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SOLVENT EFFECTS IN THE REACTION OF 2,3,6-TRI-*O*-METHYL D-GLUCOPYRANOSE AND PHENYL ISOCYANATE

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ABSTRACT

The reaction of a 3:1 mixture of 2,3,6-tri-*O*-methyl-α- and β-D-glucopyranose (**1**) with phenyl isocyanate, in acetone, benzene, dimethyl sulfoxide, 1,4-dioxane, pyridine, and tetrahydrofuran, showed the isomer ratio in the product mixture to be solvent-dependent. The ratio varied from 4.55 β/α in benzene to 0.49 in Me_2SO. It is proposed that an activated complex formed between **1** and a **1**-isocyanate complex provides for the simultaneous attack of a nucleophile on the anomeric hydroxyl proton, and of an electrophile on the ring-oxygen atom of **1**, causing mutarotation. The rate of mutarotation of the activated complex is dependent on the degree of solvation of the anomeric hydroxyl group. Solvent association is highest in Me_2SO and lowest in benzene. The reaction rate is higher in benzene than 1,4-dioxane and is slowest in Me_2SO. The hydroxyl group at C-1 is ~3 times as reactive as the one at C-4.

INTRODUCTION

Steinman[1] has described the preparation of block copolymers from cellulose triacetate blocks having hydroxyl end-groups, and diisocyanates. We are conducting similar studies employing groups other than acetyl to protect the hydroxyl groups at C-2, -3, and -6 during the chain-extension step.

The configuration at the anomeric positions of the cellulose oligomer blocks will influence the chain configuration of the copolymers. Steinman did not report the anomeric purity of his copolymers. However, on the basis of the anomeric effect[2], the α-configuration would be expected at C-1 of the cellulose triacetate block.

As part of our studies, the isomer ratio in the reaction products of 2,3,6-tri-*O*-methyl-α- and β-D-glucopyranose (**1**) with phenyl isocyanate (**2**), in a variety of solvents, was examined. The configuration at C-1 of the resulting dicarbanilates was determined by p.m.r. spectroscopy. The rate of reaction of **1** and **2**, and the relative reactivities of the C-1 and C-4 hydroxyl groups of **1**, were also determined.

RESULTS AND DISCUSSION

Compound **1** was obtained from hydrolyzed tri-*O*-methyl cellulose by column chromatography. Its 100-MHz, p.m.r. parameters in deuterated dimethyl sulfoxide (Me_2SO-d_6) solution are listed in Table I. As obtained from the column, the β-α ratio in **1** was about 0.33, as indicated by the H-1 resonance peak areas, and it melted at 105–108°. The m.p. is probably influenced by the anomeric ratio[3,4].

TABLE I

CHEMICAL SHIFTS[a], τ (p.p.m.) AND COUPLING CONSTANTS (Hz, IN PARENTHESES) OF 2,3,6-TRI-*O*-METHYL-D-GLUCOPYRANOSE AND CARBANILATES IN Me_2SO-d_6

Compd. No.	*Hydroxyl protons*			*Ring protons*			
	HO-1 (d)		*HO-4 (d)*	*H-1 (d or t)*		*H-4 (t)*	*NH (s)*
	α	β		α	β		
1	3.60 (5.0)	3.25 (6.2)	4.84 (6.0)	4.90 (4.0)	5.66 (7.0)		
3					4.36 (7.8)	5.32 (9.0)	−0.05, +0.16
4				3.26 (3.2)		5.24 (9.5)	+0.08, +0.20

[a]At 100 MHz. Peak multiplicity noted as s, singlet; d, doublet; t, triplet.

2,3,6-Tri-*O*-methyl-β-D-glucopyranose 1,4-dicarbanilate (**3**) and the α-dicarbanilate (**4**) were prepared by the reaction of **1** with **2**, and were separated by column chromatography. The reactions were conducted at either 40° or 80°, with triethylamine as catalyst, and were monitored by t.l.c. The 100-MHz p.m.r. parameters for the carbanilates in Me_2SO-d_6 solution are summarized in Table I. Assignments of hydroxyl proton resonances were verified by the addition of deuterium oxide.

In the absence of an electron-withdrawing substituent at the hydroxyl group, the ring-proton signals, with the exception of H-1, are well upfield and overlap so extensively that they cannot be differentiated. The NH signals, and the splitting of the H-1 doublet, permitted identification of the dicarbanilates.

The p.m.r. data for **1**, **3**, and **4** indicate that, in Me_2SO-d_6 solution, the molecule adopts predominantly $^4C_1$(D) conformation, as shown by the splitting of the H-1 and H-4 signals. Data not shown here indicate this is the case also in pyridine-d_5, acetone-d_6, and 1,4-dioxane-d_8, although there is some indication the boat form may also be present in 1,4-dioxane-d_8. The spectra in C_6D_6 and tetrahydrofuran were too poorly resolved to afford coupling constants. However, the $^4C_1$ conformation is energetically the more favorable and presumably in the principal form in these latter solvents also.

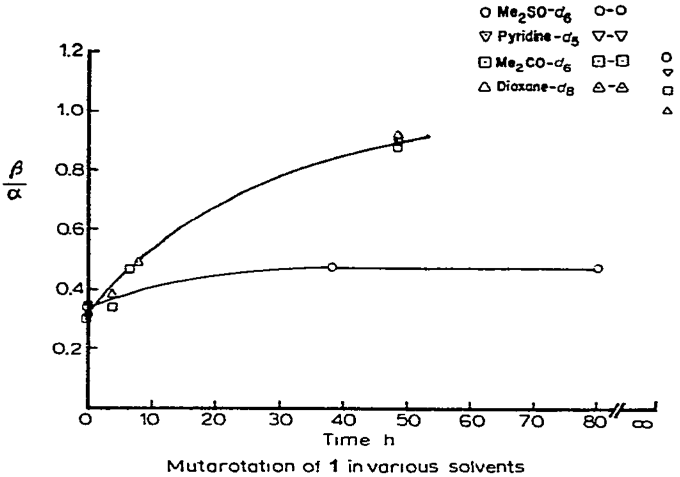
Freshly prepared solutions of **1** in D_2O, Me_2SO-d_6, Me_2CO-d_6, pyridine-d_5, and 1,4-dioxane-d_8 contained 25% of the β-isomer ($\beta/\alpha = 0.33$). Equilibrium β/α ratios in the various solvents at different temperatures are shown in Table II. The mutarotation was monitored by integration of p.m.r. spectra recorded at various time-intervals and examining the 1-OH and ring-proton resonances. The isomer ratio in the organic solvents in slightly greater than 1 and is less than 1 in D_2O, becoming very close to unity as the temperature is increased. The anomeric affect would favor the axial orientation (α-isomer).

TABLE II

EQUILIBRIUM ANOMER (β/α) RATIOS

Solvent temperature	Me_2SO-d_6	Me_2CO-d_6	*1,4-Dioxane*-d_8	*Pyridine*-d_5	D_2O
20	1.23	1.13	1.19	~1.0	0.57
40	1.20	1.09	1.13		0.69
60					0.87
80					0.92

The changes in the β-α ratio of **1** in 1,4-dioxane-d_8, Me_2SO-d_8, Me_2CO-d_6, and pyridine-d_5 at 40° are shown in Fig. 1. Mutarotation is slowest in Me_2SO-d_6, probably because of hydrogen bonding of the 1-OH group in this solvent. Similar data could not be obtained in C_6D_6 or tetrahydrofuran because of poor spectral resolution.



Mutarotation of **1** in various solvents

Fig. 1.

Compounds **1** and **2** were allowed to react in C_6H_6, 1,4-dioxane, tetrahydrofuran, pyridine, and Me_2CO at 40° and in Me_2SO at 80° with triethylamine as a catalyst. An excess of **2** was used to ensure formation of the dicarbanilates. After completion of the reaction, the solvent was removed, the reaction products were dissolved in Me_2SO-d_6, and p.m.r. spectra were recorded. The ratio of the β and α

1,4-dicarbanilates in the mixture was calculated from the areas of the H-1 signals in the respective spectra. The results are summarized in Table III.

TABLE III

REACTION PRODUCTS OF **1** AND **2** IN DIFFERENT SOLVENTS

Solvent	*Dielectric constant* (ε)	*Dipole moment* (μ)	*β/α Isomer ratio in 1*	*Ratio of 3:4*
C_6H_6	2.3	0		4.55
1,4-Dioxane	2.2	0	0.31	4.00
Tetrahydrofuran	8.2	1.63		2.84
Pyridine	12.3	2.20	0.35	0.93
Me_2CO	20.7	2.98	0.30	1.00
Me_2SO	48.9	3.96	0.33	0.49

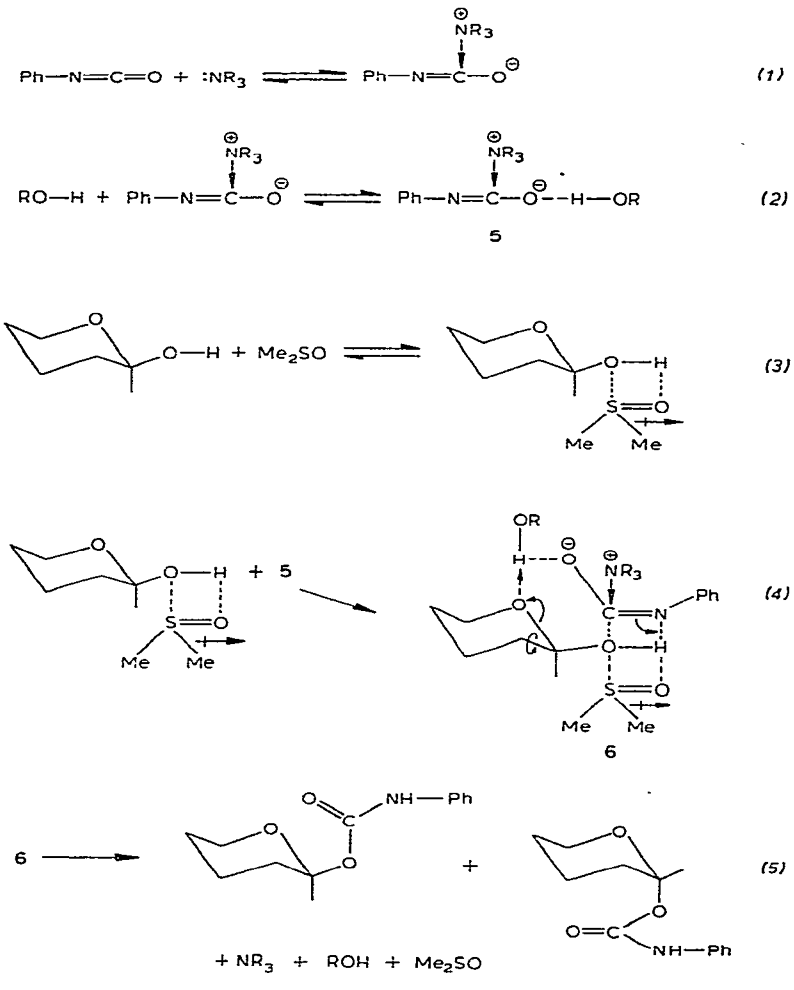
As may be noted, the proportion of **4** increases as the dielectric constant and dipole moment of the solvent increases. On the basis of the anomeric effect, the reverse might have been predicted. The isomer ratio in the reaction products should depend on the ratio of isomers in **1**, the rate constants for the reaction of the α and β 1-OH groups with **2**, the rate of mutarotation, and the relative stabilities of the isomers The latter factor may apparently be ignored. Models indicate that there is little difference in steric interference to the approach of **2** to the α or β OH group of **1**. The β-α isomer ratio in **1** at the start of the reaction is almost the same in 1,4-dioxane, pyridine, Me_2CO, and Me_2SO (Table III), and is very probably the same in C_6H_6 and tetrahydrofuran. The isomer ratio in the reaction products must, therefore, be controlled by the rate of mutarotation. Certainly, the reaction of **1** with **2** is much faster than the rate of mutarotation, and it is unlikely the relative rate-constants for reaction of the anomeric OH groups of **1** with **2** are significantly affected by the solvents employed here.

However, it cannot be the mutarotation of **1** *per se* that controls the ratio of **3**:**4**. It has been shown[5] that mutarotation in C_6H_6 is very slow, and probably occurs through the catalytic action of trace impurities. Nevertheless, the largest change in isomer ratio during the reaction occurred in C_6H_6 (Table III). With the exception of Me_2SO, the measured rates of mutarotation in the other solvents are very similar. The rate in tetrahydrofuran should not be significantly different from that in 1,4-dioxane. Interestingly, the mutarotational rate in Me_2SO is increased by the addition of C_6H_6.

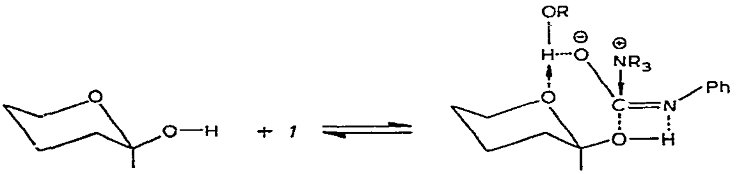
The solvents were reagent grade and were carefully dried. There was no H_2O or HOD peak apparent in the p.m.r. spectra. Water could not have catalyzed the mutarotation during the reaction of **1** with **2**, as it would have quickly reacted with **2**.

Despite many studies, the mechanism of the reaction of alcohols with isocyanates is not well understood[6], and it is difficult to speculate about the activated complex involved. However, it is well established[6–9] that complexes between the alcohol and the solvent, and the alcohol and the isocyanate, play a role in the reaction.

The following reaction-scheme is suggested to explain the results reported here. For convenience, ROH is used to represent a molecule of **1** and the solvent shown is Me_2SO. The *β*-isomer of **1** is shown in step (*4*) but, as already indicated, models suggest that there is little or no difference in steric interference for the α-isomer.



Compound **5**, a complex of the isocyanate and a molecule of **1**, complexes in turn with another molecule of **1** to form the activated complex **6**; the latter must have a lifetime sufficient for mutarotation to occur. Thus **6** provides for the simultaneous attack of a nucleophile on the proton of HO-1 and of an electrophile on the ring-oxygen atom, opening up the hemiacetal link to allow mutarotation, The rate of mutarotation (or ease of rotation about the C-2–C-1 bond) will be dependent upon the degree of solvation of HO-1. It is possible that competition between **3** and **6**, rather than solvent association in **6**, controls the rate of mutarotation. The net result



(6)

would be the same. The greater the degree of solvent association the lower will be the rate of mutarotation and the lower will be the **3**:**4** ratio in the reaction products. This interpretation agrees with the results given in Table III, namely, that the degree of solvent association is lowest in C_6H_6 and highest in Me_2SO.

The relationship[10] between the rate constant, k, and the solvent dielectric constant, ε, for the reaction of neutral molecules in solution is given by:

$$\ln k = \ln k_0 - \frac{1}{KT}\left(\frac{\mu^2}{r^3}\frac{\varepsilon-1}{2\varepsilon+1}\right)$$

where K is the Boltzmann constant, μ is the dipole moment, and r the molecular radius of the activated complex. A plot of ln k *vs* $\varepsilon - 1/2\varepsilon + 1$ should be linear, and the slope positive or negative depending on whetther the dipole moment of the activated complex is large or small in comparison with the sum of the dipole moments of the reactants. If the influence of solvation is large, the dipole moment of the activated complex may be smaller than that of the reactants, and the reaction should not be accelerated by solvents of high ε value.

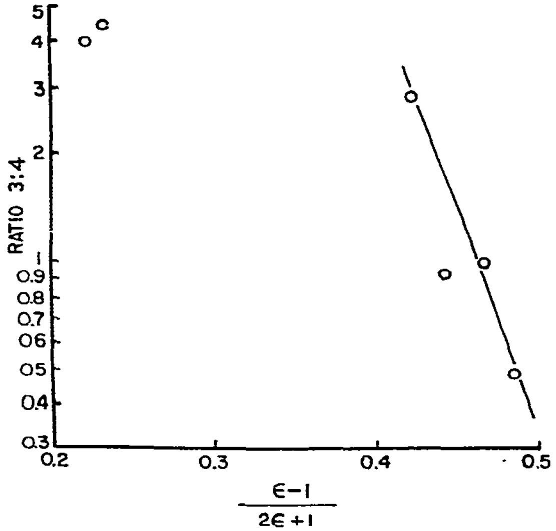
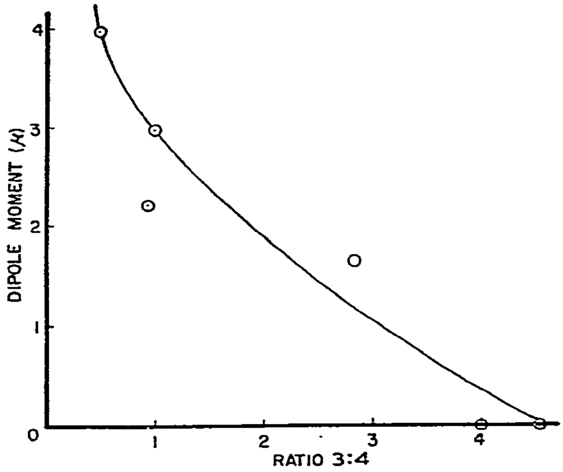


Fig. 2.

If, as already shown, the ratio of **3** to **4** in the reaction products is controlled by the rate of mutarotation of the activated complex, then the **3**:**4** value should reflect the value of the mutarotational rate-constant. A plot of **3**:**4** *vs* $\varepsilon-1/2\varepsilon+1$ is shown in Fig. 2. For the polar solvents, the plot is reasonably linear and has a negative slope that indicates influence of solvation. The rate is much greater in the non-polar solvents, indicating little solvent interference with mutarotation of the activated complex. A plot of solvent dipole-moment *vs.* the **3**:**4** ratio shows a similar trend (Fig. 3).



Ratio of 3:4 VS. solvent dipole-moment

Fig. 3.

TABLE IV

RELATIVE REACTIVITIES OF THE C-1 AND C-4 HYDROXYL GROUPS OF 2,3,6-TRI-*O*-METHYL-D-GLUCOPYRANOSE

Solvent	*Temp.* (°C)	*Reaction rate-constants* (*l/mole min.*)		k_1/k_4	*Activation energies* (*Kcal./mole*)	
		k_1	k_4		E_1	E_4
Benzene	20	0.242	0.069	3.5	1.81	4.22
	40	0.295	0.110	2.7		
1,4-Dioxane	20	0.059	0.017	3.4	6.57	8.56
	40	0.122	0.043	2.8		

Additional support for the proposal that solvent association controls the rate of mutarotation is provided by the observation that mutarotation in Me_2SO is increased by the addition of C_6H_6 (because of decreased hydrogen bonding by the solvent), and also from the 3:4 ratio in the two non-polar solvents. The ratio is lower in 1,4-dioxane than in C_6H_6. However, the hydroxyl-proton resonances of **1** may be observed in 1,4-dioxane, indicating that hydrogen bonding exists in this solvent.

Moreover, as shown in Table IV, the reaction of **1** with **2** is solvent-dependent. It is faster in C_6H_6 than in 1,4-dioxane, and is much slower in Me_2SO. It was not possible to obtain quantitative rate-data in Me_2SO because of experimental difficulties, but qualitatively, the rate is much lower in this solvent, and the temperature was increased to complete the reaction during reasonable times. The rates of mutarotation and of reaction should be similarly affected by solvent association.

The 1-OH group is about 3 times as reactive as the 4-OH group. The difference in reactivity is surprisingly small. However, this is not undesirable from the viewpoint of chain-extension reactions.

EXPERIMENTAL

General methods. — Microanalyses were made by Schwarzkopf Microanalytical Laboratory. Melting points were determined with a Kofler micro hot-stage (Arthur H. Thomas Co., Philadelphia, Pa.) and are uncorrected. P.m.r. spectra were recorded with a Varian HA-100 n.m.r. spectrometer operating at 100 MHz in the field-sweep mode. Spectra were determined with samples at a concentration of 10% (*w/v*). The solutions also contained 2% (*w/v*) of tetramethylsilane ($\tau = 10.000$) as an internal standard and to provide a lock signal. Chemical shifts are on the τ scale and were taken from the chart recording. The temperature in the probe was approximately 20°. The recorded first-order coupling constants are the measured peak spacings.

T.l.c. of the reaction products was made with Silica Gel G (E. Merck, Darmstadt, W. Germany), activated at 105°, as the absorbent. Acetone–benzene mixtures were used as developing solvents. Detection was effected with chromic acid. Activated silica gel (Davison Chemical), 100–200 mesh was employed for column chromatography. The column dimensions were 40 × 760 mm. The solvent flow-rate was maintained at 30–40 ml/h, and 10 ml fractions were collected. The fractionations were monitored by t.l.c.

Materials. — Benzene (ACS grade, Fisher Scientific) and 1,4-dioxane (histological grade, Mallinckrodt Chemical) were refluxed over metallic sodium for 4 h, distilled (benzene, b.p. 80.1°, 1,4-dioxane, b.p. 100.6–101.0°), and stored over sodium. Pyridine (Allied Chemical) was refluxed with P_2O_5 for 3 h, distilled, and collected at 115–116°. Dimethyl sulfoxide (analytical grade, Mallinckrodt Chemical) was dried over molecular sieves (Union Carbide, Type 4A, 1/16 in. size). Acetone (ACS grade, Allied Chemical) was dried over $CaCl_2$ and distilled; b.p. 56.1°. Tetrahydrofuran (Fisher Scientific) was fractionally distillled; b.p. 66.2–66.4°. Deuterated solvents from Stohler Isotope Chemical were used without further purification except that the Me_2SO-d_6 was dried with molecular sieves. Phenyl isocyanate (Matheson, Coleman & Bell) was distilled and collected at 54.0°/16 torr.

2,3,6-Tri-O-methyl-D-glucopyranose (**1**). — Tri-*O*-methyl cellulose, prepared from secondary cellulose acetate by the method of Haworth and Machemer[11], was hydrolyzed by the procedure of Croon and Manley[12]. T.l.c. showed two spots. The solid hydrolysis product was purified by column chromatography, with 3:2 (*v*/*v*) acetone–benzene as the eluant. Fractions having R_F values of 0.55, 0.33, and 0.28 were separated.

The first fraction, mp. 105–108° [lit. 114° (ref. 13); 117° (ref. 14)] was identified as 2,3,6-tri-*O*-methyl-D-glucopyranose from its p.m.r. spectrum in Me_2SO-d_6 (Table I) and elemental analysis; overall yield, 33%.

Anal. Calc. for $C_9H_{18}O_6$: C, 48.66; H, 8.11. Found: C, 48.66; H, 8.07.

2,3,6-Tri-O-methyl-β-D-glucopyranose 1,4-dicarbanilate (**3**). — Compound **1** (0.48 g, 2.16 mmoles) was dissolved in dry benzene (50 ml), and triethylamine (0.1 ml) and **2** (0.80 g, 6.7 mmoles) were added. The solution was refluxed for 3 h, and then methanol was added. On cooling, a solid precipitate formed that was filtered off. T.l.c. showed two components (R_F 0.55 and 0.48) that were separated by column chromatography with 3:7 acetone–benzene as eluant. The first fraction was identified as the "carbanilide" and the second as 2,3,6-tri-*O*-methyl-β-D-glucopyranose 1,4-dicarbanilate; yield 33%, m.p. 220–222°; p.m.r. data in Me_2SO-d_6 at 100 MHz (see Table I).

Anal. Calc. for $C_{23}H_{28}N_2O_8$: C, 60.00; H, 6.08; N, 6.08. Found: C, 60.38; H, 6.14; N, 6.46.

The filtrate was evaporated to dryness under diminished pressure. T.l.c. showed that the solid contained the "carbanilide" (R_F 0.55), **3** (R_F 0.48) and the β-monocarbanilate (R_F 0.27).

2,3,6-Tri-O-methyl-α-D-glucopyranose 1,4-dicarbanilate (**4**). — Compound **1** (0.91 g, 4.09 mmoles) and triethylamine (0.1 ml) were dissolved in dry Me_2SO (23 ml) and heated to 80°. Compound **2** (2.0 g, 1.69 mmoles) was added, and the mixture was maintained at 80° until t.l.c. showed no **1** remaining. The reaction mixture was concentrated under diminished pressure to 15–20 ml, loaded onto the column, and eluted with 1:9 (*v*/*v*) acetone–benzene. The first 80 fractions contained a mixture of **3** and **4**. Pure **4** was collected in fractions 90–100, yield 10%; m.p. 229°; p.m.r. data in Me_2SO-d_6 at 100 MHz (See Table I).

Anal. Calc. for $C_{23}H_{28}N_2O_8$: C, 60.00; H, 6.08; N, 6.08. Found: C, 59.81; H, 6.16; N, 6.28.

Reaction of compound **1** *and phenyl isocyanate in different solvents.* — In each instance, **1** (0.48 g, 2.16 mmoles), triethylamine (0.1 ml), and **2** (1.6 g, 13.4 mmoles) were dissolved in the solvent (50 ml), and the mixture was kept at 40° (80° in case of Me_2SO) until t.l.c. showed that **1** had been converted into the 1,4-dicarbanilates. MeOH was added to decompose excess **2**, and the solvents were removed under diminished pressure. The solid product was dried at 25°/1.5 torr, dissolved in Me_2SO-d_6, and its p.m.r. spectrum was recorded. The ratio of **3**:**4** was measured from the H-1 signal-areas. The results are shown in Table III.

Reaction kinetics. — The rates of reaction for **1** and **2** were determined in C_6H_6 and $C_4H_8O_2$ at 20 and 40° by measuring the rate of disappearance of **2**; the titrimetric procedure of Strafford and Stagg[15] as modified by Baker and Holdsworth[16] was used. The reaction rates of HO-1 and HO-4 were determined by using the Frost–Schwemer equation and the computer-derived tables[18]. The results are shown in Table IV.

REFERENCES

1 H. W. STEINMANN, *Polymer Preprints*, 11 (1970) 285.
2 J. F. STODDART, *Stereochemistry of Carbohydrates*, Wiley-Interscience, New York, 1971, p. 72.
3 J. C. IRVINE AND E. L. HIRST, *J. Chem. Soc.*, (1922) 1213.
4 W. N. HAWORTH AND E. L. HIRST, *J. Chem. Soc.*, (1928) 2684.
5 C. G. SWAIN AND J. F. BROWN, *J. Amer. Chem. Soc.*, 74 (1952) 2538.
6 W. G. P. ROBERTSON AND J. E. STUTCHBURY, *J. Chem. Soc.*, (1964) 4000.
7 S. EPHRAIM, A. E. WOODWARD, AND R. B. MESROBIAN, *J. Amer. Chem. Soc.*, 80 (1958) 1326.
8 M. SATO, *J. Amer. Chem. Soc.*, 82 (1960), 3893.
9 M. SATO, *J. Org. Chem.*, 27 (1962), 819.
10 S. GLASSTONE, K. J. LAIDLER AND H. EYRING, *The Theory of Rate Processes*, McGraw-Hill, New York, 1941, p. 419.
11 W. N. HAWORTH AND H. MACHEMER, *J. Chem. Soc.*, (1932) 2270.
12 I. CROON AND R. ST. J. MANLEY, *Methods Carbohyd. Chem.*, 3 (1963) 280.
13 J. C. IRVINE AND E. L. HIRST, *J. Chem. Soc.*, (1922) 1213.
14 W. N. HAWORTH AND E. L. HIRST, *J. Chem. Soc.*, (1928) 2684.
15 H. E. STRAFFORD AND E. STAGG, *Analyst*, 71 (1946) 557.
16 J. W. BAKER AND J. B. HOLDSWORTH, *J. Chem. Soc.*, (1947) 713.
17 A. A. FROST AND W. C. SCHWEMER, *J. Amer. Chem. Soc.*, 74 (1952) 1268.
18 C. A. BURKHARD, *Ind. Eng. Chem.*, 52 (1960) 678.