expected to be negligible, at the limit eq 12 will reduce to eq 18.

$$k_c = k_4/(1 + K) \quad (18)$$

Therefore, the second-order rate constant (k_4) of the reaction between PhCOCl and PNO in the organic phase can then be estimated by eq 18. The calculated values of k_4 obtained with $[PNO]_{iaq} = 2.00 \times 10^{-4}$ and 6.00×10^{-4} M (Table III, supplementary material) are 64.6 and 63.8, 99.9 and 101, 111 and 110, and 135 and 123 s^{-1} at 0, 10, 16, and 22 °C, respectively. The corresponding thermodynamic parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) obtained by the LLS fit of the Eyring plot (ln k_4/T vs $1/T$) are 19.6 ± 2.2 kJ/mol and −137 ± 8 J/mol·K and 17.6 ● 3.5 kJ/mol and −145 ± 13 J/mol·K for reactions with $[PNO]_{iaq} = 2.00 \times 10^{-4}$ M and 6.00×10^{-4} M (Table III, supplementary material), respectively. The above argument can therefore be justified by these consistent results. The negative value of entropy can be rationalized by considering that the transition state formed during the reaction between PhCOCl and PNO is much more polar than both reactant molecules. Thus, this reaction is more favorable to take place in polar solvent like CH_2Cl_2 and unfavorable in nonpolar solvents like C_6H_6 and n-C_6H_{14} as observed in the present system.

Summary

In the two-phase reaction of benzoyl chloride and benzoate ion, pyridine 1-oxide acts as an inverse phase transfer catalyst for the transport of benzoyl chloride (as (benzoyloxy)pyridinium chloride) into the aqueous phase, where it reacts with benzoate ion to produce benzoic anhydride or hydrolyzes to benzoic acid. A high yield (>95%) of benzoic anhydride can be obtained if a polar organic solvent like dichloromethane is used. Under appropriate conditions, the reaction of benzoyl chloride and pyridine 1-oxide in the organic phase is slow, and the study of the kinetics of this IPTC system becomes possible.

Abbreviations: PNO = pyridine 1-oxide, pyridine N-oxide, $PhCOONP^+Cl^-$ = 1-(benzoyloxy)pyridinium chloride, A = $PhCO_2H$, A^- = $PhCO_2^-$, B = PhCOCl, N = PNO, I = $PhCOONP^+Cl^-$, P = $(PhCO)_2O$, W = H_2O, [X] = concentration of species X, $[X]_i$ = initial concentration of species X, $[X]_s$ = steady-state concentration of species X, LLS = linear-least-squares, K = partition (equilibrium) constant, k_{obs} = observed rate constant, k_h = uncatalyzed rate constant, k_c = catalyzed rate constant, o = org = organic phase (subscript), w = aq = aqueous phase (subscript).

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Registry No. Benzoyl chloride, 98-88-4; benzoate, 766-76-7; pyridine 1-oxide, 694-59-7; benzoic anhydride, 93-97-0.

Supplementary Material Available: Figure 1 (the plot of ln [PhCOCl] vs time) and Figure 2 (the plot of k_{obs} vs $[PhCO_2Na]$) for the two-phase reaction of benzoyl chloride and benzoate ion catalyzed by pyridine 1-oxide and Table II (pseudo-first-order rate constant for the uncatalyzed) and Table III (temperature dependence of the pseudo-first-order rate constant of the uncatalyzed and pyridine 1-oxide catalyzed) for the two-phase reaction of benzoyl chloride and benzoate ion (4 pages). Ordering information is given on any current masthead page.

Stereochemical Aspects of Hydration of Carbohydrates in Aqueous Solutions. 2.[1] Kinetic Medium Effects

Saskia A. Galema,[2a] Michael J. Blandamer,[2b] and Jan B. F. N. Engberts*,[2a]

Department of Organic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands, and Department of Chemistry, University of Leicester, Leicester, LE1 7RH England

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Rate constants for the hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole in aqueous solutions of carbohydrates have been measured as a function of molality and nature of added mono- and disaccharides. The kinetic medium effects induced by the carbohydrates originate from hydration sphere overlap effects. The results are analyzed using the additivity principle and reveal specificity in the stereochemical aspects of hydration. The major effect determining the hydration of a monosaccharide appears to be the position of the OH(4) group in conjunction with OH(2). The position of the carbonyl function and the number of equatorial groups present in the molecule are of minor importance. The experimentally obtained G(C) values, which are representative of the interaction between the carbohydrate and the initial state and activated complex for the hydrolysis reaction, show that the hydration of the carbohydrates is mainly determined by the methine moieties. The G(CHOH,endo) values obtained for the dominant conformers in solution point to a similar conclusion. With an increase in compatibility of the carbohydrate molecule with the three-dimensional hydrogen-bond structure of water, the hydroxy groups become less important in determining carbohydrate–solute interactions. This might be important in molecular recognition, since under these conditions the carbohydrates are recognized as hydrophobic moieties. For disaccharides the medium effects are larger than expected on the basis of the medium effect of two monosaccharide subunits. We suggest that this is caused by a cooperativity effect, which makes the methine moieties even more dominant in governing the hydration characteristics. The G(C) values reveal that the type of linkage in the disaccharide molecule hardly influences the kinetic medium effect. Only when one of the monosaccharide subunits has an axial OH(4) or when there is a 1–3 type of linkage between the moieties is a significantly different G(C) found. It is suggested that the compatibility of the carbohydrates with the three-dimensional hydrogen-bond structure of water largely depends on the compatibility of the next nearest neighbor oxygens of the carbohydrate molecule with the nearest or next nearest neighbor oxygens of liquid water.

Carbohydrates play an important role in life processes. Not only do they serve as structural and protective materials and as an energy source[3] but they are also very important moieties in glycoproteins[4] and play a significant

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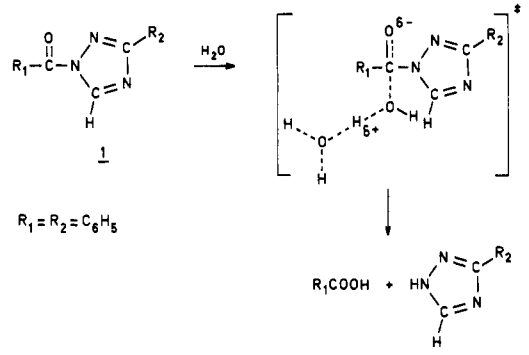
Scheme I. Reaction Scheme for the Neutral Hydrolysis of 1

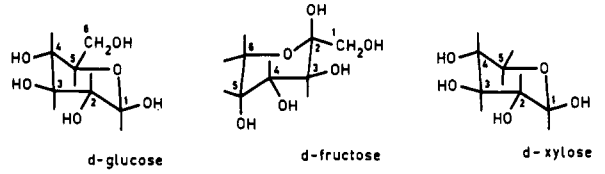


role in (bio)molecular recognition.[5] The source of the specificity of carbohydrates (and particularly carbohydrates in aqueous solution) has been a subject of study over a long period of time.[6] Neither crystallographic data nor data obtained in other solvents or solvent mixtures can be readily extrapolated to aqueous solutions,[7] due to the special solvent characteristics of water. Nonbonding interactions in aqueous solutions of carbohydrates determine the thermodynamics of the solution and can be treated in terms of hydration numbers[8,9] or in terms of carbohydrate–solute interactions mediated by the solvent.[10]

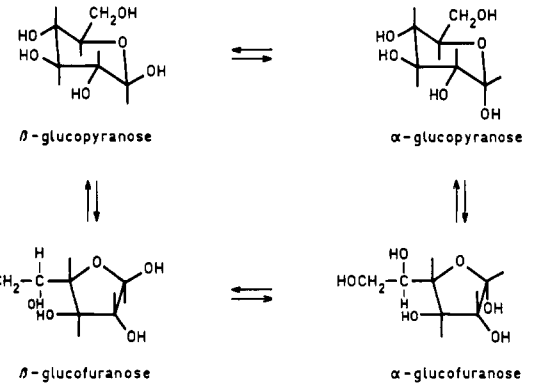
This paper deals primarily with the specificity of carbohydrate–solute interactions mediated by water. These interactions will cause a kinetic medium effect on the medium-dependent, water-catalyzed hydrolysis reaction of 1 (Scheme I). These medium effects find their origin in hydration shell overlap effects.[11] This means that the observed medium effects are primarily the result of a reordering of hydration shells during the activation process. The magnitude of these effects reflects the hydration characteristics of the carbohydrate.

Attempts have been made to rationalize the hydration characteristics of carbohydrates by using concepts such as hydration numbers,[8,9,12] the anomeric effect,[13] the ratio of axial versus equatorial hydroxy groups,[12,14,15] the hydrophobic/hydrophilic index,[16] the hydrophobic volume of the carbohydrate,[17] and the compatibility with water structure depending on the position of the next nearest neighbor

Chart I. Dominant Conformers in Aqueous Solutions for D-Glucose, D-Fructose, and D-Xylose



Scheme II. Equilibrium of D-Glucose in Water



hydroxy groups of a carbohydrate molecule.[18,19] However, studies of aqueous solutions of carbohydrates are complicated because of the fact that carbohydrates are present in aqueous solution in several forms.[20] This makes it preferable to study aqueous solutions of carbohydrates over a small temperature and pressure range[21] and at low concentrations of carbohydrate.[22] Previous results have shown that kinetic medium effects are useful in studies of the hydration of alcohols, diols and polyols[11] as well as stereochemical aspects of hydration.[1]

Results

Kinetic Analysis. Kinetic medium effects on the hydrolysis of 1 in water in the presence of carbohydrates are interpreted in terms of solvent effects since no carbohydrate-derived esters are found in the reaction products. These solvent effects are analyzable in terms of the additivity principle. The theoretical background of this approach has been delineated previously.[11,23,24] Accordingly:

$$\ln (k_{obs}/k^{\circ}_{obs}) = (2/RT)[G(\text{C–IS}) - G(\text{C–TS})]m_c - n\Phi M_1 m_c \quad (1)$$

Herein k_{obs} is the pseudo-first-order rate constant for hydrolysis of 1 in the aqueous binary mixture in which the molality of carbohydrate is m_c, k°_{obs} is the rate constant in pure water ($m_c = 0$), n is the number of water molecules involved in the activated complex (for 1, $n = 2$), and Φ is the practical osmotic coefficient of water ($\Phi = 1$ for highly dilute solutions).[25] M_1 is the molar mass of water. G(C–

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Table I. Tautomeric and Anomeric Equilibrium Compositions of Carbohydrates in D_2O, Conformation of Dominant Conformer, and Medium Effects on the Neutral Hydrolysis of 1 in Highly Aqueous Solutions of Carbohydrates at 298 K

	pyranose[b]		furanose				
carbohydrate[a]	α	β	α	β	conf[b] pos OH	G(C)[c] J kg mol^{-2}	G(CHOH,endo)[d] J kg mol^{-2}
2a, D-galactose	29	64	3	4	1e2e3e4a6e	−142 (11)	−31 (3)
2b, D-gulose	16	81		3	1e2e3a4a6e	−131 (30)	−22 (7)
2c, D-glucose[e]	38	62			1e2e3e4e6e	−201 (12)	−45 (3)
2d, D-mannose	66	34			1a2a3e4e6e	−227 (12)	−52 (3)
2e, D-allose	16	76	3	5	1e2e3a4e6e	−228 (15)	−52 (4)
2f, D-altrose	27	43	17	13	1e2a3a4e6e	−244 (10)	−56 (3)
2g, D-talose	37	32	17	14	1a2a3e4a6e	−280 (10)	−65 (3)
2h, D-idose	39	36	11	14	1a2a3a4a6e	−330 (40)	−72 (10)
3a, D-fructose[e]		75	4	21	1e2a3e4e5a	−222 (12)	−51 (3)
3b, L-sorbose	98		2		1e2a3e4e5e	−255 (10)	−51 (3)
3c, D-psicose	22	24	39	15	1e2a3e4a5e	−247 (10)	−57 (3)
3d, D-tagatose	79	16	1	4	1e2a3a4e5e	−203 (10)	−46 (3)
4a, D-arabinose	60	35	3	2	1a2e3e4a	−98 (8)	−13 (2)
4b, L-arabinose	60	35	3	2	1a2e3e4a	−129 (10)	−21 (4)
4c, D-xylose[e]	37	63			1e2e3e4e	−253 (18)	−52 (5)
4d, D-lyxose	70	28	2		1a2a3e4e	−241 (18)	−49 (5)
4e, D-ribose	22	59	6	13	1e2e3a4e	−223 (10)	−45 (4)

[a] Molality always below 1 mol kg^{-1}. [b] From ref 20. [c] Experimental value, error is given between parentheses. The error in the G(C) value is calculated with aid of the GraphPad linear regression program. [d] Calculated CHOH, endo value from G(C) = 4G(CHOH,endo) + x-(CHOH,exo) + G(–O–) + G(CH_2); x = 1 for hexoses and x = 0 for pentoses. [e] The dominant conformer of D-glucose, D-fructose, and D-xylose and the numbering of the ring carbon atoms are shown in Chart I.

IS) is the pairwise Gibbs energy interaction parameter for the interaction between carbohydrate and the initial state of the reaction, whereas G(C–TS) is the corresponding interaction parameter for the activated complex of the reaction. Earlier this has been described as G(C) = G(C–IS) – G(C–TS)[24] or as – 3G(C–OH),[23] since according to Scheme I the difference between the initial state and activated complex of the reaction is interpreted as being three hydroxy groups pointing toward the medium in the activated complex. Thus, G(C) will be representative for the overall effect of the carbohydrate on the Gibbs energy of activation of the hydrolytic process. Its value is directly obtained by adding the value of $n\Phi M_1$ to the value of the slope of the linear plot of $\ln(k_{obs}/k^{o}_{obs})$ vs the molality of the carbohydrate. The term G(C) can be written as the sum of the functional group contributions. For example, for D-glucose we have:

$$G(\text{D-glucose}) = 4G(\text{CHOH,endo}) + G(\text{CHOH,exo}) + G(\text{CH}_2) + G(\text{–O–}) \quad (2)$$

In this equation CHOH,endo represents a CHOH moiety present in the pyranose ring, whereas CHOH,exo is the CHOH group attached to the ring and part of the hydroxymethyl moiety.

Kinetics. In this paper, we make an endeavor to understand the hydration characteristics of different isomeric aldohexoses (**2a–2h**), ketohexoses (**3a–3d**), and aldopentoses (**4a–4e**) by using 1-benzoyl-3-phenyl-1,2,4-triazole as a kinetic probe. The numbering of carbon atoms as used for the monosaccharides is shown in Chart I, whereas the conformational equilibrium for D-glucose is presented in Scheme II. Stereochemical details and interaction parameters for the monosaccharides are listed in Table I. Representative plots of ln (k_{obs}/k^{o}_{obs}) vs molality of carbohydrate (eq 1, vide supra) are shown for hexoses and pentoses in Figures 1 and 2. Comparable data for methyl glycopyranosides (**5a–5f, 6a, 6b**) and for disaccharides (**7a–7d, 8a-8c, 9a-9c**) are listed in Tables II and III, respectively. A representative plot of ln (k_{obs}/k^{o}_{obs}) versus molality of some methyl glycopyranosides is given in Figure 3.

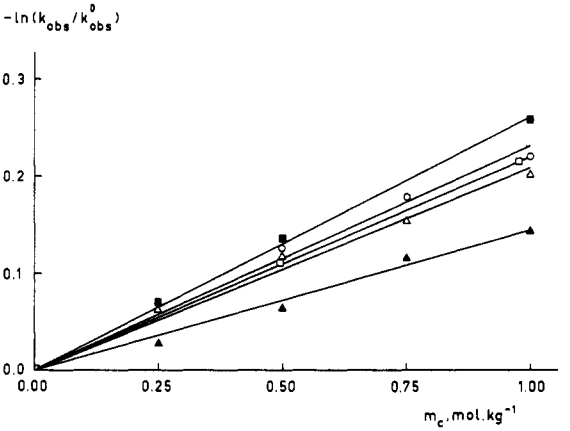

Figure 1. Plots of $-\ln (k_{obs}/k^{o}_{obs})$ vs molality of carbohydrate for the neutral hydrolysis of 1: D-galactose (–▲–); D-allose (–□–); D-talose (–■–); D-glucose (–△–); D-mannose (–○–).

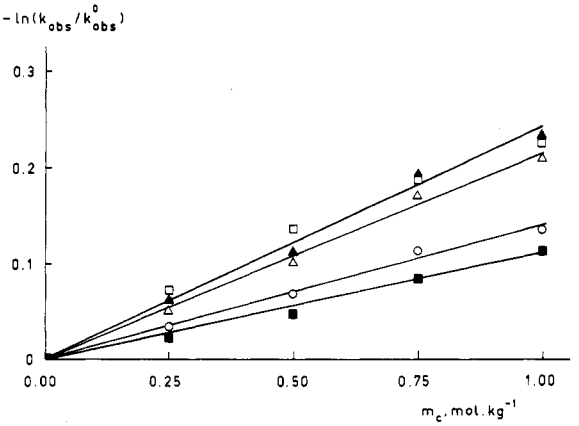

Figure 2. Plots of $-\ln (k_{obs}/k^{o}_{obs})$ vs molality of carbohydrate for the neutral hydrolysis of 1: D-arabinose (–■–); L-arabinose (–○–); D-ribose (–△–); D-lyxose (–□–), D-xylose (–▲–).

(25) Osmotic coefficients are only known for few carbohydrates in aqueous solution. See, for example, ref 8. In the concentration range 0–1 mol kg^{-1} osmotic coefficients vary by about 2% for monosaccharides and by about 5% for disaccharides. The kinetic medium effects can, therefore, not be explained on the basis of these changes in Φ. In the calculation of G(C) values we have chosen to take Φ = 1 for all carbohydrate solutions.

Table II. Medium Effects of Methyl Glycopyranosides on the Neutral Hydrolysis of 1 in Highly Aqueous Solutions at 298 K

carbohydrate[a]	$G(C)$[b], J kg mol^{-2}
5a, methyl α-D-galactopyranoside	−244 (10)
5b, methyl β-D-galactopyranoside	−228 (13)
5c, methyl α-D-glucopyranoside	−276 (10)
5d, methyl β-D-glucopyranoside	−326 (19)
5e, 3-*O*-methylglucopyranose	−389 (16)
5f, methyl α-D-mannopyranoside	−343 (10)
6a, methyl β-D-arabinopyranoside	−260 (10)
6b, methyl β-D-xylopyranoside	−428 (10)

[a] Molality always below 1 mol kg^{-1}. [b] Experimental value, error given between parentheses. The error was calculated with aid of GraphPad linear regression method.

Table III. Medium Effects of Disaccharides on the Neutral Hydrolysis of 1 in Highly Aqueous Solutions at 298 K

disaccharide[a]	subunits[b]	type of linkage	$G(C)$,[c] J kg mol^{-2}
7a, maltose	gl-gl	1-4α	−659 (49)
7b, cellobiose	gl-gl	1-4β	−649 (62)
7c, trehalose	gl-gl	1-1αα	−637 (37)
7d, gentiobiose	gl-gl	1-6α	−575 (37)
8a, sucrose	gl-fr	1-5α	−541 (25)
8b, turanose[d]	gl-fr	1-3α	−440 (25)
8c, palatinose	gl-fr	1-6α	−540 (15)
9a, lactose	gl-ga	1-4β	−472 (37)
9b, melibiose	gl-ga	1-6α	−467 (20)
9c, lactulose	fr-ga	1-4β	−482 (25)

[a] Molality always below 0.5 mol kg^{-1}. [b] gl = glucose, fr = fructose, ga = galactose. [c] Experimentally obtained, error in parentheses. The error was calculated with aid of the GraphPad linear regression method. [d] Fructose in pyranose form.

The mechanism of hydrolysis of the activated amide 1 has been studied in detail.[26] The pH-independent hydrolysis proceeds through a dipolar transition state containing two water molecules and in which three protons are in flight (Scheme I).

Rate constants were determined at 25 °C at low carbohydrate concentrations (0–1 mol kg^{-1}). Typically, the measurements were performed at four different molalities. All carbohydrates cause a rate retardation of the hydrolytic process as expressed in the negative slopes of the linear plots of ln (k_{obs}/k^{o}_{obs}) vs molality of carbohydrate.

Aldohexoses. To the best of our knowledge, the present study is the first one (except for the NMR investigation by Angyal et al.[20]) that considers a complete set of D-aldohexoses in an attempt to delineate stereochemical aspects of hydration.

According to the additivity principle of Savage and Wood,[27-30] all aldohexoses should exert the same kinetic medium effect. However, the kinetic medium effects of the aldohexoses (**2a–2h**, Table I) suggest that the interactions of the hexoses depend on their stereochemistry. Three different classes of medium effects can be distinguished, depending on the stereochemistry of the aldohexose. We observe a very small, but negative kinetic medium effect ($G(C)$ = −108 and −142 J kg mol^{-2}) for aldohexoses which have an axial hydroxy group on the C4 position and an equatorial OH(2) (**2a**, D-galactose and **2b**, D-gulose). A moderately negative kinetic medium effect ($G(C)$ = −201 to −244 J kg mol^{-2}) is found for aldohexoses for which OH(4) is equatorial and OH(2) is either equatorial or axial (**2c**, D-glucose, **2d**, D-mannose, **2e**, D-allose, **2f**, D-altrose). Finally, aldohexoses with both an axial OH(4) and an axial OH(2) show the largest negative kinetic medium effect (**2g**, D-talose and **2h**, D-idose); in these cases the $G(C)$ values range from −280 to −307 J kg mol^{-2}. This is in accord with preliminary results obtained previously.[1]

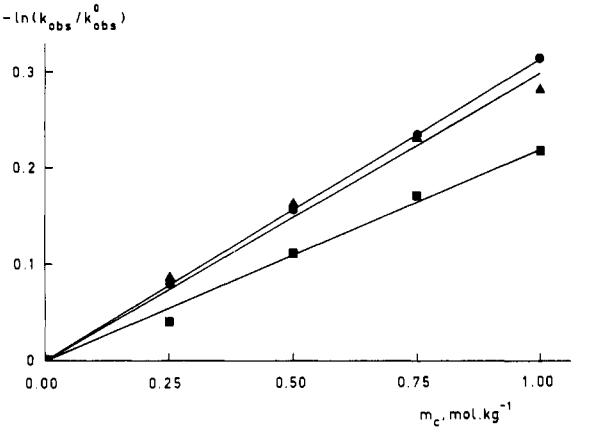

Figure 3. Plots of −ln (k_{obs}/k^{o}_{obs}) vs molality of carbohydrate for the neutral hydrolysis of 1: methyl β-D-galactopyranoside (-■-), methyl α-D-mannopyranoside (-●-), methyl β-D-glucopyranoside (-▲-).

Ketohexoses. All ketohexoses (**3a–3d**, Table I) exhibit the same type of hydration independent of their stereochemistry. Although their hydration characteristics seem to be different from those of the aldohexoses, overall they show a $G(C)$ value (−203 to −255 J kg mol^{-2}) similar to that of the aldohexoses. We suggest that the relative insensitivity of the hydration of ketohexoses for their stereochemistry is caused by the presence of the exocyclic −CHOH moiety on the anomeric center.

Aldopentoses. We find that the type of hydration of the aldopentoses (**4a–4e**, Table I) depends on the stereochemistry of the pentose in the same way as was found for the hexoses. The pentoses can be divided into two groups with different extents of hydration. Both D- and L-arabinose (**4a** and **4b**) which have an axial hydroxy group at the 4-position and an equatorial OH(2) show a small negative $G(C)$ value (−98 and −129 J kg mol^{-2}), while D-xylose (**4c**), D-lyxose (**4d**), and D-ribose (**4e**) exhibit a more negative $G(C)$ value (−233 to −253 J kg mol^{-2}). The latter compounds possess an equatorial OH(4) and either an axial or an equatorial OH(2). Again the position of the hydroxy groups on position 4 (and 2) appears to determine the magnitude of the kinetic medium effect.

Methyl Glycopyranosides. The methyl glycopyranosides (**5a–5f**, **6a**, **6b**, Table II) exert a stronger rate retarding effect than their "parent" aldopyranoses due to the presence of the methoxy group at the anomeric center.

Again the $G(C)$ values depend on the stereochemistry of the carbohydrate. We observe that the methyl hexopyranosides can be divided into two groups depending on the position of the OH(4) relative to OH(2). A moderately large and negative kinetic medium effect is found for the methyl hexopyranosides which have an equatorial OH(4) (**5d**, **5f**) and either an axial or an equatorial OH(2) ($G(C)$ = −326 and −343 J kg mol^{-2}, respectively), while **5b**, which has an axial OH(4) and an equatorial OH(2), shows a

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smaller negative G(C) value (−228 J kg mol^{-2}). When there is an equatorial OH(4), the G(C) values depend also on the relative position of the methoxy group (**5c**, **5d**, and **5e** all have significantly different G(C) values: −276, −326, and −389 J kg mol^{-2}, respectively). This is not found when the OH(4) is axial and OH(2) is equatorial; **5a** and **5b** induce approximately the same kinetic medium effect (G(C) = −244 and −228 J kg mol^{-2}, respectively). Also for the methyl pentopyranosides (**6a**, **6b**) the G(C) values differ depending on the relative position of OH(4); compare **6b** (G(C) = −428 J kg mol^{-2}) with **6a** (G(C) = −260 J kg mol^{-2}).

Disaccharides. The composition of the disaccharides and the relevant G(C) values are listed in Table III. All disaccharides have a more negative G(C) value than anticipated on the basis of the individual monosaccharide moieties. We suggest that this is caused by a cooperativity effect.[31] The results will be discussed on the basis of the composition of the disaccharides. The most negative kinetic medium effect is found for disaccharides which consist of two glucose units (**7a–7d**) and the G(C) value is not much influenced by the type of linkage between the glucose moieties (G(C) = −575 to −659 J kg mol^{-2}). The disaccharides which consist of a glucose and a fructose moiety have a slightly smaller negative G(C) value (**8a–8c**) (G(C) = −541, −440, and −540 J kg mol^{-2}, respectively). Their kinetic medium effect is not sensitive to the type of linkage either, except in the case of a 1–3 type of linkage (**8b**, turanose) for which a significantly different G(C) value is found. Apart from the type of linkage, this difference could also be caused by the fact that the fructose moiety resides in the pyranose form. All disaccharides which have a moiety with an axial OH(4) (**9a–9c**) have the least negative G(C) values compared to those of the other disaccharides (G(C) = −467 to −482 J kg mol^{-2}). Differences in type of linkage or identity of monosaccharide moiety other than the galactose have no significant effect.

Quantitative Analysis and Comparison. Since in most equilibrium mixtures of the monosaccharides the pyranose form is the dominant conformer present in solution,[20] all calculations for the monosaccharides have been performed assuming that the carbohydrate resides in the pyranose form. All carbohydrates cause a rate retardation, which is expressed quantitatively in a negative G(C) value. Now the value of G(CHOH,exo) can be obtained by comparison of the data of aldohexoses with those for aldopentoses, the only difference being the exocyclic −CHOH group. This provides a G(CHOH,exo) value of about 25 J kg mol^{-2}, which means that this group has the hydration characteristics of a similar group in a vicinal dihydric alcohol.[11] The hydration characteristics of the group are still mainly determined by the hydroxy group which is dominant over the methine moiety. Evaluation of the G(CHOH,endo) values (Table I) shows that these values depend on the stereochemistry of the carbohydrate (as their "parent G(C) values" from which they were calculated). The G(CHOH,endo)[32] values range from −65 to −72 J kg mol^{-2} for aldoses which have an axial hydroxy group on both C-2 and C-4, −45 to −52 J kg mol^{-2} for aldoses with an equatorial OH(4) and either an equatorial or axial OH(2), to values of −13 to −31 J kg mol^{-2} for aldoses with an axial OH(4) and an equatorial OH(2). The G(CHOH,endo) values for the ketoses are in the range from −46 to −59 J kg mol^{-2}, comparable to those found for aldoses with an equatorial OH(4) and either an axial or equatorial OH(2). These negative values show that the hydration of the endocyclic CHOH group is largely determined by the methine moiety, which explains why sometimes carbohydrates are found to behave like "hydrophobic" solutes in aqueous solutions.[33,34]

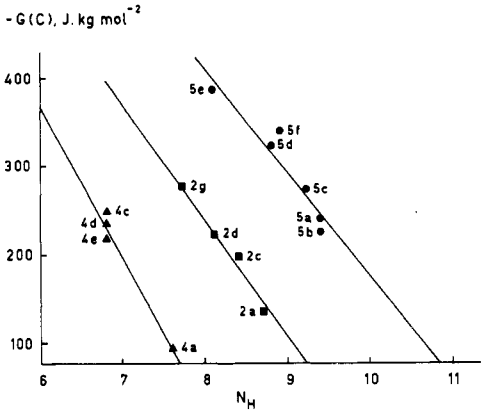

Figure 4. Kinetic medium effects vs hydration number of aldopentoses, aldohexoses, and methyl glycopyranosides: D-arabinose (**4a**), D-xylose (**4c**), D-lyxose (**4d**), D-ribose (**4e**), D-galactose (**2a**), D-glucose (**2c**), D-mannose, (**2d**) D-talose (**2g**), methyl α-D-galactopyranoside (**5a**), methyl β-D-galactopyranoside (**5b**), methyl α-D-glucopyranoside (**5c**), methyl β-D-glucopyranoside (**5d**), 3-*O*-methylglucopyranose (**5e**), methyl α-D-mannopyranoside (**5f**).

Discussion

Based upon previous results,[11,23,24] we assume that the carbohydrate-induced medium effects are caused by hydration shell overlap of the initial and transition state of the reaction with the carbohydrate dissolved in the aqueous medium. The present results suggest that the different kinetic medium effects found for the aldoses are solely determined by the relative stereochemistry of the OH(4) and OH(2) groups. Studies of partial molar isentropic compressibilities,[35,36] which have been performed previously and concurrently with this study, have already shown that the relative position of the OH(2) and OH(4) is a major factor determining the compatibility of the carbohydrate with the three-dimensional hydrogen-bond network of water. Therefore, we contend that the more compatible a carbohydrate is with the three-dimensional hydrogen-bond structure of water, the more negative the experimentally obtained G(C) values and the calculated G(CHOH,endo) values are. An illustration hereof is given in Figure 4 in which the experimentally obtained G(C) values are plotted against the hydration numbers of the carbohydrates.[36] Our theory is further supported by the finding that *m*-inositol has hardly any effect on the rate of hydrolysis of **1**,[37] while it has a large negative partial molar isentropic compressibility.[38]

The smaller the hydration number, the better the carbohydrate fits into the water structure. We observe a linear dependence of the G(C) values with the compatibility of the carbohydrates within every set of isomers (unfortunately, hydration numbers for hexoses other than

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(32) For comparison: using the data of ref 24 for arabitol, sorbitol, and mannitol one can calculate (taking G(polyol) = nG(CHOH) + G(CH_2)) a G(CHOH) value, which ranges from −4 to −19 J kg mol^{-2}.
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Table IV. Through-Space Oxygen Distances[a] in Carbohydrate Crystals[b] (in Angstroms)

carbohydrate	O_2–O_4	O_2–O_5	O_4–O_5	O_1–O_3
β-D-galactose	4.284	3.657	2.826	4.820
β-D-glucose	4.874	3.666	3.664	4.754
α-D-mannose	4.270	2.774	3.687	4.123
β-D-allose	4.821	3.672	3.660	4.126
α-D-talose	2.657	2.926	2.870	4.170

[a] See Experimental Section. [b] In water: O–O (nearest neighbor) = 2.95 Å, O–O (next nearest neighbor) = 4.82 Å.

those in the plot were not available). Also, a smaller hydration number within a certain set of isomers accompanies a more negative $G(C)$ value. This means that a greater compatibility causes a more pronounced camouflage effect[38,39] and the hydroxy groups start to resemble hydroxy groups of water. Hence, another solute will predominantly "see" methine moieties. In this respect, it is interesting to note that the $G(C)$ value for D-talose is even more negative than that for the relatively hydrophobic monohydric alcohol 1-propanol.[11] Thus, D-talose is recognized by the hydrolytic probe as a relatively hydrophobic solute. This peculiar situation should be considered in studies aimed at an understanding of molecular recognition of carbohydrates in aqueous solution.

As yet there is no firm theory which explains why the relative positions of the OH(4) and OH(2) are so important for the compatibility of the aldohexoses in the three-dimensional hydrogen-bond structure of water. Explanations in terms of the Lemieux effect or the occurrence of complex mutarotation[40] seem unlikely. For a Lemieux effect the OH(4) is often involved in a complicated network of intramolecular hydrogen bonds between OH(4), OH(6), and O(5). This can be facilitated when an OH(4) is axial. However, similar trends in kinetic medium effects are still observed when there is no OH(6) present (in the case of the pentoses). Also, an axial OH(4) can give rise to complex mutarotation (see Table I). Under these conditions, more furanose forms will be present in solution which could cause a different kinetic medium effect. But this seems unlikely too. First, the methyl glycopyranosides, which have an anomeric center which is blocked for mutarotation, show the same trend in kinetic medium effects as their "parent" aldoses. Second, D-glucose and D-gulose exert different kinetic medium effects despite the fact that the equilibrium compositions for both aldoses are comparable. For aldoses, which possess a similar equilibrium composition and which have a fairly large preference for furanose forms in solution (D-idose, D-talose, and D-altrose), we observe a different $G(C)$ value for D-idose and D-talose compared to that for D-altrose. This also suggests that the furanose forms present in the equilibrium mixture are not crucial in determining the kinetic medium effect. Accordingly, we suggest that the difference in water compatibility is mainly governed by the relative distances of the next nearest neighbor oxygens in the carbohydrate molecule compared to the relevant oxygen distances in liquid water as proposed by Danford and Warner.[18,19] In Table IV these distances are given for the crystalline state of some aldohexoses (the anomers are the dominant ones in aqueous solutions). It is striking that for D-talose all the next nearest neighbor oxygen distances are comparable to the nearest neighbor oxygens in water. This opens the possibility for efficient intramolecular hydrogen bonding interactions. However, in aqueous solutions these interactions will be in competition with carbohydrate–water hydrogen bond formation. For the other aldoses some oxygen distances are comparable to next nearest neighbor oxygens in water. Clearly, some aldohexoses have a greater number of similar next nearest neighbor oxygen distances than others. We therefore suggest that the next nearest neighbor oxygens of the carbohydrate can either be compatible with the nearest neighbor oxygens or with the next nearest neighbor oxygens of water and if not, they will not be compatible at all. Presently, this aspect is under further investigation. It is striking that these nonbonding carbohydrate–solute interactions as determined by hydration shell overlap seem to be governed by the same stereochemical details as the complexation of ions;[41] the best compatibility with water structure is found when there is an axial–equatorial–axial hydroxy group sequence in the carbohydrate molecule.

Conclusion

Kinetic medium effects on a hydrolysis reaction in aqueous solutions of carbohydrates are found to be a powerful tool in studying the stereochemical aspects of hydration. For the monosaccharides the different extents of hydration depend on the relative position of the next nearest neighbor hydroxy groups OH(4) and OH(2). The results for the methyl glycopyranosides and disaccharides further support this conclusion. The position of the carbonyl moiety in the carbohydrate as well as the number of equatorial hydroxy groups are clearly of minor importance in determining the medium effect. The present quantitative analysis shows that the better a carbohydrate fits into the three-dimensional hydrogen-bond structure of water, the more the hydroxy groups will be camouflaged for interaction; hence, the more the carbohydrate will be recognized as a "hydrophobic" solute. These results require special consideration in studies of molecular recognition by carbohydrate molecules.

Experimental Section

Materials. All carbohydrates were dried overnight in vacuum before use. This does not apply for D-idose, D-gulose, and D-psicose, which are colorless syrups. In these cases solutions were made by dissolving them in water and subsequent freeze–drying of the solution. After several days of drying under vacuum the amount of carbohydrate was weighed and solutions of the proper pH were made.

The water used in all experiments was demineralized and distilled twice in an all-quartz distillation unit. All solutions were made up by weight using water to which approximately 1 mM of HCl was added in order to suppress hydroxide ion catalysis in the hydrolytic process. The molalities of monosaccharide were in all cases below 1 mol kg^{-1} to minimize the role of triplet and higher order interactions. For the disaccharides the molalities were kept below 0.50 mol kg^{-1}.

The carbohydrates were obtained from the following: Merck (D-glucose, D-xylose), Sigma (D-mannose, D-galactose, D-talose, D-allose, D-idose, D-gulose, D-altrose, D-tagatose, D-psicose, D-lyxose, 3-*O*-methylglucose, trehalose, gentiobiose, methyl β-D-arabinopyranoside, methyl β-D-xylopyranoside, maltose, cellobiose, methyl α-D-galactopyranoside, methyl α-D-glucopyranoside, sucrose, turanose, palatinose, lactose, melibiose, lactulose), Janssen (D-arabinose, L-arabinose, D-ribose), and Aldrich (methyl β-D-glucopyranoside, methyl β-D-galactopyranoside, methyl α-D-mannopyranoside).

Kinetic Measurements. Pseudo-first-order rate constants for the neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole (1) were obtained by using a Perkin-Elmer λ5 spectrophotometer

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equipped with a data station. Substrate concentrations were approximately 10^{-5} mol dm^{-3}, and the substrate was added as a concentrated solution in 10^{-5} dm^3 of acetonitrile to a volume of 2.5 10^{-3} dm^3 of the aqueous solution. Rate constants were obtained by recording the change in absorbance at 273 nm at pH 3 for about 10 half-lives. The end value method was used to calculate the rate constants. All measurements were done in triplicate, and the rate constants were found to be reproducible to within 2% for the aqueous solutions of monosaccharides and to within 3% for the aqueous solutions of disaccharides.

Product Analysis. The reaction mixtures were analyzed for the presence of carbohydrate-derived esters. Aqueous solutions of D-glucose, D-galactose, and methyl β-D-glucopyranoside were employed. In a typical experiment 10^{-3} M of the substrate was hydrolyzed in the presence of 0.01 mol kg^{-1} of carbohydrate. The small concentration of carbohydrate is necessitated by experimental limitations. After the hydrolysis had gone to completion, the mixture was freeze-dried. The samples were silylated with hexamethyldisilazane–chlorotrimethylsilane–pyridine (1:1:5) for 30 min at room temperature. Combined GLC and GLC/MS experiments showed that no carbohydrate-derived esters had been formed.

Gas–Liquid Chromatography. GLC was performed on a Varian 3700 gas chromatograph equipped with a capillary SE-30 fused silica column (25 m, 0.32 mm, Pierce) and FID. The oven temperature was programmed from 130 to 220 °C at 4 °C per min. The injector temperature was 210 °C. The detector temperature was 230 °C.

Gas–Liquid Chromatography/Mass Spectrometry. Combined GLC–MS was performed on a Carlo-Erba GC/Kratos MS 80/Kratos DS 55 system; electron energy, 70 eV; accelerating voltage, 2.7 kV; ionizing current, 100 μA; ion source temperature, 225 °C; capillary CP sil 5 column (25 m, 0.32 mm); oven temperature program, 140 °C during 2 min, 140–260 °C at 4 °C per min.

Through-Space Oxygen Distances. The through-space oxygen distances (Table IV) were obtained by introducing the crystallographic data from the Cambridge Crystallographic Database into a CHEMX program.[42]

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Supplementary Material Available: Pseudo-first-order rate constants for the hydrolysis of 1 in aqueous solutions of carbohydrates at 298 K (3 pages). Ordering information is given on any current masthead page.

(42) CHEMX, developed and distributed by Chemical Design Ltd. Oxford, England.

Cobalt(II) Chloride Catalyzed Acylation of Alcohols with Acetic Anhydride: Scope and Mechanism

Javed Iqbal* and Rajiv Ranjan Srivastava

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

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Cobalt(II) chloride catalyzes the acetylation of a variety of alcohols with acetic anhydride in excellent yield. Primary hydroxyl groups can be selectively acylated in the presence of secondary and tertiary ones while the secondary hydroxyl groups can be preferentially acetylated in the presence of tertiary ones. Tertiary alcohols have been found to give ketones, acetoacetates, olefins, and diketene in addition to the acetate. The β-hydroxy esters and ketones can be acylated under these conditions without any elimination, and this reaction has been compared with 4-(dimethylamino)pyridine (DMAP)-mediated acylations where elimination of the resulting β-acetoxy carbonyl compound is observed. A detailed investigation of the acylation of tertiary alcohols has revealed that these reactions proceed via a tertiary alkoxy radical and ketene. A mechanism for these acylations is proposed by invoking an electron-transfer process.

Introduction

The acylation of alcohols by acetic anhydride or acetyl chloride is very routinely carried out[1,2] with amine bases such as triethylamine, pyridine, or 4-(dimethylamino)-pyridine (DMAP). In these reactions the base is considered to provide activation[2b,3] to the acylating reagent (nucleophilic activation) whereas in some cases the base, e.g., triethylamine, is mainly used to trap the generated acid. Primary and secondary alcohols can be very easily acylated with acetic anhydride by using pyridine or triethylamine whereas the tertiary alcohols show very little tendency to undergo acylations in presence of these bases. However, the acylation of tertiary alcohols can be efficiently carried out in the presence of DMAP.[2] When we attempted to acylate a β-hydroxy carbonyl compound using the protocol followed in the DMAP method, a mixture of the acetate and α,β-unsaturated carbonyl compound was obtained (Table II). This may be attributed to the basic medium which causes elimination of the resulting acetate. To circumvent this problem, the acylation under nonbasic conditions seemed an attractive alternative although this has received little attention[4] in the past. This consideration for selectivity prompted us to search for a Lewis acid-based acylation catalyst, and in a preliminary communication we have shown[5] that cobalt(II) chloride is

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