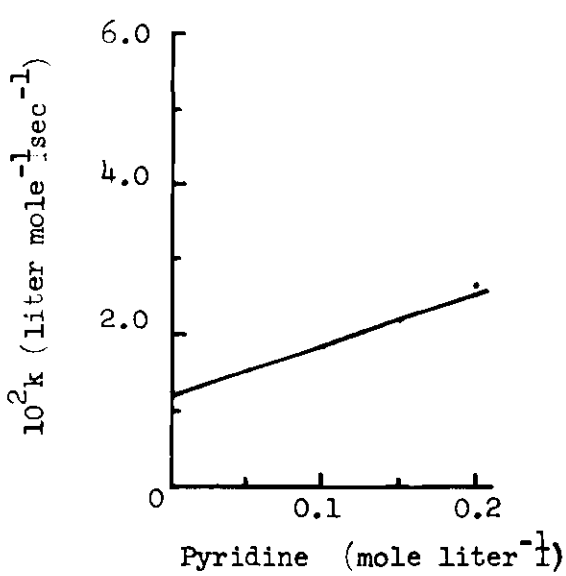


Figure 9 Reaction of N-Methylbenzylamine with DNFB in Benzene at 25°C (Addition of Pyridine)

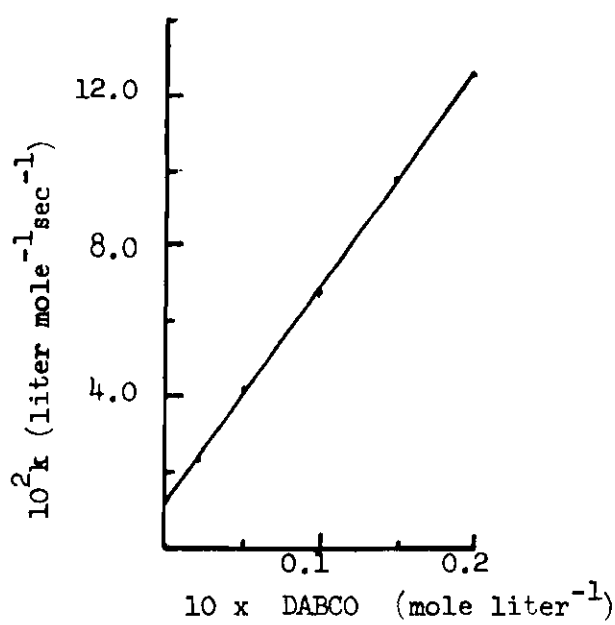


Figure 10 Reaction of N-Methylbenzylamine with DNFB in Benzene at 25°C (Addition of DABCO)

It is difficult to speculate on the unsubstituted benzylamine reactions in the presence or absence of catalysts since the curvature of the plots obscure the values of the catalyzed and uncatalyzed rate coefficients. On the other hand, the N-methylbenzylamine reactions are quite similar to studies conducted on the reactions of other nucleophiles with this substrate (58,59).

The reaction of morpholine with 2,4-dinitrofluorobenzene is rather interesting since it is a weaker base than piperidine and, according to the theory suggested by Bernasconi and Zollinger (80) should be more sensitive to base catalysis. The rate data for the morpholine-DNFB reaction are listed in Table 21 and the plots of this data are illustrated in Figures 11, 12 and 13. Finally, the comparison of the catalytic coefficients of piperidine and morpholine with this substrate are in Table 22.

Table 21. Data for the Reaction of Morpholine with 2,4-Dinitrofluorobenzene in Benzene at 25°C

(a) DNFB (3.72×10^{-5} M), Morpholine								
10^3 Morpholine (moles liter^{-1})	0.98	1.96	2.94	3.92	4.90	7.66	7.85	8.82
10^2 k (liter mole^{-1} sec^{-1})	0.99	1.43	2.12	2.62	3.36	4.32	4.85	5.04
(b) DNFB (3.72×10^{-5} M), Morpholine (2.08×10^{-3} M)								
Pyridine (moles liter^{-1})	0.10	0.201	0.251	0.251	0.301	0.402	0.502	
10^2 k (liter mole^{-1} sec^{-1})	4.36	7.83	9.90	9.89	11.83	16.72	22.10	
(c) DNFB (3.72×10^{-5} M), Morpholine (2.08×10^{-3} M)								
10^2 DABCO (moles liter^{-1})	0.42	1.06	2.12	3.17	3.60	4.23		
10^2 k (liter mole^{-1} sec^{-1})	4.12	6.73	11.67	15.94	19.29	22.20		

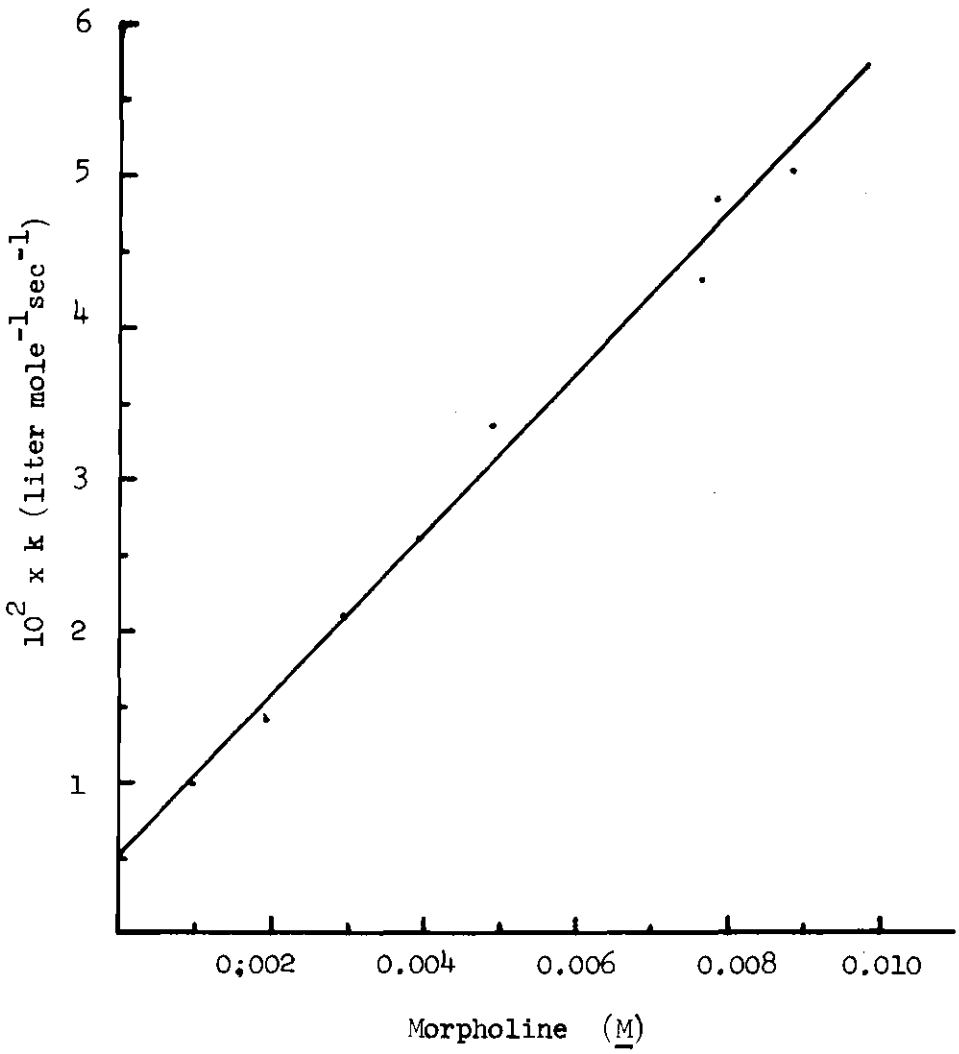


Figure 11 Reaction of Morpholine with 2,4 - Dinitrofluorobenzene in Benzene at 25°C
(No Additives)

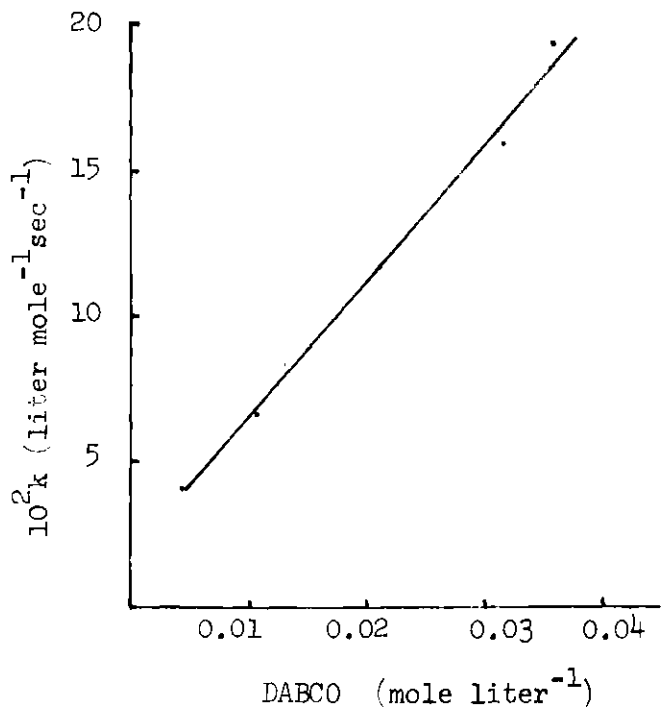


Figure 12 Reaction of Morpholine with 2,4-Dinitrofluorobenzene in Benzene at 25°C (DABCO Added)

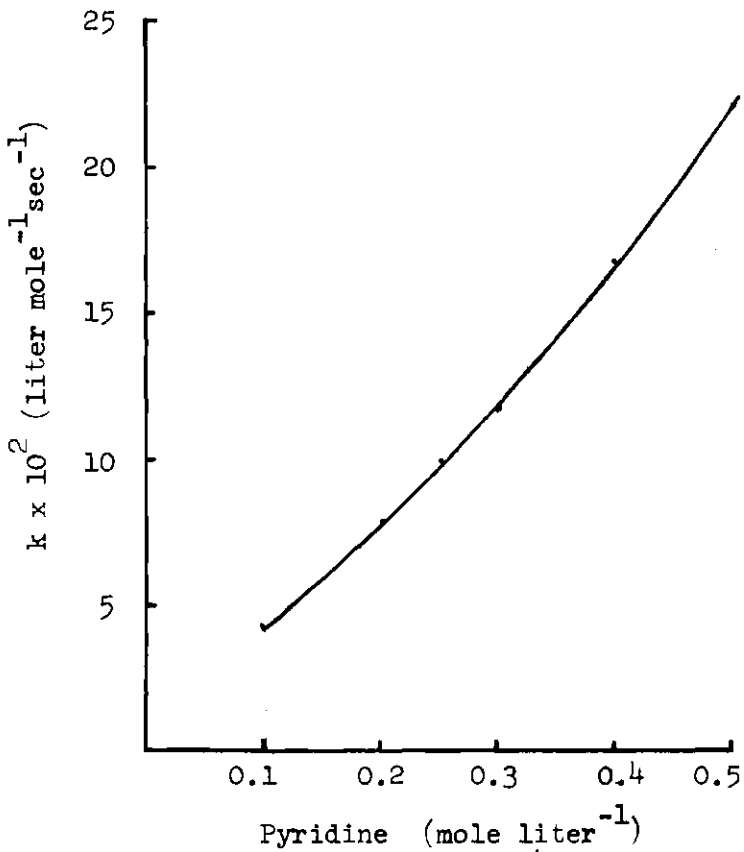


Figure 13 Reaction of Morpholine with 2,4 - Dinitrofluorobenzene in Benzene at 25°C (Pyridine Added)

Table 22. Catalysis Ratios in the Reaction of 2,4-Dinitrofluorobenzene with Piperidine and Morpholine in Benzene

Amine	pK_b	$\frac{k_{3(amine)}}{k_{o(uncat)}}$	$\frac{k_{3(pyridine)}}{k_{o(uncat)}}$	$\frac{k_{3(DABCO)}}{k_{o(uncat)}}$
Piperidine	2.94	1230	4.3	64.5
Morpholine	5.64	982	58	444

Aside from the medium effect apparently exhibited by pyridine (as evident from the abnormal curvature of the plot) the trends in the catalytic coefficients are similar to that shown by piperidine and additives in the reaction of the latter amine with 2,4-dinitrofluorobenzene in benzene. The catalytic ratios in the absence of additives for both piperidine and morpholine are large and of almost the same magnitude. However, in the case of pyridine and especially of DABCO the catalysis appears to be significantly greater for the morpholine reactions. This appears to substantiate the theory that higher catalyzed to uncatalyzed ratios are obtained for the amine with the reduced basicity.

CHAPTER II

EXPERIMENTAL

Chemicals

A.C.S. Spectranalyzed isooctane (Fisher) was used without further purification. A VPC of the liquid using an OV-17 phenyl silicone column showed only one peak; however, the VPC of the vapor showed two peaks which were almost superimposable.

Piperidine (Fisher) was purified by distillation from sodium (14). About 250 ml of piperidine (2.52 moles) and six grams (0.26 g atoms) of sodium metal were placed in a 500 ml round-bottomed flask and refluxed 6-12 hours using a two-foot distilling column which was packed with glass beads and insulated with aluminum foil. Upon distillation the first 30 ml of distillate was discarded and the next 150 ml was collected, b.p. 105°C/740 mm (lit. 105°C/760 mm) and stored in a brown bottle under nitrogen. This piperidine contained approximately one percent pyridine (as determined from VPC).

Piperidine-N-d was prepared according to the method of Hawthorne (73). A mixture of 102 g of piperidine (1.2 moles), 30 ml (1.5 moles) of 99.8 percent deuterium oxide and 3 ml of deuterated phosphoric acid (prepared by making a syrup of phosphorous pentoxide and deuterium oxide) was refluxed overnight. The solution was then added dropwise to a 1 liter flask equipped with a reflux condenser and containing three grams (0.13 g atoms) of sodium metal in 300 ml of ether. The contents of the flask were cooled with an ice bath while stirring was maintained with a

magnetic stirrer. The addition required several hours. The piperidine-ether solution was then distilled until most of the ether was removed. The remainder of the mixture was distilled under reduced pressure (b. p. 40°C/4 mm) into a trap cooled with dry ice. To this solution was added two grams of sodium metal and the mixture was distilled again. A forerun of seven milliliters was discarded and 71 grams (70%) of the fraction boiling between 104-106° (740 mm) was collected (lit. b. p. 106.3°C/760 mm) (73). An n.m.r. spectrum of the product showed that a small amount of piperidine-N-h was present. The entire process was repeated with the deuterated piperidine. No piperidine-N-h peak was observed in the final product (n.m.r.).

The compounds in Table 23 were refluxed over sodium for 3-5 hours and then distilled (14). The procedure followed was the same as that described for the purification of piperidine-N-h.

Table 23. Physical Data on the Purification of the Catalysts

Compound	Boiling point (exp) (°C)	Boiling point (lit.) (°C)	Source
Pyridine	114-115° @ 740 mm	115.3° @ 760 mm(81)	Fisher
Triethylamine	87-89° @ 740 mm	89.5° @ 760 mm(81)	Fisher
1-Aminobutane	76-78° @ 735 mm	77.8° @ 760 mm(81)	Fisher
1,2-Ethanediamine	115-116° @ 745 mm	116.1° @ 760 mm(81)	Fisher
*2,6-Dimethylpiperidine	124-126° @ 740 mm	127-128°@768 mm(81)	Aldrich
2-Methyl-2-propanol	81-82° @ 740 mm	82.8° @ 760 mm(81)	Fisher
1-Butanol	116-118° @ 740 mm	117.7° @ 760 mm(81)	Fisher

*A mixture of cis and trans isomers

Methanol (Fisher) was purified by distillation from magnseium metal. About 400 ml (10 moles) of methanol was placed in a 1 liter round-bottomed flask containing three grams (0.125 g atoms) of magnesium metal and a crystal of iodine. The flask was then attached to a reflux condenserequipped with a drying tube filled with calcium chloride, and the mixture was warmed with a heat gun until the reaction was initiated. After refluxing over the magnesium metal for three hours the methanol was distilled into a 500 ml round-bottomed flask. The first 30 ml of distillate was discarded and the fraction boiling at 63.5-64°C/740 mm was collected (lit. b. p. 64.6°C/760 mm (81).

Methanol-O-d was previously prepared by Dr. C. L. Liotta and shown to be of high deuterium content by n.m.r.

Tetrahydrofuran (Fisher) was purified by distillation from lithium aluminum hydride. About 500 ml (6.17 moles) of tetrahydrofuran was placed in a 1 liter flask containing five grams (0.132 mole) of lithium aluminum hydride. The contents of the flask were refluxed for three hours and then distilled. The fraction boiling at 64-65°C/740 mm (lit. b. p. 64-66°C/760 mm) (81) was collected.

Purification of tetrahydropyran (Aldrich) was accomplished by distillation from sodium hydroxide. About 200 ml (1.99 moles) of tetrahydropyran was dried in a 500 ml round-bottomed flask over sodium hydroxide for 12 hours at room temperature. The flask was then attached to a spinning band column of the Nester Faust apparatus and distilled. The third fraction boiling at 80-81°C/740 mm (lit. b. p. 81-2°C/760 mm) (81) was collected.

A.C.S. Spectranalyzed acetone (Fisher) was dried over potassium

carbonate and distilled, b. p. 55-56°C/740 mm (lit. b. p. 56.5°C/760 mm) (81).

2-Azacyclononanone (Aldrich) was sublimed at room temperature under 2 mm pressure, m. p. 77-78°C (lit. m. p. 77-79°C) (82).

Benzyl alcohol (Fisher) was distilled using Bantam Ware apparatus. The fraction boiling at 203-205°C/740 mm (lit. b. p. 205.2°C) (81) was collected. m-Chlorobenzyl alcohol (Aldrich) was also distilled using the Bantam Ware apparatus. The fraction boiling at 105°C/0.7 mm (lit. b. p. = 85°C/0.5 mm) (83) was collected.

p-Chlorobenzyl alcohol (Aldrich) was recrystallized from isooctane, m. p. 73-74°C (lit. m. p. 75°C) (81). p-Methylbenzyl alcohol (Aldrich) was also recrystallized from isooctane, m. p. 60-61°C (lit. m. p. 61-62°C) (81).

6-Chloro-9-ethylpurine was prepared in the manner described by Montgomery and Temple (84). The 6-chloropurine (Nutritional Biochemicals Corp.) was used without further purification. Dimethylsulfoxide (Fisher) was dried by refluxing over calcium hydride for three hours and then distilling (b. p. 52-54°C/15 mm). Ethyl iodide (Fisher) and anhydrous potassium carbonate (Fisher) were used without further purification. Two grams (0.013 mole) of 6-chloropurine, 130 ml (1.83 moles) of dimethylsulfoxide, 1.88 g (0.0136 mole) of potassium carbonate and 4.05 g (0.026 mole) were placed in a 200 ml Erlenmeyer flask at room temperature. The flask was stoppered and the contents stirred for three hours using a magnetic stirrer. After this time period the solution was diluted with 130 g of ice and extracted with two 100 ml portions of benzene and two 100 ml portions of ether. The extracts were each extracted

with two 50 ml portions of distilled water, then dried over anhydrous magnesium sulfate. Finally the ether and benzene were removed using the rotary flash evaporator. The yellow solid material which remained in each flask were combined and chromatographed. The 50 ml burette was made up with benzene (dried over sodium metal) and silica gel (70-325 mesh ASTM E. Merck Ag. Dormstadt, Germany). The yellow solid was put on the column with benzene and 20 ml aliquots of benzene were used until the yellow color was eluted from the column. Then 100 ml of ether (dried over sodium metal) was added to 100 ml of benzene and 15 ml aliquots of this solution were used to dissolve the product on the column. About 200 mg (10%) of the white, crystalline 6-chloro-9-ethylpurine was collected and recrystallized from isooctane, m. p. 81-82°C (lit. m. p. 81-84°C).

Instrumentation

Ultraviolet Spectrophotometer

The UV spectra and kinetic measurements were run on a Cary Model 14 Recording Spectrophotometer equipped with a Lauda Thermostated Constant Temperature Unit (range 0 to 100°C). The temperature of the reactions was measured with an NBS calibrated 100°C thermometer inserted into the sample compartment of the instrument. The cuvettes used were 1.0 cm Beckman standard silica cells.

Melting Point Apparatus

A Mel-temp unit was used to obtain melting points. Fisher capillary tubes were used. The values are uncorrected.

Nuclear Magnetic Resonance Spectrometer

The n.m.r. data were obtained on a Varian A-60 D with the RF field

at 0.01 or less.

Constant Temperature Baths

Solutions were prepared and slow reactions were studied using a thick-walled pyrex glass bath obtained from Fisher Scientific Co. A Sargent thermonitor unit (Model nl. NSI-12) was used along with an NBS calibrated 100° thermometer. For the vapor-pressure studies a Precision Scientific Water Bath Model 161 was employed. A mercury thermoregulator capable of an accuracy of $\pm$ 0.03°C was used along with the NBS calibrated 100° thermometer.

Weighing Balances

Reaction samples were weighed out on a Mettler Type H15 balance and micro samples on a Mettler Type B 6 balance.

Mass Spectrometer

All mass spectra were obtained on a Varian M 66 instrument.

Gas-Liquid Chromatography Instruments

The vapor pressure studies were determined on a Varian Model 204-C instrument with a flame ionization detector and a Model 20 Varian Recorder. An OV-17 phenyl silicone column was used in the vapor pressure studies.

Wang 700 A/B Electronic Calculator

The slopes used in calculating the pseudo or second order rate constants were determined using the standard linear regression program of the Wang 700 A/B Electronic Calculator.

Identification of 6-Chloro-9-ethylpurine and the 1-Aminobutane Addition Product

In addition to the agreement of the experimental with the literature

melting point for 6-chloro-9-ethylpurine (see p.42), other data was used to characterize this compound. A mass spectrum of the compound gave a parent ion peak of 182 mass units which agrees with the molecular weight of 6-chloro-9-ethylpurine. The UV spectrum for this chloropurine in water was found to be similar to that reported in the literature, λmax 264 mμ ϵ8500 (lit.λ max 266 mμ ϵ9400) (84).

Finally, 1-aminobutane was reacted with the prepared chloropurine in isooctane. A solution prepared by mixing 5 ml of 1.0×10^{-4} M 6-chloro-9-ethylpurine with 5 ml of 0.4 M 1-aminobutane (solvent-isooctane) was allowed to stand at room temperature for several days. Periodic checks on the amount of product formation were made on the solution using UV spectroscopy to determine the extent of reaction. After four days the spectrum of the reaction mixture (6-n-butylamino-9-ethylpurine) remained unchanged (λmax 269 mμ, ϵ17,440). To determine the spectral value of λmax and ϵ in aqueous solution the reaction mixture was placed in a 1.0 cm cuvette and the solution was evaporated to dryness using dry nitrogen (care was taken to avoid blowing the product out of the cuvette). Water was then added to the same level as the original solution. The UV spectrum of this aqueous solution of 6-n-butylamino-9-ethylpurine was thus obtained, λmax 269 mμ, ϵ18000 (lit. λmax 269 mμ ϵ 17500) (85).

Kinetic Procedures

The following procedure was used for the preparation of the piperidine solutions. The stock solution was made up in a 50 ml volumetric flask. The flask was weighed and then piperidine was weighed into the flask. Approximately 40 ml of isooctane was added and the contents of

the flask were equilibrated in the water bath at 25°C for 15 minutes. After this time period the flask was filled to the mark with isooctane also at 25°. Using 10 ml volumetric flasks and 5 ml pipettes the piperidine stock solution was used to prepare all concentrations of piperidine solutions by a series of dilutions with isooctane at 25°C.

The purine stock solution was prepared by first weighing a 10 ml volumetric flask on the micro balance. Then, 36.46 mg of 6-chloro-9-ethylpurine was weighed into the flask. Approximately 9 ml of isooctane was added to dissolve the purine and the contents of the flask were poured into a 100 ml volumetric flask. The 10 ml flask was washed five times with 10 ml portions of isooctane and the washings were combined with the contents of the 100 ml volumetric flask. The contents of this flask were then equilibrated in the water bath for 15 minutes at 25°C followed by addition of isooctane at 25° to the mark on the flask. The concentration of this 6-chloro-9-ethylpurine solution was 1.998×10^{-3} moles liter^{-1}. Five milliliters of the purine stock solution was added to another 100 ml volumetric flask and the contents were diluted to the mark on the flask with isooctane at 25°C. The final concentration of this purine reaction solution was 9.990×10^{-5} moles liter^{-1}.

The solutions containing the catalysts (except for 2-azacyclononanone, 1,2-ethanediamine and the benzyl alcohols) were prepared in the same manner as that described for the preparation of the piperidine solutions using isooctane as the solvent. The appropriate ratios of catalyst and piperidine solutions were mixed in order to give the desired concentration of piperidine and catalyst prior to reaction with the purine.

The solutions of 2-azacyclononanone, 1,2-ethanediamine and the benzyl alcohols had to be prepared in a slightly different manner due to their low solubilities in isooctane. A 10 ml volumetric flask was weighed, and the catalyst and piperidine were then weighed into the flask. Finally, the contents were diluted to the mark on the flask with isooctane at 25°C. Serial dilutions were not used in preparing these solutions; therefore, a different weight of catalyst was introduced into a 10 ml flask for each concentration desired.

All reaction rates were followed by means of UV spectroscopy. A sample solution was run to determine the maximum wavelength absorption and the extinction coefficient of the piperidine-purine product. Five milliliters of 0.4 M piperidine solution and 5 ml of 6-chloro-9-ethylpurine (9.990×10^{-5} M) solution were mixed at room temperature and allowed to react for 12 hours. Periodic checks on the amount of product formation were determined by the examination of UV spectra. After this period of time it was assumed reaction was complete since the spectrum had remained unchanged for several hours. Based on the concentration of starting purine, the UV spectral characteristics of the product could be determined using Lambert's and Beer's Laws (86), $\epsilon = A/cl$, where ϵ is the molar extinction coefficient, c is the molar concentration and l is the path length in centimeters. The absorbance (A) was obtained directly from the spectrum (0.978 absorbance units), the path length was 1 cm. and the concentration of the product was 4.998×10^{-5} moles l^{-1}. The values obtained for the product (6-piperidino-9-ethylpurine) were λ max 283.5 mμ and ϵ 19,579.

Since the piperidine always contained a very small amount of

pyridine (about one percent) it was necessary to balance the solution in the sample compartment with the same concentration of piperidine in the reference compartment. The solvent used was always isooctane. For solutions containing catalysts, an equal concentration of catalyst was maintained in the reference and sample cuvettes. All catalysts were mixed at the reaction temperature with the substrate in the highest concentration range to be studied. These solutions were permitted to remain for the longest reaction time which would be observed. It was found that none of the catalysts reacted with the 6-chloro-9-ethylpurine under these conditions.

The spectrum of 6-piperidino-9-ethylpurine was checked after each kinetic run and the absorbance was found never to deviate more than two percent from the predicted value based on the concentration of the starting purine. Some evaporation of the purine solution did occur over the 1.5 years that the solution was used (about a five percent change in concentration over this period of time). However, the concentration of starting purine was verified by UV before each kinetic run.

The following procedure was employed for all the kinetic runs except those at high piperidine concentrations (greater than 0.3 M). The 10 ml volumetric flask containing the piperidine (or piperidine-catalyst) solutions, the 100 ml flask containing the 9.990×10^{-5} M purine reaction solution and an empty 10 ml volumetric flask were placed in the sample compartment of the Cary 14 Spectrophotometer. The compartment temperature was regulated by adjustment of the Lauda Thermostated Constant Temperature Unit. The solutions were permitted to remain in the compartment for at least thirty minutes in order for them to equilibrate

with the compartment temperature. The solutions were quickly removed and using pipettes, 5 ml of each solution was transferred to the empty flask. The flask was shaken vigorously for approximately three seconds and the sample cuvette which had also been equibrating in the sample compartment was filled with this reaction solution. After replacement of the cuvette in the sample compartment, the compartment lid was replaced and the master switch was thrown; adjustment of the baseline was quickly made to the desired setting. This entire process required no more than 30 seconds. Reproduction of the kinetic results was excellent (see p. 67 ff).

The reactions of piperidine solutions at greater than 0.3 moles liter^{-1} were studied in a slightly different manner since even the short period of time required in the above process using pipettes was found to be too slow compared to the rate of reaction. Therefore, the following method was adopted for these reactions. Three 10 ml flasks, one empty and two containing the purine and piperidine solutions, respectively, were placed in the sample compartment of the instrument. A 2.5 ml gas syringe with a Chaney adaptor was adjusted to deliver 1.7 ml of solution (this would half-fill the cuvette) and placed in the sample compartment with the flasks. After equilibration for at least 20 minutes (the reactions run at 50° were equilibrated for about 30 minutes) and without removing the cuvette from the cell holder, the gas syringe was used to inject the 1.7 ml purine sample into the sample cuvette. The cuvette was then tightly stoppered and the compartment lid replaced. The syringe was washed with isooctane and dried with dry nitrogen gas; then, it was returned to the sample compartment. After 15-20 minutes 1.7 ml of the piperidine solution

was drawn into the gas syringe and the sample was quickly injected into the purine solution in the cuvette. The force of the injection proved to be sufficient to cause complete mixing of the solutions. The cover was quickly replaced, the master switch was thrown, and the baseline was adjusted. The mixing of the solutions and adjustment of the instrument required less than ten seconds to perform. This procedure was found to be adequate to study reactions with half-lives as short as 15 seconds. The results obtained by the pipette method were able to be reproduced by the gas syringe method for the lower concentrations of piperidine (see data).

The kinetic studies were followed by observing the rate of formation of the purine product (6-piperidino - 9-ethylpurine) in the UV spectrum. The UV spectrum of this compound in isooctane contained three principle absorptions at 274.0 mμ, 283.5 mμ and 294 mμ; however, the maximum wavelength absorption was at 283.5 mμ (ϵ19,579). This was the wavelength setting used for most of the kinetic runs. Moreover, it was observed that the spectra of the starting purine and product overlapped about 3 percent in this region. Thus it was necessary to determine if this extent of overlap altered the results of the kinetic studies. The absorption of 294 mμ, although only about 0.65 as intense as the absorption at 283.5 mμ, did not overlap with the spectrum of the starting purine. Therefore, the kinetics of the reaction of 6-chloro-9-ethylpurine with piperidine was studied at the two different wavelength settings 283.5 mμ and 294.0 mμ. The results in the following table clearly indicate that the extent of overlap in this particular case does not alter the kinetics of the reaction significantly.

Table 24. Kinetic Studies of Purine and Piperidine at Two Different Wavelengths

Wavelength (mμ)	Concentration of Piperidine (moles liter^{-1})	Concentration of 6-Chloro-9-ethyl-purine (moles liter^{-1})	k_{pseudo}	$\frac{k_{pseudo}}{[Pip]} = k_{obs}$
283.5	0.3762	5×10^{-5}	0.1113 min^{-1}	0.00495 M^{-1} sec^{-1}
294.0	0.3762	5×10^{-5}	0.1089 min^{-1}	0.00484 M^{-1} sec^{-1}

All kinetic studies were run under pseudo first order conditions except for the experiment in which the reaction order was determined (see p. 54). The nucleophile (piperidine) was always at least 500 times in excess of the purine (molar concentrations). It was necessary to prove that the reaction order was genuinely pseudo first order under these conditions. Therefore, the reaction of piperidine with 6-chloro-9-ethylpurine was run at two different concentrations of purine. The results of these reactions are illustrated in Table 25. From these results it is obvious that true pseudo kinetics are being observed.

Table 25. Kinetics of the Reaction of Piperidine and 6-Chloro-9-ethyl-purine at Different Purine Concentrations

Concentration of Piperdine (moles liter^{-1})	Concentration of Purine (moles liter^{-1})	k_{pseudo}	$k_{pseudo}/[Pip] = k_{obs}$
0.3762	5×10^{-5}	0.1113	0.00495
0.3762	2.5×10^{-5}	0.1103	0.00490

The kinetic data was treated using the Guggenheim method (87) which permits the determination of the rate constant without knowing the absorbance at "infinite time". Readings were taken at times t_1, t_2, t_3, etc., and at times $t_1 + \Delta$, $t_2 + \Delta$, $t_3 + \Delta$, etc., where Δ is a constant increment of time equal to at least two half-lives. Then, $\ln(A_{t+\Delta} - A_t) = kt + \text{constant}$, where $A_{t+\Delta}$ is the absorbance at $(t + \Delta)$ and A_t is the absorbance at initial time (t). A plot of $\log (A_{t+\Delta} - A_t)$ against time gives a straight line of slope $\frac{-k}{2.303}$. Since the piperidine is at least 500-fold in excess over the purine the k which is obtained from the Guggenheim plot is k_{pseudo}. This rate constant, k_{pseudo}, is then divided by the piperidine concentration to obtain the second order rate constant. The following sample calculation demonstrates this procedure. The plot of $\log (A_{t+\Delta} - A_t)$ versus time is illustrated in Figure 14.

Table 26. The Reaction of Piperidine (0.2916 M) with 6-Chloro-9-ethylpurine (5×10^{-5} M) at 29.75 ± 0.25 C: Calculation of log $(A_{t+\Delta} - A_t)$ and the Second Order Rate Constant (Δ = 20 minutes)(two half-lives)

Time (min)(t)	A_t	$t + \Delta$	$A_{t+\Delta}$	$\log (A_{t+\Delta} - A_t)$
4	0.206	24	0.700	-0.2958
8	0.362	28	0.738	-0.4248
12	0.483	32	0.767	-0.5452
16	0.578	36	0.789	-0.6757
20	0.649	40	0.803	-0.8125
24	0.700	44	0.816	-0.9318
28	0.738	48	0.824	-1.0655
32	0.767	52	0.832	-1.1871

Slope = 3.196×10^{-2}; $k_{pseudo} = 3.196 \times 10^{-2} \times 2.303 = 7.361 \times 10^{-2}$ min^{-1}

$k_{obs} = k_{pseudo/\ piperidine} = 7.361 \times 10^{-2}$ min^{-1}/0.2916 mole liter^{-1}
$= 0.2524$ M^{-1} min^{-1}; $k_{obs} = 4.22 \times 10^{-3}$ M^{-1} sec^{-1} (after density correction)

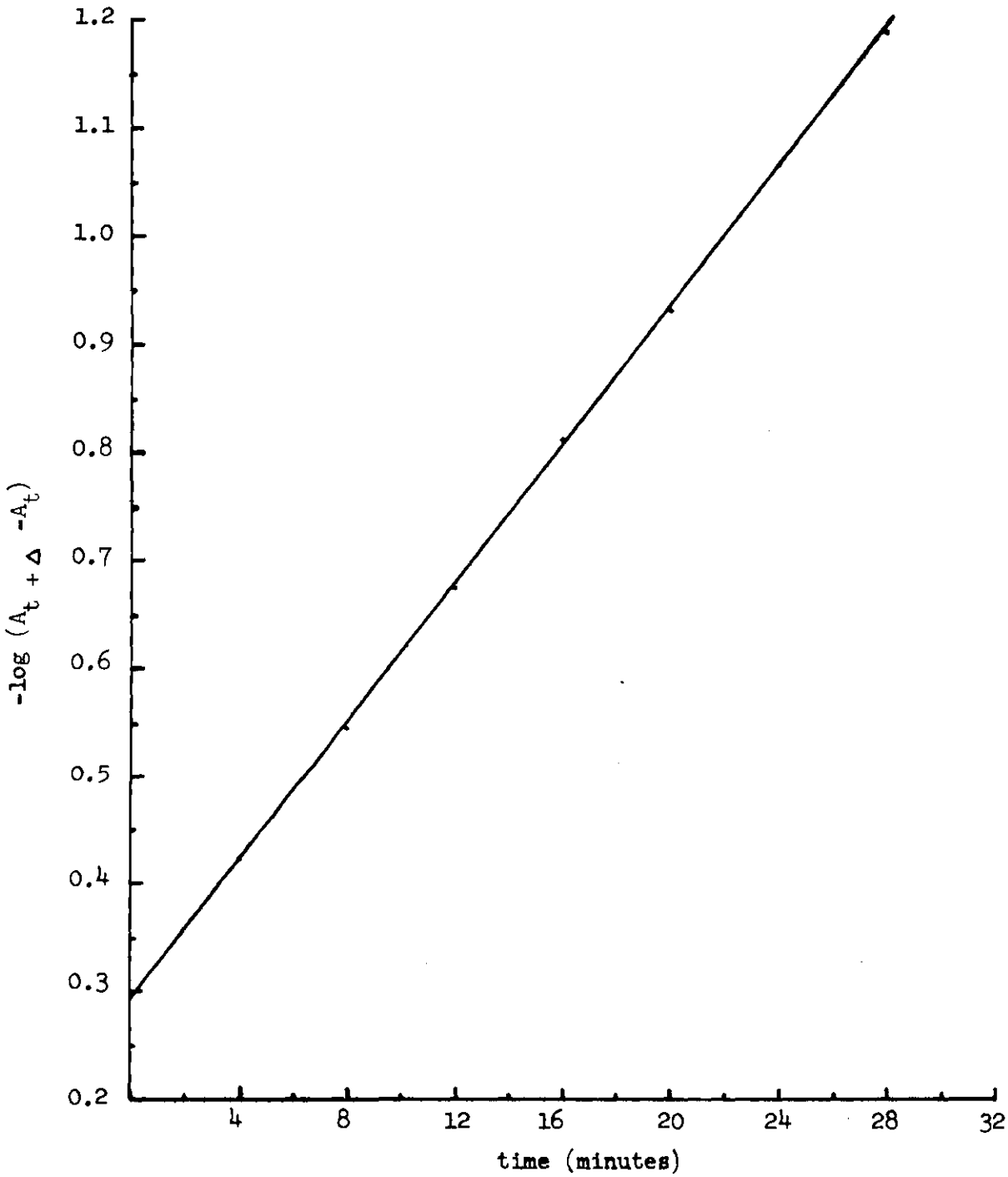


Figure 14 Reaction of Piperidine (0.2916M) with 6-Chloro-9-ethylpurine in Isooctane at 29.75 ± 0.25° C: Calculation of k pseudo

The pseudo first order rate constant was determined for several reactions by a second method. The absorbance at "infinite time" (A_∞) and various intermediate time intervals (A_t) was obtained. Then, the plot of log ($A_\infty - A_t$) against time is linear with a slope of $\frac{-k}{2.303}$ (87). The "infinite time" was obtained by running the reaction until the extinction coefficient of the product remained unchanged. Thus, the reaction was assumed to go to 100 percent completion. This appears to be a valid assumption since the pseudo constants calculated by this method agree very well with those obtained by the Guggenheim method. Several of these constants calculated by both methods are in Table 27. The reactions run under pseudo first order conditions were followed to 70-90 percent completion.

Table 27. Comparison of Data Calculated Using the Guggenheim and "Infinite Time" Methods [6-Chloro-9-ethylpurine] = 5×10^{-5} M

Reaction Temperature (°C)	Piperidine (moles liter^{-1})	k_{obs} (M^{-1} sec^{-1})	Method
4.75 ± 0.25	0.3010	1.84×10^{-3}	Guggenheim
4.75 ± 0.25	0.3010	1.89×10^{-3}	Infinite Time
29.75 ± 0.25	0.2916	4.22×10^{-3}	Guggenheim
29.75 ± 0.25	0.2916	4.25×10^{-3}	Infinite Time
49.5 ± 0.3	0.2657	7.46×10^{-3}	Guggenheim
49.5 ± 0.3	0.2657	7.30×10^{-3}	Infinite Time

In order to establish the order of the reaction of piperidine with

6-chloro-9-ethylpurine in isooctane the following experiment was devised. Five milliliters of a 1.104×10^{-4} M 6-chloro-9-ethylpurine solution was mixed in a 10-ml volumetric flask with 5 ml of a 3.488×10^{-4} M piperidine solution at 29.75 ± 0.25 °C. A 1000 minute Precision Scientific timer graduated in hundredths of a minute was used to record the reaction time. The cuvettes were standard silica with teflon stopcocks. The wavelength setting was 283.5 mμ, and the baseline was balanced before each reading with isooctane in the sample and reference compartments of the Cary 14 Recording Spectrophotometer. Readings were taken at various time intervals and the reaction was followed to approximately 20 percent completion. The concentration of purine starting material and piperidine can be obtained at time intervals from the absorbance of the purine product. Therefore, ϵ pdt = 19,579 = A/cl (Beer-Lambert's Law), A is the absorbance, l is the pathlength (1.0 cm) and c is the concentration of the purine product. The kinetic expression which is used to calculate the second order rate constant for a reaction of this type is the following (88):

$$kt = \frac{1}{2A_o - B_o} \ln \frac{B_o (A_o - x)}{A_o (B_o - 2_x} = \frac{2.303}{2A_o - B_o} \log \frac{B_o (A_o - x)}{A_o (B_o - 2_x)}$$

A_o and B_o are the initial purine and piperidine concentrations, respectively, and x (c in the Beer-Lambert equation) is the concentration of purine product formed. Since the stoichiometry of this reaction is: $A + 2B \rightarrow C + D$, the concentration of 6-chloro-9-ethylpurine at time (t) is $(A_o - x)$ and the concentration of piperidine at time (t) is $(B_o - 2x)$. Thus, if the log $(A_o - x/B_o - 2x)$ is plotted against time, the slope is $\frac{k}{2.303}(2A_o - B_o)$. The data for this reaction is given in Table 28, and the plot of log $(A_o - x/B_o - 2x)$ versus time is in Figure 15.

Table 28. Determination of the Second Order Rate Constant for the Reaction of Piperidine with 6-Chloro-9-ethylpurine in Isooctane at 29.75°C

Time (minutes)	Absorbance	Concentration of Product (M) (Absorbance) / 19579	Concentration of Purine (M) $(A_o - x)$	Concentration of Piperidine $(B_o - 2x)$	Log $\frac{A_o - x}{B_o - 2x}$
54	0.024	1.23×10^{-6}	5.394×10^{-5}	1.719×10^{-4}	-0.5034
170	0.040	2.04×10^{-6}	5.313×10^{-5}	1.703×10^{-4}	-0.5058
348	0.050	2.55×10^{-6}	5.262×10^{-5}	1.693×10^{-4}	-0.5074
953	0.068	3.47×10^{-6}	5.170×10^{-5}	1.674×10^{-4}	-0.5103
1667	0.080	4.09×10^{-6}	5.108×10^{-5}	1.662×10^{-4}	-0.5124
2437	0.088	4.50×10^{-6}	5.068×10^{-5}	1.654×10^{-4}	-0.5136
3856	0.097	4.95×10^{-6}	5.022×10^{-5}	1.645×10^{-4}	-0.5152
6723	0.112	5.72×10^{-6}	4.945×10^{-5}	1.630×10^{-4}	-0.5178
10323	0.129	6.59×10^{-6}	4.858×10^{-5}	1.612×10^{-4}	-0.5208
12510	0.138	7.05×10^{-6}	4.812×10^{-5}	1.603×10^{-4}	-0.5225
13930	0.143	7.30×10^{-6}	4.787×10^{-5}	1.598×10^{-4}	-0.5234
15896	0.151	7.71×10^{-6}	4.746×10^{-5}	1.590×10^{-4}	-0.5249
17263	0.160	8.17×10^{-6}	4.700×10^{-5}	1.580×10^{-4}	-0.5266
18406	0.167	8.53×10^{-6}	4.664×10^{-5}	1.573×10^{-4}	-0.5280
20395	0.172	8.78×10^{-6}	4.638×10^{-5}	1.568×10^{-4}	-0.5290
22796	0.187	9.55×10^{-6}	4.562×10^{-5}	1.553×10^{-4}	-0.5319
25725	0.201	10.27×10^{-6}	4.490×10^{-5}	1.539×10^{-4}	-0.5348
27655	0.210	10.73×10^{-6}	4.444×10^{-5}	1.529×10^{-4}	-0.5367

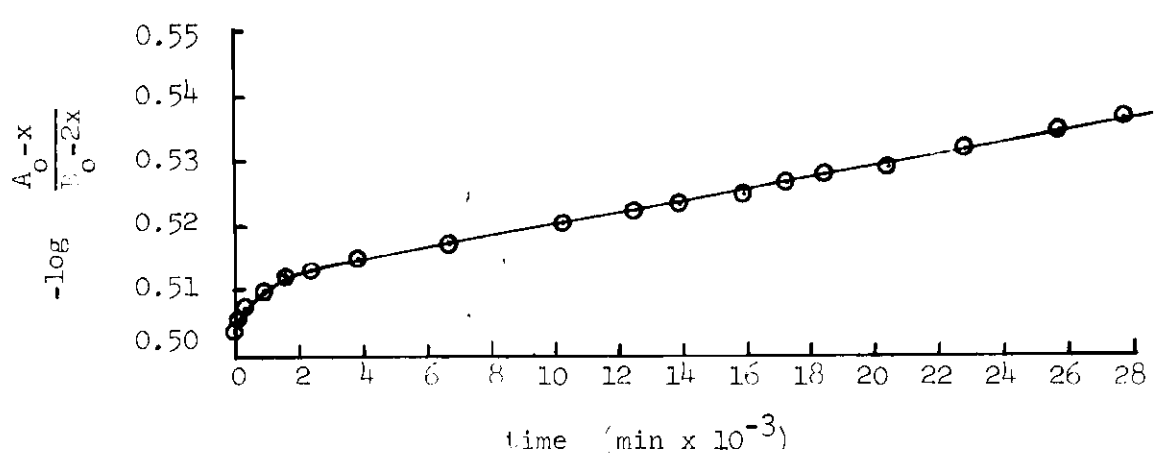


Figure 15 Reaction of Piperidine and 6-Chloro-9-ethylpurine under true second order conditions

The initial curvature of the graph during the first few percent of reaction is possibly due to a side reaction of an impurity in the starting purine. The remainder of the plot is linear with a slope of -9.107×10^{-7}. From this slope the second order rate constant is thus determined.

$$k = \frac{2.303 \times (-)\ 9.017 \times 10^{-7}}{(2 \times 5.517 \times 10^{-5} \text{ moles liter}^{-1}) - 1.744 \times 10^{-4} \text{ moles liter}^{-1}}$$

$$= \frac{2.303 \times 9.017 \times 10^{-7}}{0.641 \times 10^{-4}} = 0.0324\ M^{-1}\ min^{-1}$$

$$k = 5.4 \times 10^{-4}\ M^{-1}\ sec^{-1}$$

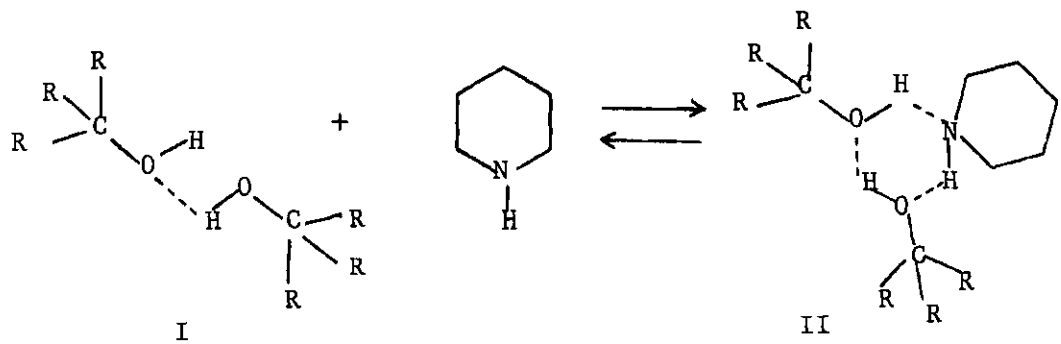
The reaction was repeated at a wavelength of 294 mμ and the concentrations of the starting materials after mixing was as follows (initial concentrations): 6-chloro-9-ethylpurine = 5.577×10^{-5} mole liter^{-1}, piperidine = 1.744×10^{-4} mole liter. The "extinction coefficient" at this wavelength was found to be 12,086 (determined from examination of the spectrum after the reaction of the purine with 0.2 M piperidine). The plot of log $(A_o - x/B_o - 2x)$ versus time for this particular setting (294 mμ) was essentially identical to that obtained at the previous setting (283.5 mμ). The second order rate constant for the 294 mμ setting was 6.28×10^{-4} M^{-1} sec^{-1}.

It appears that there was approximately one percent of impurity in the purine sample. However, in the piperidine concentration range of the kinetic studies the reaction with 6-chloro-9-ethylpurine was so fast that this side reaction was not observable in the pseudo first order reaction plots (all of the pseudo first order plots had a correlation coefficient of better than 0.9999). The two experimental values,

5.40×10^{-4} $\underline{M}^{-1}$ sec^{-1} and 6.28×10^{-4} $\underline{M}^{-1}$ sec^{-1} are comparable to the extrapolated rate constant, $4.45 \times 10^{-4} \pm 1.9 \times 10^{-4}$ $\underline{M}^{-1}$ sec^{-1} obtained from the plot of k_{obs} versus the concentration of excess piperidine at 29.75°C and extrapolated to zero piperidine concentration (see Figure 19, p. 70). The variations in the rate constants obtained under true second order conditions and the deviation from the extrapolated rate constant were possibly due to a small amount of evaporation of the solution over the long reaction time. Thus, it is concluded that the reaction of piperidine with 6-chloro-9-ethylpurine is essentially first order in piperidine and first order in purine at very low piperidine concentrations.

Determination of the Concentration of Unassociated Piperidine and Catalytic Alcohol in Isooctane

Several workers have postulated that alcohols and amines in sufficient concentration will associate in varying degrees in non-polar solvents. Equilibrium constants have been proposed for many of these systems (89-102). Therefore, it was necessary to determine the concentration of free piperidine in solution in the reactions in which alcoholic catalysts were employed. In order to simplify the calculations it was assumed that the alcohol exists only in the dimeric form in the concentration range examined. Thus, the equilibrium that is of concern here is the following (R = H or alkyl group or phenyl group):



The product (II) is neither nucleophilic or catalytic. Using equilibrium constants ranging from K = 1 to K = 6 the initial concentrations of methanol and 1-butanol were substituted into the expression:

$$K = (\text{alcohol}_{\text{dimer}}\text{-piperidine})/(\text{alcohol}_{\text{dimer}})(\text{piperidine})$$

The values for the concentrations of $\text{alcohol}_{\text{dimer}}$ and piperidine were then obtained. Using these "free" concentrations of piperidine, k'_{obs} was calculated. Subtraction of the "second order rate constant" for the "free" piperidine concentration (see Figure 19, p. 70) from k'_{obs} gives the "second order rate constant" for the concentration of dimeric alcohol. The rate constants for the alcohol were then plotted against the concentration of the dimeric species. The best correlation of data was obtained for K = 5. Actually, the linearity of the plot did not deviate appreciably for K = 4, 5 or 6; however, the value of K = 5 was chosen as the equilibrium constant for the determination of all alcohol and piperidine concentrations. The following calculations illustrate the method of determining k_{obs} for the methanol dimer:

Initial concentration of piperidine = 0.1055 M

Initial concentration of methanol = 0.1027 M

Initial concentration of dimeric alcohol = 0.0513 M

Let x = concentration of alcohol-piperidine complex,

then, $K = 5 = \frac{(\text{alcohol}_{\text{dimer}}\text{-piperidine})}{(\text{alcohol}_{\text{dimer}})(\text{piperidine})} = \frac{x}{(0.0513-x)(0.1055-x)}$,

and x = 0.0159 M

The concentration of free piperidine = 0.1055 - 0.0159 = 0.0896 M and the concentration of dimeric alcohol that is unassociated with piperidine is 0.0513 - 0.0159 = 0.0354 M. If $k_{pseudo} = 0.0662\ \text{min}^{-1}$, then $k'_{obs} = 0.0662/0.0896 = 0.7388\ \text{M}^{-1}\ \text{min}^{-1}$, or $k'_{obs} = 0.0124\ \text{M}^{-1}\ \text{sec}^{-1}$ (after the density correction). The value of $k_{obs(piperidine)}$ for this concentration of piperidine is $0.0017\ \text{M}^{-1}\ \text{sec}^{-1}$. Therefore, $k'_{obs} = k_{obs(piperidine)} + k_{obs(methanol)}$ and $k_{obs(methanol_{dimer})} = 0.0124 - 0.0017 = 0.0107\ \text{M}^{-1}\ \text{sec}^{-1}$ (for 0.0354 M methanol_{dimer}). All alcohol rate constants were calculated in this manner.

Density Corrections

A 50 ml volumetric flask whose stem was marked at various exact intervals was used for the density corrections. A 50 ml pipette was used to deliver exactly 50 ml of isooctane at 25°C to the flask. The liquid was now at the 50 ml mark on the stem. Then, 3 ml of isooctane (also at 25°C) was added to the flask using a 3 ml pipette. This process was repeated several times to determine accurately the final volume at 25°C. It was found by this method that each large marking on the flask corresponded to 0.65 ml and each small unit was 0.065 ml. Thus, the flask was calibrated. Now, the contents of the flask were discarded and the flask was again filled to about the 50 ml mark at 25°C. This

volume was recorded. Finally, the flask was stoppered and transferred to a water bath maintained at the reaction temperature. After equilibration for ten minutes the volume of the solution was recorded. The values for the volume of the isooctane solution before and after expansion were recorded for the three reaction temperatures and the appropriate ratio was obtained (see Table 29). The process was also repeated at these three temperatures for a solution of isooctane and piperidine at the highest piperidine reaction concentration used (1.0 M). The values obtained were essentially the same as those in Table 29. Therefore, all of the second order rate constants were divided by the ratio for the appropriate temperature illustrated in the table.

Table 29. Density Correction Data

Reaction Temperature (°C)	Volume (Reaction Temperature) (°C) (V_{Rxn})	Volume (25°) (V_{25})	Correction Factor (V_{25}/V_{Rxn})
5	50.44	51.69	1.025
30	51.88	51.69	0.996
50	53.15	51.69	0.972

Vapor Pressure Studies of Piperidine in Isooctane

It was necessary to determine the extent of self-association of piperidine in isooctane in the experimental concentration range used for the kinetic studies. The following apparatus and procedure were utilized for this determination.

A 2 liter cylinder equipped with a stopcock sampling valve and attached in series by means of heavy-walled rubber tubing to a manometer,

McCloud gauge, cold trap and vacuum pump, respectively, was used to contain the test solutions. The isooctane-piperidine solutions were placed in the cylinder and cooled, using liquid nitrogen, to slightly above the melting point of the solution. The system was evacuated until the McCloud gauge reading was 0.08 mm pressure, and then the gauge, cold trap and vacuum pump were disconnected from the manometer and cylinder. The cylinder was immersed in a water bath at 25°C and the solution permitted to equilibrate until the manometer indicated a constant pressure. Gas samples were removed using a 5 ml gas syringe and injected into a Varian 204-C flame-ionization gas chromatograph equipped with an OV-17 (phenyl silicone) column. Samples of the liquid were injected into the gas chromatograph after the gas studies were completed. The area of the piperidine and isooctane peaks in both the gas and liquid samples were calibrated with a solution of piperidine in isooctane of known concentration.

Three concentrations of piperidine in isooctane were investigated, 0.1147, 0.0884, and 0.0694 mole fraction, respectively. The following Table 30 illustrates the calibration of the peak area for a particular piperidine concentration.

Table 30. Calibration of the Peak Area Using a 0.8756 M Piperidine Solution

Attenuation of Recorder	Compound	Peak Area	Grams of Compound Corresponding to Peak Area
512	Isooctane	94 units	3.146×10^{-4}
8	Piperidine	465 units	3.728×10^{-5}

Using the calibration data in the previous table the mole fractions of the components in the vapor and in the solution (after withdrawal of the vapor samples) were calculated.

Table 31. Mole Fractions of Piperidine and Isooctane in the Vapor and Liquid Phases

Phase	Peak Area (Units)	Compound	Grams of Compound	Mole Fraction	Vapor Pressure
Vapor	131	Isooctane	4.385×10^{-4}	-	53.5
Vapor	510	Piperidine	4.089×10^{-5}	0.1112	53.5
Vapor	121	Isooctane	4.050×10^{-4}	-	53.5
Vapor	551	Piperidine	4.418×10^{-5}	0.1276	53.5
Vapor	150	Isooctane	5.020×10^{-4}	-	53.0
Vapor	541	Piperidine	4.337×10^{-5}	0.1039	53.0
Vapor	103	Isooctane	3.447×10^{-4}	-	54.0
Vapor	327	Piperidine	2.622×10^{-4}	0.0926	54.0
	Average			0.1089	53.5
Liquid	91	Isooctane	3.046×10^{-4}	-	
Liquid	381	Piperidine	3.054×10^{-5}	0.1186	
Liquid	86	Isooctane	2.878×10^{-4}	-	
Liquid	385	Piperidine	3.086×10^{-5}	0.1258	
Liquid	144	Isooctane	4.820×10^{-4}	-	
Liquid	521	Piperidine	4.177×10^{-5}	0.1041	
Liquid	92	Isooctane	3.079×10^{-4}	-	
Liquid	383	Piperidine	3.070×10^{-5}	0.1180	
Liquid	98	Isooctane	3.280×10^{-4}	-	
Liquid	448	Piperidine	3.592×10^{-5}	0.1281	
Liquid	86	Isooctane	2.878×10^{-4}	-	
Liquid	277	Piperidine	2.221×10^{-5}	0.0938	
	Average			0.1147	

From the product of the mole fraction of piperidine in the vapor and the total pressure exerted by the corresponding solution, the partial pressure of piperidine is obtained. Table 32 summarizes these results.

Table 32. Data for the Determination of the Henry's Law Constant

Total Pressure	Mole Fraction of Piperidine (Vapor)	Partial Pressure of Piperidine (P_2)	Mole Fraction of Piperidine (Solution) (X_2)	P_2/X_2
53.5 mm	0.1089	5.82 mm	0.1147	50.74 mm
55.0 mm	0.0880	4.82 mm	0.0884	54.75 mm
55.7 mm	0.0676	3.76 mm	0.0694	54.18 mm

A classical plot (103) was then used to determine the Henry's law constant at infinite dilution. The value for this constant (K_2) was 60.6 mm at a temperature of 25°C.

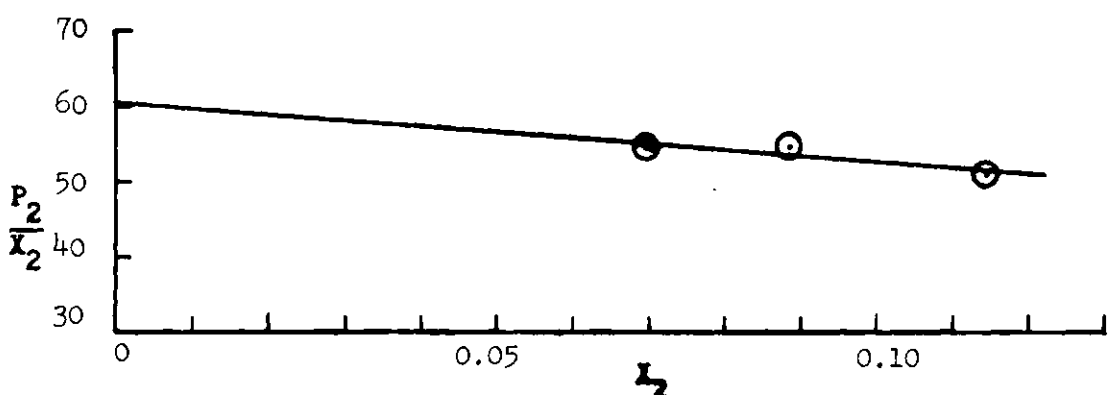


Figure 16 Determination of the Henry's Law Constant for the Piperidine-Isooctane Solutions at 25°C

Using the general expression (104) $\log_{10} P = (-0.2185\ A/K) + B$, where for piperidine: A = 8911.8 and B = 8.0325, the vapor pressure of pure piperidine at 25°C is calculated to be 31.5 mm. The results of these relationships are illustrated in Figure 17.

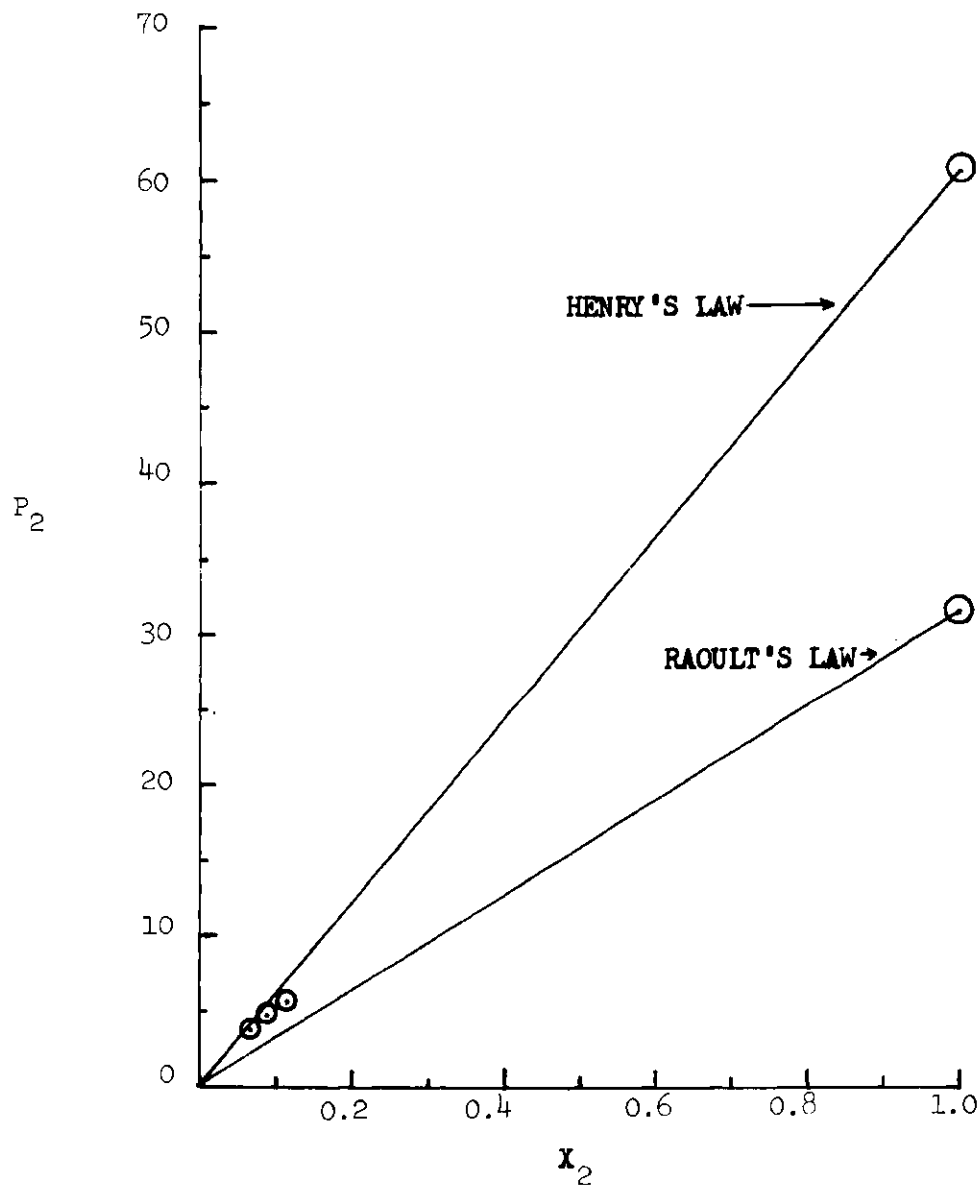


Figure 17 Determination of the Extent of Association of Piperidine as a Function of Partial Pressure and Mole Fraction

The experimental partial pressure at a given mole fraction divided by the theoretical partial pressure from the Henry's law extrapolation is the activity coefficient of piperidine for the specified concentration. The activity coefficients for the three concentrations are given in Table 33.

Table 33. Activity Coefficients for Piperidine in Isooctane

Mole Fraction (X_2)	Activity Coefficient
0.1147	0.80 ± 0.04
0.0884	0.86 ± 0.04
0.0694	0.85 ± 0.04

The results of these studies indicate activity coefficients for 0.069, 0.088, and 0.115 mole fraction piperidine which do not deviate appreciably from the ideal case. It is also interesting that the calculated partial pressure of pure piperidine is actually one-half that determined by the plot of Henry's law. This appears to demonstrate a high degree of association for liquid piperidine. We have made two assumptions in our data: (1) that we are dealing only with monomeric species in the gas phase, (2) that our data are far enough within the Henry's law region to obtain an acceptable Henry's law constant. Both of these assumptions appear to be valid for the data presented. Therefore we feel that there is only a low degree of association of piperidine in isooctane for the concentration range studied.

CHAPTER III

RESULTS AND DISCUSSION

The following kinetic study is an attempt to elucidate the mechanism of nucleophilic aromatic substitution by piperidine on 6-chloro-9-ethylpurine in the non-polar, aprotic solvent, isooctane. Table 34 gives the second order rate coefficients as obtained from the pseudo first order rate constants for the reaction of piperidine with 6-chloro-9-ethylpurine in isooctane at temperatures of 4.75°, 29.75°, and 49.5°C. The maximum error in the rate constants is approximately ± 3 percent for the higher concentrations of piperidine (greater than 0.4 M) and ± 2 percent for the lower concentrations (less than 0.4 M).

Table 34. Second Order Rate Constants for the Piperidine-Purine Reactions in the Absence of Additives (the concentration of 6-chloro-9-ethylpurine is 5×10^{-5} M)

Molarity of Piperidine (moles liter^{-1})	Rate Constant (M^{-1} sec^{-1})	Temperature
0.1016	7.44×10^{-4}	4.75 ± 0.25 C
0.1922	1.180×10^{-3}	4.75 ± 0.25 C
0.2481	1.57×10^{-3}	4.75 ± 0.25 C
0.2916	1.78×10^{-3}	4.75 ± 0.25 C
0.3010	1.840×10^{-3}	4.75 ± 0.25 C
0.3961	2.340×10^{-3}	4.75 ± 0.25 C
0.0518	1.09×10^{-3}	29.75 ± 0.25 C
0.1035	1.82×10^{-3}	29.75 ± 0.25 C
0.2070	3.10×10^{-3}	29.75 ± 0.25 C
0.2916	4.22×10^{-3}	29.75 ± 0.25 C
0.2706	3.70×10^{-3}	29.75 ± 0.25 C
0.2762	3.81×10^{-3}	29.75 ± 0.25 C
0.3890	5.06×10^{-3}	29.75 ± 0.25 C
0.5461	6.33×10^{-3}	29.75 ± 0.25 C
0.5455	5.93×10^{-3}	29.75 ± 0.25 C

Table 34. (Continued)

Molarity of Piperidine (moles liter^{-1})	Rate Constant (M^{-1} sec^{-1})	Temperature
0.5444	6.04×10^{-3}	29.75 ± 0.25 C
0.7535	7.71×10^{-3}	29.75 ± 0.25 C
0.7723	7.80×10^{-3}	29.75 ± 0.25 C
0.7215	7.26×10^{-3}	29.75 ± 0.25 C
0.7230	7.47×10^{-3}	29.75 ± 0.25 C
0.7334	7.71×10^{-3}	29.75 ± 0.25 C
1.1138	10.15×10^{-3}	29.75 ± 0.25 C
1.1103	10.06×10^{-3}	29.75 ± 0.25 C
1.0989	10.13×10^{-3}	29.75 ± 0.25 C
1.1326	10.25×10^{-3}	29.75 ± 0.25 C
0.0253	1.47×10^{-3}	49.5 ± 0.3 C
0.0507	2.14×10^{-3}	49.5 ± 0.3 C
0.1014	3.26×10^{-3}	49.5 ± 0.3 C
0.2027	5.67×10^{-3}	49.5 ± 0.3 C
0.2459	7.02×10^{-3}	49.5 ± 0.3 C
0.2657	7.46×10^{-3}	49.5 ± 0.3 C
0.5020	12.47×10^{-3}	49.5 ± 0.3 C
0.5041	12.15×10^{-3}	49.5 ± 0.3 C
0.4989	12.05×10^{-3}	49.5 ± 0.3 C
0.6468	15.78×10^{-3}	49.5 ± 0.3 C
0.6618	15.16×10^{-3}	49.5 ± 0.3 C
0.6501	15.87×10^{-3}	49.5 ± 0.3 C
0.9636	21.10×10^{-3}	49.5 ± 0.3 C
1.0040	21.51×10^{-3}	49.5 ± 0.3 C
0.9834	20.69×10^{-3}	49.5 ± 0.3 C
0.9874	20.91×10^{-3}	49.5 ± 0.3 C

On examination of these data, it is obvious that the second order rate constant (k_{obs}) is changing with a variation in the concentration of piperidine. The plot of k_{obs} against the piperidine concentrations is illustrated for the three experimental temperatures in Figures 18, 19, and 20.

These three graphs demonstrate that at low piperidine concentrations there is an increasing linear dependence of the second order rate "constant" on the concentration of piperidine. However, at higher piperidine concentrations curvature develops (Figures 19 and 20). This

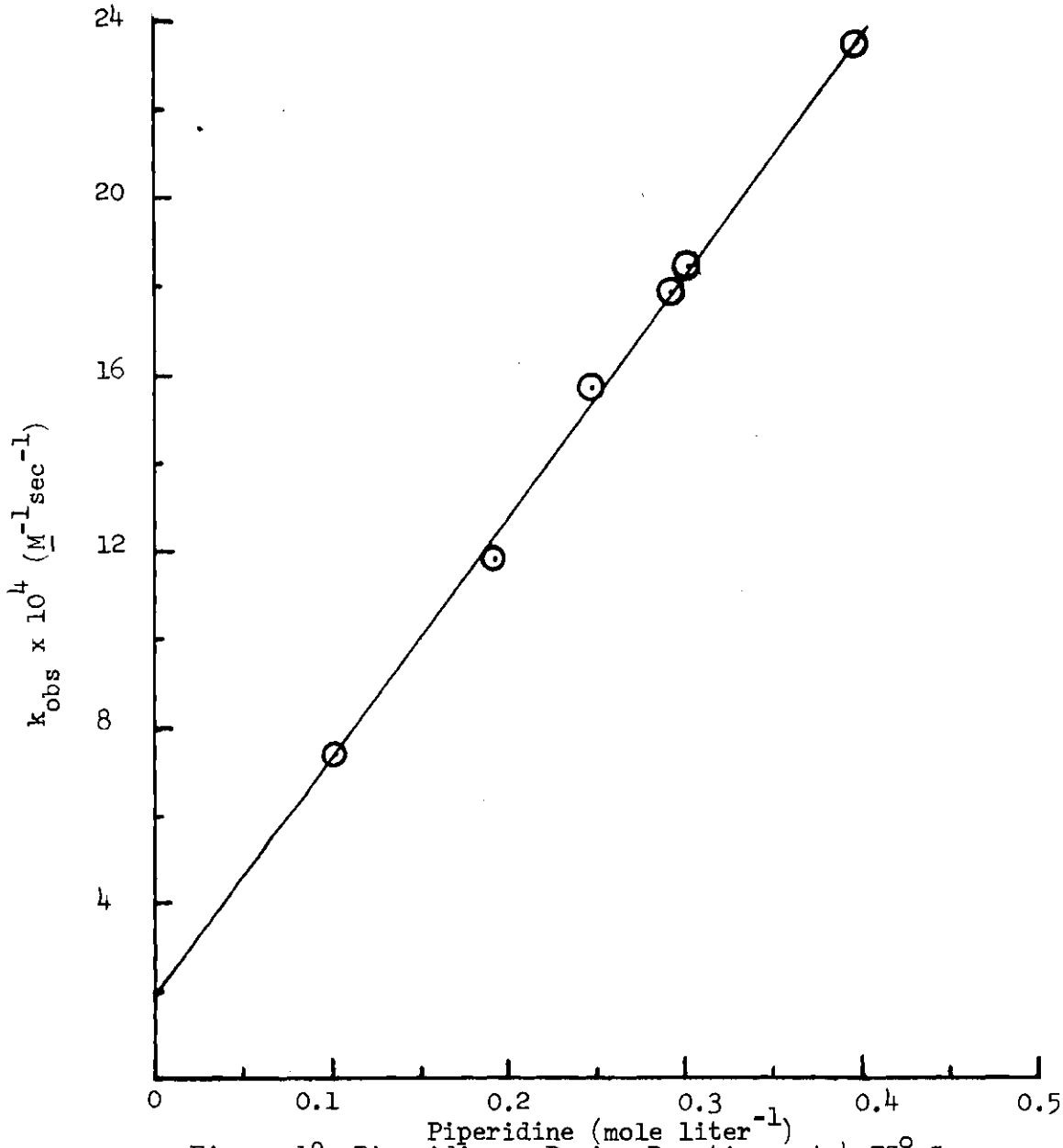


Figure 18 Piperidine - Purine Reactions at 4.75° C

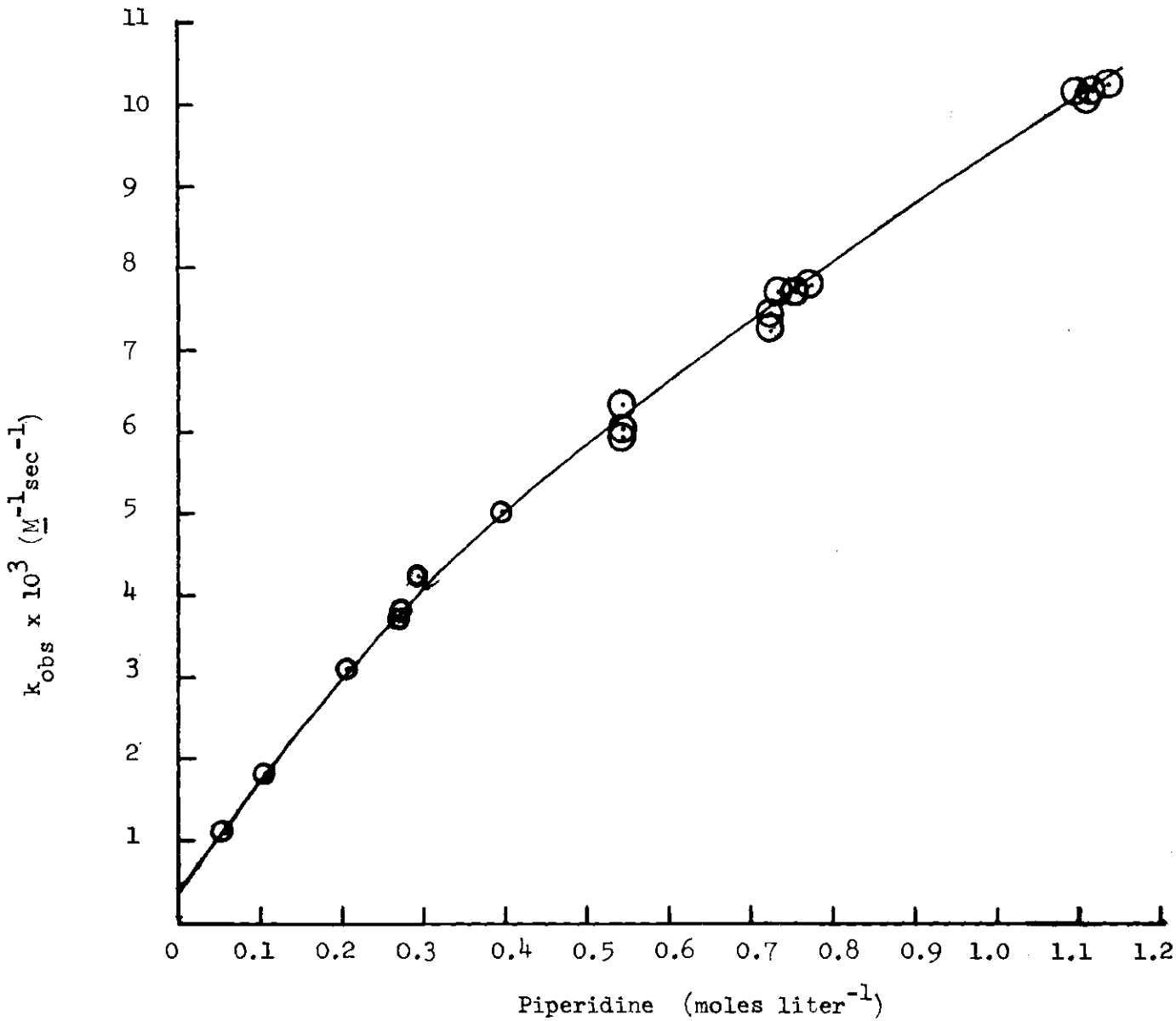


Figure 19 Piperidine - Purine Reactions at 29.75° C

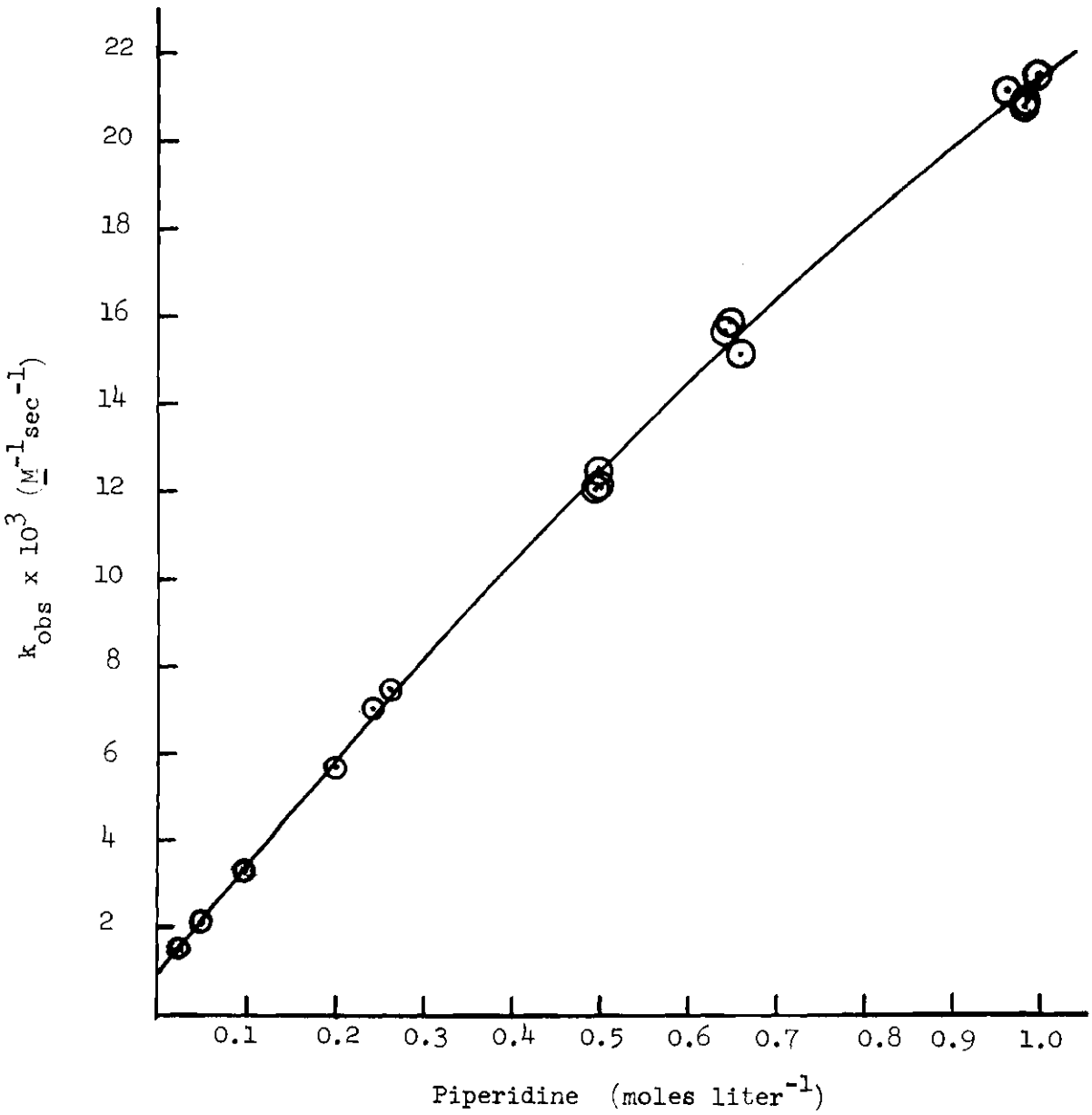
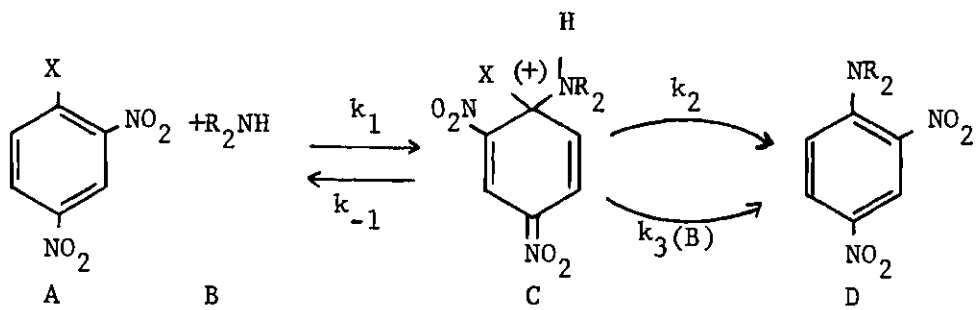
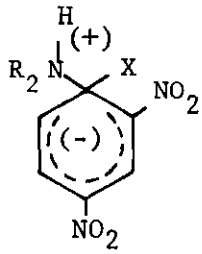


Figure 20 Piperidine - Purine Reactions at 49.5°C

behavior is reminiscent of the catalysis described by Bunnett and other workers in the nucleophilic aromatic substitution reactions of amines with substituted nitrobenzenes and nitronaphthalenes. The mechanism (discussed on pp. 1-3) involves attack by the nucleophile on the substrate to form the intermediate (C), followed by either catalyzed or uncatalyzed decomposition of the intermediate to give the final product (D). It should be noted here that the intermediate may be represented



as a Meisenheimer complex, 

which can either proceed to products or revert back to reactants (14).

Using the steady-state approximation (105) the following relationship is obtained.

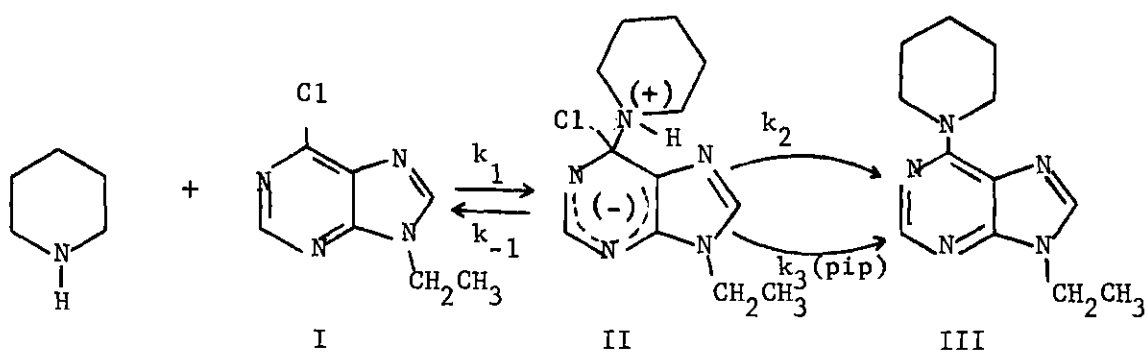
$$k_{obs} = \frac{k_1k_2 + k_1k_3(B)}{k_{-1} + k_2 + k_3(B)}$$

Now if $K_{-1} \gg k_2 + k_3(B)$ this equation becomes:

$$k_{obs} = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3 (B)}{k_{-1}} .$$

It was then shown that at lower concentrations of amine a plot of k_{obs} versus the concentration of amine was linear with a slope of $\frac{k_1 k_3}{k_{-1}}$ and an intercept of $\frac{k_1 k_2}{k_{-1}}$ defined as the catalyzed (k_3') and uncatalyzed (k_2') rate "constants", respectively. At higher concentrations of amine $k_{-1} \approx k_2 + k_3(B)$, resulting in curvature of the plot. Bunnett in his most recent publications (21) concerning this subject has postulated that acid catalysis is responsible for the change in the second order rate coefficient (k_{obs}) with increasing amine concentrations. Earlier (10) and more recent (18) reports concerning the explanation of these effects have dealt with base or "bifunctional" catalysis.

This multi-step, addition-elimination mechanism based on the kinetic treatment of the data also appeared most attractive for the reaction of piperidine with 6-chloro-9-ethylpurine. The exact nature of the catalysis remained to be determined, however.



There was also concern that the piperidine in the experimental concentration range was associated in some manner through hydrogen bonding. Thus, it was apparent that the state of association of piperidine was important in order to interpret the kinetics. While the literature (106-113) contains a significant number of nmr studies dealing with the state of association of amines, most of these investigations deal with chlorinated solvents at rather high concentrations of amine where association via hydrogen bonding becomes important. A few nmr studies have been conducted in the solvent cyclohexane where both monomer-dimer and monomer-tetramer equilibria have been postulated for a variety of amines (111) (113). Investigations utilizing infrared techniques indicate the possible presence of some self-associated species (114-116). In order to obtain more definitive information concerning the state of association of piperidine in isooctane at the more dilute end of the concentration spectrum, vapor pressure studies were undertaken. Activity coefficients of 0.80 $\pm$ 0.04, 0.86 $\pm$ 0.04, and 0.85 $\pm$ 0.04 for 0.1147, 0.0884, and 0.0694 mole fraction of piperidine, respectively, (see p. 61 for experimental procedure) were obtained.

In spite of the huge amount of work published on the association of amines in various aprotic, non-polar solvents very little is known concerning the state of association of amines at relatively low concentrations. The results here appear to indicate that piperidine is primarily monomeric in concentrations ranging up to 0.8 M since deviations from Henry's law are quite small. It is interesting to note that the calculated partial pressure of pure piperidine is approximately one-half that determined by the Henry's law plot.

The rate coefficients and activation data for the reaction of piperidine with 6-chloro-9-ethylpurine in isooctane are listed in the Table 35. The data were treated by assuming the multi-step, addition-elimination mechanism as proposed by Bunnett and co-workers (1-21). Thus, the slope of the linear portion of the plot of k_{obs} against the concentration of piperidine is the rate coefficient for the "catalyzed" reaction and the intercept is the rate coefficient for the "uncatalyzed" breakdown of the intermediate. It is interesting that the catalyzed and uncatalyzed activation parameters are of almost the same magnitude for the catalyzed and uncatalyzed steps of the reaction. The low values of $\Delta E^{\ddagger}$ seem to indicate that the reaction is not greatly temperature dependent.

Table 35. Rate and Activation Data for the Reaction of Piperidine with 6-Chloro-9-ethylpurine.

Reaction Step	Rate Coefficient*			$\Delta E^{\ddagger}$	$\Delta S^{\ddagger}$(29.75 C)
Considered	4.75°C	29.75°	49.5°	(kcal $mole^{-1}$)	(cal deg^{-1} $mole^{-1}$)
Catalyzed	5.50×10^{-3}	1.29×10^{-2}	2.35×10^{-2}	5.69±0.11	-34±0.7
Uncatalyzed	1.72×10^{-4}	4.45×10^{-4}	9.07×10^{-4}	6.60±2.84	-41.0±17.6

*The units of the catalyzed step are ($M^{-2}sec^{-1}$) and the units of the uncatalyzed step are ($M^{-1}sec^{-1}$)

Primary deuterium isotope effects in which proton transfer occurs in the rate-determining step have rather large values (k_{H/k_D} = 7 to 9) (71). Secondary deuterium isotope effects, on the other hand, exhibit much smaller values, on the order of $K_{H/K_D} \leq 1.2$ (72). In the latter case, the bond to the isotopic hydrogen is not broken, but anharmonicity of the

vibrations involving motion of the hydrogen atoms leads to different average bond lengths and angles in deuterated and normal molecules and hence to different reactivities of the deutero and protio compounds. Thus, such isotope effects can be valuable tools in deducing the mechanism of a reaction. In order to determine if isotope effects are important in the reactions under investigation piperidine-N-d was reacted with 6-chloro-9-ethylpurine in isooctane at reaction temperatures of 29.7 ± 0.25°C, and 49.5 ± 0.3°C. The results are recorded in Tables 36 and 37. The plots of k_{obs} versus the concentration of piperidine-N-d and piperidine-N-h are shown in Figures 21 and 22.

Table 36. Data for the Reaction of Piperidine N-d with 6-Chloro-9-ethylpurine at Temperatures of 29.75 and 49.5°C in Isooctane.

Molarity of Piperidine-N-d (moles liter^{-1})	k_{obs} ($M^{-1}sec^{-1}$) ± 3 percent-high conc., ± 1.5 percent-low conc.,	Temperature (°C) ± 0.25°C or ± 0.30°C
0.0496	1.18×10^{-3}	29.75
0.0992	1.84×10^{-3}	29.75
0.1984	3.35×10^{-3}	29.75
0.2389	3.77×10^{-3}	29.75
0.4978	6.52×10^{-3}	29.75
0.4738	6.29×10^{-3}	29.75
0.4620	6.14×10^{-3}	29.75
0.6166	7.31×10^{-3}	29.75
0.6344	7.19×10^{-3}	29.75
0.6364	7.70×10^{-3}	29.75
0.6234	7.33×10^{-3}	29.75
0.9444	9.71×10^{-3}	29.75
0.9454	9.84×10^{-3}	29.75
0.9585	10.07×10^{-3}	29.75
0.9457	10.04×10^{-3}	29.75
0.0248	1.64×10^{-3}	49.50
0.0496	2.24×10^{-3}	49.50
0.0992	3.68×10^{-3}	49.50
0.1984	6.30×10^{-3}	49.50
0.1287	4.61×10^{-3}	49.50
0.2526	7.40×10^{-3}	49.50

Table 36. (Continued)

Molarity of Piperidine-N-d (moles liter^{-1})	k_{obs} ($\underline{M}^{-1}sec^{-1}$) ± 3 percent-high conc., ± 1.5 percent-low conc.,	Temperature (°C) ± 0.25°C or ± 0.30°C
0.2526	7.45×10^{-3}	49.50
0.4812	11.49×10^{-3}	49.50
0.4736	11.06×10^{-3}	49.50
0.6808	13.98×10^{-3}	49.50
0.6975	14.38×10^{-3}	49.50
0.6766	14.26×10^{-3}	49.5
0.6865	14.15×10^{-3}	49.5
1.0694	19.75×10^{-3}	49.5
1.0405	19.20×10^{-3}	49.5
1.0671	19.54×10^{-3}	49.5

Table 37. Catalytic Rate Coefficients from the Reaction of Piperidine (-N-h and -N-d) with 6-chloro-9-ethylpurine in Isooctane at 29.75° and 49.5°C.

Catalyst	Reaction Step	Rate Coefficient (k_3')* (29.75°)	Rate Coefficient* (49.5°C)
Piperidine-N-h	Catalyzed(Slope)	1.29×10^{-2}	2.35×10^{-2}
Piperidine-N-h	Uncatalyzed(Intercept)	4.45×10^{-4}	9.07×10^{-4}
Piperidine-N-d	Catalyzed(Slope)	1.43×10^{-2}	2.71×10^{-2}
Piperidine-N-d	Uncatalyzed(Intercept)	4.61×10^{-4}	9.46×10^{-4}

*The units of the catalyzed step are ($\underline{M}^{-2}sec^{-1}$) and the units of the uncatalyzed step are ($\underline{M}^{-1}sec^{-1}$).

The ratio of the slopes in Figure 21 for the concentration range 0 to 0.3 $\underline{M}$ piperidine (linear portion of the plot) indicates a k_{H/k_D} = 0.90 ± 0.03. In Figure 22 it is obvious that the increase in the reaction temperature has a bearing on the k_{H/k_D} ratio. The initial linear portion of the plots have an isotopic ratio comparable to that at 29.75° (k_{H/k_D} =

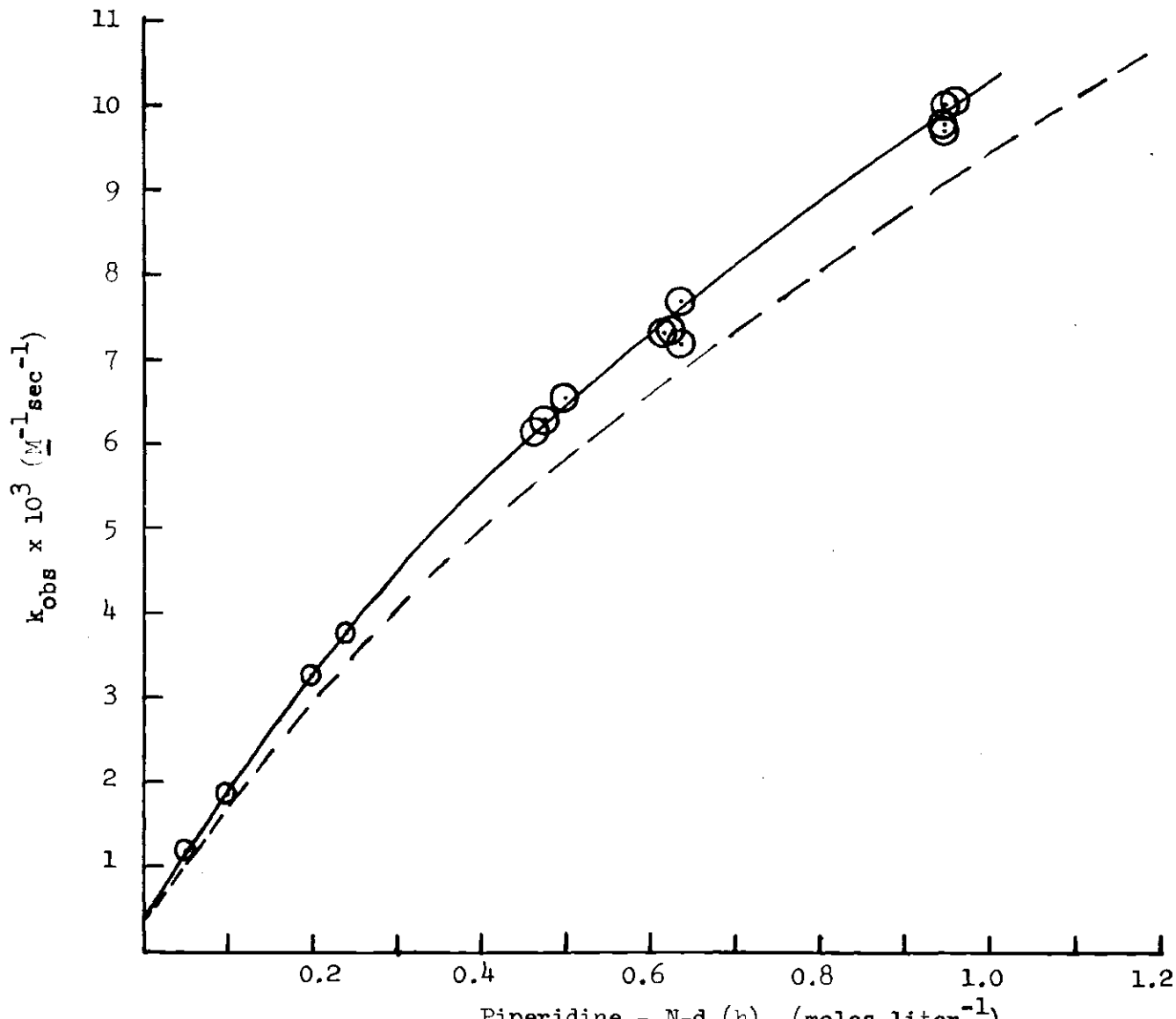


Figure 21 Piperidine - N-d - Purine Reactions at 29.75°C

——————— Piperidine-N-d
---------- Piperidine-N-h

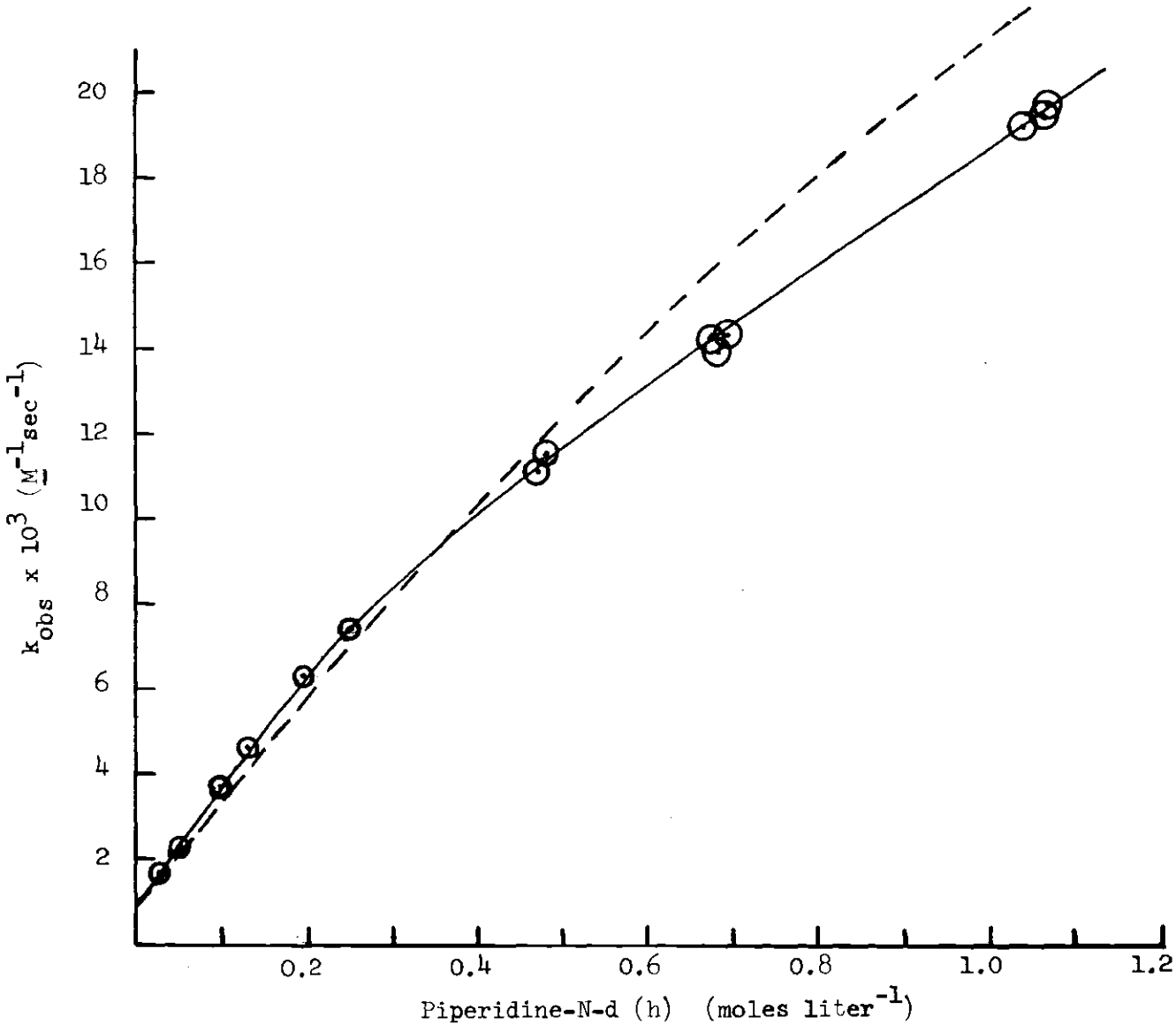


Figure 22 Piperidine-N-d - Purine Reactions at 49.5°C

———————Piperidine-N-d
----------Piperidine-N-h

0.87 ± 0.03). However, as the concentration of piperidine is increased the lines cross and a value of k_{H/k_D} greater than unity is obtained. In the case of the intercepts k_{H/k_D} = 0.96 ± 0.03 for both reaction temperatures (these values are thus within experimental error of 1.00). This behavior may be interpreted as a secondary deuterium isotope effect similar to that described by Bernasconi and Zollinger (70) in the study of the reaction of p-anisidine with dinitrohalobenzenes in benzene solution. Other workers (74) have found analogous results in the reaction of piperidine with the dinitronaphthalene system. One might rationalize that the increased nucleophilicity of the deutero over the protio amine could contribute to this effect. This is not really a substantial argument since the k_{H/k_D} ratio for the reaction of p-anisidine with 2,4-dinitrofluorobenzene was found to be slightly greater than unity (70). Pietra (75) found a k_{H/k_D} = 1.27 for the displacement of the ether group in 2,4-dinitrophenyl phenyl ether by piperidine. Perhaps a more suitable explanation lies in the possible bifunctional nature of the nucleophile-catalyst which can assist in proton and halide removal in a more or less synchronous manner (IV). This, of course, would result in a primary deuterium isotope effect. The "uncatalyzed" reaction might be depicted as a four-center transition state such as (V). This explanation has also been suggested by Bernasconi and Zollinger (58) and Pietra (54) in their nucleophilic aromatic substitution studies in benzene solution. Such a transition state as (IV) could certainly explain the results obtained thus far. Therefore, the multi-step, addition-elimination mechanism is still logical and can incorporate these isotopic studies.

The observed second order rate coefficient for the reaction of

piperidine with 6-chloro-9-ethylpurine is defined by the following equation:

$$k_{obs} = \frac{k_1k_2 + k_1k_3(B)}{k_{-1} + k_2 + k_3(B)} ,$$

where B is piperidine.

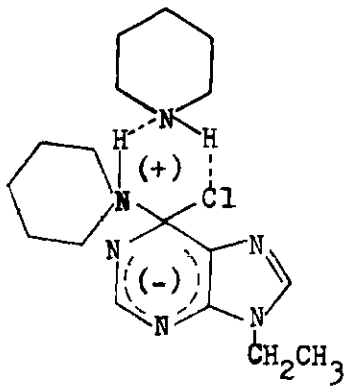
Therefore,

$$\frac{1}{k_{obs}} = \frac{k_{-1} + k_2 + k_3(B)}{k_1k_2 + k_1k_3(B)}$$

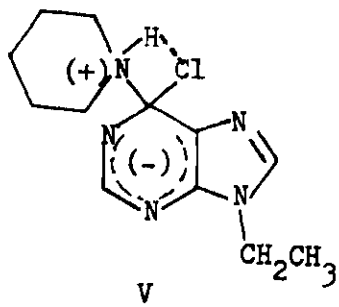
$$= \frac{k_{-1}}{k_1k_2 + k_1k_3(B)} + \frac{k_2 + k_3(B)}{k_1k_2 + k_1k_3(B)}$$

Now if $k_1k_3(B) >> k_1k_2$ (at high concentrations of piperidine), then $\frac{1}{k_{obs}} = \frac{k_{-1}}{k_1k_3}\left[\frac{1}{(B)}\right] + \frac{1}{k_1}$. A plot of $\frac{1}{k_{obs}}$ versus $\frac{1}{pip}$ gives a linear plot of slope = k_{-1}/k_1k_3 and intercept = $1/k_1$. Therefore, the value of k_1 for the reaction of piperidine with 6-chloro-9-ethylpurine can be extracted from this relationship. The values of k_1 obtained by this method were 0.0277 ± 0.0138 $\underline{M}^{-1}$ sec^{-1} and 0.0599 ± 0.0260 $\underline{M}^{-1}$ sec^{-1} for 29.75° and 49.5°C, respectively. In the situation where the nucleophile is piperidine-N-d, k_1 was found to be 0.0231 ± 0.0115 $\underline{M}^{-1}$ sec^{-1} (29.75°C) and 0.0345 ± 0.0172 $\underline{M}^{-1}$ sec^{-1} (49.5°C). The error in k_1 is particularly large since a small variation in the slope produces a significant change in the intercept. However, the values for $k_{1(H)}$ and $k_{1(D)}$ appear to be the same, within experimental error, for the respective temperature.

A study of the effects of a variety of catalysts on the piperidine-purine reaction was undertaken. The catalysts which were chosen did not react with the purine in the concentration range studied.



IV



V

Triethylamine, 2,6-dimethylpiperidine (a mixture of cis- and trans-isomers), tetrahydrofuran, tetrahydropyran, and acetone failed to have any noticeable effect on the reaction of piperidine with 6-chloro-9-ethylpurine in isooctane. Pyridine had a very small catalyzing influence, but 1-aminobutane and 1,2-ethanediamine had a more pronounced effect, comparable to the catalysis by piperidine. Finally, the lactam, 2-azacyclononanone was found to have a huge influence on the reaction rate; however, due to solubility problems, only a limited amount of this amide catalyst could be added to the reaction solution. The rate coefficients in the presence of these compounds are listed in Table 38. The plots of k_{obs} against the concentration of the additives are shown in Figures 23 to 31. The error in the rate constants is approximately $\pm$ 2.0 percent.

According to the results thus far, the mechanism for the piperidine-purine reaction may be viewed as a multi-step addition-elimination process such as the following (k_4 is the catalysis step due to the additive).

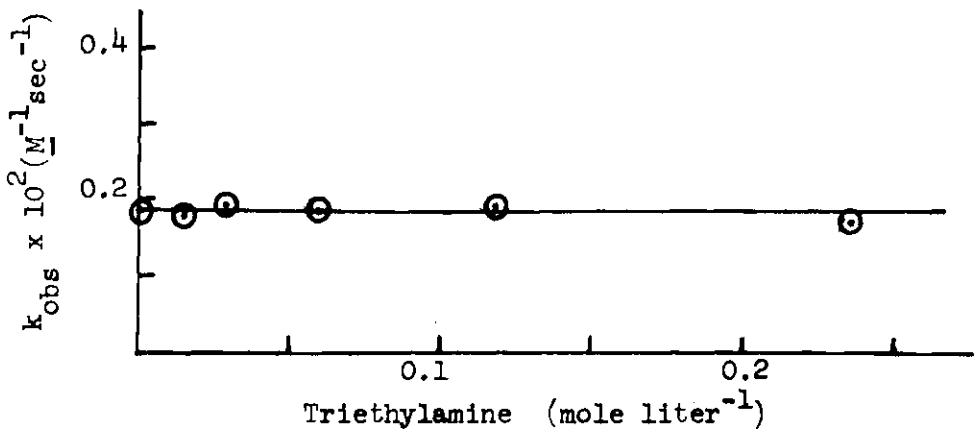


Figure 23 Addition of Triethylamine to the Purine-Piperidine Reaction Solution

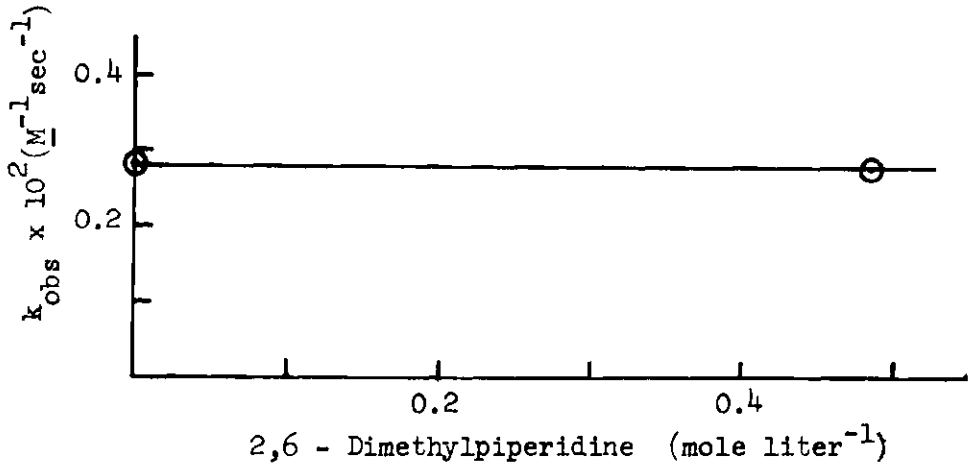


Figure 24 Addition of 2,6-Dimethylpiperidine to the Piperidine-Purine Reaction Solution

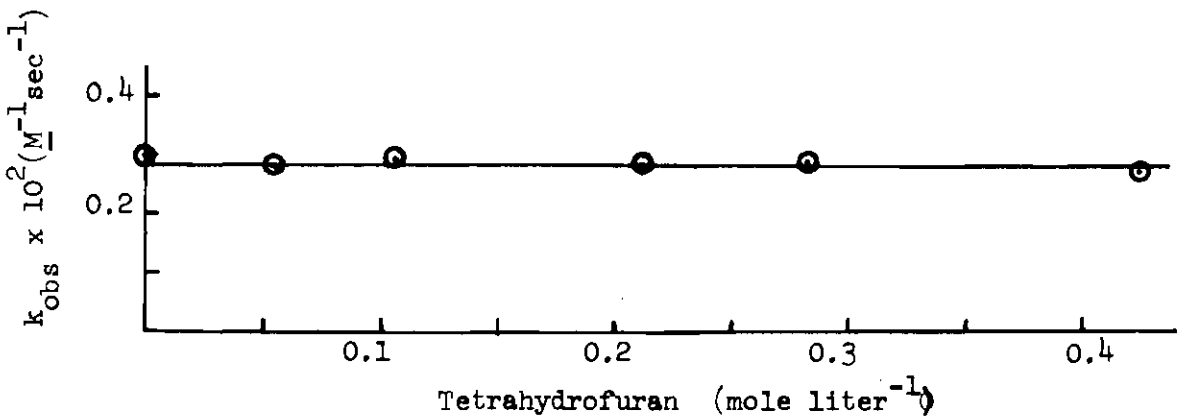


Figure 25 Addition of Tetrahydrofuran to the Piperidine-Purine Reaction Solution

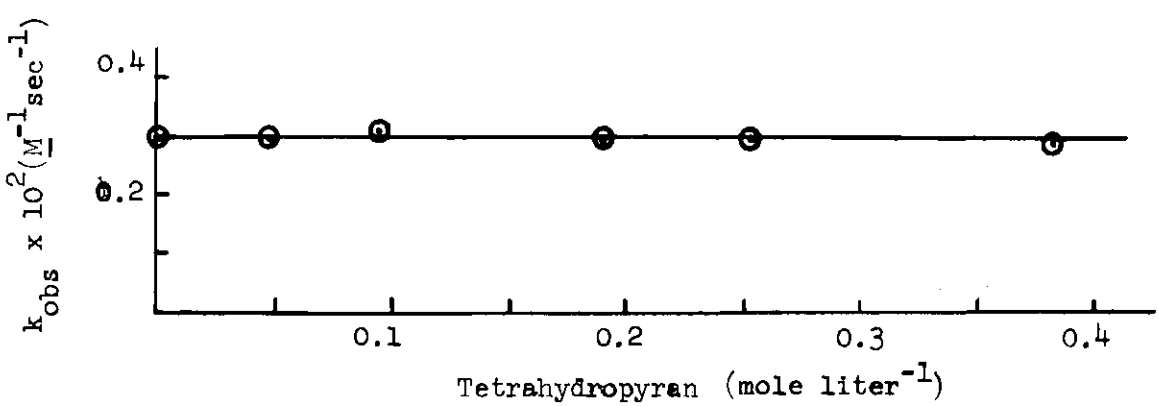


Figure 26 Addition of Tetrahydropyran to the Piperidine-Purine Reaction Solution

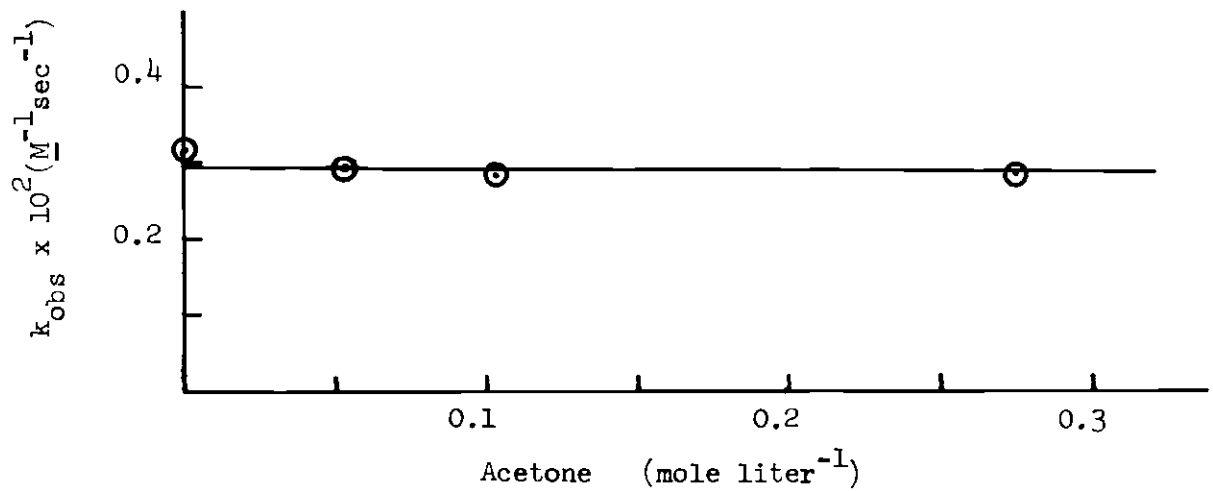


Figure 27 Addition of Acetone to the Piperidine-Purine Reaction Solution

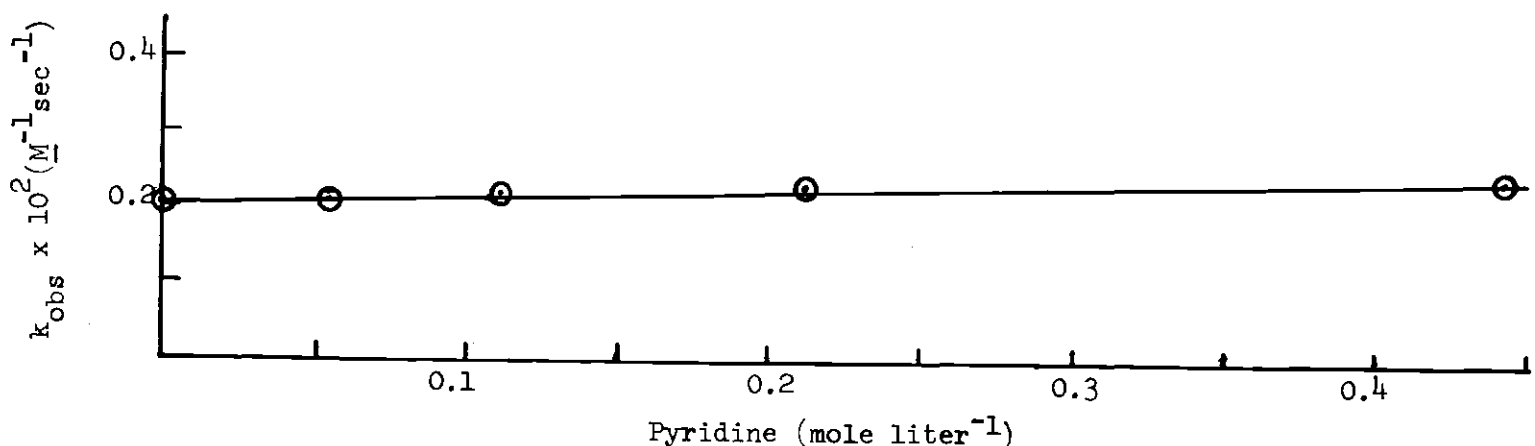


Figure 28 Addition of Pyridine to the Purine-Piperidine Reaction Solution

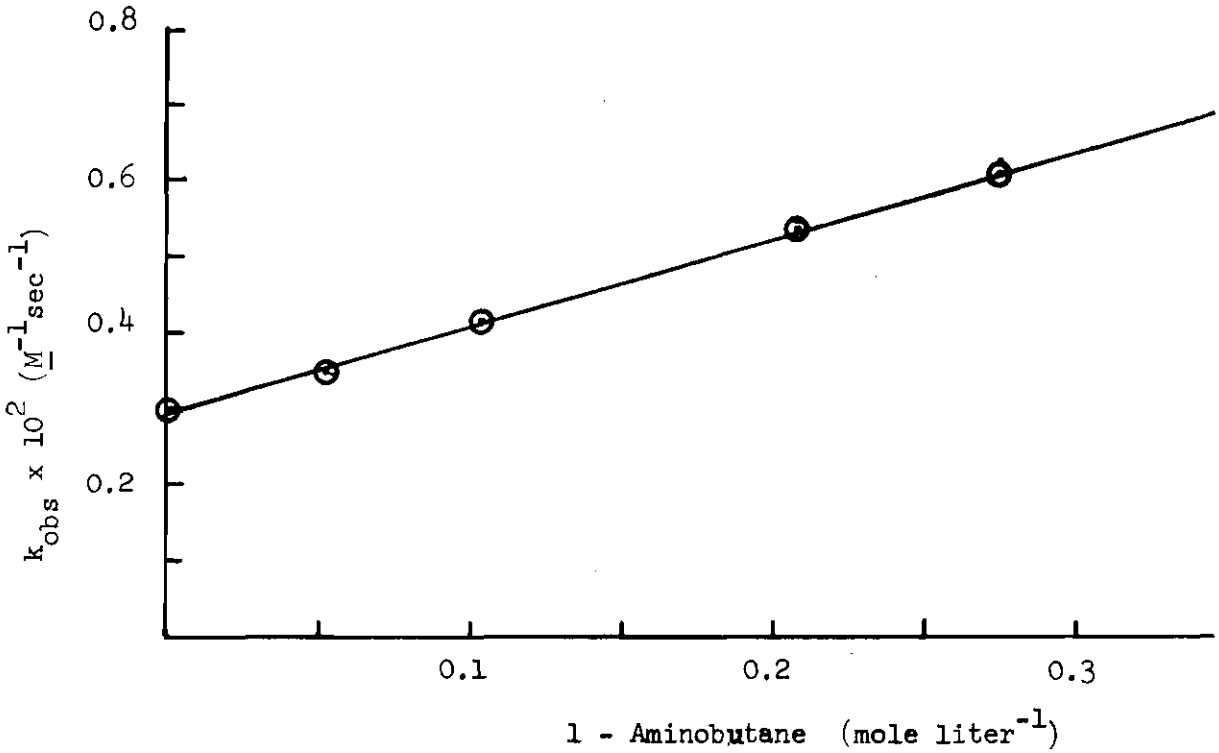


Figure 29 Addition of 1 - Aminobutane to the Piperidine-Purine Reaction Solution

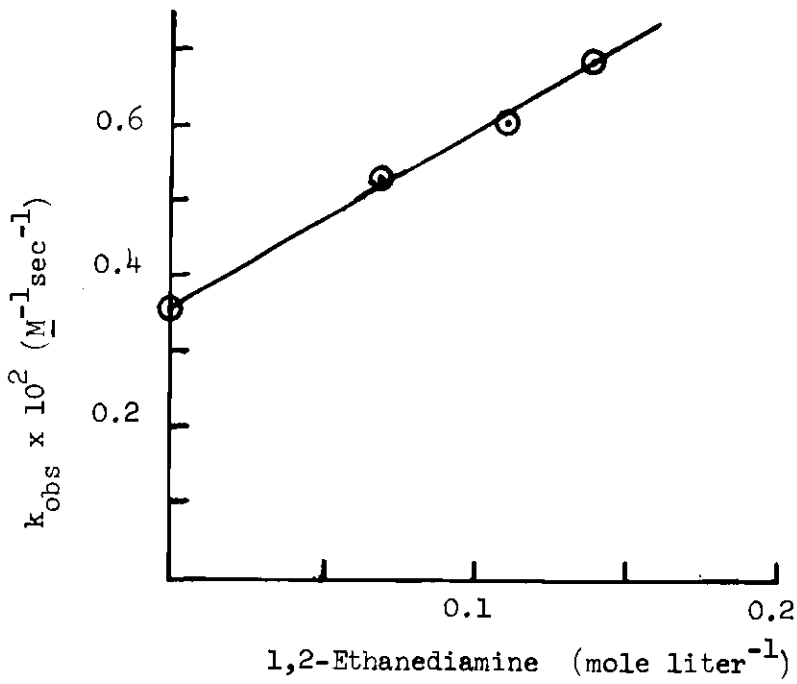


Figure 30 Addition of 1,2-Ethanediamine to the Piperidine-Purine Reaction Solution

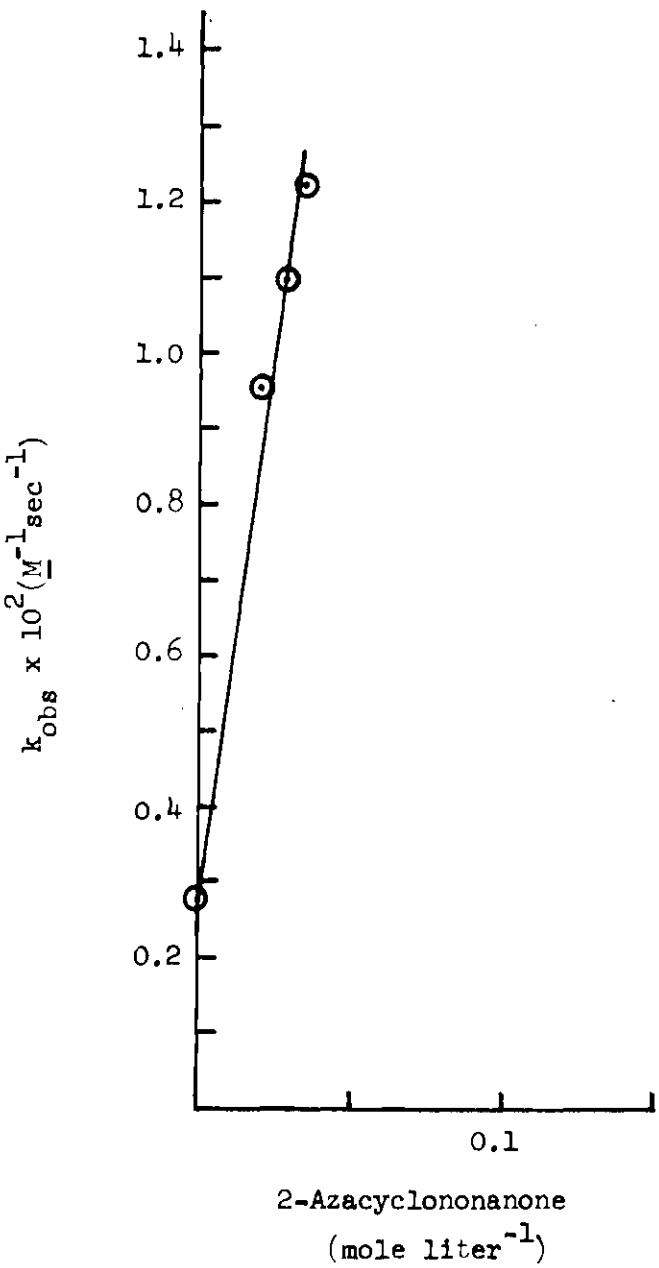
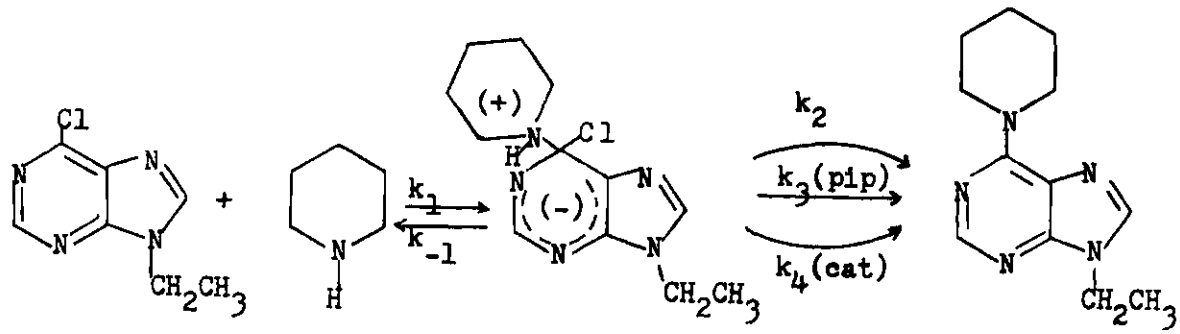


Figure 31 Addition of 2-Azacyclononanone to the Piperidine-Purine Reaction Solution

Table 38. Effect of Various Catalysts on the Reaction of Piperidine with 6-Chloro-9-ethylpurine in Isooctane.

Piperidine Concentration (moles liter^{-1})	Catalyst	Catalyst Concentration (moles liter^{-1})	k_{obs} ($M^{-1}sec^{-1}$)
0.0960	Triethylamine	0.0000	1.84×10^{-3}
0.0960	Triethylamine	0.0147	1.80×10^{-3}
0.0960	Triethylamine	0.0294	1.87×10^{-3}
0.0960	Triethylamine	0.1175	1.93×10^{-3}
0.0960	Triethylamine	0.2350	1.72×10^{-3}
0.1989	2,6-Dimethyl-Piperidine	0.0000	2.86×10^{-3}
0.1989	2,6-Dimethyl-Piperidine	0.4851	2.76×10^{-3}
0.1906	Tetrahydrofuran	0.0000	2.96×10^{-3}
0.1906	Tetrahydrofuran	0.0531	2.82×10^{-3}
0.1906	Tetrahydrofuran	0.1061	2.96×10^{-3}
0.1906	Tetrahydrofuran	0.2121	2.79×10^{-3}
0.1906	Tetrahydrofuran	0.2828	2.84×10^{-3}
0.1906	Tetrahydrofuran	0.4242	2.64×10^{-3}
0.1881	Tetrahydropyran	0.0000	2.94×10^{-3}
0.1881	Tetrahydropyran	0.0477	2.92×10^{-3}
0.1881	Tetrahydropyran	0.0954	3.08×10^{-3}
0.1881	Tetrahydropyran	0.1909	2.95×10^{-3}
0.1881	Tetrahydropyran	0.2545	2.95×10^{-3}
0.1881	Tetrahydropyran	0.3818	2.88×10^{-3}
0.2042	Acetone	0.0000	3.18×10^{-3}
0.2042	Acetone	0.0517	2.90×10^{-3}
0.2042	Acetone	0.1034	2.84×10^{-3}
0.2042	Acetone	0.2758	2.86×10^{-3}
0.1261	Pyridine	0.0000	2.04×10^{-3}
0.1261	Pyridine	0.0554	2.08×10^{-3}
0.1261	Pyridine	0.1108	2.18×10^{-3}
0.1261	Pyridine	0.2217	2.29×10^{-3}
0.1261	Pyridine	0.4433	2.44×10^{-3}
0.1881	1-Aminobutane	0.0000	2.94×10^{-3}
0.1881	1-Aminobutane	0.0516	3.48×10^{-3}
0.1881	1-Aminobutane	0.1033	4.14×10^{-3}
0.1881	1-Aminobutane	0.2066	5.37×10^{-3}
0.1881	1-Aminobutane	0.2754	6.09×10^{-3}
0.1881	1-Aminobutane	0.4131	7.45×10^{-3}
0.2445	1,2-Ethanediamine	0.0000	3.51×10^{-3}
0.2442	1,2-Ethanediamine	0.0686	5.30×10^{-3}
0.2429	1,2-Ethanediamine	0.1103	6.08×10^{-3}
0.2448	1,2-Ethanediamine	0.1392	6.82×10^{-3}
0.1860	2-Azacyclononanone	0.0000	2.79×10^{-3}
0.1852	2-Azacyclononanone	0.0199	9.56×10^{-3}
0.1861	2-Azacyclononanone	0.0286	10.96×10^{-3}
0.1857	2-Azacyclononanone	0.0345	12.21×10^{-3}



At low concentrations of piperidine in the absence of added catalyst $k_2 + k_3$ (piperidine) $< k_{-1}$ and the breakdown of the intermediate is rate-determining, while at high concentrations of amine, catalysis is a maximum ($k_{-1} < k_2 + k_3$) (piperidine) and k_1 becomes rate determining. At intermediate concentrations $k_{-1} \cong k_2 + k_3$ (piperidine) thus, a sloping of the linear plot occurs.

If an additional catalyst other than the nucleophile is present, then the rate equation expands to (see p. 4):

$$k_{obs} = \frac{k_1k_2 + k_1k_3(\text{piperidine}) + k_1k_4(\text{catalyst})}{k_{-1} + k_2 + k_3(\text{piperidine}) + k_4(\text{catalyst})}$$

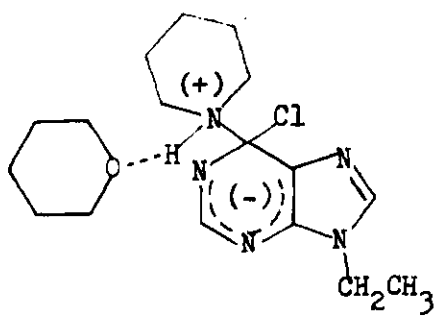
and if $k_{-1} \gg k_2 + k_3(\text{piperidine}) + k_4(\text{catalyst})$:

$$k_{obs} = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3(\text{piperidine})}{k_{-1}} = \frac{k_1k_4(\text{catalyst})}{k_{-1}}$$

At constant piperidine concentration a plot of k_{obs} against the catalyst concentration gives a line of slope = $\frac{k_1k_4}{k_{-1}}$ and an intercept =

$$\frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3 (\text{piperidine})}{k_{-1}}$$

Now it becomes necessary to speculate further on the nature of the catalyst. This was accomplished by adding a variety of compounds to the reaction solution in an attempt to observe the extent of the catalytic effect. Triethylamine, which had been found to be a good catalyst in the reaction of cyanuric chloride with aniline (52), failed to produce any noticeable catalytic effect. This may be attributed to a steric problem since 2,6-dimethylpiperidine, likewise, did not catalyze the reaction. Tetrahydrofuran, tetrahydropyran, and acetone were also ineffective as catalysts. If proton removal alone were the rate-determining feature, then one might anticipate that the latter three additives could enhance the rate since they are all Lewis bases:



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Thus, failure to produce any noticeable effect on the reaction rate by the addition of these compounds suggests that something other than simple proton removel or "base" catalysis may be involved (60).

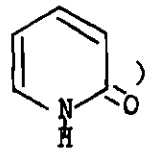
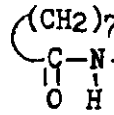
Pyridine was found to exhibit a weak to strong catalytic effect on the reactions studied by Bernasconi and Zollinger (58) and by Pietra and Vitali (69) in benzene solution. The results here indicate that pyridine is, at best, only a poor catalyst in the reaction of piperidine with 6-chloro-9-ethylpurine. Both 1-aminobutane and 1,2-ethanediamine catalyze the piperidine-purine reaction to an extent comparable to that of piperidine itself (after the statistical correction for the two amine groups in the diamine). The values of the catalytic constants were obtained from the slopes of the plots in Figures 19, 28, 29, and 30, and are listed in Table 39. It is obvious in comparing the pyridine to the amine catalysis that the proton attached to the nitrogen of the additive is necessary for effective participation in the catalytic effect.

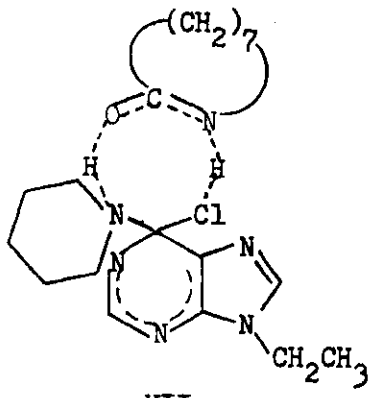
Table 39. Catalytic Constants for the Reaction of Piperidine with 6-Chloro-9-ethylpurine in Isooctane at 29.75 .

Catalyst	Catalytic Coefficient (k_4')*(or k_3')
Pyridine	9.16×10^{-4} $M^{-2}sec^{-1}$
1-Aminobutane	1.16×10^{-2} $M^{-2}sec^{-1}$
1,2-Ethanediamine	1.17×10^{-2} $M^{-2}sec^{-1}$
Piperidine	1.29×10^{-2} $M^{-2}sec^{-1}$

$*k_4' = \frac{k_1 k_4}{k_{-1}}$

A considerable amount of information concerning the nature of the piperidine-purine reaction was obtained by a kinetic study of the reaction in the presence of small amounts of lactam, 2-azacyclononanone. The

lactam α-pyridone () has been found to accelerate the reaction of cyanuric chloride with aniline in benzene solution (52). Furthermore, it was discovered to be an excellent catalyst in the reaction of 2,4-dinitrofluorobenzene with piperidine, also in benzene solution (53). The argument that lactams such as α-pyridone can assist in proton-halide removal with minimum charge accumulation during the transition state in non-polar solvents certainly has merit (53). Moreover, this same rationale can be applied to the effect of 2-azacyclononanone () on the reaction of piperidine with 6-chloro-9-ethylpurine in isooctane. This "bifunctional" catalysis by the lactam can be represented in the following manner:



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The value of the catalysis constant (k_4') for this amide is calculated from the slope of the line in Figure 31 to be 27.6 x 10^{-2} M^{-1} sec^{-1}. Therefore, for the reaction under investigation it is apparent that an effective

catalyst is one which at least possesses a proton bound to an electronegative atom; it may also contain a "bifunctional" center which can assist in both removal of a proton and the halide leaving group. Thus, as it has already been shown, amines and lactams which contain an "acidic" proton can act as bifunctional catalysts.

By studying the effect of acids on the piperidine-purine reaction it was hoped that more information might be obtained regarding the breakdown of the intermediate complex. However, mineral acids and carboxylic acids react with piperidine even in dilute concentrations. Phenols were also found to complicate such studies by salt formation (54). Therefore, various alcohols were chosen as the catalysts in this particular phase of the investigation.

Methanol (O-h and O-d), 1-butanol, and 2-methyl-2-propanol were found to accelerate the reaction of piperidine with 6-chloro-9-ethylpurine as shown in the following Table 40 and Figures 32, 33, 34 and 35 (piperidine-N-d was used in the methanol-O-d solutions).

Table 40. Addition of Alcohols to the Piperidine-Purine Solutions at 29.75 ± 0.25 C.

Piperidine (moles liter^{-1})	Alcohol	Alcohol (moles liter^{-1})	k_{obs} ($\underline{M}^{-1}$ sec^{-1})
0.0537	Methanol	0.0000	1.06×10^{-3}
0.0537	Methanol	0.0513	6.03×10^{-3}
0.0537	Methanol	0.1027	10.93×10^{-3}
0.0537	Methanol	0.2738	22.34×10^{-3}
0.0537	Methanol	0.4108	27.02×10^{-3}
0.1055	Methanol	0.0000	1.73×10^{-3}
0.1055	Methanol	0.0513	5.69×10^{-3}
0.1055	Methanol	0.1027	10.50×10^{-3}
0.1055	Methanol	0.2054	16.78×10^{-3}
0.1055	Methanol	0.4108	23.62×10^{-3}
0.2290	Methanol	0.0000	3.32×10^{-3}
0.2290	Methanol	0.0521	5.98×10^{-3}

Table 40. (Continued)

Piperidine (moles liter^{-1})	Alcohol	Alcohol (moles liter^{-1})	k_{obs} ($\underline{M}^{-1}sec^{-1}$)
0.2290	Methanol	0.1042	8.77×10^{-3}
0.2290	Methanol	0.2085	13.08×10^{-3}
0.2290	Methanol	0.2780	15.07×10^{-3}
0.2290	Methanol	0.4170	18.18×10^{-3}
0.0282*	1-Butanol	0.0000	9.00×10^{-4}
0.0282	1-Butanol	0.0483	7.15×10^{-3}
0.0282	1-Butanol	0.0966	13.26×10^{-3}
0.0282	1-Butanol	0.1932	20.31×10^{-3}
0.0282	1-Butanol	0.2576	22.99×10^{-3}
0.0282	1-Butanol	0.3864	25.33×10^{-3}
0.0537	1-Butanol	0.0483	6.52×10^{-3}
0.0537	1-Butanol	0.0966	12.29×10^{-3}
0.0537	1-Butanol	0.1932	19.18×10^{-3}
0.0537	1-Butanol	0.2576	21.40×10^{-3}
0.0537	1-Butanol	0.3863	24.28×10^{-3}
0.0972	1-Butanol	0.0000	1.64×10^{-3}
0.0972	1-Butanol	0.0483	6.09×10^{-3}
0.0972	1-Butanol	0.0966	10.76×10^{-3}
0.0972	1-Butanol	0.1932	16.63×10^{-3}
0.0972	1-Butanol	0.2576	19.46×10^{-3}
0.0972	1-Butanol	0.3863	22.21×10^{-3}
0.1906	1-Butanol	0.0000	2.96×10^{-3}
0.1906	1-Butanol	0.0509	6.11×10^{-3}
0.1906	1-Butanol	0.1018	9.64×10^{-3}
0.1906	1-Butanol	0.1018	9.40×10^{-3}
0.1906	1-Butanol	0.2035	14.40×10^{-3}
0.1906	1-Butanol	0.2035	14.33×10^{-3}
0.1906	1-Butanol	0.2714	15.62×10^{-3}
0.1906	1-Butanol	0.4070	18.82×10^{-3}
0.0972	2-Methyl-2-propanol	0.0000	1.64×10^{-3}
0.0972	2-Methyl-2-propanol	0.0509	4.58×10^{-3}
0.0972	2-Methyl-2-propanol	0.1019	7.00×10^{-3}
0.0972	2-Methyl-2-propanol	0.2037	10.14×10^{-3}
0.0972	2-Methyl-2-propanol	0.2716	11.34×10^{-3}
0.0972	2-Methyl-2-propanol	0.4074	12.81×10^{-3}
0.1989	2-Methyl-2-propanol	0.0000	2.87×10^{-3}
0.1989	2-Methyl-2-propanol	0.0518	5.13×10^{-3}
0.1989	2-Methyl-2-propanol	0.1036	6.97×10^{-3}
0.1989	2-Methyl-2-propanol	0.2072	9.65×10^{-3}
0.1989	2-Methyl-2-propanol	0.2763	10.73×10^{-3}
0.1989	2-Methyl-2-propanol	0.4144	12.18×10^{-3}
0.2271	Methanol-O-d	0.0000	3.34×10^{-3}

*(obtained by extrapolation)

Table 40. (Concluded)

Piperidine (moles liter^{-1})	Alcohol	Alcohol (moles liter^{-1})	k_{obs} ($M^{-1}sec^{-1}$)
0.2271	Methanol-0-d	0.0513	6.26×10^{-3}
0.2271	Methanol-0-d	0.1026	9.12×10^{-3}
0.2271	Methanol-0-d	0.2053	13.23×10^{-3}
0.2271	Methanol-0-d	0.2737	15.54×10^{-3}
0.2271	Methanol-0-d	0.4106	18.63×10^{-3}

It is evident from examination of the following graphs (Figures 33, 34 and 35) that the rate coefficient due to the catalysis by the alcohols (k_4') is changing with a variation in the concentration of piperidine. Table 41 and Figure 36 illustrates that the apparent rate coefficient decreased linearly with increasing piperidine concentration. Only the linear portion of the plots were used to calculate the rate coefficients.

Table 41. Change in the Rate Coefficient with a Variation in the Concentration of Piperidine

Piperidine (moles liter^{-1})	Alcohol	Rate Coefficient due to Catalysis by Alcohol (k_4')
0.0537	Methanol-0-h	9.61×10^{-2} $M^{-2}sec^{-1}$
0.1055	Methanol-0-h	8.54×10^{-2} $M^{-2}sec^{-1}$
0.2290	Methanol-0-h	5.23×10^{-2} $M^{-2}sec^{-1}$
0.0282	1-Butanol	12.80×10^{-2} $M^{-2}sec^{-1}$
0.0537	1-Butanol	11.63×10^{-2} $M^{-2}sec^{-1}$
0.0972	1-Butanol	9.44×10^{-2} $M^{-2}sec^{-1}$
0.1906	1-Butanol	6.47×10^{-2} $M^{-2}sec^{-1}$
0.0972	2-Methyl-2-propanol	5.18×10^{-2} $M^{-2}sec^{-1}$
0.1982	2-Methyl-2-propanol	3.96×10^{-2} $M^{-2}sec^{-1}$
0.2271	Methanol-0-d	5.53×10^{-2} $M^{-2}sec^{-1}$

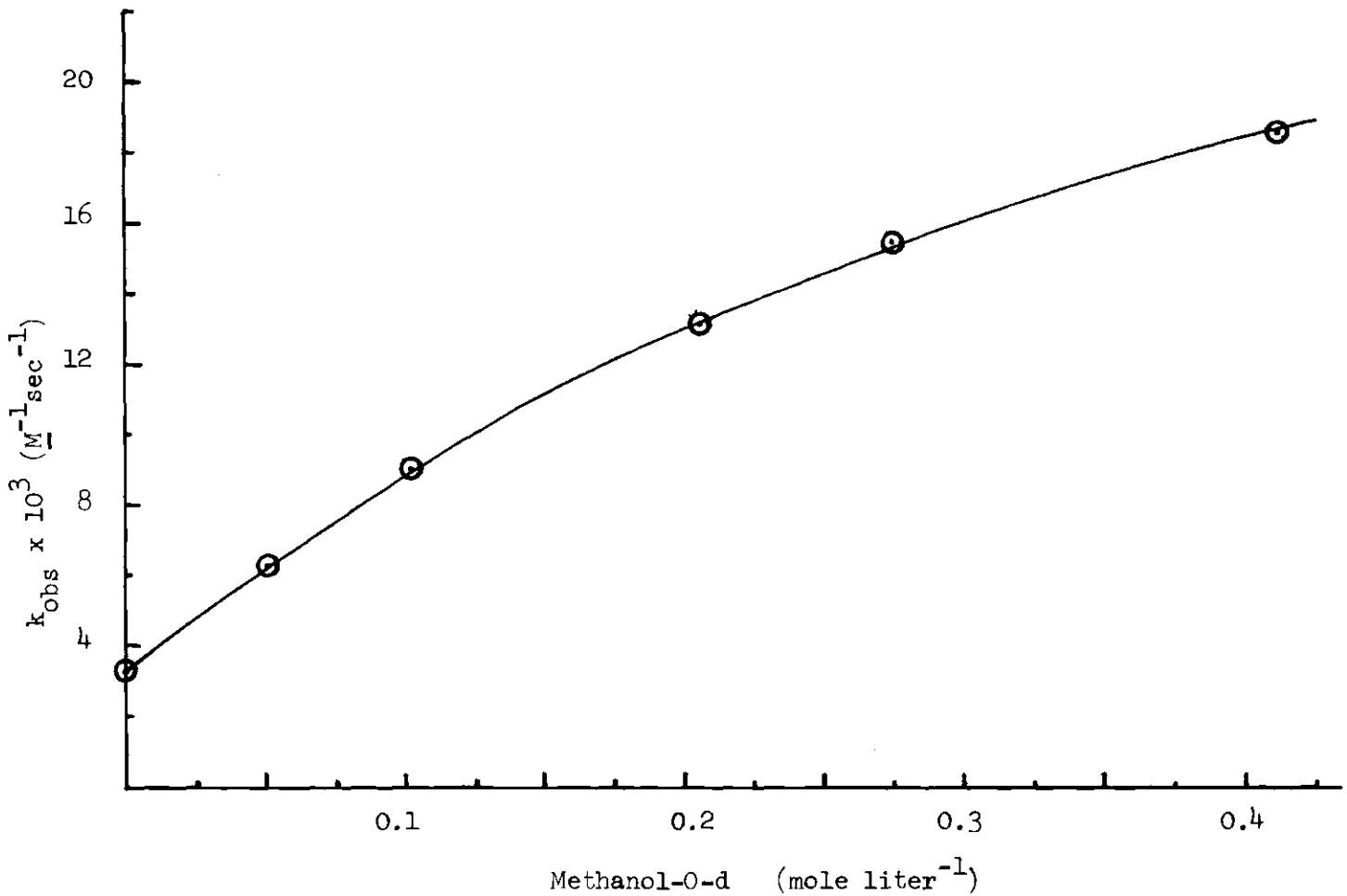


Figure 32 Addition of Methanol-O-d to the Piperidine-Purine Reaction at 29.75° C

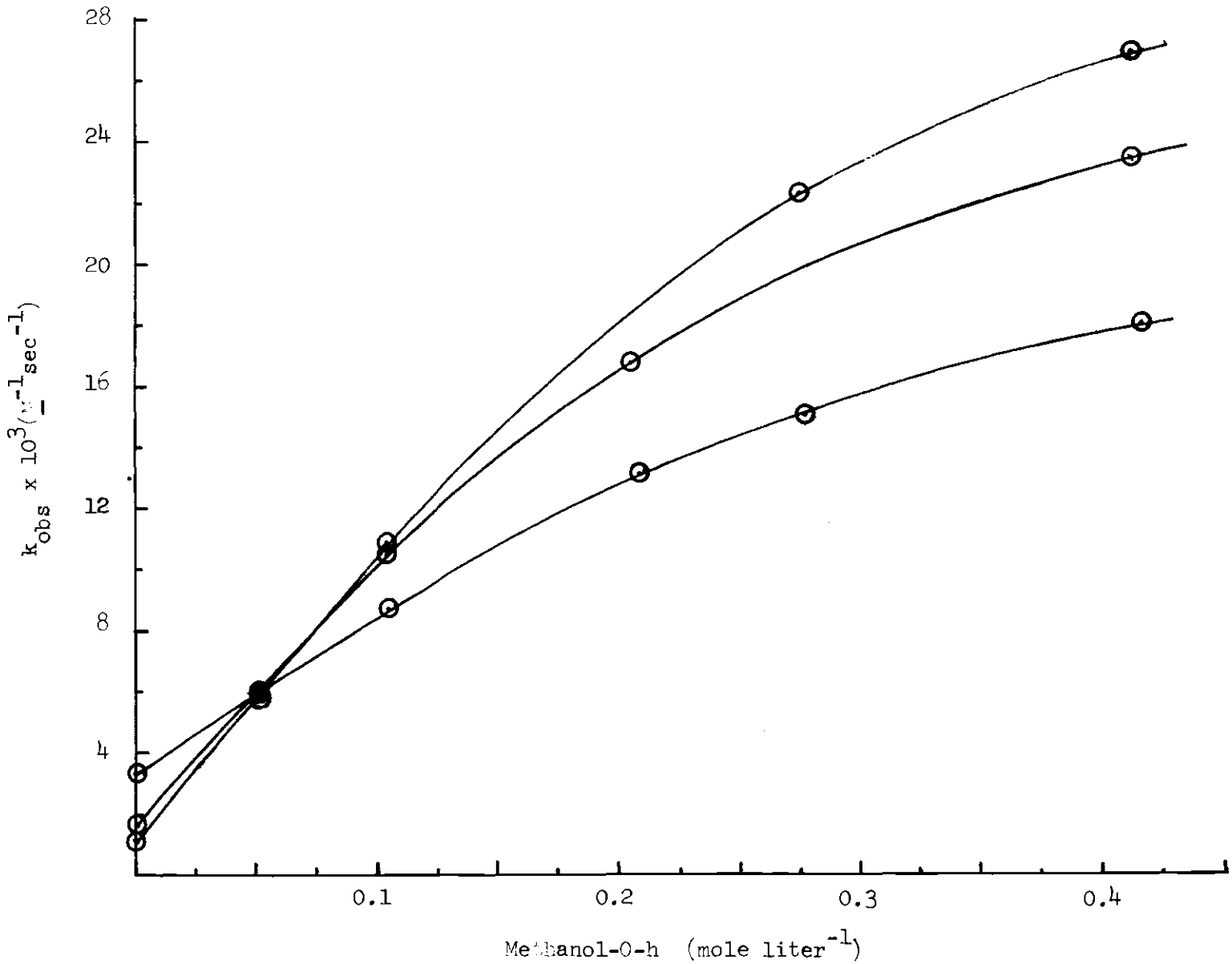


Figure 33 Addition of Methanol-O-h to the Piperidine-Purine Reaction at 29.75° C

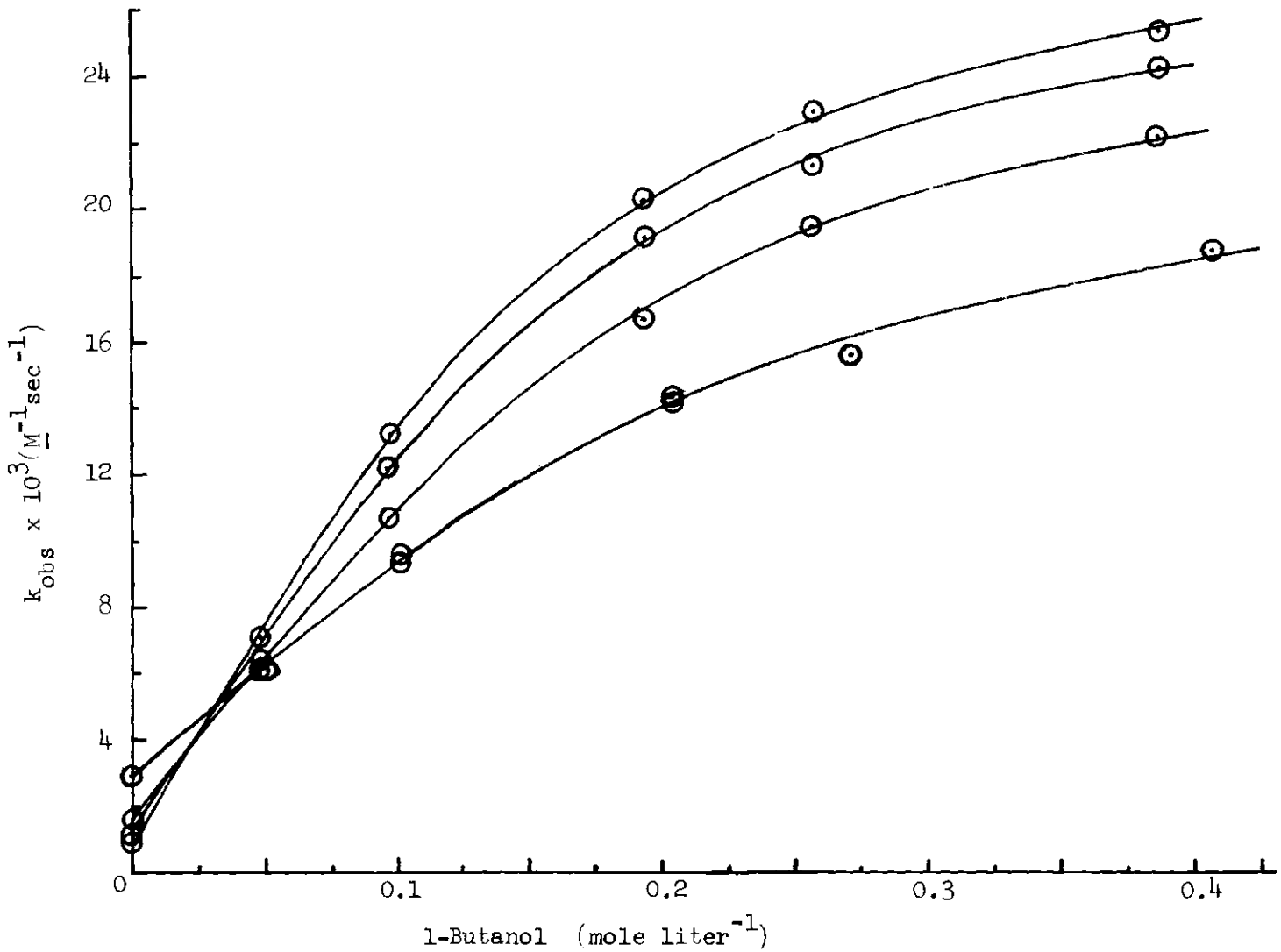


Figure 34 Addition of 1-Butanol to the Piperidine-Purine Reaction Solution at 29.75° C.

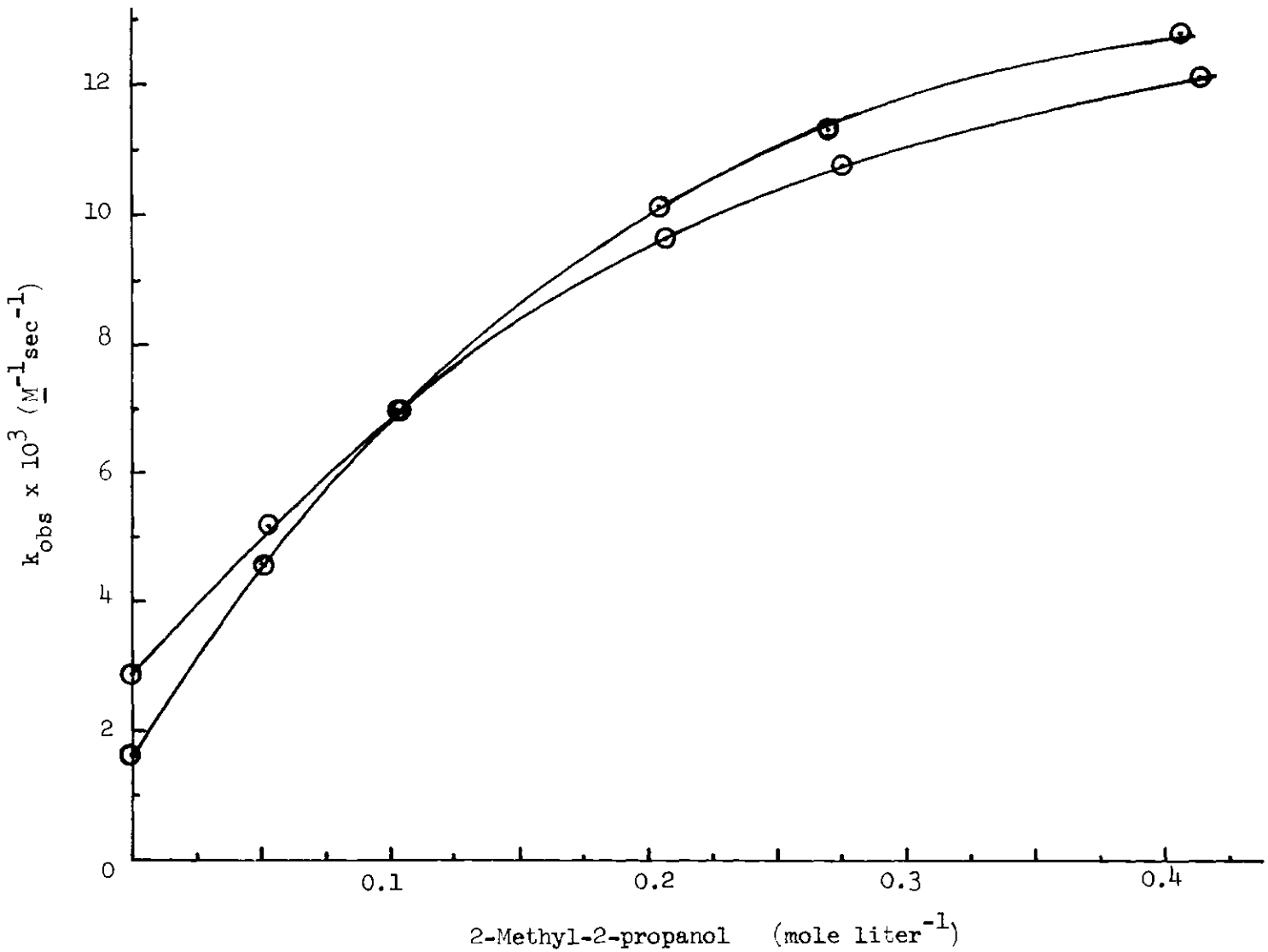


Figure 35 Addition of 2-Methyl-2-propanol to the Piperidine-Purine Reaction Solution at 29.75° C

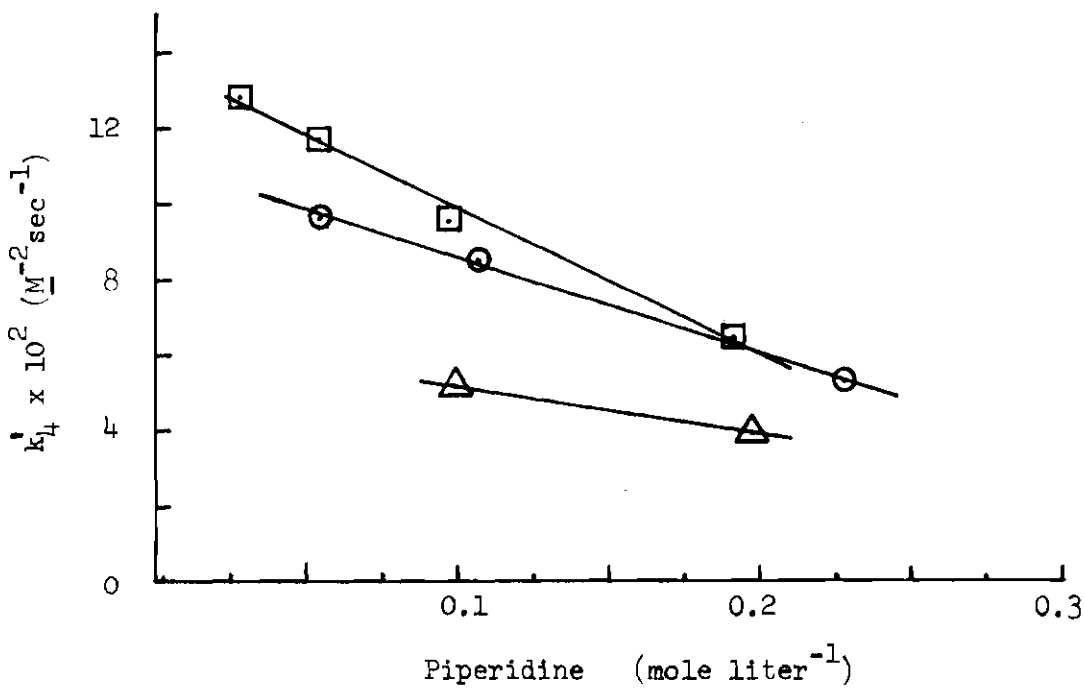


Figure 36 Change in the Rate Coefficient with a Variation in Piperidine Concentration

□ 1 - Butanol

○ Methanol

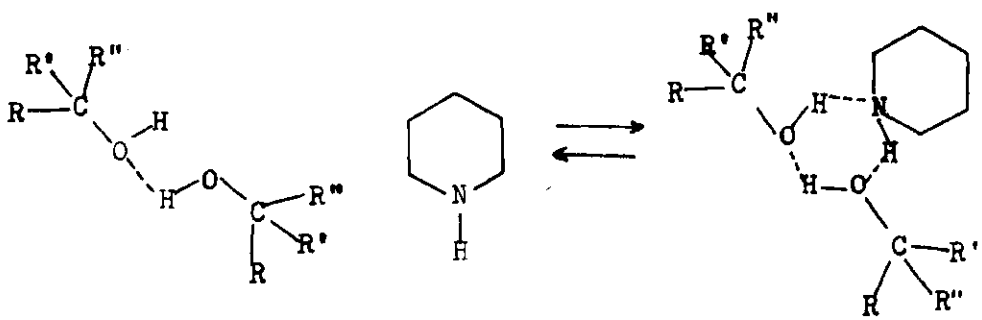
△ 2-Methyl-2-propanol

This behavior seemed to indicate that some medium effect was occurring, possibly association between piperidine and the corresponding alcohol. A variety of techniques have been reported for the study of the formation of alcohol-alcohol and alcohol-amine hydrogen-bonded complexes in non-polar media. Unfortunately, the amount of useful data obtained from such studies is very limited. Using nmr spectroscopy, monomer-tetramer and monomer-trimer equilibria have been postulated for methanol and 2-methyl-2-propanol, respectively, in carbon tetrachloride (91). Others (96,97) have suggested that monomer-dimer complexes are also important. In fact, studies in the far ultra-violet absorption spectrum of hydrogen-bonded methanol in n-hexane have indicated that at least 28 percent of the molecules are associated at a concentration of 0.0247 moles liter^{-1}, the extent of association then increases to 74 percent at a concentration of 0.247 moles liter^{-1} (99) (assuming a dimeric species in both cases). Formation constants for all the normal, straight chain alcohols dispersed in non-polar solvents have been reported to be essentially the same (95). However, Pitzer and coworkers, (96) using nmr investigations have proposed that the presence of higher polymers makes it impossible to obtain a satisfactory equilibrium constant for the monomer-dimer association of alcohols in benzene or carbon tetrachloride. In general, though, it is thought that alcohols in non-polar solvents such as benzene and n-hexane are extensively associated even at low mole fractions of the alcohol (96).

Confusion has also arisen regarding the association of alcohols with amines via hydrogen-bonding. Using infrared techniques, association constants for the alcohol-amine systems of a type similar to those utilized here range from K = 1, to K = 5 for carbon tetrachloride solutions (for

instance, K = 3.4 has been reported for the 1-butanol-diethylamine complex) (89). Difficulty in interpretation of the data has been encountered due to extensive overlap of the spectrum peaks.

In view of all of the conflicting and confusing information regarding these association studies, the following treatment of the data was undertaken. First, in consideration of the consensus and in order to simplify the calculations, the alcohols were assumed to be entirely dimeric in isooctane in the concentration range studied. Second, a series of equilibrium constants ranging from K = 1 to K = 6 were used in determining the concentration of "free" piperidine and dimeric alcohol in solution. Thus, the equilibrium which appears likely is the following (the species (IX) is neither nucleophilic or catalytic). The best correlation of data was obtained for K = 5;



however, the linearity of the plot in determining (k_3') did not deviate appreciably for K = 4, 5 or 6. Therefore, the value of K = 5 was used as the association constant for all of the alcohol studies (including the case of the benzyl alcohols to be discussed, subsequently). The results

of this treatment of the data are presented in Table 42, 43, 44, 45 and 46 and in Figures 37, 38, 39 and 40. The catalytic coefficient due to the alcohol catalysis was obtained from the slope of the plot of k_{obs} (alcohol) against the alcohol concentrations.

It is obvious that several of the points in the following figures deviate from the linear plot (see the points "blocked in"). These discrepancies are only found for the higher concentrations of alcohol and/or piperidine. There are at least two possible reasons that might be offered to explain these variations: (1) Higher associated species may be occurring at these elevated concentrations which would tend to cause lower rate values than anticipated; and (2) A change in the rate-determining step for the higher concentrations of alcohol or piperidine where catalysis should be a maximum ($k_2 + k_3(pip) + k_4(Cat) \geq k_{-1}$) would produce similar results. It is difficult to predict, with the data presented, which of these effects is predominating. However, for the catalysis by methanol and 1-butanol it is tempting to attribute the discrepancies to more extensive association than dimers since not all of the "fast" reactions deviate from the linear relationship.

It is possible that the "acid" catalysis demonstrated by the alcohols is really a type of bifunctional catalysis which could be represented by the (X) or (XI). Since most of the alcohols appear to be associated, the latter transition state might be more appropriate.

Table 42. Determination of the Observed Second Order Rate Coefficient Due to the Addition of Methanol to the Reaction of Piperidine with 6-Chloro-9-ethylpurine in Isooctane at 29.75 ± 25°C.

Initial Piperidine (moles liter^{-1})	Initial Methanol (moles liter^{-1})	Equilibrium Piperidine (moles liter^{-1})	Equilibrium Methanol (moles liter^{-1})	k'_{obs} (M^{-1} sec^{-1})	k_{obs} Piperidine (M^{-1} sec^{-1})	Methanol (M^{-1} sec^{-1})
0.1055	0.1027	0.0896	0.0354	0.01236	0.00173	0.01063
0.0537	0.1027	0.0445	0.0421	0.01319	0.00110	0.01209
0.2290	0.1042	0.2028	0.0259	0.00989	0.00303	0.00686
0.2290	0.2085	0.1797	0.0549	0.01665	0.00274	0.01391
0.1055	0.2054	0.0769	0.0741	0.02301	0.00150	0.02151
0.0537	0.4108	0.0283	0.1800	0.05127	0.00090	0.05037
0.1055	0.4108	0.0588	0.1587	0.04239	0.00127	0.04112
0.1055	0.0513	0.0971	0.0172	0.00618	0.00172	0.00446
0.0537	0.0513	0.0487	0.0206	0.00665	0.00115	0.00550
0.2290	0.0521	0.2157	0.0123	0.00634	0.00319	0.00315
0.2290	0.2780	0.1659	0.0759	0.02079	0.00258	0.01821
0.0537	0.2738	0.0339	0.1192	0.03539	0.00097	0.03443
0.0278	0.0494	0.0244	0.0213	0.00722	0.00083	0.00639
0.0336	0.0494	0.0298	0.0209	0.00743	0.00102	0.00641
0.0282	0.0513	0.0249	0.0223	0.00825	0.00085	0.00740
0.2290	0.4170	0.1423	0.1218	0.02923	0.00230	0.02693

Table 43. Determination of the Observed Second Order Rate Coefficient Due to the Addition of 1-Butanol to the Reaction of Piperidine with 6-Chloro-9-ethylpurine in Isooctane at 29.75 ± 25°C.

Initial Piperidine (moles liter^{-1})	Initial 1-Butanol (moles liter^{-1})	Equilibrium Piperidine (moles liter^{-1})	Equilibrium 1-Butanol (moles liter^{-1})	k'_{obs} (M^{-1} sec^{-1})	k_{obs} Piperidine (M^{-1} sec^{-1})	k_{obs} 1-Butanol (M^{-1} sec^{-1})
0.1906	0.0509	0.1786	0.0134	0.00652	0.00272	0.00380
0.1906	0.1018	0.1674	0.0277	0.01096	0.00258	0.00838
0.1906	0.1018	0.1674	0.0277	0.01068	0.00258	0.00810
0.1906	0.2035	0.1474	0.0586	0.01862	0.00233	0.01629
0.1906	0.2035	0.1474	0.0586	0.01851	0.00233	0.01618
0.1906	0.2714	0.1357	0.0808	0.02193	0.00220	0.01973
0.1906	0.4070	0.1159	0.1288	0.03092	0.00198	0.02894
0.0972	0.0483	0.0896	0.0166	0.00661	0.00163	0.00498
0.0972	0.0966	0.0830	0.0341	0.01260	0.00158	0.01102
0.0972	0.1932	0.0717	0.0711	0.02254	0.00142	0.02112
0.0972	0.2576	0.0654	0.0970	0.02892	0.00134	0.02758
0.0972	0.3863	0.0553	0.1513	0.03904	0.00121	0.03783
0.0537	0.0483	0.0489	0.0194	0.00716	0.00115	0.00601
0.0537	0.0966	0.0449	0.0394	0.01470	0.00110	0.01360
0.0537	0.1932	0.0382	0.0811	0.02696	0.00100	0.02596
0.0537	0.2576	0.0347	0.1098	0.03312	0.00098	0.03214
0.0537	0.3863	0.0291	0.1686	0.04480	0.00090	0.04390
0.0282	0.0483	0.0256	0.0214	0.00788	0.00087	0.00701
0.0282	0.0966	0.0233	0.0433	0.01606	0.00083	0.01523
0.0282	0.1932	0.0196	0.0880	0.02922	0.00079	0.02843
0.0282	0.2576	0.0177	0.1183	0.03662	0.00076	0.03586
0.282	0.3864	0.0148	0.1798	0.04828	0.00072	0.04756

Table 44. Determination of the Observed Second Order Rate Coefficient Due to the Addition of 2-Methyl-2-propanol to the Reaction of Piperidine with 6-Chloro-9-ethylpurine in Isooctane at 29.75 ± 25°C

Initial Piperidine (moles liter^{-1})	Initial 2-methyl-2-propanol (moles liter^{-1})	Equilibrium Piperidine (moles liter^{-1})	Equilibrium 2-methyl-2-propanol (moles liter^{-1})	k'_{obs} ($M^{-1}sec^{-1}$)	k_{obs}(pip) ($M^{-1}sec^{-1}$)	k_{obs}(alc) ($M^{-1}sec^{-1}$)
0.1989	0.0518	0.1864	0.0134	0.00548	0.00281	0.00267
0.1989	0.1036	0.1747	0.0276	0.00793	0.00268	0.00525
0.1989	0.2072	0.1539	0.0580	0.01248	0.00242	0.01006
0.1989	0.2763	0.1416	0.0809	0.01507	0.00228	0.01279
0.1989	0.4144	0.1209	0.1292	0.02009	0.00202	0.01807
0.0973	0.0509	0.0894	0.0176	0.00498	0.00163	0.00335
0.0973	0.1019	0.0825	0.0361	0.00825	0.00158	0.00667
0.0973	0.2037	0.0707	0.0753	0.01394	0.00140	0.01254
0.0973	0.2716	0.0643	0.1028	0.01715	0.00133	0.01582
0.0973	0.4074	0.0540	0.1604	0.02306	0.00120	0.02186

Table 45. Determination of the Observed Second Order Rate Coefficient Due to the Addition of Methanol-O-d to the Reaction of Piperidine with 6-Chloro-9-ethylpurine in Isooctane at 29.75 ± 25°C

Initial Piperidine (moles liter^{-1})	Initial Methanol-O-d (moles liter^{-1})	Equilibrium Piperidine (moles liter^{-1})	Equilibrium Methanol-O-d (moles liter^{-1})	k'_{obs} ($\underline{M}^{-1}sec^{-1}$)	k_{obs}(pip) ($\underline{M}^{-1}sec^{-1}$)	$k_{obs}(CH_3OD)$ ($\underline{M}^{-1}sec^{-1}$)
0.2271	0.0513	0.2139	0.0124	0.00665	0.00312	0.00353
0.2271	0.1026	0.2014	0.0256	0.01029	0.00300	0.00729
0.2271	0.2053	0.1787	0.0542	0.01681	0.00270	0.01411
0.2271	0.2737	0.1652	0.0749	0.02137	0.00256	0.01881
0.2271	0.4106	0.1419	0.1201	0.02981	0.00200	0.02781

Table 46. Summary of the k'_4 Values of the Alcohols

Alcohol	Rate Coefficient due to Catalysis by Alcohol (k'_4) (Assuming Association of the Components)
Methanol-O-h	27.35×10^{-2} ($\underline{M}^{-2}sec^{-1}$)
1-Butanol	30.22×10^{-2} ($\underline{M}^{-2}sec^{-1}$)
2-Methyl-2-propanol	18.84×10^{-2} ($\underline{M}^{-2}sec^{-1}$)
Methanol-O-d	25.69×10^{-2} ($\underline{M}^{-2}sec^{-1}$)

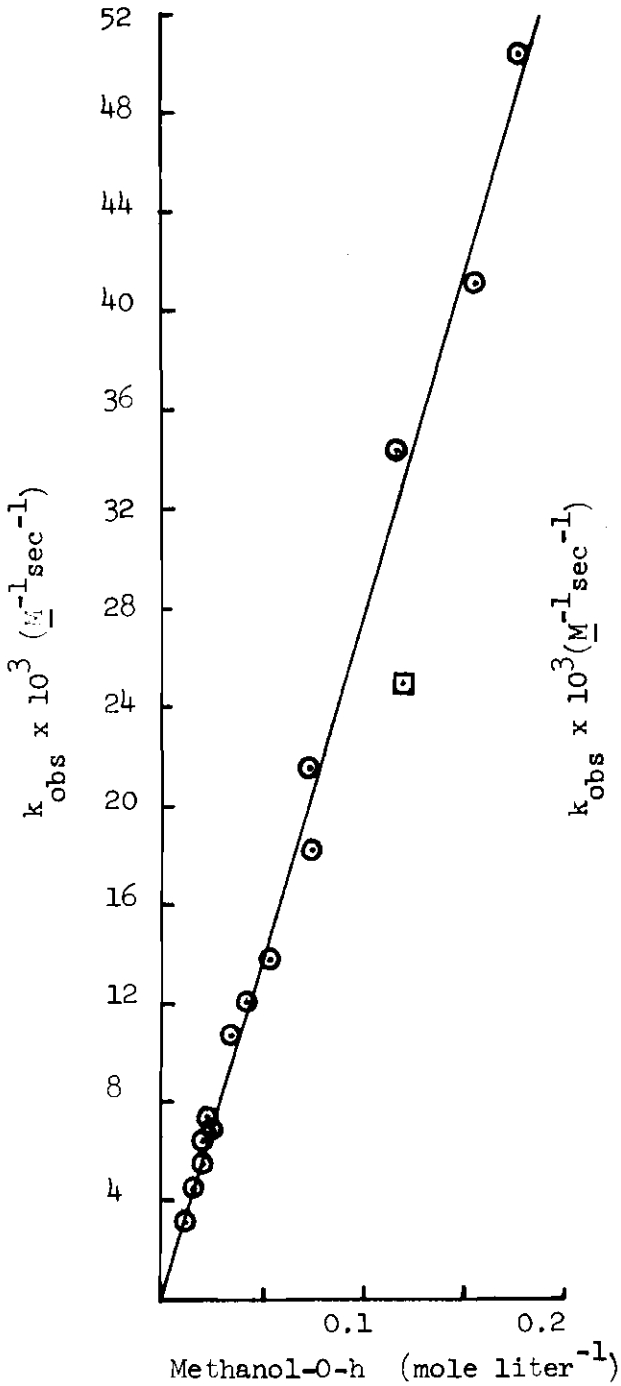


Figure 37
Addition of Methanol-O-h to the Purine-Piperidine Reaction at 29.75° C (Corrected for Association)

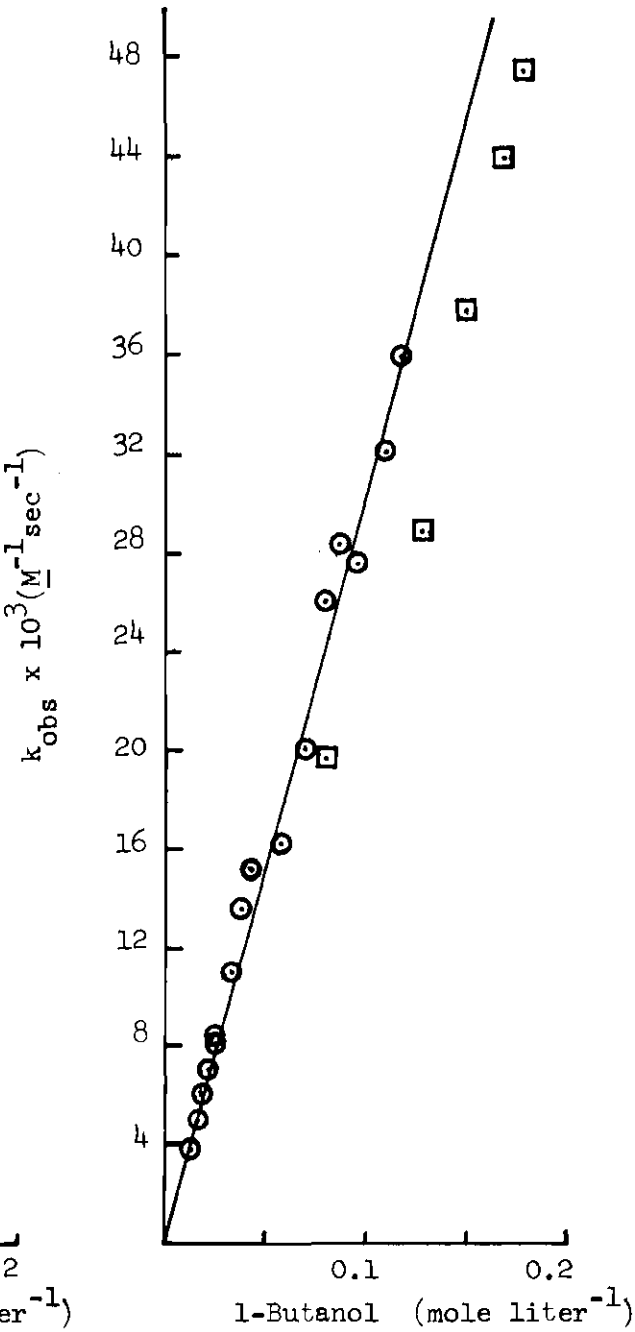


Figure 38
Addition of 1-Butanol to the Piperidine-Purine Reaction at 29.75° C (Corrected for Association)

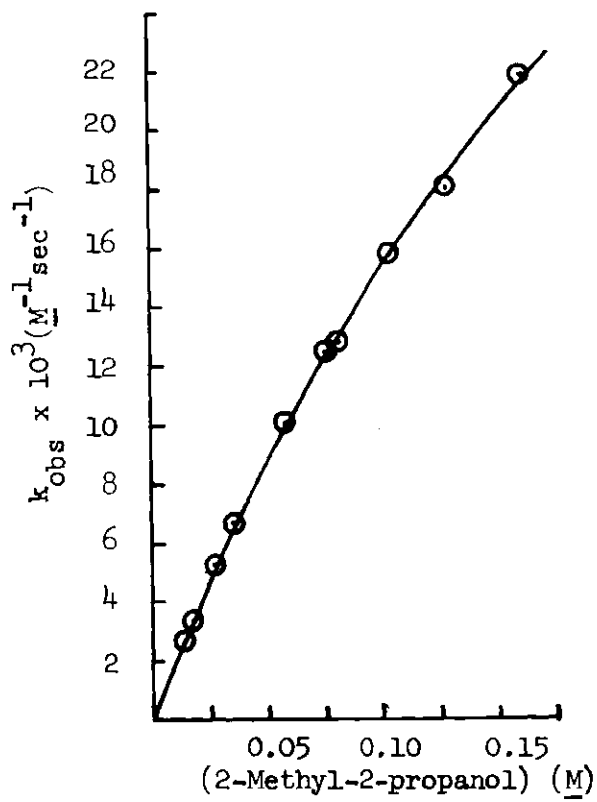


Figure 39 Addition of 2-Methyl-2-propanol to the Piperidine-Purine Reaction at 29.75° C (Corrected for Association)

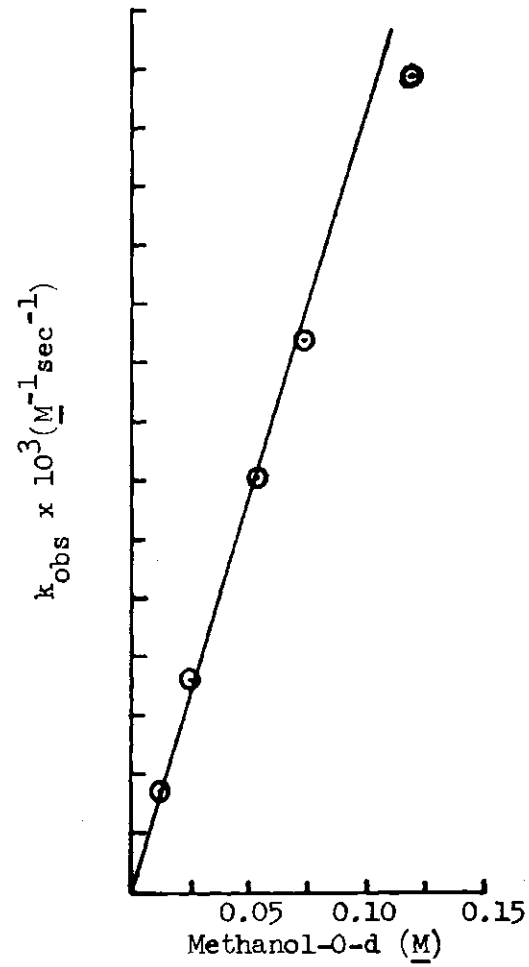
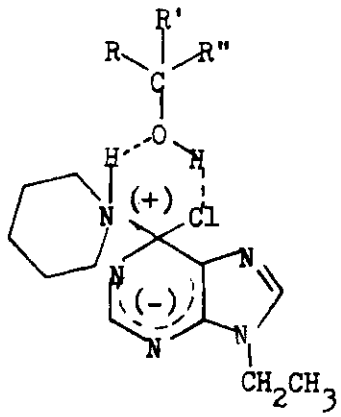


Figure 40 Addition of Methanol-O-d to the Piperidine-Purine Reaction at 29.75° C (Corrected for Association)



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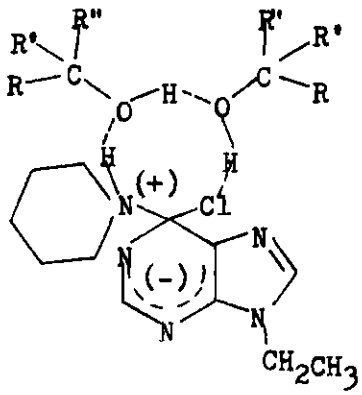


XI

In order to gain additional insight into the nature of the catalysis a Hammett plot was constructed using the data from catalysis studies on four benzyl alcohols. A Hammett plot is, of course, a mechanistic tool. If all the points lie on a straight line, the compounds are assumed to react by the same mechanism. In the case of catalysis by additives which possess both an acidic hydrogen and a non-bonded pair of electrons and display a linear Hammett relationship one (or variations) of three distinct possibilities can exist:

(1) The plot has a large negative rho value which indicates that electron-donating groups attached to the catalyst accelerate the reactions. Electron-donating groups would increase the availability of the electron-pair and decrease the acidity of the acidic proton attached to the electro-negative atom; thus base catalysis predominates.

(2) The plot has a large positive rho value. This demonstrates that electron-withdrawing groups attached to the catalyst accelerate the

reactions. The electron-withdrawing groups would increase the acidity of the acidic proton and decrease the availability of the electron pair of the catalyst. This implies acid catalysis.

(3) The plot is parallel to the abscissa indicating that the nonbonded pair of electrons and the acidic hydrogen of the catalyst play an essentially equal role in the catalytic process; this is bifunctional catalysis.

Since the benzyl alcohols used in this study have similar steric requirements, only different electronic effects should be encountered. The rate coefficients were treated by assuming no association as shown in Table 47 and Figure 41, and also, by assuming dimeric alcohol with an equilibrium between the alcohol dimer and amine (K_{eq} = 5) which is shown in Table 48 and Figure 42. The catalytic coefficients and sigma values are listed in Table 49 and the Hammett plots are shown in Figures 43 and 44.

From the small rho values obtained $\rho = +0.22$ (assuming no association) and $\rho = +0.26$ (assuming dimeric alcohol and an equilibrium between alcohol and amine), it appears that bifunctional catalysis with a small emphasis on the acidity of the catalyst is occurring in these reactions.

Table 47. Rate Coefficients for the Addition of Various Benzyl Alcohols to the Piperidine-Purine Reaction Solution at 29.75° (Assuming No Association)

Piperidine (moles liter^{-1})	Alcohol (moles liter^{-1})	k_{obs} ($M^{-1}sec^{-1}$)
0.1852	0.0000[1]	0.00289
0.1854	0.0650[1]	0.00736
0.1855	0.0871[1]	0.00905
0.1854	0.1221[1]	0.01128
0.1857	0.1470[1]	0.01283
0.1856	0.1800[1]	0.01507
0.1853	0.2600[1]	0.01924
0.1855	0.3066[1]	0.02142
0.1856	0.4242[1]	0.02580
0.1867	0.0000[2]	0.00286
0.1874	0.0818[2]	0.00977
0.1875	0.0932[2]	0.01080
0.1872	0.1114[2]	0.01234
0.1872	0.1551[2]	0.01614
0.1876	0.1795[2]	0.01801
0.1875	0.2648[2]	0.02380
0.1871	0.3022[2]	0.02611
0.1876	0.4753[2]	0.03419
0.1868	0.0000[3]	0.00282
0.1872	0.0410[3]	0.00554
0.1868	0.0765[3]	0.00798
0.1876	0.1124[3]	0.01018
0.1877	0.1724[3]	0.01325
0.1876	0.2242[3]	0.01588
0.1870	0.2801[3]	0.01829
0.1878	0.3954[3]	0.02194
0.1868	0.0000[4]	0.00282
0.1877	0.0478[4]	0.00672
0.1867	0.1032[4]	0.01096
0.1872	0.1446[4]	0.01453
0.1871	0.1951[4]	0.01789

[1]Benzyl Alcohol, [2]m-Chlorobenzyl Alcohol, [3]p-Methylbenzyl Alcohol
[4]p-Chlorobenzyl Alcohol

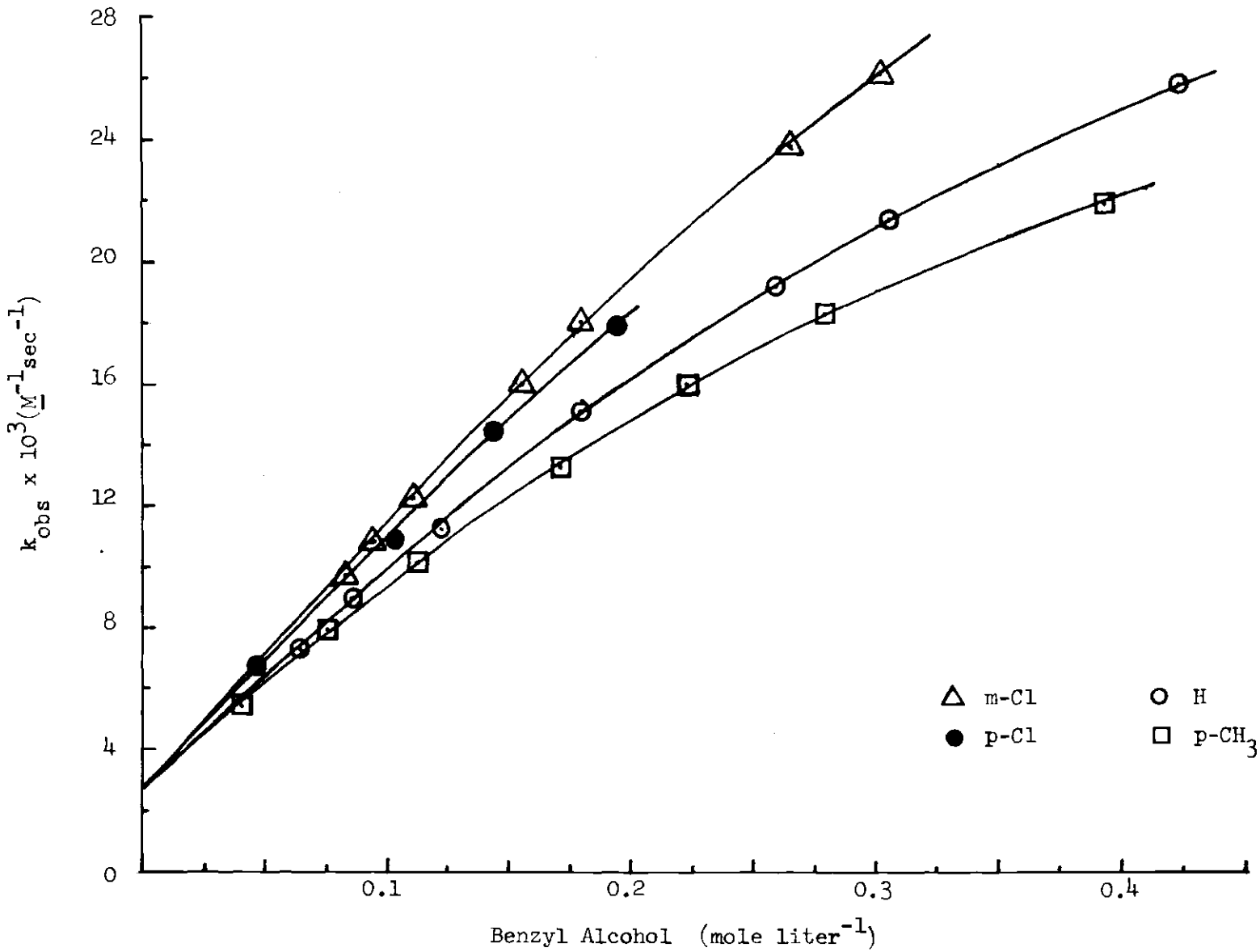


Figure 41 Addition of Benzyl Alcohols to the Piperidine-Purine Reaction Solution at 29.75°C (Assuming No Association)

Table 48. Rate Coefficients for the Addition of Various Benzyl Alcohols to the Piperidine-Purine Reaction Solution at 29.75°C (Assuming Association of the Components)

Initial Piperidine (moles liter^{-1})	Initial Alcohol (moles liter^{-1})	Equilibrium Piperidine (moles liter^{-1})	Equilibrium Alcohol (moles liter^{-1})	k'_{obs} ($M^{-1}sec^{-1}$)	$k_{obs(pip)}$ ($M^{-1}sec^{-1}$)	$k_{obs(Alc)}$ ($M^{-1}sec^{-1}$)
0.1854	0.0650[1]	0.1704	0.0175	0.00801	0.00261	0.00540
0.1855	0.0871[1]	0.1657	0.0238	0.01013	0.00259	0.00754
0.1854	0.1221[1]	0.1584	0.0340	0.01320	0.00248	0.01072
0.1857	0.1470[1]	0.1538	0.0416	0.01549	0.00242	0.01307
0.1865	0.1800[1]	0.1474	0.0518	0.01972	0.00231	0.01741
0.1853	0.2600[1]	0.1333	0.0780	0.02675	0.00219	0.02456
0.1855	0.3066[1]	0.1262	0.0940	0.03149	0.00210	0.02939
0.1856	0.4242[1]	0.1102	0.1367	0.04346	0.00190	0.04156
0.1874	0.0818[2]	0.1687	0.0228	0.01085	0.00260	0.00825
0.1875	0.0932[2]	0.1663	0.0254	0.01217	0.00258	0.00959
0.1872	0.1114[2]	0.1622	0.0307	0.01427	0.00251	0.01173
0.1872	0.1551[2]	0.1535	0.0439	0.01969	0.00241	0.01728
0.1876	0.1795[2]	0.1492	0.0514	0.02265	0.00236	0.02029
0.1875	0.2648[2]	0.1393	0.0842	0.03203	0.00223	0.02980
0.1871	0.3022[2]	0.1281	0.0921	0.03813	0.00210	0.03603
0.1876	0.4753[2]	0.1055	0.1555	0.06078	0.00185	0.05893
0.1872	0.0410[3]	0.1776	0.0109	0.00584	0.00271	0.00313
0.1868	0.0765[3]	0.1691	0.0207	0.00881	0.00260	0.00621
0.1877	0.1724[3]	0.1507	0.0492	0.01651	0.00240	0.01411
0.1876	0.2242[3]	0.1412	0.0657	0.02110	0.00228	0.01882
0.1870	0.2801[3]	0.1315	0.0845	0.02600	0.00216	0.02384
0.1878	0.3954[3]	0.1154	0.1253	0.03571	0.00195	0.03376
0.1876	0.1129[4]	0.1623	0.0311	0.01176	0.00250	0.00926
0.1877	0.1032[4]	0.1635	0.0284	0.01251	0.00235	0.00996
0.1877	0.0478[4]	0.1765	0.0127	0.00115	0.00270	0.00445
0.1872	0.1446[4]	0.1556	0.0407	0.01748	0.00245	0.01503
0.1871	0.1951[4]	0.1459	0.0564	0.02294	0.00231	0.02063

[1]Benzyl Alcohol, [2]m-Chlorobenzyl Alcohol, [3]p-Methylbenzyl Alcohol, [4]p-Chlorobenzyl Alcohol

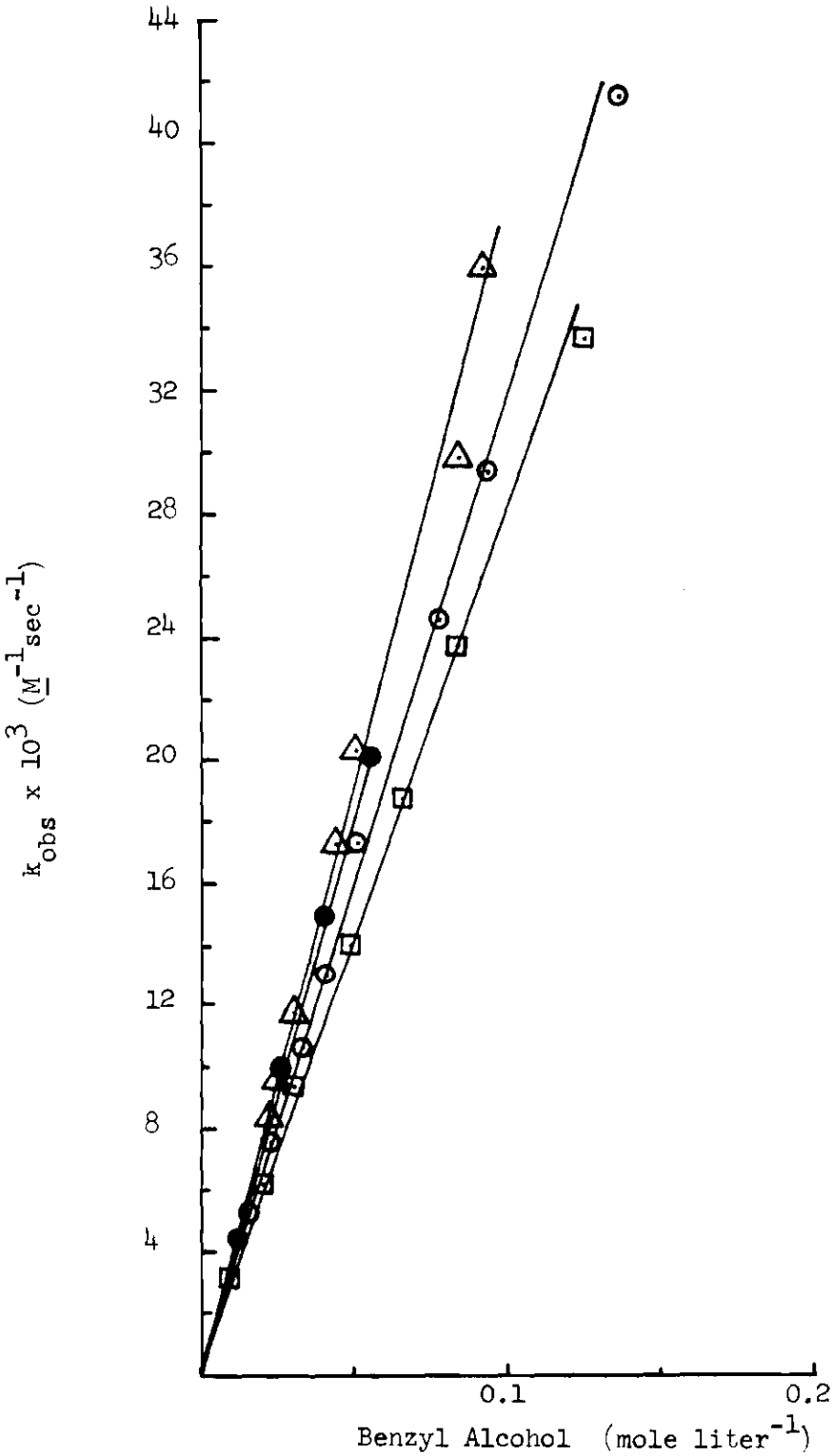


Figure 42 Addition of Benzyl Alcohols to the Piperidine-Purine Reaction Solution at 29.75° C (Assuming Association of the Components)

△ m-Cl, ● p-Cl, ○ H, □ p-CH_3

Table 49. Hammett Plot Data for the Benzyl Alcohols

Substituent	Sigma Value (117)	$k'_{(alc)}$ ($M^{-2}sec^{-1}$) (assuming no association)	$k'_{(alc)}$ ($M^{-2}sec^{-1}$) (assuming association)
p-CH_3	-0.17	6.58×10^{-3}	27.74×10^{-3}
H	0.00	6.75×10^{-3}	31.07×10^{-3}
p-Cl	+0.227	8.04×10^{-3}	36.42×10^{-3}
m-Cl	+0.373	8.49×10^{-3}	37.89×10^{-3}

rho value (no association) = +0.22
rho value (association = +0.26

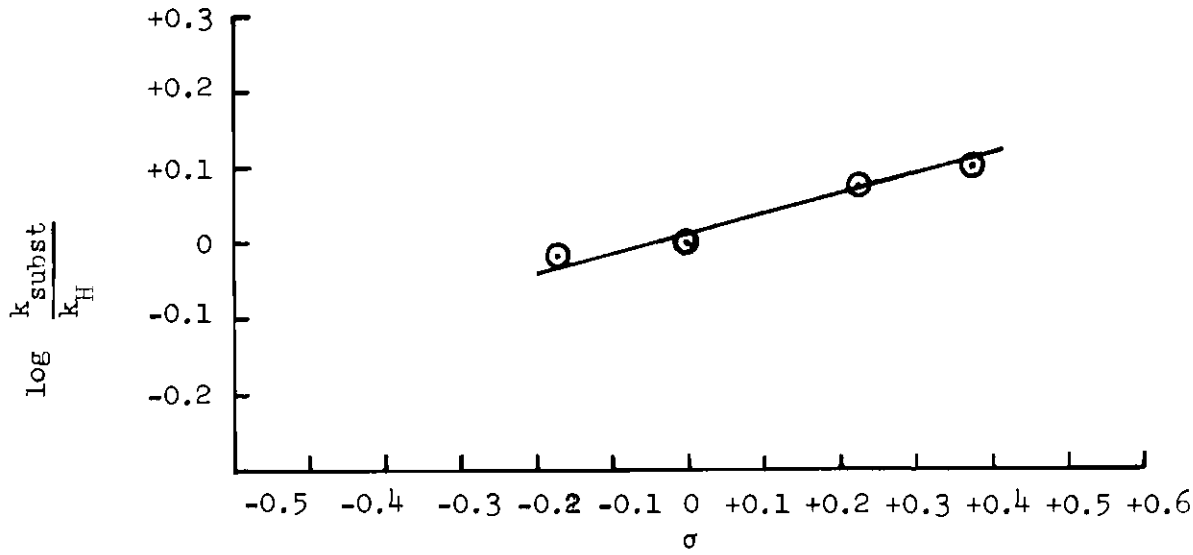


Figure 43 Hammett Plot for the Addition of Benzyl Alcohols to the Piperidine-Purine Reaction in Isooctane at 29.75°C (Assuming No Association of the Components)

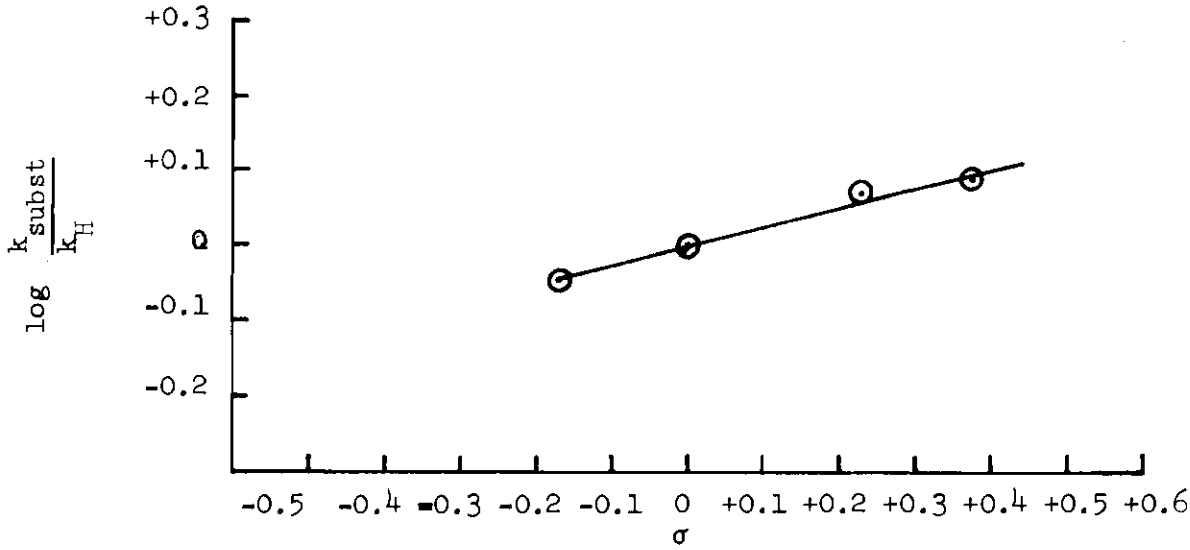
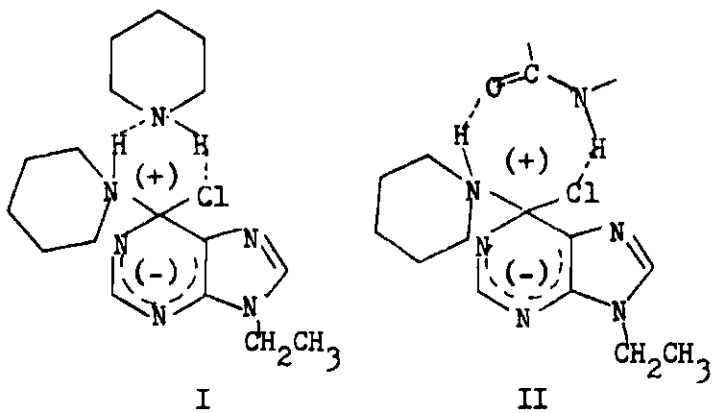


Figure 44 Hammett Plot for the Addition of Benzyl Alcohols to the Piperidine-Purine Reaction in Isooctane at 29.75°C (Assuming Association of the Components)

CHAPTER IV

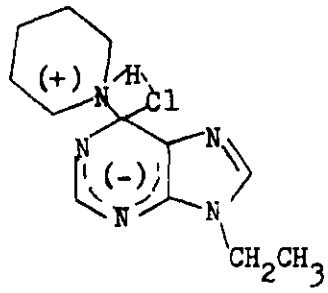
CONCLUSIONS

The results in Chapter 3 indicate that the mechanism of the reaction of piperidine with 6-chloro-9-ethylpurine in isooctane goes through an intermediate complex whose breakdown to products may be either catalyzed or uncatalyzed. The catalyzed decomposition is accomplished by primary and secondary amines, alcohols and lactams which contain acidic protons and non-bonded electrons attached to the electronegative atoms. Compounds which do not contain acidic protons such as ethers and ketones have no influence on the rate of reaction. Tertiary amines also appear to have no catalytic effect. The catalysis appears to be bifunctional in nature and may be represented by either of the following diagrams:



I II

The observation of a small deuterium isotope effect supports this representation of the catalysis step. The uncatalyzed process may involve a four-center transition state such as the following:



III

A linear Hammett plot constructed from the catalytic rate coefficients of a series of meta and para substituted benzyl alcohols indicates that there is only a small emphasis on the acidity of the catalyst.

CHAPTER V

RECOMMENDATIONS

It would be desirable if the extent of association of the alcohols employed in these reactions were known in greater experimental detail. Vapor pressure studies similar to those undertaken in the investigation of the extent of association of piperidine in isooctane will be useful in obtaining this information.

The same catalysts used in the 6-chloro-9-ethylpurine-piperidine reaction could be employed in the reaction of piperidine with 6-fluoro-, 6-bromo- and 6-iodo-9-ethylpurine in isooctane. A comparison of these results with those obtained from the 6-chloro-9-ethylpurine reactions would be interesting.

BIBLIOGRAPHY*

1. J. F. Bunnett, Quart. Rev. (London), 12, 1 (1958).

2. J. F. Bunnett and R. E. Zahler, Chem. Rev., 49, 273 (1951).

3. J. F. Bunnett, R. J. Morath, and T. Okamoto, J. Am. Chem. Soc., 77, 5055 (1955).

4. J. F. Bunnett and R. J. Morath, J. Am. Chem. Soc., 77, 5051 (1955).

5. J. F. Bunnett, J. Am. Chem. Soc., 79, 5969 (1957).

6. J. F. Bunnett and G. T. Davis, J. Am. Chem. Soc., 76, 3011 (1954).

7. J. F. Bunnett and H. D. Crockford, J. Chem. Education 33, 552 (1956).

8. J. F. Bunnett and K. M. Pruitt, J. Elisha Mitchell Sci. Soc., 73, 297 (1957).

9. J. F. Bunnett and G. T. Davis, J. Am. Chem. Soc., 80, 4337 (1958).

10. J. F. Bunnett and J. J. Randall, J. Am. Chem. Soc., 80, 6020 (1958).

11. J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, J. Am. Chem. Soc. 79, 385 (1957).

12. J. D. Reinheimer and J. F. Bunnett, J. Am. Chem. Soc., 81, 315 (1959).

13. J. F. Bunnett and R. H. Garst, J. Am. Chem. Soc., 87, 3875 (1965).

14. J. F. Bunnett and R. H. Garst, J. Am. Chem. Soc., 87, 3879 (1965).

15. J. F. Bunnett and C. Bernasconi, J. Am. Chem. Soc., 87, 5209 (1965).

16. J. F. Bunnett and D. A. R. Harper, J. Org. Chem., 31, 2369 (1966).

17. J. F. Bunnett and R. H. Garst, J. Org. Chem.,33, 2320 (1968).

18. J. F. Bunnett and C. F. Bernasconi, J. Org. Chem. 35, 70 (1970).

19. J. F. Bunnett, T. Kato, and N. S. Nudelman, J. Org. Chem., 34, 785 (1969).

*Periodical abbreviations follow those in Access, 1969.

20. J. F. Bunnett and N. S. Nudelman, J. Org. Chem. 34, 2038 (1969).

21. J. A. Orvik and J. F. Bunnett, J. Am. Chem. Soc., 92, 2417 (1970).

22. A. J. Kirby and W. P. Jencks, J. Am. Chem. Soc., 87, 3217 (1965).

23. C. R. Hart and A. N. Bourns, Tetrahedron Letters, 2995 (1966).

24. J. D. Reinheimer, W. F. Kieffer, S. W. Frey, J. C. Cochran, and E. W. Barr, J. Am. Chem. Soc., 79, 1263 (1957).

25. J. D. Reinheimer, W. F. Kieffer, S. W. Frey, J. C. Cochran, and E. W. Barr, J. Am. Chem. Soc., 80, 164 (1958).

26. J. D. Reinheimer, R. C. Taylor, and P. E. Rohrbaugh, J. Am. Chem. Soc., 83, 835 (1961).

27. C. W. L. Bevan, J. Chem. Soc., 2340 (1951).

28. G. S. Hammond and L. R. Parks, J. Am. Chem. Soc., 77, 340 (1955).

29. J. C. Lockhart, J. Chem. Soc., 1980 (1959).

30. F. Pietra, Quart. Rev. (London), 23, 504 (1969).

31. C. F. Bernasconi and P. Schmid, J. Org. Chem., 32, 2953 (1967).

32. C. F. Bernasconi, J. Org. Chem., 32, 2947 (1967).

33. C. F. Bernasconi, J. Am. Chem. Soc., 90, 4982 (1968).

34. C. F. Bernasconi, J. Org. Chem., 35, 1214 (1970).

35. C. F. Bernasconi, J. Am. Chem. Soc., 92, 129 (1970).

36. C. F. Bernasconi, J. Am. Chem. Soc., 92, 4682 (1970).

37. S. D. Ross in A. Streitwieser, S. G. Cohen, and R. W. Taft (Eds.), Progress in Physical Organic Chemistry, Vol. 1, Interscience, New York, N. Y., 1963, p. 31.

38. S. D. Ross and I. Kuntz, J. Am. Chem. Soc., 76, 3000 (1954).

39. N. B. Chapman, R. E. Parker and P. W. Soanes, J. Chem. Soc., 2109 (1954).

40. D. H. D. Elias and R. E. Parker, J. Chem. Soc., 2616 (1962).

41. S. D. Ross and M. Finkelstein, J. Am. Chem. Soc., 79, 6547 (1957).

42. S. D. Ross, Tetrahedron, 25, 4427 (1969).

43. S. D. Ross, J. Am. Chem. Soc., 81, 2113 (1959).

44. S. D. Ross and R. C. Peterson, J. Am. Chem. Soc., 80, 2447 (1958).

45. S. D. Ross, M. Finkelstein, and R. C. Petersen, J. Am. Chem. Soc., 81, 5336 (1959).

46. S. D. Ross and M. Finkelstein, J. Am. Chem. Soc., 85, 2603 (1963).

47. W. Greizerstein and J. A. Brieux, J. Am. Chem. Soc., 84, 1032 (1962).

48. N. E. Sbarbati, T. H. Suarez and J. A. Brieux, Chem. Ind. (London), 1754 (1964).

49. F. Pietra and F. Del Cima, Tetrahedron Letters, 4573 (1967).

50. F. Pietra, D. Vitali, F. Del Cima, and G. Cardinali, J. Chem. Soc. (B), 1659 (1970).

51. F. Pietra and F. Del Cima, J. Org. Chem., 33, 1411 (1968).

52. B. Bitter and H. Zollinger, Helv. Chim. Acta, 44, 812 (1961).

53. F. Pietra and D. Vitali, Tetrahedron Letters, 5701 (1966).

54. F. Pietra and D. Vitali, J. Chem. Soc. (B), 1318 (1968).

55. P. D. Bartlett in A. R. Todd, Perspectives in Organic Chemistry, Interscience, New York, N. Y. 1956, p. 9.

56. C. G. Swain, J. Am. Chem. Soc., 70, 1119 (1948).

57. F. Pietra and A. Fava, Tetrahedron Letters, 1535 (1963).

58. C. Bernasconi and H. Zollinger, Tetrahedron Letters, 1083 (1965).

59. C. Bernasconi and H. Zollinger, Helv. Chim. Acta, 49, 103 (1966).

60. C. F. Bernasconi, M. Kaufmann, and H. Zollinger, Helv. Chim. Acta, 49, 2563 (1966).

61. D. B. Weser, Unpublished Results.

62. H. Suhr, Ber. Bunsenges Phys. Chem., 67, 893 (1963).

63. F. Pietra and F. Del Cima, Tetrahedron Letters, 4453 (1966).

64. S. D. Ross, J. E. Barry, and R. C. Petersen, J. Am. Chem. Soc., 83, 2133 (1961).

65. F. Pietra, Tetrahedron Letters, 745 (1965).

66. F. Pietra and F. Del Cima, Tetrahedron Letters, 1925 (1966).

67. E. Sanhueza, R. L. Toranzo, R. V. Caneda and J. A. Brieux, Tetrahedron Letters, 4917 (1969).

68. P. Beltrame, L. Bonomi, P. Da. Re, and M. Simonetta, Gazzetta, 67, 470 (1967).

69. F. Pietra and D. Vitali, J. Chem. Soc. (B), 1200 (1968).

70. C. F. Bernasconi and H. Zollinger, Helv. Chim. Acta, 49, 2570 (1966).

71. K. Wiberg, Chem. Rev., 55, 713 (1955).

72. E. A. Halevi in A. Streitwieser, S. G. Cohen and R. W. Taft (Eds.), Progress in Physical Organic Chemistry, Vol. 1, Interscience, New York, N. Y., 1963, p.109.

73. M. F. Hawthorne, J. Am. Chem. Soc., 76, 6358 (1954).

74. F. Pietra, D. Vitali, and S. Frediani, J. Chem. Soc. (B), 1595 (1968).

75. F. Pietra, Tetrahedron Letters, 2405 (1965).

76. F. Pietra and D. Vitali, Chem. Commun., 692 (1968).

77. R. L. Toranzo, R. V. Caneda and J. A. Brieux, J. Am. Chem. Soc., 88, 3651 (1966).

78. F. Pietra and F. Del Cima, Tetrahedron Letters, 1041 (1970).

79. C. F. Bernasconi and H. Zollinger, Helv. Chim. Acta, 50, 3 (1967).

80. G. Becker, C. F. Bernasconi and H. Zollinger, Helv. Chim. Acta, 50, 10 (1967).

81. G. Harris, J. R. A. Pollock and R. Stevens, eds., Dictionary of Organic Compounds, Oxford University Press, New York, 1965, p. 11 ff.

82. G. Rapp and O. Schilichting, German Patent, 1,046,623, Dec. 18, 1958; Chem. Abstr. 55, 9441 c (1961).

83. R. L. Huang and S. Singh, J. Chem. Soc., 3183 (1959).

84. J. A. Montgomery and C. Temple, Jr., J. Am. Chem. Soc., 83, 630 (1961).

85. J. A. Montgomery and C. Temple, Jr., J. Am. Chem. Soc., 79. 5238 (1957).

86. J. R. Dyer, Applications of Absorption Spectroscopy of Organic Compounds, Prentice-Hall, Englewood Cliffs, N. J., 1965, p. 5.

87. K. B. Wiberg, Physical Organic Chemistry, John Wiley and Sons, New York, 1964, p. 312.

88. S. W. Benson, The Fundamentals of Chemical Kinetics, McGraw-Hill Book Company, Inc., New York, 1960, p. 18.

89. T. Zeegers-Huyskens, L. Lamberts, and P. Huyskens, J. Chim. Phys. Physicochim. Biol., 59, 521 (1962).

90. W. C. Coburn and E. Grunwald, J. Am. Chem. Soc., 80, 1318 (1958).

91. M. Saunders and J. B. Hyne, J.Chem. Phys. 29, 1319 (1958).

92. A. B. Littlewood and F. W. Willmott, Trans. Faraday Soc., 62, 3287 (1966).

93. T. Gramstad, Acta Chem. Scand., 16, 807 (1962).

94. M. Martin, Ann. Phys. (Paris), 7, 35 (1962).

95. T. Higuchi, E. Shami, S. Chulkaratana, and J. JaLee, Sci. Sect. Am. Pharm. Ass. Prepr. Pap., L. V., Nev., 1962; Chem. Abstr., 60, 9968f (1964).

96. J. C. Davis, Jr., K. S. Pitzer and C. N. R. Rao, J. Phys. Chem., 64, 1744 (1960).

97. E. D. Becker, J. Chem. Phys. 31, 269 (1959).

98. M. Saunders and J. B. Hyne, J. Chem. Phys., 31, 270 (1959).

99. W. Kaye and R. Poulson, Nature, 193, 675 (1962).

100. T. Zeegers-Huyskens, Bull. Soc. Chim. Belg., 69, 282 (1960).

101. T. Zeegers-Huyskens, Spectrochim. Acta, 21, 221 (1965).

102. R. L. Denyer, A. Gilchrist, J. A. Pegg, J. Smith, T. E. Tomlinson and L. E. Sutton, J. Chem. Soc., 3889 (1955).

103. F. Daniels and R. A. Alberty, Physical Chemistry, John Wiley and Sons, Inc., New York, 1966, p. 146.

104. Robert C. Weast, ed., Handbook of Chemistry and Physics, The Chemical Rubber Co., Cleveland, Ohio, 1970, p. D-146.

105. M. Bodenstein, Z. Physik. Chem., 85, 329 (1913).

106. H. Suhr, Ber. Bunsenges. Phys. Chem., 71, 1104 (1967).

107. J. Feeney and L. H. Sutcliffe, J. Chem. Soc., 1123 (1962).

108. J. Feeney and L. H. Sutcliffe, Proc. Chem. Soc., 118 (1961).

109. J. L. Mateos, R. Cetina, and O. Chao, Chem. Commun., 519 (1965).

110. V. F. Bystrov and V. P. Lezima, Opt. and Spectrosc., 16, 430 (1964).

111. R. A. Murphy and J. C. Davis, Jr., J. Phys. Chem., 72, 3111 (1968).

112. James A. Happe, J. Phys. Chem., 65, 72 (1961).

113. C. S. Springer, Jr. and D. W. Meek, J. Phys. Chem., 70, 481 (1966).

114. A. E. Lutskii and E. I. Goncharova, Russ. J. Phys. Chem. 41, 271, (1967).

115. H. Linnell, M. Aldo, and F. Raab, J. Chem. Phys., 36, 1401 (1962).

116. E. L. Shaman'ko, Opt. Specktrosk., 25, 500 (1968); Chem. Abstr. 70. 24379 (1969).

117. J. Hine, Physical Organic Chemistry, McGraw-Hill Book Company, New York, 1962, p. 87.

VITA

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