

## PRNC020

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PUERTO RICO NUCLEAR CENTER

BASE CATALYZED FORMATION OF IMIDATES

?OPERATED BY UNIVERSITY OF PUERTO RICO UNDER  
NNO. AT (401-1893 FOR U. \$. ATOMIC ENERGY COMNISKION

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Contribution from the Puerto Rico Nuclear Center and  
Department of Chemistry, University of Puerto Rico, Rio Piedras, P. R,

?BASE CATALYZED FORMATION OF IHIDATES

by

4H, Harry Szmant and Eusebio P, Olavarra

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From Thesis submitted by E. P. O. in partial fulfillment of the requirements for the M. Se. Degree, August, 1963,

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

?The reaction chosen for this purpose is the nucleophilic substitution of the hydroxyl group

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arc tort Se ae + Ret te

No So

where  $X^\ominus$  is a poor nucleophile, and  $3^\circ$  is a good nucleophile

To augment the driving force of the substitution reaction, the imidates were derived from negatively substituted nitriles such as the 2-pyridones, and in order to minimize undesired and complex side reactions in the case of the polyfunctional alcohols, the formation of imidates was chosen to be catalyzed by bases rather than acids

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

## RESULTS.

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

Sound the variations in the initial concentrations of the different alcohols,

The expression 7 .

$k(a-x)(b-x)$  (base), where  $x$  = concentration of nitrate at time  $t$  &

$a$  = initial concentration of nitrile

$b$  = initial concentration of alcohol

gives, upon integration, the expression

$\frac{1}{b-a} \ln \frac{a(b-x)}{b(a-x)}$  and from the slope of the linear plots

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

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Tables I and II List the results obtained at 27°C with several

alcohols and the dimeric cyanopyridine. Since the rate of nitrate

formation of *t*-butyl alcohol is very low and the use of  $\phi$ -SOK in place

of the corresponding alkoxide introduced relatively insignificant changes

ip the rate constants (vide infra), ic was convenient to euploy ?-BudK catalyst in these experinents.

Taser

Base Dependence in the Reaction of Methenol®/ and 3-cysnopyridine®/ at 27.0%

(e-BuOK) x 107k (e=BuOK) x 10 kx 1

pote x17? Lnmole? sec! 1° oie? see

6.0 0.618 1.03

8 0.80 oon

18.9 184 0.97

23.2 2a 0.2

BY Concentration 1.0 mole x 1

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

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see

TAS 31

Reactions of Alcohols with Cyanopyridines?/ at 27.0%

Meonate?????febaey x 10? 1? Tinidate Kx le

ole x 1" sole xi"! i2sotenZace"! | (equittsetun)

SCyanopyridine

Methyl (20) 28-232 0,96 + 0.06 ay 13 ana

Bethyl (15) a2? 9140 2

AsPropylt (12) 6.02200 0:18 o.08 4.8.

e-Butylt (11) 8.2 max. 0,016 023

Ethylene glycol (16) 82+ 31,2 C1037 40.007 3.75

1,3-Propanediol

23) 42-152 0.11 0.0L 8.7

2-Syanopyeidine

Methyl (20) 6.0 033 £0.13 98,9 (979 473 (soph

Eethyl (15) a0 0.69 0.12 76:3 23

A-Propyl (12) 134-260 82 011s ato 38

AsCyanopyridine

Methyl (20) 64-128 5,840.2 - -

Ethyl (15) 64 = 98 1313" 013 95.0

A-Propyl (12) toe = 132 713 a2 35.7

2/ Concentration  $1.0 \text{ ole} \times 10^{-1}$ . b/ Values reported in Ref. (1). of At 30%,

The ANCE She ePprectable variation in the rate constants vith chang  
fhe structure of both the alcohol and the cyanopyridine, it say conneeey  
spor taesmeatte effect of temperature on the razes of reactions aed sent  
equilibrium concentrations of the intdates,

io

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as

TARE IE

Reactions of Alcohols with Cyanopyridines®/ at Different Temperatures

?Alcohol Temps Kx 10 i ietdate mg e 10

(aole x 17) (40.3°C) 12 mole?Zeee"! (equilibrium)

2-Cyanopyetdine

Methyt (20) 88 38

? 98.9 (9798/4673 (asoye/

36

Eehyl (15)

76.3 23



98.0 350

t-Propylt (22)

90 %6

os %

Yathy (20) ce

27 RODS 13 CALs

225 v3

Behyl (15) 910 0:29 78.0 as

29 tan 63 2

ais uo

4-Propyl (12) 10.0 oon

Be ois

a's 053

Eethylene 50:0 0:30

slycol (9.2)8/ as or

\$9 170

1,3-Fropanedton (7.0% 30:0 036

20 rn

20 533

Lb-tucanedion (5.69% 30.0 289

in

3 any

snopr i

Methyt (20) Ls

57 95.0 99.7

?3

Renyt (15) 26

33 95.0 99.7

aa

s-Propyl (12) 15

mB

10

ie of 4.55 mole x 1<sup>o</sup> of dioxane and using the X salt of the

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=e

ue date presented in Table IIT gave Linear plots of log k ve. 1/T-

Zoe snthalpien and entropies of activation vere calculated by masts cf the

Byring equation

ke at

(tere snd M are the Boltzmann and Planck constante, respectively) and

are Listed in Table IV.

mas 1

The Kothatnies and Ratroptes of Activation for the  
Reaction of Alcohols with Cyenopyridine

A (13)

A-Propyl (12)

S-Propyl (12)

Behylene glycot (9,2)

1,3-Prevanadiol (7.8)8/

1,4-Bur! af

Mathyl (20)

ndlol (3.

4-tyen0

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Table 11 and IIL include information concerned with the equ!

Teated arte, forastion of imidaces. ?wnerever comparisons are sonsibiee the

Trtulte of thie vork agree well with thoue reported previously), tect

iteference between the 2- and 4-cyanopyridines, o

sta nae saztae toner on the other, with the latter compound betag

niger Vorsble for the formation of the imidates. It ie also contivend than

higher temperatures tend to repress the formation of the intaacce?

rica tvoscesnastit ERS experiments performed co teat the effect of using

Teaetais Erbutoxide as base catalyst in place of the approprincs sedvea

alkoxide, and there 1s noted a consistent im the reaction velocity

When the sodiua alkoxide 1s employed,

TABLE v

Hffect of Different Bane Catalyst on the Reaction Rat

Mathanol2/ and Cyanopyridines?/

Pridine

e-Buoe Moonta

0.90 0.57

3+cyano 0.96 0.31

4-yano 5.7 48

£/ Concentration 20 mole x l! at 27°C, bf concentration 1.0 mole x 1°,

22 7At" of the snterest to employ polyfunctional and possibly solid

fatale, ta, cle sesearch chere was investigated che formacion op tevaicen

seaseneearsnce OF Sfferene solvente rather then exceasive emcees sete

Tetaseeyescohels Te war dtacovered that the equtlibriun concontseteea ot

Fensles rapotenatly affected by the nature of the solvent, an shows to ent

Feaulte reported io Table VI and summarised to Pigs ty

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-Te

TABLE VI

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

eee

Methanol % Imtdare

Solvent Mole x17) (equilibrium)

ee

Dimethyl sulfoxide 3 2

2s as

10 25

Dimethyl formamide 5 a

1s 26

10 36

is 52.5

Dioxane 1 n

25 1.5

5 3010

10 53.0

ans 65:0

t-Butyl alcohol 1 w

4 30

° a

2 80

Toluene

eee

4 Concentration 1.0 mole x 1". Variable amounts of  $\phi$ -Buk did not affect the equilibria values,

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a

4 \$6 7 8 9 to th w 13 a6 tp

Fig. 2

(Hoon) / (aren)

Boutlibriua of Tmidate Fornation an Function of (MeG)/(ArGN) ?nm

Different Solvents (Sable ¥I)-

The observed affect of solvents on the position of the equilibrium

Guting the formation of inidates is beltevad to be of great patenctal ealus

a# @ neans to promote better yields in the ayntheste of lai

It vas mentioned to the Introduction that the proposed study of the

ae termntlts substitution reactions of isidacce pronuaes the avalabiitey

SEafahdete alee derived from acide contataing an anion of low mucieopnitictty,

sa the PHerace ion ts an example of such an anion. Also, the iaideees eee

fo be liquids that are normally isolated by rather? te.

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=0

## TABLE VII

Bicrates of Inidates Derived fro 3-Cyanopyridine®/

Alcohol Foraul® ke aoa

Methy) 137-138 yy 5M507 Caled. 42.75 3,06 19.17

Found 42:87 2.98 15.28

A-Propyl 139-140 455850, Caled, 45183 3.81 17.83,

ASS 7 Found 43.63 3.57 14109

Behylene glycol 134-135 Gy4lly 850g Caled, 42154 331 A772

Pound 42:11 3.19 14.23,

A,3-Propanediol 122-123 Gy 3HijsNg0g Caled. 44.02 3:70 17:12

Found 44:62 3.45 15.75

EE

Af Wicroanetyesen by De. Alfred Becabarde, Nilheim, caramny.

The low nitrogen analyses indicate partial hydrolysis of the iodide to the ether during the repeated crystallizations of the picrates from acetone.

Since the change of the NA group for an oxygen produces practically no change in the molecular weight, and the picrate can still be formed by virtue of the Pyridine ring, the C and H analyses suffer no alterations as a consequence of the hydrolysis.

## Discussion

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

ky

Reon + eeBuo? KY Ge ROT RT oun,

a

1

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

cently

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= 10

The reaction of the alkoxide with the nitrile 4 mor

Rate-determining step than the subsequent

molecule of alcohol, since the latter

Likely to be the

formation of the anion with another

relatively stable proton transfer

process involving an anion expected to be highly solvated by an alcohol, i.e.

the first place,

and since  $k_1 \gg k_2$  (ROR) (B00),

$k_1 \gg k_2$  (R-OH) (t-BuOK)

It is true that  $k_1$  must vary from one alcohol to another, because

the fact that the proton transfer in alcohols is many magnitudes greater (3)

than the rate of imide formation, one can assume that the rate of the latter

Reaction is affected very little by the relatively small differences in acidity  
of different alcohols (4).

As would be seen from the data reported in Table II for 3- and 4-cyanopyridines,  
that in the series methyl, ethyl, and isopropyl alcohols, the reaction rate  
increases at first because of the greater nucleophilicity of the alkoxide ion,  
but that this trend does not continue. However, it is  
difficult to arrive at conclusions along these lines because of dif-

ferences primarily as the variations in the entropies of

activation in the case of imidate formation by S-cyano-

pyridine, the progressive increase in the negative entropy of activation

(one proceeds from methyl to isopropyl alcohol) can be interpreted to arise

progressively as a loss of freedom of the system (comparing the initial and

transition states) when we go from a more highly organized alcohol, such as

methanol, (to an alcohol in which the intermolecular forces of attractions are

Relatively small. The notable increase in the enthalpy of activation for the  
Reaction of the glycols is most likely due to chelation that tends to the  
steric hindrance of the  $9^\circ$   $\text{KT OH}$  less reactive, and the large negative entropy of activation

requires

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such

The equilibrium constants for the imine formation were shown (1)

According to the Hammett equation and to be favored by negative substituents

(positive  $\rho$  value). In line with the greatest positive  $\rho$  constant

for the  $\text{S-pyridyl}$  group (5), it is expected that the Sveyane component is

the most favorable reagent among the isomeric cyanopyridines for the, for

ion of imidates. The incomplete data listed in Table I based on the  
spectrum, but there is an indication that 2-cyanopyridine may be  
used in the formation of imidates derived from secondary alcohols  
(note the high equilibrium value for isopropyl alcohol), should that  
result be confirmed by additional work, it will be an example of an  
ortho-acceleration effect (6),

The results shown in Table VI and Figure 1 indicate the profound  
effect on the imidate equilibrium exerted by different solvents

for imidate formation ( $K_{eq}$ ) listed in Tables VI and  
in a manner analogous to that described previously (1)

Table VI and Figure 1 are suitable for the calculation  
of imidate equilibrium constants in the presence of different solvents in  
the following fashion.

For a given equilibrium concentration of imidate ( $a$ ) and known



Sritical concentrations of the alcohol (b) and nitrile (ec), ene eqellibe

Flum constant 1# given by

(atdace) .

Big = = , sere x represents the concen

(ROH) (CaroN) ~ (b-a-x) (ena)

tration of the alechol which is ?inactive? in che equilibrium due to

strong involenent vith the solvent solecui

fone can ignore the quantity x end eatin for atfferent

(ROD CarcH) ration, Then we can plor the apparent Kya valves agciaat

the mole fraction of the given solvent and extcepolats'to tere contest rae

ion of RO to obtain an isproved Kiq value. This operation ts jectieied

Jos eatasis that wich decreasing anounte of alcohol the value of + beteees

seve egisntficant. Figure 2 shows this application of this procedure te

rel solvents, and Table VIII Lists the Kim values obtained foc the

SEEGSG, formation from nechanol and 3-cyanopyridine in different worcente

at 27%,

t, on the other hand, the use of  
displacements of the equilibrium even in the absence,  
of the alcohol,

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ABLE VEIT

Equilibrium Constants for Unidate Formation from Methanol and  
S-Cyanopyridine at 27°C in Different Solvents,

Solvent

Dimechyl sulfoxide 3

Diwechel foraemide

Methyl aleohois/

Dioxane

E-Butyl ateonol

Toluene °

af Fron Table 11,

© e-BuoH

g =<

oN oo © Dioxane

SS ee ee ?\_

es eee o???

oS

0.90 0.89 0.70 2.60 0.50 0.40

mole fraction

Fig. solvent

Estimate of  $K_e$  for the Reaction of Methanol and  
S-Cyanopyridine at 27°C in Different Solvents

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