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Regioselective Acylation of Diols and Triols: The Cyanide Effect

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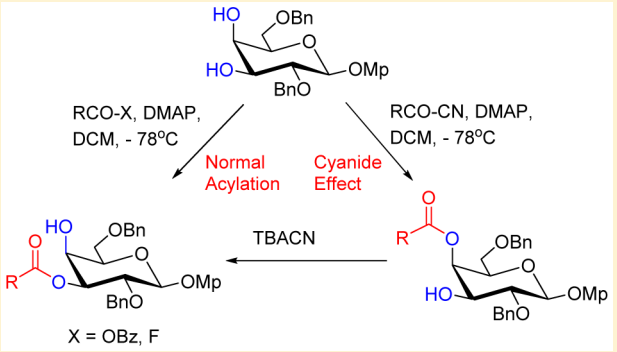
Supporting Information

ABSTRACT: Central topics of carbohydrate chemistry embrace structural modifications of carbohydrates and oligosaccharide synthesis. Both require regioselectively protected building blocks that are mainly available via indirect multistep procedures. Hence, direct protection methods targeting a specific hydroxy group are demanded. Dual hydrogen bonding will eventually differentiate between differently positioned hydroxy groups. As cyanide is capable of various kinds of hydrogen bonding and as it is a quite strong sterically nondemanding base, regioselective *O*-acylations should be possible at low temperatures even at sterically congested positions, thus permitting formation and also isolation of the kinetic product. Indeed, 1,2-*cis*-diols, having an equatorial and an axial hydroxy group, benzoyl cyanide or acetyl cyanide as an acylating agent, and DMAP as a catalyst yield at −78 °C the thermodynamically unfavorable axial *O*-acylation product; acyl migration is not observed under these conditions. This phenomenon was substantiated with 3,4-*O*-unproteced galacto- and fucopyranosides and 2,3-*O*-unprotected mannopyranosides. Even for 3,4,6-*O*-unprotected galactopyranosides as triols, axial 4-*O*-acylation is appreciably faster than *O*-acylation of the primary 6-hydroxy group. The importance of hydrogen bonding for this unusual regioselectivity could be confirmed by NMR studies and DFT calculations, which indicate favorable hydrogen bonding of cyanide to the most acidic axial hydroxy group supported by hydrogen bonding of the equatorial hydroxy group to the axial oxygen. Thus, the "cyanide effect" is due to dual hydrogen bonding of the axial hydroxy group which enhances the nucleophilicity of the respective oxygen atom, permitting an even faster reaction for diols than for mono-ols. In contrast, fluoride as a counterion favors dual hydrogen bonding to both hydroxy groups leading to equatorial *O*-acylation.



INTRODUCTION

Regioselective *O*-protection of hydroxy groups of diols and triols, in particular in carbohydrates, plays an important role, as it gives direct access to intermediates required for structural modifications and as building blocks for chain extension in glycosidation reactions.[1−4] Thus, cumbersome protection and deprotection procedures, often required to attain regioselective protection, are dispensable. Such direct regioselective protection procedures are also regarded as an important aspect of "green" or "sustainable" chemistry.[2,5] As under standard partial *O*-acylation conditions, i.e. using acyl halide or acid anhydride as an acylating agent and trialkylamines or pyridines, respectively, as a base,[6] mainly mixtures of *O*-acylated products are generated; reagents interacting with two hydroxy groups of a 1,2-*cis*-diol or 1,3-diol system were studied. Thus, inherent differences in acidity, nucleophilicity, and/or steric congestion at the hydroxy groups can be amplified, which in turn results in increased regioselectivities for *O*-acylation. Thus, with the help of oxophilic organotin[7−9] and organoboron[10,11] reagents, very good regioselectivities, for instance, for the primary 6-hydroxy group and, particularly noteworthy, for the equatorial secondary 3-hydroxy group of galacto-, gluco-, and mannopyranosides were obtained. Because of toxicity problems[12] and the cost of such reagents the search for other regioselectivity-mediating reagents continued. Hence, organosilicon reagents,[11] various metal salts,[13−17] and organocatalysts[18−22] as well as enzymes[23] were studied. However, other drawbacks were often encountered with these reagents.

Recently, besides acid−base catalysis via hydrogen-bonding effects,[24] dual hydrogen bonding gained considerable interest for the regioselective activation of hydroxy groups.[5,17,25−27] For instance, dual hydrogen bonding in an acetate anion supported deprotonation of a hydroxy group and acetic anhydride based *O*-acetylation was studied. This apporach led to excellent regioselectivities for the primary 6-hydroxy group and the secondary 3-hydroxy group, respectively, of galacto-, gluco-, and mannopyranosides.[5,28] Although the axial 4-hydroxy group of galactopyranosides is more acidic than the equatorial 3-hydroxy group[29] (as also confirmed by theoretical studies)[5] and therefore strong hydrogen bonding to the 4-hydroxy group increasing the oxygen nucleophilicity is expected, the often desirable but thermodynamically unfavorable 4-*O*-acylation of 3,4-*O*-unprotected galactopyranosides, if found at all, is not the main reaction under these conditions. Commonly, steric effects are put forward to explain the preference for 3-*O*-acylation over 4-*O*-acylation.

It was found that the basicity of the counterion of the acylating agent influences the acylation rate, thus revealing the importance

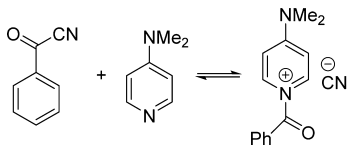
Received: March 7, 2016
Published: April 22, 2016

DOI: 10.1021/jacs.6b02454
J. Am. Chem. Soc. 2016, 138, 6002−6009

of the deprotonation of the hydroxy group in the *O*-acylation reaction. The cyanide ion is rather basic and increases the rate of acylation reactions more than acetate or the halides chloride, bromide, and iodide, respectively. As a consequence, cyanide-supported acylation reactions can be carried out at lower temperatures. Besides preferential hydrogen bonding to the most acidic hydroxy group, ambident cyanide is also capable of dual hydrogen bonding via the carbon or the nitrogen atom or concomitantly via both, the carbon and the nitrogen atoms. Hence, differences in the acidities of the two hydroxy functions of diols should lead to increased differences in oxygen nucleophilicities and thus to higher regioselectivities, particularly at low temperatures. Due to the small size of the cyanide counterion, steric effects are also minimized. Preferential *O*-acylation at the axial hydroxy group should thus be accessible, which is of great importance for the direct regioselective protection of the readily available 3,4-*O*-unprotected galacto- and fucopyranosides, 2,3-*O*-unprotected manno- and rhamnopyranosides, 1,2-/2,3-*O*-unprotected inositols, or the 1,2-*O*-unprotected α-anomeric hydroxy groups in gluco- and galactopyranoses and related compounds. With cyanide as a quite strong base in organic solvents (see below) the desired formation of the kinetically controlled axial *O*-acyl product could be followed by a thermodynamically controlled acyl migration; yet, acyl migration is not expected at low temperatures. Hence, there are good prospects to replace the indirect ortho-ester procedure[30] to obtain 4-*O*-acylated galactopyranosides by a convenient direct method, with cyanide as the base at low temperatures.

RESULTS AND DISCUSSION

Cyanide as Counterion in *O*-Acylation Reactions of Diols. Our first experiments were performed with 2,6-di-*O*-benzyl protected galactopyranoside **1a** as the substrate, benzoyl cyanide (BzCN, 1 equiv) as the acyl donor, and 4-dimethylaminopyridine (DMAP, 0.1 equiv) as the catalyst. As BzCN and DMAP lead to a cationic adduct with cyanide as the counterion (eq 1),[31,32] cyanide is available for hydrogen bonding to the



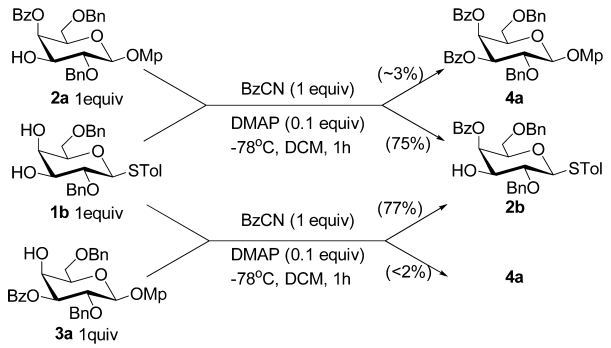
(1)

hydroxy groups of **1a**. Indeed, with these reagents, even at room temperature mainly axial 4-*O*-benzoylation takes place, leading to **2a** and to the 3,4-di-*O*-benzoylated product **4a** (Table 1, entry 1). In accordance with our expectations, at −78 °C essentially only **2a** was formed (entry 2).

Competition studies between substrate **1b** and 4-*O*-benzoylated **2a** and between **1b** and 3-*O*-benzoylated **3a**, respectively, with BzCN and DMAP at −78 °C showed that 4-*O*-benzoylation of **1b** is by far faster than 3-*O*-benzoylation of **2a** or 4-*O*-benzoylation of **3a** (Scheme 1). The use of more polar nonprotic solvents (acetonitrile or DMF) for the benzoylation reaction did not change regioselectivities (Table 1, entries 3, 4).

As cyanide not only is able to form hydrogen bonds but also is a rather strong base, particularly in organic solvents (H_2O: pK_a 9.4; DMSO: pK_a 12.9),[33] we applied the same procedure to benzoyl chloride. The chloride anion released on adduct formation is less prone to hydrogen bonding and also much less basic (H_2O: pK_a −8.0; DMSO: pK_a 1.8).[33] Yet no reaction was observed with DMAP as the catalyst at −78 °C (entry 5). At

Scheme 1. Competition Reactions between 1b/2a and 1b/3a, Respectively



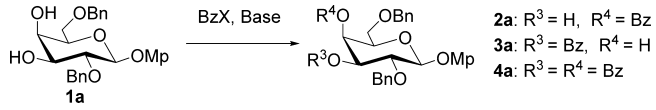
room temperature the reaction was still slow; after 48 h only 3-*O*-benzoylated **3a** was obtained in low yield (entry 6). Selection of benzoic acid anhydride as the acylating agent increased the basicity of the counterion (H_2O: pK_a 4.2; DMSO: pK_a 11.1)[33] compared with benzoyl chloride, and as expected, the reaction rate was increased. In accordance with previous results,[5] also with DMAP as the catalyst, practically exclusive 3-*O*-benzoylation (→ **3a**) took place (entry 7). With 0.1 equiv of tetrabutylammonium cyanide (TBACN) as the base at −78 °C no reaction was attained. However, with 1 equiv of TBACN the preference for axial 4-*O*-benzoylation was observed again, though **2a** was obtained only in modest yields (entries 8, 9). As in organic solvents the small fluoride anion is a particularly strong base (H_2O: pK_a 3.17; DMSO: pK_a 15)[33] and fluoride is also capable of dual hydrogen bonding, TBAF was selected as the base for the benzoylation with benzoic acid anhydride. At −10 °C some reaction was observed; however, the "fluoride effect", favoring 4-*O*-benzoylation, was only modest (entries 10, 11). Therefore, benzoyl fluoride as the acylation agent and DMAP as the catalyst were selected; however, then a clear preference for 3-*O*-benzoylation of **1a** was attained (entries 12, 13).

Transesterification of **2a** or **3a** with DMAP or TBACN as the base was not observed at −78 °C. At 0 °C with **2a** as the substrate and TBACN as the base after 24 h, a 1:1.1 ratio of **2a**:**3a** was obtained. No isomerization took place with DMAP at 0 °C. From these results it is evident that a cyanide-specific effect supports kinetic 4-*O*-benzoylation of **1a**. This effect is particularly efficient with BzCN as the acylating agent and DMAP as the catalyst. At ambient temperatures these high regioselectivities may be compromised by some 4-*O*- ⇌ 3-*O*-migration of the acyl group.

In order to demonstrate the hydrogen bonding between hydroxy and nitrile groups or the cyanide ion, the effect of addition of 1 equiv of BzCN, acetonitrile, and cyanide, respectively, to a solution of **1a** in $CDCl_3$ was studied by ^{1}H NMR spectroscopy (Figure 1). Noncharged BzCN and acetonitrile had practically no effect on the chemical shifts of **1a** (Figure 1A–C). However, as expected, cyanide addition had a dramatic effect on not only the proton shifts of the 3,4-*cis* hydroxy groups but also the shift of the C–H protons (Figure 1D). The same observations were also made for the 2,3-*O*-unprotected β-D-galactopyranoside **5** where the two hydroxy groups are in the *trans*-orientation (Figure 1E, 1F). However, competition between **1a** and **5** for the cyanide ion (addition of 1 equiv of TBACN to 1 equiv each of **1a** and **5**) is clearly in favor of **1a**, as the C–H shifts in Figure 1G indicate. Hence, hydrogen bonding to the *cis*-diol in **1a** is much stronger than hydrogen bonding to the 1,2-*trans*-diol in **5**.

DOI: 10.1021/jacs.6b02454
J. Am. Chem. Soc. 2016, 138, 6002–6009

Table 1. Regioselectivity of the Benzoylation of 3,4-*O*-Unprotected Galactopyranoside 1a



						Product [%][a]			
entry	BzX (equiv)	base (equiv)	solvent	temp [°C]	time [h]	**2a**	**3a**	**4a**	ratio **2a**/**3a**
1	BzCN (1.0)	DMAP (0.1)	DCM	rt	4	82	<3	8	>20:1
2	″	″	″	−78	4	90	<3	<3	>20:1
3	″	″	DCM/MeCN (5:1)	−78	4	92	<3	<3	>20:1
4	″	″	DCM/DMF (5:1)	−78	4	86	<3	<3	>20:1
5	BzCl (1.1)	DMAP (0.1)	DCM	−78	4		no reaction		
6	″	″	″	rt	48	–	23	–	<1:20
7	Bz_2O (1.1)	″	″	−78	10	<3	90	<2	<1:20
8	″	TBACN (0.1)	″	−78	3		no reaction		
9	″	TBACN (1.0)	″	−78	3	44	<3	–	>14:1
10	″	TBAF[b] (1.0)	″	−78	4		no reaction		
11	″	″	″	−10	1.5	27	9	~20	3:1
12	BzF (1.1)	DMAP (0.1)	″	−78	1	6	57	–	1:10
13	″	″	″	−78 to −10	4	7	84	–	1:12

[a]Yields are based on isolated material. [b]1 M solution in THF.

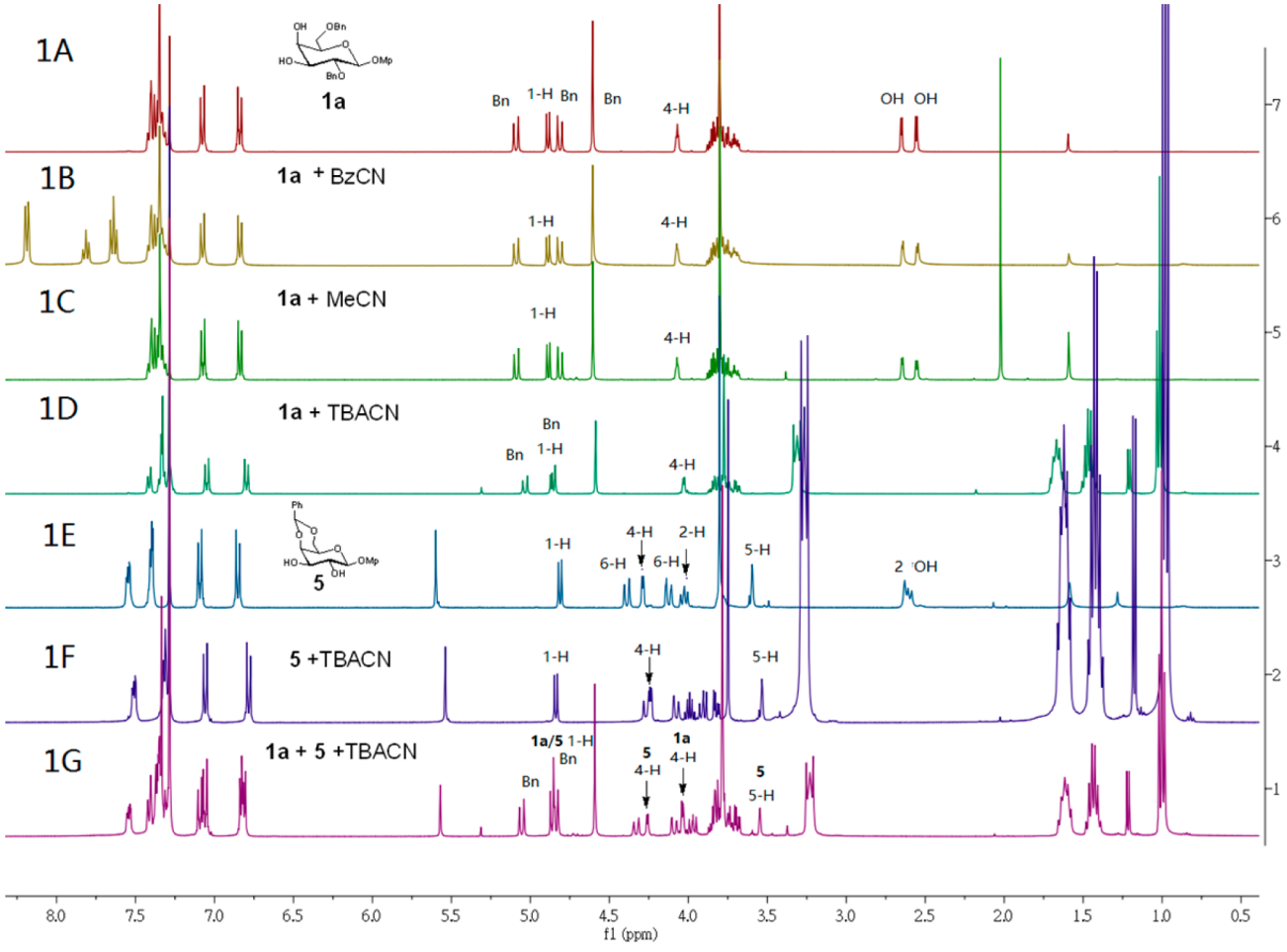
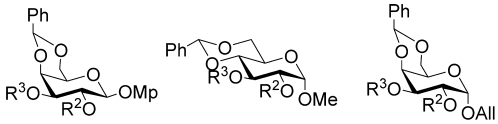


Figure 1. ^{1}H NMR spectra of **1a** and **5** (1A, 1E) with addition of BzCN (1B), MeCN (1C), and TBACN (1D, 1F, 1G).

These observations prompted us to also investigate the regioselectivity of the benzoylation of *β*-galactoside **5** possessing a *trans*-diol moiety. With BzCN (1.0 equiv) and DMAP (0.1 equiv) in DCM at −78 °C, practically exclusive 3-*O*-benzoylation to compound **6a** was observed (Table 2, entry 1). With *α*-glucopyranoside **7** 2-*O*-benzoylation to **8b** and with *α*-galactopyranoside **9** a 2:5 mixture of 2-*O*- and 3-*O*-benzoylation (**10a**, **10b**) was obtained (entries 2, 3). These results are in accordance with previous findings that equatorial *trans*-diols, having a vicinal axial alkoxy group, react preferentially at the

DOI: 10.1021/jacs.6b02454
J. Am. Chem. Soc. 2016, 138, 6002−6009

Table 2. Regioselectivity of the Benzoylation of 2,3-*O*-Unprotected Glycosides 5, 7, and 9[a]



5: $R^2 = R^3 = H$ **7**: $R^2 = R^3 = H$ **9**: $R^2 = R^3 = H$
6a: $R^2 = H$, $R^3 = Bz$ **8a**: $R^2 = H$, $R^3 = Bz$ **10a**: $R^2 = H$, $R^3 = Bz$
6b: $R^2 = Bz$, $R^3 = H$ **8b**: $R^2 = Bz$, $R^3 = H$ **10b**: $R^2 = Bz$, $R^3 = H$

entry	substrates	products (yield in %)[b]	
1	**5**	**6a** (99%)	**6b** (−)
2	**7**	**8a** (−)	**8b** (89%)
3	**9**	**10a** (64%)	**10b** (25%)

[a]The reactions are carried out with substrate (1 equiv), BzCN (1.0 equiv), DMAP (0.1 equiv) at −78 °C in DCM for 4 h. [b]Yields are based on isolated material.

hydroxy group next to the axial alkoxy group, as accumulation of the lone pair orbitals of the *cis*-oxygens leads to increased nucleophilicity of the hydroxy group.[34] The high regioselectivities found for **5** and **7** in comparison to **9** are therefore not due to a specific cyanide effect.

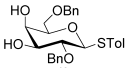
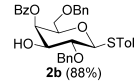
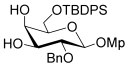
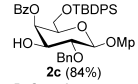
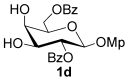
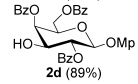
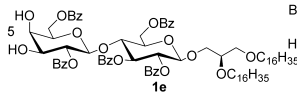
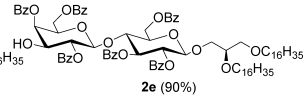
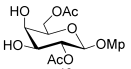
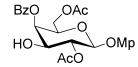
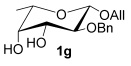
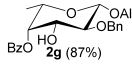
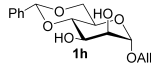
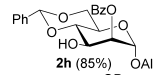
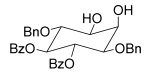
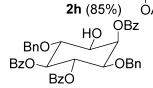
Regioselective *O*-Acylation of Other 1,2-*cis*-Diols. To further demonstrate the generality and usefulness of the cyanide effect for the thermodynamically unfavorable regioselective axial *O*-benzoylation of vicinal *cis*-diols, different substrates, also with different protecting group patterns, were studied under the reaction conditions that were successful for the transformation of **1a** into **2a** (see Table 1, entry 2 and Table 3, entry 1). Replacement of the methoxyphenoxy group by the tolylthio group at C-1, as in **1b** (entry 2), or variation of the steric bulk of 6-*O*-protection, as in **1c** (entry 3), did not change the regioselectivity, thus leading in high yields to **2b** and **2c**, respectively. Also electron-withdrawing 2,6-di-*O*-benzoyl protection of the galactose moiety, as in **1d** and **1e** (entries 4, 5), had no negative influence on the regioselective formation of **2d** and **2e**, respectively. Even the 2,6-di-*O*-acetyl protected β-D-galactopyranoside **1f** (entry 6) led to practically exclusive formation of the 4-*O*-benzoylated product **2f** when DCM/MeCN (2:1) was used as solvent; under the reaction conditions practically no detrimental acetyl group migration was observed. However, in DCM as solvent, due to the low solubility of **1f**, only a modest yield of **2f** (60%) was obtained, as the good solubility of **2f** in DCM permitted the competing formation of the 3,4-di-*O*-benzoylated product.

Also the reactions of 3,4-*O*-unprotected β-L-fucopyranoside **1g** (entry 7) and 2,3-*O*-unprotected α-D-mannopyranoside **1h** (entry 8) were in complete accordance with our expectations and led, in very good yields, to 4-*O*-benzoylated fucoside **2g** and to the 2-*O*-benzoylated mannopyranoside **2h**, respectively.[35]

After investigation of substrates with (i) different groups at the anomeric position, (ii) different anomeric configurations, (iii) electron-donating and -withdrawing protecting groups, (iv) sterically demanding protecting groups, and (v) different sugars including a deoxysugar, the important carbohydrate-related *myo*-inositol was studied. To this end, derivative (±)-**1i** with a 1,2-*cis*-diol moiety was prepared. With BzCN and DMAP at −78 °C, the desired axial *O*-benzoyl derivative (±)-**2i** was also preferentially obtained in good yield.

Extension of this method to an aliphatic acyl cyanide, namely to acetyl cyanide as the acetylating agent and DMAP as the

Table 3. Regioselective Benzoylation of Different *cis*-Diols[a]

Entry	Substrates **1**	Products (yields)[b] **2**
1	**1a**	**2a** (90%)
2	 **1b**	 **2b** (88%)
3	 **1c**	 **2c** (84%)
4	 **1d**	 **2d** (89%)
5	 **1e**	 **2e** (90%)
6[c]	 **1f**	 **2f** (92%)
7	 **1g**	 **2g** (87%)
8	 **1h**	 **2h** (85%)
9[d]	 (±)-**1i**	 (±)-**2i** (73%)

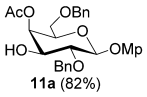
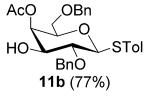
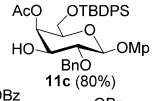
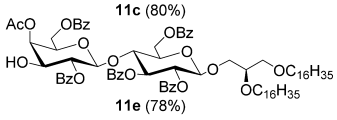
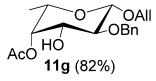
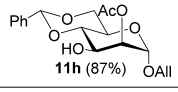
[a]All reactions are performed at ∼0.03 M concentration in DCM with BzCN (1.0 equiv), DMAP (0.1 equiv), at −78 °C for 4 h. [b]Yields are based on isolated material. [c]DCM/MeCN (v/v = 2:1) was used as solvent. [d]The reaction is performed at 0.004 M concentration in DCM with BzCN (1.05 equiv), DMAP (0.3 equiv), at −78 °C for 10 h (**2i**/**3i** = 5:1). **3i**: benzoylation of the equatorial OH group.

catalyst, led under the standard reaction conditions to similar regioselectivities (see Table 4). Thus, 3,4-*O*-unprotected galactopyranosides **1a**, **1b**, **1c**, and **1e** furnished the 4-*O*-acetyl products **11a**, **11b**, **11c**, and **11e** in very good yields (entries 1−4). Similarly, 3,4-*O*-unprotected fucopyranoside **1g** and 2,3-*O*-unprotected mannopyranoside **1h** furnished 4-*O*- or 2-*O*-acetyl protection in compounds **11g** and **11h**, respectively. Hence, the generality of the cyanide effect, strongly favoring axial *O*-acylation of 1,2-*cis*-diols with an equatorial and an axial hydroxy group, is evident.

Studies with Triols. The unexpected preference for the axial *O*-acylation of *cis*-1,2-diols with the help of cyanide as the anion was by no means expected to hold for 6-*O*-unprotected hexopyranosides, as generally the primary 6-hydroxy group is (by far) more reactive than any of the secondary hydroxy groups. Surprisingly, reaction of a 3,4,6-*O*-unprotected 2-azido-2-deoxy-galactopyranoside with 2 equiv of benzoyl cyanide in pyridine at 0 °C resulted in the preferential formation of the 4,6-di-*O*-benzoylated product, as reported by the Paulsen group.[30c,36] The authors neither discussed nor further investigated the origin of this unusual result. Therefore, we studied the regioselectivity of the *O*-benzoylation of 3,4,6-tri-*O*-unprotected galactopyranoside **12a** with BzCN/DMAP (Table 5). In accordance with the results described above, addition of 2 equiv of BzCN led exclusively to the 4,6-di-*O*-benzoyl derivative **15a** (entry 1). However, with 1 equiv of BzCN, primarily not 6-*O*-benzoylation to **14a** but 4-*O*-benzoylation to **13a** and then further benzoylation to 4,6-di-*O*-benzoylated **15a** took place (entry 2). Hence, the rate of 4-*O*-benzoylation is not only by far faster than that of 3-*O*-

DOI: 10.1021/jacs.6b02454
J. Am. Chem. Soc. 2016, 138, 6002−6009

Table 4. Regioselective Acetylation of Different *cis*-Diols with Acetyl Cyanide and DMAP[a]

Entry	Substrates 1	Products (yields)[b] 11
1	**1a**	 **11a** (82%)
2	**1b**	 **11b** (77%)
3	**1c**	 **11c** (80%)
4	**1e**	 **11e** (78%)
5	**1g**	 **11g** (82%)
6	**1h**	 **11h** (87%)

[a]All reactions are performed in DCM with AcCN (1.1 equiv), DMAP (0.1 equiv), at −78 °C for 4 h. [b]Yields are based on isolated material.

benzoylation but also faster than that of 6-*O*-benzoylation. By performing the reaction in DCM/MeCN as solvent the reaction rates were slowed down and 6-*O*-benzoylation competed even less successfully with 4-*O*-benzoylation leading to **13a** and **14a** in a 4:1 ratio (entry 3). Also the amount of **15a** was reduced. By increasing the amount of acetonitrile in the solvent and raising the temperature, a higher yield of **13a** was accessible, yet the isomer ratio decreased to 7:3 (entry 4). The desired direct regioselective formation of the 4-*O*-benzoylated product could be almost achieved with **12b** as a triol substrate: compound **13b** was obtained with high preference (entry 5), thus providing a very useful building block for oligosaccharide synthesis with the help of the cyanide effect in a straightforward manner. With 2 equiv of BzCN, **12b** could be readily transformed into the 4,6-di-*O*-benzoyl derivative **2d** (entry 6); still no 3-*O*-benzoylation was observed.

DFT Calculations. In order to understand the "cyanide effect" on the mechanism and the regiochemical outcome of the reaction, DFT-calculations were performed on the B3LYP/6-311++G(d,p)/PCM(dichloromethane) level of theory, which is known to be a reliable combination for the conformational analysis of carbohydrates and the analysis of hydrogen bonding.[37−40] 2,3-*O*-Unprotected mannopyranoside **1h** (Table 3) was chosen as a test substrate. As a starting point for the investigations and in order to test if discrimination between the *cis* aligned hydroxy functions is observable already at the stage of deprotonation, the association of the cyanide ion with the carbohydrate was studied. Considering that the ambident cyanide base may approach a hydroxy function via its carbon and/or nitrogen terminus, eight possible intermediates may be formed. In structures $\mathbf{3_{eq}}$-**C**, $\mathbf{2_{ax}}$-**C**, $\mathbf{3_{eq}}$-**N**, and $\mathbf{2_{ax}}$-**N** (Figure 2),

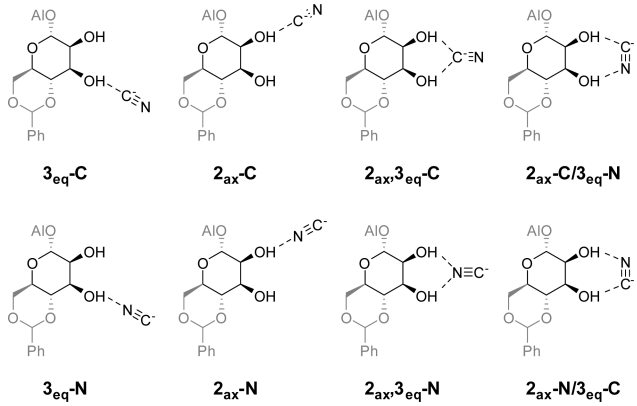
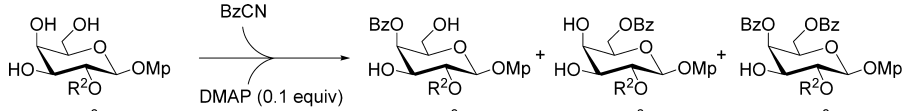


Figure 2. Schematic structures of cyanide adducts and their naming scheme.

the cyanide approaches one hydroxy function, forming an O−H···C or an O−H···N hydrogen bond. In structures $\mathbf{2_{ax}}$,$\mathbf{3_{eq}}$-**C**, and $\mathbf{2_{ax}}$,$\mathbf{3_{eq}}$-**N** the cyanide ion associates with both hydroxy functions through either the carbon or the nitrogen atom, forming a seven-membered ring. Alternatively, the cyanide ion may bridge both hydroxy functions in a "side-on" fashion, forming an eight-membered ring (structures $\mathbf{2_{ax}}$-**C**/$\mathbf{3_{eq}}$-**N** and $\mathbf{2_{ax}}$-**N**/$\mathbf{3_{eq}}$-**C**). This multitude of association modes will likely result in a shallow, complex, and multiwelled potential energy surface (PES) with many intermediates that rapidly interconvert.

The energy surface was explored starting from structure $\mathbf{2_{ax}}$,$\mathbf{3_{eq}}$-**C** by placing a cyanide in close proximity to the preoptimized substrate **1h**. The C···H or N···H distances were decreased in an internal redundant coordinate (IRC) scan calculation in order to identify the most stable associate and to model the

Table 5. Regioselective Benzoylation of 3,4,6-*O*-Unprotected Galactopyranosides 12a, b



12a: R^2 = Bn
12b: R^2 = Bz
13a: R^2 = Bn
13b: R^2 = Bz
14a: R^2 = Bn
1d: R^2 = Bz
15a: R^2 = Bn
2d: R^2 = Bz

entry	substrate (1 equiv)	BzCN (equiv)	solvent	temp [°C]	time [h]	13	product (%)[a] 14	15
1	**12a**	2.1	DCM	−78	7	**13a** (<3%)	**14a** (<3%)	**15a** (86%)
2	**12a**	1	DCM	−78	4	**13a** (20%)	**14a** (<3%)	**15a** (40%)
3	**12a**	1	DCM/MeCN (1:1)	−78	7	**13a** (40%)	**14a** (11%)	**15a** (20%)
4	**12a**	1	DCM/MeCN (1:4)	−60 to −50	4	**13a** (53%)	**14a** (24%)	**15a** (10%)
5	**12b**	1	DCM/MeCN (1:2)	−40 to −20	4	**13b** (61%)	**1d** (7%)	**2d** (10%)
6	**12b**	2.1	DCM/MeCN (1:1)	−40 to 0	10	**13b** (<3%)	**1d** (<3%)	**2d** (70%)

[a]Yields are based on isolated material.

DOI: 10.1021/jacs.6b02454
J. Am. Chem. Soc. 2016, 138, 6002−6009

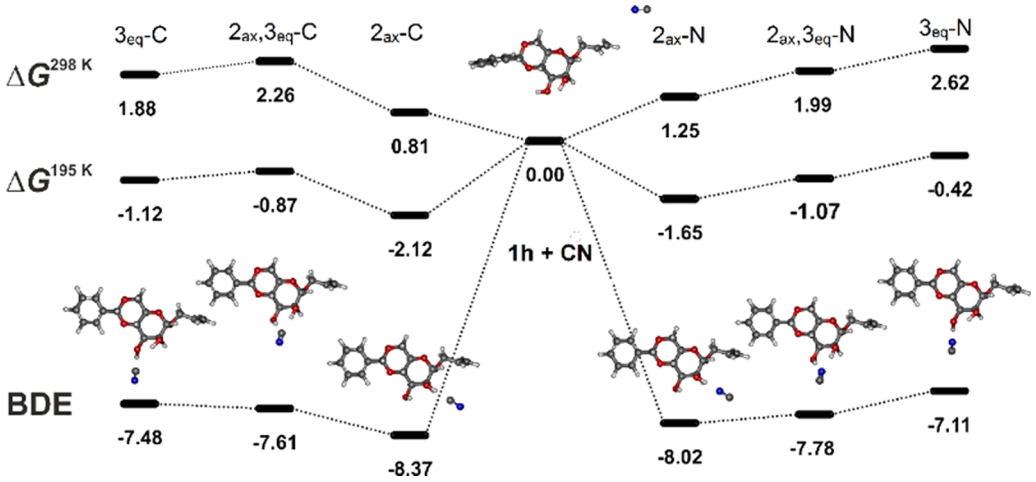


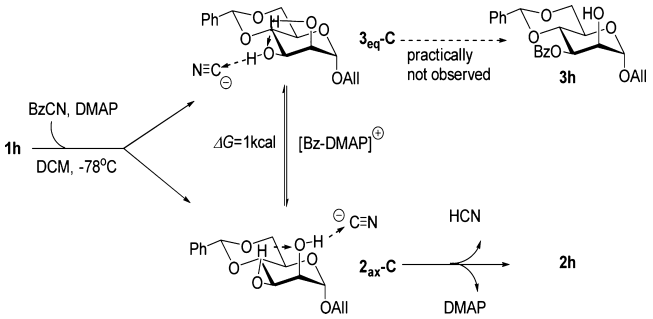
Figure 3. Energy level diagram of the calculated local minima for **1h**···CN^-; energies are given in kcal mol^{-1}, relative to the unassociated educts.

deprotonation of the axial or equatorial OH-functions (the IRC-Scans are printed in Figure RW1 of the Supporting Information). Figure 3 displays the energy level diagram and the structures of the possible intermediates. The association of the cyanide with the diol is exothermic. All association modes are local minima and are lower in energy than the unassociated starting compounds. The two association modes **2_{ax}-C/3_{eq}-N** and **2_{ax}-N/3_{eq}-C** were found to be the transition states for the conversion of **2_{ax},3_{eq}-C** to **2_{ax},3_{eq}-N** and were therefore not considered any further (see Figure RW2 in the Supporting Information for an IRC scan). The most stable associate **2_{ax}-C** has a BDE of 8.37 kcal mol^{-1} (bond dissociation energy calculated from the energy difference to the separated fragments in their optimized structures in the PCM model). It is 0.35 kcal mol^{-1} lower in energy than the next stable associate **2_{ax}-N** (which would provide the same product selectivity though) and 0.59 kcal mol^{-1} lower in energy than the next stable associate **2ax,3eq-N**, which would not show any selectivity for one of the possible products. However, at room temperature, association is an endergonic process, as all associates have higher Δ*G*-values than their separated constituents. The entropy term in the Gibbs free energy exceeds the enthalpy term because associates shown in Figure 2 offer substantially fewer degrees of freedom. **2_{ax}-C** remains the most favorable associate, lying 0.81 kcal mol^{-1} above the minimum representing the separate reaction partners. Additional thermochemistry calculations were performed to model a reaction temperature of −78 °C. At this temperature association is an exergonic process and **2_{ax}-C** is again the most stable associate, lying 0.47 kcal mol^{-1} below **2_{ax}-N**. The most stable associate to H-3_{eq} (**3_{eq}-C**) lies 1.00 kcal mol^{-1} above the minimum.

Upon cyanide coordination to H-2_{ax}, the hydroxyl proton of the 2-hydroxy functionality, a partial negative charge is induced at the oxygen atom O-2_{ax}, favoring acylation at that position. The associate of the cyanide carbon with H-3_{eq} (**3_{eq}-C**) is less stable by 1.00 kcal mol^{-1}. This corresponds to an equilibrium constant K_{eq} = 13 at −78 °C. Similar results are obtained for cyanide nitrogen coordination at −78 °C to H-2_{ax} (**2_{ax}-N**) and to H-3eq (**3_{eq}-N**). Under the reasonable assumption that the energy barrier for the interconversion of intermediates **2_{ax}-C** and **3_{eq}-C** is small compared with the transition state energy for their *O*-benzoylation and that the *O*-acylation transition state energy differences are reflected in the different energies of the intermediates, these calculated energy differences will also determine the corresponding differences in reaction rates. Hence, in accordance with the experimental observations the rate for the axial *O*-acylation at −78 °C should be >10 times higher than that for equatorial *O*-acylation.[41]

The increasing reaction rates when using a diol as compared to a simple alcohol (Scheme 1) can be rationalized with a glance at the structures of the associates in Figure 2. In **2_{ax}-C** and **2_{ax}-N** intramolecular hydrogen bonds are formed from negatively charged O-2_{ax} to H-3_{eq} with a bond distance of 2.12 Å (Table RW1, Supporting Information). Similar distances are found for **3_{eq}-C** and **3_{eq}-N** (2.08−2.09 Å). Upon deprotonation by cyanide, this strong hydrogen bond, forming a highly stable five-membered ring, will stabilize the resulting anion, hence, resulting in the driving force and the rate increase. The regioselectivity of the *cis*-diol *O*-acylation is thus not due to dual hydrogen bonding of cyanide to both hydroxy groups but to hydrogen bonding to the most acidic axial hydroxy group supported by hydrogen bonding of the equatorial hydroxy group to the axial oxygen atom (Scheme 2). Thus, dual hydrogen bonding in a different manner as initially assumed seems to be responsible for the cyanide effect.

Scheme 2. Calculated Structures of Lowest Energy Intermediates 2_{ax}-C and 3_{eq}-C of 1h



The same kind of calculations were performed for the reaction of mannopyranoside **1h** with fluoride to distinguish general effects arising from the association of a hard anion from specific cyanide effects, in particular as cyanide and fluoride are not too different with respect to their basicities, at least in DMSO solution. However, the results for fluoride are quite different from the cyanide case (Figure 4). The strong hydrogen-bonding ability of fluoride makes association exergonic at all temperatures

DOI: 10.1021/jacs.6b02454
J. Am. Chem. Soc. 2016, 138, 6002−6009

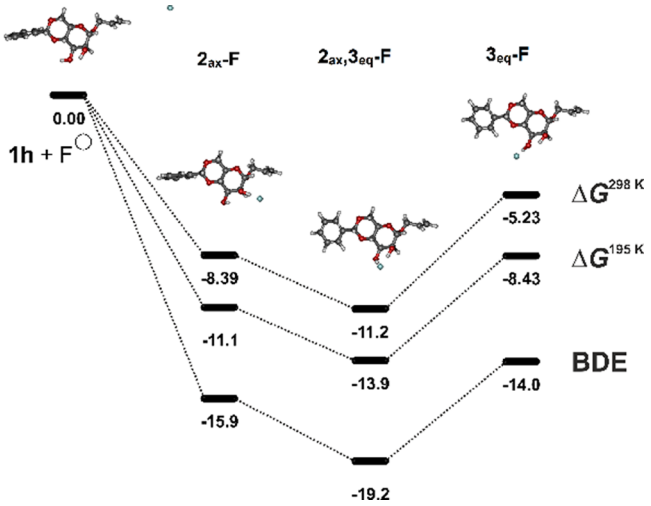


Figure 4. Energy diagram of the calculated local minima for **1h**···F^-.

considered. In contrast to cyanide, the bridging $\mathbf{2_{ax},3_{eq}}$-**F** association mode is the most stable one at all temperatures with a ΔG-value of −13.9 kcal mol^{-1} at −78 °C. $\mathbf{2_{ax}}$-**F** ($\Delta G^{195\ K}$ = 2.80 kcal mol^{-1}) and $\mathbf{3_{eq}}$-**F** ($\Delta G^{195\ K}$ = 5.49 kcal mol^{-1}) are considerably less stable at both temperatures. Partial charges are equally induced on both oxygen atoms O-3_{eq} and O-2_{ax}. The resulting, different selectivities for the acylation in the presence of fluoride as compared to cyanide are obvious. Strong hydrogen bonding to both hydroxy groups of a *cis*-diol does not seem to promote reactivity differences.

CONCLUSION

Cyanide as the counterion in *O*-acylations of *cis*-diols and triols leads to an increase in overall reaction rate and to a strong preference for regioselective axial *O*-acylation. This "cyanide effect", supporting formation of the thermodynamically unfavorable product, could be confirmed for partially protected galacto-, fuco-, and mannopyranosides as well as for *myo*-inositol. Particularly noteworthy is the faster reaction rate of the axial 4-*O*-acylation of 3,4,6-*O*-unprotected galactopyranosides over the 6-*O*-acylation of the primary 6-hydroxy group; *O*-acylation of the 3-hydroxy group was not observed. Thus, a wide scope for this unprecedented reaction is available. DFT calculations revealed that this effect is due to hydrogen bonding of the basic cyanide ion to the more acidic axial hydroxy group, which in turn is supported by hydrogen bonding of a vicinal equatorial hydroxy group to the axial oxygen atom. Thus, the axial oxygen undergoes dual hydrogen bonding. Fluoride as the counterion favors dual hydrogen bonding to both hydroxy groups leading, in the presence of DMAP as the catalyst, to preferred formation of the equatorial *O*-acylation product. Thus, either the axial or the equatorial *O*-acyl products are directly accessible. Hence, the proper choice of reagents and reaction conditions, enhancing subtle differences between identical functional groups, permits highly regioselective reactions.

EXPERIMENTAL SECTION

Acylation with Acyl Cyanide and DMAP. To a solution of compound **1a** (70.8 μmol) and 4 Å molecular sieves in 3 mL of dry DCM was added benzoyl cyanide (76.3 μmol) at room temperature under a nitrogen atmosphere. After the reaction mixture was cooled to −78 °C, 4-dimethylaminopyridine (DMAP) (7.1 μmol) was added. The reaction was further stirred for 4 h at this temperature. After the TLC analysis showed the reaction was complete, the reaction was quenched by addition of NH_4Cl (aq) and 100 μL of MeOH. Then the mixture was diluted with 100 mL of DCM, and the precipitate was filtered off through a pad of Celite. The organic layer was washed with NH_4Cl (aq) and $Na_2S_2O_3$ (aq), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel.

DFT Calculations. The ground state electronic structures were calculated by density functional theory (DFT) methods using the Gaussian 09 program packages.[42,43] The 6-311++G(d,p) polarized triple-ζ basis sets[44−47] were employed for all atoms together with the B3LYP hybrid functional.[48−51] Solvent effects werde described by the polarizable conductor model (PCM) in dichloromethane.[52] The GaussSum program package was used to analyze the results,[53] while visualization of the results was performed with the Avogadro program package.[54] Graphical representations of molecular orbitals were plotted using the Gabedit program package in combination with POV-Ray.[55,56]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02454.

Full experimental details and ^1H and ^{13}CNMR spectra forall new compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the University of Konstanz for the support of this work.

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DOI: 10.1021/jacs.6b02454
J. Am. Chem. Soc. 2016, 138, 6002−6009