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Note

A mechanistic study of the reaction of phenyl isocyanate with methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside

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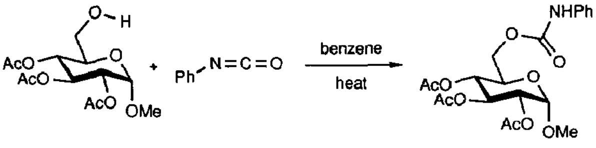
The reaction of carbohydrate hydroxyl groups with isocyanates is a useful way to prepare carbamate-functionalized[1], -derivatized[2–5], and -crosslinked sugars[6,7]. Despite the myriad studies of the reaction of simple alcohols with isocyanates[8–13], little is known about the intrinsic reactivity of carbohydrate hydroxyl groups relative to "ordinary" ones. In addition, the mechanism of carbamate formation is far from being well understood, and may even differ in the carbohydrate examples[14]. We have therefore undertaken a kinetic and mechanistic investigation of the reaction of an archetypal carbohydrate alcohol (**1**) with phenyl isocyanate (**2**) under conditions where meaningful comparisons with simple alcohols can be made.



1 **2** **3**

Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[15] (**1**) was selected as a suitable carbohydrate substrate for kinetic studies, as (*a*) its reaction with **2** gives quantitatively a single product, the carbamate[16] **3**, (*b*) the carbamylation reaction may be conveniently monitored by n.m.r. spectroscopy, (*c*) the relative reactivity of the glucopyranose hydroxyl groups is known[17], and (*d*) the solubility and rate of reaction of **1** in benzene are sufficient to allow comparison with the recent work of Sivakamasundari and Ganesan on simple alcohols under very similar conditions[9]. The i.r. spectra of neat **1** (thin film) and a 0.125M solution of **1** in benzene-d_6 show at room temperature a strong, broad absorbance at 3550 cm^{-1} for the OH group intramolecularly hydrogen-bonded[18] to the pyranose-ring oxygen atom, and no non-hydrogen-bonded OH. N.m.r. spectra of **1** in benzene-d_6 reveal the 6-OH proton signal as a triplet, even in the presence of traces of

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water. At 75°, the triplet broadens slightly, still indicating slow proton exchange because of hydrogen bonding.

A dilute solution of **1** was allowed to react with an excess of **2** under pseudo-first-order conditions at three different temperatures. The resulting rate constants are displayed in Table I. Calculation of the activation parameters[19] gives the values shown in Table II, alongside those of Sivakamasundari and Ganesan[9] for three representative alcohols.

The data in Table II reveal that the reactivity of **1** is qualitatively similar to that of the simple alcohols, but differs quantitatively in some respects. The relatively low Arrhenius activation energy indicates that the reaction of **1** with **2** in benzene is not highly temperature-dependent, and is even less so than the reaction of **2** with simple alcohols. The relatively low values of $\Delta H^{\neq}$ for all of the substrates suggest that little bond breaking occurs prior to attainment of the transition state. For the case of carbohydrate **1**, the large negative value of $\Delta S^{\neq}$ indicates a highly ordered transition-state (even more than for the simple alcohols).

To probe the role of the pyranose-ring oxygen, the relative reactivity of **1** and its β anomer **4** was examined. Overlap of one of the lone pairs of electrons of the pyranose oxygen with the σ^* orbital of the C-1–OMe bond (the anomeric effect[20]) should decrease its basicity and hydrogen-bonding ability to a greater extent in the α anomer **1**, whereas the steric environments of the C-6 hydroxyl groups of **1** and **4** should be similar. A

TABLE I

Rate constants[a] for the reaction of **1** with **2**

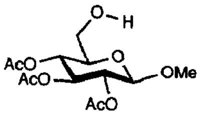
Temp. (°)	*$10^5 k_1, s^{-1}$*	*$10^5 k_2, s^{-1} M^{-1}$*
30 (extrap'd)	-	1.41
80	6.25	7.18
100	10.7	12.3
125	19.3	22.2

[a] Initial [**1**] = 0.125M; initial [**2**] = 0.870M.

TABLE II

Activation parameters for the reaction of alcohols with **2**

Alcohol	*t (°)*	*E_a (kcal·mol)*	*$\Delta H^{\neq}$ (kcal·mol)*	*$-\Delta S^{\neq}$ (eu)*	*$\Delta G^{\neq}$ (kcal·mol^{-1})*
CH_3OH	30	9.0	8.4	46.9	22.6
CH_3CH_2OH	30	8.6	8.0	48.2	22.6
$CH_3O(CH_2)_2OH$	30	11.4	10.8	44.3	24.3
1 (data)	100	7.0	6.2	60.2	28.6
1 (extrap'd)	30	7.0	6.4	59.8	24.5



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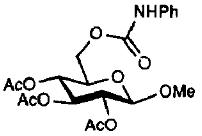

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competition experiment with **1** and **4** was performed with **2** in benzene at 100°. Analysis of the mixture of products **3** and **5** by n.m.r. reveals that the β anomer **4** is only ~1.1 times more reactive than **1**.

The timing of the proton transfer during carbamate formation was examined by looking for a deuterium isotope effect. In this series of experiments, **1** and **1**-d_1 were treated with **2** under conditions of second-order kinetics. The results are presented in Table III. The values of k^H/k^D show that this reaction exhibits a modest but unmistakable kinetic isotope effect. This result is consistent with the results of other workers[10,11] on similar isocyanate–alcohol systems. Moodie[10] has made the point that reactions featuring proton transfer between hetero atoms in the rate-determining step, and those in which other covalency changes are taking place in the transition state, are expected to show a primary isotope effect of about this magnitude.

The reaction of **1** with **2** shows the same general kinetic behavior as simple alcohols under these conditions, namely first order in the alcohol substrate. The mechanism of the alcohol–isocyanate condensation in nonpolar solvent and in the absence of added catalyst is normally formulated[9–11,21] as a concerted bond-reorganization through a four-membered cyclic transition-state **6**. A two-step mechanism[11] passing through an intermediate **7** (followed by proton transfer) seems less likely under these conditions, based on the charge separation required and the observed high negative $\Delta S^{\neq}$. The two-step process would certainly be more pausible in polar medium or in the presence of an acidic or basic catalyst.

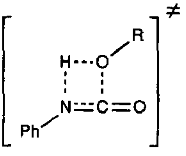
We suggest that a third mechanism, passing through the cyclic transition-state **8** (followed by proton transfer), should also be considered. This mechanism is consistent

TABLE III

Kinetic isotope effect on rate of carbamylation

Alcohol	*t* (°)	*[Alcohol]*	*[**2**]*	*10^4k_2*	k^H/k^D	*Ref.*
1	100	0.105	0.342	133 ±1		
1-d_1	100	0.113	0.341	68 ±9	1.93 ±0.25	this work
MeOH(D)	25.1	(with 4,4′di-isocyanatodiphenylmethane in DMF)			1.58 ±0.08	11
MeOH(D)	25	(with **2** in carbon tetrachloride with pyridine catalyst)			1.70 ±0.08	10

with the kinetic evidence (bimolecular reaction, kinetic isotope effect, high negative $\Delta S^{\neq}$), although it has the apparent drawback that the O–H and N=C=O bond dipoles[21] are aligned almost parallel in **8**, as shown.



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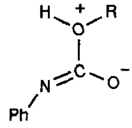

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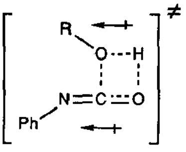

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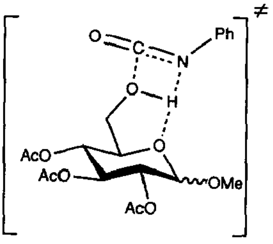
Comparison of the kinetic parameters of the reaction of carbohydrate substrate **1** with simple alcohols (Table II) reveals that the lower reactivity of **1** may be accounted for by differences in the entropy term. The greater steric hindrance about the hydroxyl group of **1** would be expected to contribute to the high negative $\Delta S^{\neq}$ value. Whereas the low reactivity of methoxyethanol relative to methanol and ethanol (Table II) has been ascribed to the electron-withdrawing C–O bond vicinal to the reacting hydroxyl group[9], carbohydrate **1**, which also has this structural feature, does not show nearly so high an E_a value. This difference indicates that there may be compensating factors present in the reaction of **1** that do not occur with the simple alcohols. One such factor might be the interaction of the pyranose ring oxygen of **1** with its reacting hydroxyl group either before or during the rate-determining step[14]. The possible presence of a pre-existing hydrogen bond between these groups (whose rupture is necessary for attaining the transition state) does not manifest itself as a higher $\Delta H^{\neq}$ value. Likewise, the possible stabilization of an intermediate **7** by an intramolecular hydrogen-bond is not reflected in a decreased kinetic isotope effect or a less-negative $\Delta S^{\neq}$ value relative to the simple alcohols, and changing the anomeric configuration (**1** *vs.* **4**) has negligible effect. Thus the reaction of **1** and **2** may simply proceed through the non-hydrogen-bonded form of **1**, or if the hydrogen bond is present in the transition state, it may simply orient or partially polarize the reacting hydroxyl group (as shown in **9**) rather than changing the mechanism or accelerating the reaction.



9

EXPERIMENTAL

Materials and equipment. — Proton nuclear magnetic resonance (n.m.r.) spectra were obtained with a Varian Associates XL-400 instrument. Chemical shifts are reported in p.p.m. downfield from Me_4Si. I.r. spectra were recorded by using a Mattson Instruments Expert-FT i.r. spectrophotometer. Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[15] (**1**) and its β anomer[22] (**4**) were prepared from the respective methyl D-glucopyranosides following the literature procedure[15]. Phenyl isocyanate (98+%), benzene-d_6 (99.5% D), and methanol-d_1 (99.5%D) were purchased from Aldrich and used as received. Deuterated **1** was prepared by dissolving **1** in methanol-d_1 and evaporating *in vacuo* several times until n.m.r. analysis revealed >98% deuteration.

Kinetic studies. — A 0.125M solution of **1** in benzene-d_6 was mixed with 7.0 equiv of phenyl isocyanate (**2**) in an n.m.r. tube, which was then sealed and placed in a constant-temperature bath (± 1°). The extent of reaction was determined by integrating the C-6 methylene protons (δ 4.28) of the product **3** against the total OCH_3 signal. N.m.r. analysis of the mixture at 400 MHz indicated only the presence of starting materials and product; no complicating side-reactions were observed. Plots of $\ln\{[1]/([1]-x)\}$ *vs.* time gave good correlation to a straight line (r = 0.99+) over 90% of the reaction, indicating a pseudo-first-order reaction.

The relative reactivity of **1** and its β anomer **4** was established by treating an equimolar mixture of the two with **2** as described above for **1**. The reaction was carried out at 100° and stopped after 2 h (12% completion). The reaction products (as the mixture of **3** and **5**) were separated from the starting materials by column chromatography on silica, and analyzed by n.m.r. by integration of the respective OCH_3 and anomeric proton signals.

The deuterium isotope-effect experiments were carried out by simultaneously but separately treating **1** and **1**-d_1 in the same constant-temperature bath with **2** under the conditions described already for **1**, except that the initial concentrations were 0.105, 0.113, and 0.342M for **1**, **1**-d_1, and **2**, respectively. The progress of the reactions was monitored by n.m.r. as before.

ACKNOWLEDGMENTS

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