LN N PUERTO RICO NUCLEAR CENTER BASE CATALYZED FORMATION OF IMIDATES OPERATED BY UNIVERSITY OF PUERTO RICO UNDER NNO. AT (401-1893 FOR U. S. ATOMIC ENERGY COMMISSION ---Page Break--- Contribution from the Puerto Rico Nuclear Center and Department of Chemistry, University of Puerto Rico, Rio Piedras, P. R, BASE CATALYZED FORMATION OF IMIDATES by 4H, Harry Szmant and Eusebio P. Olavarría Research sponsored by U. S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health. From Thesis submitted by E. P. O. in partial fulfillment of the requirements for the M. Sc. Degree, August, 1963, ---Page Break--- INTRODUCTION The ultimate aim of this research is the preparation of potential antimetabolites by the selective replacement of a hydroxyl group in polyfunctional alcohols and carbohydrates. The reaction chosen for this purpose is the nucleophilic substitution of imidates where X is a poor nucleophile, and Y is a good nucleophile. To augment the driving force of the substitution reaction, the imidates were derived from negatively substituted nitriles such as the sympyridines, and in order to minimize undesired and complex side reactions in the case of the polyfunctional alcohols, the formation of imidates was chosen to be catalyzed by bases rather than acids. In the first phase of this work there were investigated the factors which affect the base-catalyzed formation of the imidates, dealing exclusively with this aspect of the problem. RESULTS. The formation of the imidates was followed using the method described recently by Schaeffer and Peters (1). Using an excess of the alcohol, the reaction kinetics obeyed the pseudo-first-order rate law, and the specific reaction rate gave linear dependence on the concentration of the substrate. However, in order to achieve better comparisons of the reaction rates of different alcohols and of systems containing inert diluents, the rates were calculated on the basis of the

pscudo-binolecular cate law by taking ines ee Sount the variations in the initial concentrations of the different aleshols. The expression 7 . k (a-x) (b-X) (base), where x = concentration of taidate at tine & 4 = initial concentration of nitrile b= intetal concentration of aleshol ‘ives, upon integration, the expression 7k (base) t, and from the slope of the linear plots of log axx ve. t there can be calculated the rate constants k- ---Page Break --- Tables I and IT List the results obtained at 27C with several alcohols and the dsoseric eyanopyrid Since the rate of inidate formation of t-butyl alcohol 1s very lov and the use of ¢-S0K in place gf the corresponding alkoxide introduced relatively insignificant chacges 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 Tee petults Listed in table T agree with the vork of Schaeffer and Peters (1) snd desonstrate that the rates are directly dependent on the concentestion oy the base catalyse, ---Page Break --- sae TAS 31 Reactions of Aicohols with Cyenopyridines’/ at 27.0% Meonat————“febaey x 10? 1? Tinidate Kx Ie ole x 1" sole xi"! i2sotenZace"l | (equtttsetun) SCyanopyridine Methyl (20) 28-232 0,96 + 0.06 ay 13 ana Bebyl (15) a2” 9140 2 AsPropyt (12) 6.02200 0:18 o.08 4.8. e-Butyt (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 Eehyl (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 ole x 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 says concerning the effect of temperature on the rates of reactions and equilibrium concentrations of the intermediates, io ---Page Break--- as

TARE IE Reactions of Alcohols with Cyanopyridines® at Different Temperatures ‘Alcohol Temps Kx 10 i intermediate mg e 10 (mole x 17) (40.3°C) 12 mole™Zeee"! (equilibrium) 2-Cyanopyridine Methyl (20) 88 38 ” 98.9 (9798/4673 (above/ 36 Ethyl (15) 76.3 23 98.0 350 t-Propyl (22) 90 %6 os % Yathy (20) ce 27 RODS 13 CALs 225 v3 Benzyl (15) 910 0:29 78.0 as 29 tan 63 2 ais uo 4-Propyl (12) 10.0 con Be ois a's 053 Ethylene 50:0 0:30 glycol (9.2)8/ as or $9 170 1,3-Propanediol (7.0) 30:0 036 20 rn 20 533 Lb-butanedione (5.69) 30.0 289 in 3 any support i Methyl (20) Ls 57 95.0 99.7 “3 Benzyl (15) 26 33 95.0 99.7 aa s-Propyl (12) 15 mB 10 ie of 4.55 mole x 1°! of dioxane and using the X salt of the ---Page Break--- =e ue date presented in Table IIT gave Linear plots of log k vs. 1/T- The enthalpies and entropies of activation were calculated by means of the Eyring equation k at (T) and M are the Boltzmann and Planck constants, respectively) and are listed in Table IV. mas 1 The Kothatnies and Rates of Activation for the Reaction of Alcohols with Cyanopyridine A (13) A-Propyl (12) S-Propyl (12) Ethylene glycol (9.2) 1,3-Propanediol (7.8) 1,4-Butanediol (20) ndiol (3. 4-tyen0 ---Page Break--- -6- Table II and III include information concerning the equilibrium treated rates, formation of imidates. “wherever comparisons are sensible, the results of this work agree well with those reported previously), tect reference between the 2- and 4-cyanopyridines, o sta nae saztae toner on the other, with the latter compound being more favorable for the formation of the imidates. It is also contended that higher temperatures tend to repress the formation of the intermediates’ rica tvoscesnastit ERS experiments performed to test the effect of using tert-Butoxide as base catalyst in place of the appropriate sodium alkoxide, and there.

1s noted a consistent im the reaction velocity When the sodium alkoxide 1s employed, TABLE v Effect of Different Base Catalyst on the Reaction Rate Methanol2/ and Cyanopyridines?/ Pyridine e-Buoe Moonta 0.90 0.57 3-cyano 0.96 0.31 4-cyano 5.7 48 £/ Concentration 20 mole x I! at 27°C, bf concentration 1.0 mole x 1°, 22 7At" of the interest to employ polyfunctional and possibly solid fatale, ta, cle sesearch chere was investigated che formacion op tevaicen seaseneearsnce OF Sfferene solvente rather than excessive emcees sete Tetaseeyescohels Te war dtacovered that the equilibrium concentration ot Fensles rapotenatly affected by the nature of the solvent, an shows to ent Feaulte reported io Table VI and summarised to Pigs ty ---Page Break--- -Te TABLE VI Effect of Solvents on the Equilibrium Concentration of Tmidates Derived from Methanol and 3-Cyanopyridine®/ et 27°C with varying Methanol/ Nitrile Concentrations. eee Methanol % Imtdare Solvent Mote 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 ¢-Buk did not affect the equilibrium values, ---Page Break--- a 4 $6 7 8 9 to th w 13 a6 tp Fig. 2 (Hoon) / (aren) Boutlibriua of Tmidate Formation an Function of (MeG)/(ArGN) ‘nm Different Solvents (Sable ¥I)- The observed effect of solvents on the position of the equilibrium Guting the formation of inidates is believed to be of great potential value as a means to promote better yields in the synthesis of Iai It was mentioned in the Introduction that the proposed study of the ae termntlts substitution reactions of isidacce pronuaes the availability SEafahdete alee derived from acids containing an anion of low nucleophilicity, sa the PHerace ion is an example of such an anion. Also, the iaideees eee fo be liquids that are normally isolated by rather’ te. ---Page Break--- =o TABLE VIL Bicrates of Inidates Derived from 3-Cyanopyridine®/

Alcohol Foral® 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 Wicroanetysen by

De. Alfred Becabarde, Nilheim, caramny. The lov nitrogen analyses indicate parcial hydrolyate of the iatdate to the eater during the repeated crystallizations of the picrates from acetone. Since the change of the NA group for an oxygen produces practically no change im the molecular weight, and the picrace can still be formed by virtue of the Pyridine ring, the C and H analyses suffer no alterations ## @ consequence of the hydrolyste. Discussion A mechanism of the imidace formation constatent with the results described above involves a rapid equiltbration of the reacting alcohol with Potassius t-butoxide, ky Reon + eeBuo™ KY Ge ROT RT oun, a 1 The fact that the reactions of methanol catalyzed by t-Bu0K are cons! ‘ore rapid than those catalyzed by sodium methoxide (Fable V) indicates thay the nature of the metal ts of greater significance than that of the alkoxide introduced as the base catalyst, and this requlr is in agreement (2) withthe Kecognized difference in the degree of dissociation of the alkall metal alkoxides. cently ---Page Break--- = 10 The reaction of the alkoxide with the nitrile 4 mor Tate-deternining step than the subsequent molecule of alcohol, since the latter Likely to be the ‘tion of the anton vith ancther relatively staple proton transfer process involving an anion expected to by highly solvated by en alechel, ie the firat place, and since (R0") {ky (ROR) (B00), ky CArON) (R-OH) (€-Bu0"K"Y Mile 4¢ is true that ky must vary from one alcohol to another, because Sf tie, fact that the proton Eransfer in alcohols is many magnitudes’ greater (3) fhéa the rate of imidate formation, one can assume that the rate of the Lecter Fesotion is

affected vary little by the relatively small differences in acidity of different alcohols (4). It would be seen from the data reported in Table II for 3- and 4-cyanopyridines, that in the series of methyl, ethyl, and isopropyl alcohols, the reaction rate increases at first because of the greater nucleophilicity of the alkoxide ion, but that this trend is more than offset. However, it is difficult to arrive at conclusions along these lines because of difficulties primarily as the variations in the entropies of activation. In the case of imidate formation by 3-cyanopyridine, the progressive increase in the negative entropy of activation (one proceeds from methyl to isopropyl alcohol) can be interpreted to signify a progressively greater loss of freedom of the system (comparing the initial and transition states) when we go from a more highly organized alcohol, such as methanol, to an alcohol in which the intermolecular forces of attraction 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 make the enolate ion less reactive, and the large negative entropy of activation requires ---Page Break --- . The equilibrium constants for the imidate formation were shown (1) to obey the Hammett equation and to be favored by negative substituents (positive rho value). In line with the greatest positive sigma constant for the 3-pyridyl group (5), it is expected that the 3-cyanopyridine component is the most favorable reagent among the isomeric cyanopyridines for the formation of imidates. The incomplete data listed in Table II bespeak one such expectation, but there is an indication that 2-cyanopyridine may see some special use 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 (Kyq) listed in Tables Tt and in a manner analogous to that described previously (1) VI and Figure 1 are suitable for the calculation of imidate equilibrium constants in the presence of different solvents in the following fashion. For a given equilibrium concentration of imidate (a) and known initial concentrations of the alcohol (b) and nitrile (c), the equilibrium constant K is given by (atdace). K = (ROH)(CaroN) / (b-a-x)(c) where x represents the concentration of the alcohol which is “inactive” in the equilibrium due to strong involvement with the

solvent molecules. One can ignore the quantity x and calculate for different (ROH)(CaroN) ratios. Then we can plot the apparent K values against the mole fraction of the given solvent and extrapolate to zero concentration of ROH to obtain an improved K value. This operation is justified by the hypothesis that with decreasing amounts of alcohol the value of K becomes significant. Figure 2 shows this application of this procedure to relevant solvents, and Table VIII lists the K values obtained for the imidate formation from methanol and 3-cyanopyridine in different solvents at 27°C. On the other hand, the use of displacements of the equilibrium even in the absence of the alcohol. ---Page Break --- TABLE VIII Equilibrium Constants for Imidate Formation from Methanol and 3-Cyanopyridine at 27°C in Different Solvents, Solvent Dimethyl sulfoxide, Dimethyl formamide, Methyl alcohol, Dioxane, t-Butyl alcohol, Toluene ° from Table 11. © t-Butyl 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 for the Reaction of Methanol and 3-Cyanopyridine at 27°C in Different Solvents ---Page Break --- =e (D. F. Schaefer and G. A. Peters, J. Org. Chem. 26, 412 (1961) (2) S. Betthetaer, J. T. certs and J. C. Cochran, J. Am. Chem. Soc. 83, 2873 (1961) ©) F. Grumald, C.F. Jumper and S. Hetboos, Ibid., 84, 4666 (1962) mp Linger and P. A. Long, Ibid., 82, 795 (1960) G) W. H. Safte, Chem. Rev., 53, 191

(1953) (9) () Ro. c, Rorman and G. K. Radda, J. Chem. Soc., 1961, 3030 (8G: Shepard: W. B. Taft and H. M. Krastorki, J. Org. Chem., 26, 2764 (1961) ---Page Break---