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Synthesis of Allophanate-Derived Branched Glycoforms from Alcohols and *p*-Nitrophenyl Carbamates

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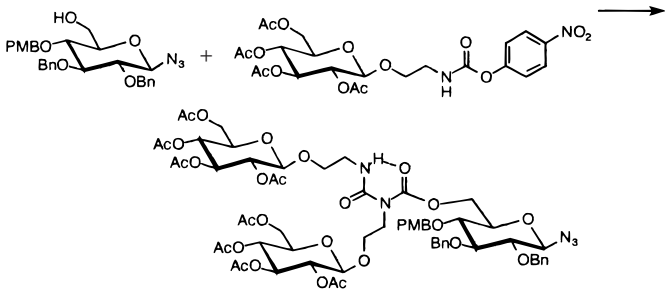
ABSTRACT



The formation of saccharide-derived carbamates and alkyl 2,4-dialkylallophanates from alcohols and *p*-nitrophenyl carbamates is described. Optimization of allophanate formation has led to the synthesis of branched glycoforms with inter-saccharide allophanate linkages that are rigidified by intramolecular hydrogen bonds.

The generation of glycoforms that display multiple copies of a saccharide ligand at their periphery has been the subject of much investigation due to their potential as high-affinity inhibitors of carbohydrate-binding proteins involved in biologically relevant recognition processes.[1] Although a structurally diverse range of scaffolds can and has been used to assemble synthetic glycoclusters, a more rigid or ordered scaffold would allow for a greater degree of control over the spatial arrangement of the saccharide ligands and minimize the entropic penalty of binding.[2] Such a design should allow multivalent glycoforms to be "tailored" to complement the arrangement of the specific target receptors.

We now report the generation of saccharide-derived alkyl 2,4-dialkylallophanates as secondary products of base-induced carbamoylations and their optimization for the generation of branched glycoforms with inter-saccharide allophanate linkages. These allophanates are intramolecularly hydrogen bonded branched glycoforms that can be incorporated into the design of glycoclusters with multivalent saccharide ligands. In these allophanate systems, the rigidity imparted by the hydrogen bond may be an important design element for glycoclusters with a more ordered or well-defined ligand arrangement.

The synthesis of allophanates[3] is generally achieved by two routes. The first utilizes the treatment of a carbamate with an isocyanate or isocyanate equivalent[4] while the second relies on reaction between a urea and a chloroformate or chloroformate equivalent.[5] It is known that organic iso-

(1) Representative references regarding the design and use of multivalent glycoforms for enhancing carbohydrate-protein binding: (a) Kiessling, L. L.; Pohl, N. L. *Chem., Biol.* **1996**, *3*, 71−77. (b) Roy, R. *Curr. Opin. Struct. Biol.* **1996**, *6*, 692−702. (c) Jayaraman, N.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Eur. J.* **1997**, *3*, 1193−1199. (d) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754−2794. (e) Fulton, D. A.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 1113−1116 and references therein. (f) Roy, R. Recent Developments in the Rational Design of Multivalent Glycoconjugates. In *Glycoscience*; Driguez, H., Thiem, J., Eds.; Springer-Verlag: Berlin, 1999; p 241−274.

(2) (a) Kitov, P. I.; Sadowska, J. M.; Mulvey, G.; Armstrong, G. D.; Ling, H.; Pannu, N. S.; Read, R. J.; Bundle, D. R. *Nature* **2000**, *403*, 669−672. (b) See ref 1a.

(3) The majority of the allophanates reported are endocyclic.

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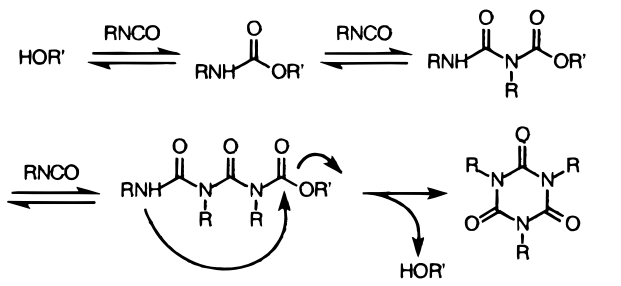
cyanates react with alcohols in a sequence of reactions to give carbamates, allophanates, and isocyanurates (Scheme 1).[6] The rate constants have been found to depend strongly

Scheme 1. Reaction of Alcohols with Isocyanates



on the tertiary amine base and substrates. While the synthesis of 2,4-diarylallophanates may be achieved by the consecutive reaction of two aryl isocyanates with an alcohol,[7] a mixture of carbamate, allophanate, and isocyanurate is typically afforded by the base-catalyzed reactions of alkyl isocyanates with alkyl alcohols, making optimization of the allophanate difficult.[8]

In a recent report on the cyclooligomerization of a saccharide-based isocyanato alcohol to produce carbamate-containing cyclodextrin analogues,[9] we demonstrated the high-yielding formation of inter-saccharide carbamate linkages from saccharide-derived *p*-nitrophenyl carbamates. This "transcarbamoylation", which occurs by in situ activation of the *p*-nitrophenyl carbamate to the isocyanate, proceeded in good yields for several model systems. Continued studies on this transformation led to the discovery of the potential of this methodology for generating saccharide-derived allophanates.

We previously described the base-catalyzed conversion of the activated carbamate **1** to its isocyanate.[9] "Transcarbamoylations" of **1** with alcohols derived from saccharides may be achieved in high yields with the use of NaH and Et_3N at 40 °C.[10] During the course of further investigations into this reaction, we found that the carbamates were capable of undergoing further reaction with the isocyanate to generate allophanates when excess isocyanate and higher reaction temperatures were employed. Thus, treatment of the glycosyl azide **2** with 1.3 equiv of *p*-nitrophenyl carbamate **1** at 50 °C for 1 h afforded the carbamate **3** in 80% yield (Table 1) and the allophanate **4** in 9% yield.

The identity of allophanate **4** was established by NMR spectroscopic, mass spectral, and IR spectral analyses.[11] The NMR spectra clearly showed incorporation of two saccharide units of **1** for each unit of **2**. The anomeric azide remained intact[12] during the reaction as judged by the presence of the N═N═N IR stretch at 2117.16 cm^{-1} of **4**. The distinctive triplet corresponding to the NH proton of **4** appears at 8.7 ppm, significantly downfield shifted with respect to the carbamate NH signal at 5.2 ppm for **3**.[13] The magnitude of this downfield shift is a strong indicator that the allophanate is largely or wholly hydrogen-bonded.[14] Both the chemical shift range and the magnitude of the shift in $CDCl_3$ are very similar to those observed for hydrogen bonded NH protons in other systems including Nowick's oligourea scaffolds and artificial β-sheets.[15] Mass spectral analyses confirmed the molecular composition of **4**. To maximize allophanate formation, the reaction temperature was elevated to 60 °C and a greater excess of **1** was used (3.9 equiv). Under these conditions, allophanate **4** was isolated in 94% yield after 6 h (Table 1).[16]

The rates of formation of the carbamate and in turn the allophanate vary with the nature of the substrate, presumably due to differences in the reactivity of the pyranose alcohol

(4) For examples see: (a) Dyer, E.; Reed, R. E. *J. Org. Chem.* **1959**, *24*, 1788−1789. (b) Krieg, B.; Lautenschläger, H. *Liebigs Ann. Chem.* **1976**, 208−220. (c) Shimasaki, C.; Murai, A.; Sakai, Y.; Tsukurimichi, E. *Chem. Lett.* **1988**, 1009−1012. (d) Shimasaki, C.; Hayase, S.; Murai, A.; Takai, J. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1074−1079. (e) Botella, J.-M.; Klaebe, A.; Perie, J.; Monnier, E. *Tetrahedron* **1992**, *48*, 5111−5122. (f) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48*, 2520−2527. Isocyanate generated from amide by Hoffman rearrangement: (g) Müller, J. H.; Donin, M. N.; Behnke, W. E.; Hofman, K. *J. Am. Chem. Soc.* **1951**, *73*, 2487−2491. Isocyanate generated from acyl azide by Curtius rearrangement: (h) Misiti, D.; Santaniello, M.; Zappia, G. *Synth. Commun.* **1992**, *22*, 883−891. Phosgene followed by amine: (i) see ref 4f. Trichloromethyl chloroformate followed by amine: (j) Turconi, M.; Nicola, M.; Quintero, M. G.; Maiocchi, L.; Micheletti, R.; Giraldo, E.; Donetti, A. *J. Med. Chem.* **1990**, *33*, 2101−2108.

(5) For examples see: (a) Kamata, S.; Haga, N.; Matsui, T.; Nagata, W. *Chem. Pharm. Bull.* **1985**, *33*, 3160−3175. (b) Yamashita, J.; Yamakawi, I.; Ueda, S.; Yasumoto, M.; Unemi, N.; Hashimoto, S. *Chem. Pharm. Bull.* **1982**, *30*, 4258−4267. (c) Kondo, H.; Miura, K.; Seki, E.; Sunamoto, J. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2801−2804. (d) Sundberg, S. A.; Barrett, R. W.; Pirrung, M.; Lu, A. L.; Kiangsoontra, B.; Holmes, C. P. *J. Am. Chem. Soc.* **1995**, *117*, 12050−12057. Phosgene followed by alcohol: (e) Ulrich, H.; Tilley, J. N.; Sayigh, A. A. R. *J. Org. Chem.* **1964**, *29*, 2401−2404. Trichloromethyl chloroformate followed by alcohol: (f) see ref 4b and (g) Kuroda, T.; Hisamura, K.; Matsukuma, I.; Nishikawa, H.; Nakamizo, N. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 674−681.

(6) Schwetlick, K.; Noack, R. *J. Chem. Soc., Perkin Trans. 2* **1995**, 395−402.

(7) With aryl isocyanates: (a) Kogon. I. C. *J. Am. Chem. Soc.* **1956**, *78*, 4911−4914. (b) Ellzay, S. E.; Mack, C. H. *J. Org. Chem.* **1962**, *27*, 7, 2655−2656.

(8) (a) Ulrich, H.; Tucker, B.; Sayigh, A. A. R. *J. Org. Chem.* **1967**, *32*, 3938−3941. (b) Farkas, E.; Swallow, J. A. *J. Med. Chem.* **1964**, *7*, 739−741.

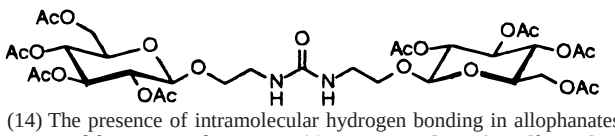
(9) Chong, P. Y.; Petillo, P. A. *Org. Lett.* **2000**, *2*, 1093−1096.

(10) The use of NaH and Et_3N was found to be optimal for carbamate formation. NaH plays an important role in driving the reaction to completion by precipitating the *p*-nitrophenol out of solution as the phenolate salt (see ref 9).

(11) The allophanate was formed by reaction of the carbamate with the isocyanate at the carbamate N as expected based on existing literature. The appearance of a second C═O stretch (at 1721−1728 cm^{-1}) in the IR spectra supports the formation of the allophanates. The alternative structure, resulting from reaction at the carbamate C═O, is discounted based on the absence of a C═N stretch (at 1690−1645 cm^{-1}). In support of this, we observe the appearance of isocyanurate **11** upon disappearance of the allophanate.

(12) Under these conditions, the azides remained intact although azides have been shown to undergo reduction under NaH/refluxing THF conditions: Lee, J.-Y.; Closson, W. D. *Tetrahedron Lett.* **1974**, *4*, 381−384.

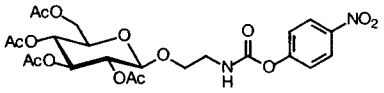
(13) The NH resonance for the symmetrical urea is also at 5.2 ppm.



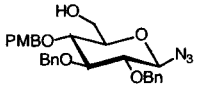
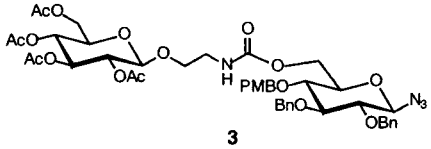
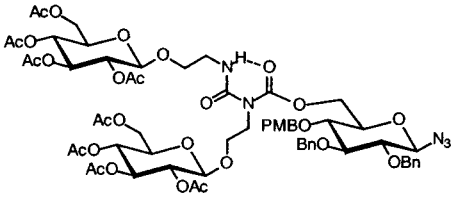
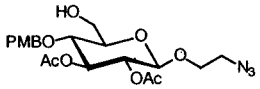
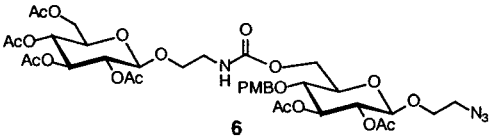
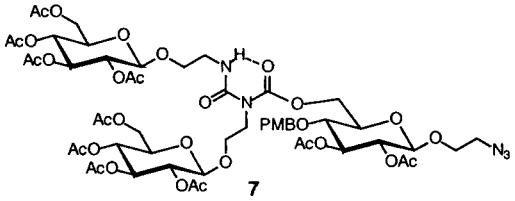
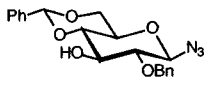
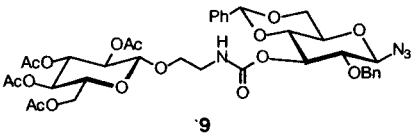
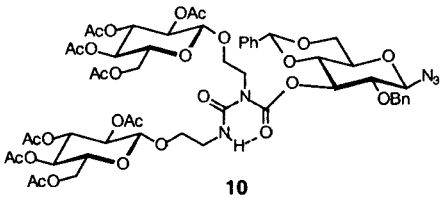
(14) The presence of intramolecular hydrogen bonding in allophanates is supported by existing literature: (a) Kogon, I. C. *J. Am. Chem. Soc.* **1957**, *79*, 2253. (b) Bloodworth, A. J.; Davies, A. G. *J. Chem. Soc., B* **1966**, 125−127. (c) See ref 4b.

(15) (a) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287−296 and references therein. (b) Kim, K.; Germanas, J. P. *J. Org. Chem.* **1997**, *62*, 2847−2852. (c) Liang, G. B.; Rito, C. J.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 4440−4442.

Table 1. Synthesis of Carbamates and Allophanates from Alcohols and *p*-Nitrophenyl Carbamate **1**



1

Alcohol	Reaction conditions (eq of **1**)	Product	δ (NH) (ppm)[a]	Yield
 **2**	Et_3N, NaH, THF 50 °C, 1 h (1.3)	 **3**	5.2	80%
	Et_3N, NaH, THF 60 °C, 6 h (3.9)	 **4**	8.7	94%
 **5**	Et_3N, NaH, CH_2Cl_2 40 °C, 1 h (1.1)	 **6**	5.2	92%
	Et_3N, NaH, THF 60 °C, 6 h (3.3)	 **7**	8.7	73%
 **8**	Et_3N, NaH, THF 50 °C, 3 h (1.3)	 **9**	5.1	85%
	Et_3N, NaH, THF 60 °C, 5 h (3.8)	 **10**	8.6	75%

[a] ^1H NMR chemical shifts in $CDCl_3$ at 25 °C.

groups. While the reaction between **1** and **5** led to carbamate **6** in 92% yield after 1 h at 40 °C, the corresponding reaction with **8** led to carbamate **9** in 85% yield after 3 h at 50 °C (Table 1).

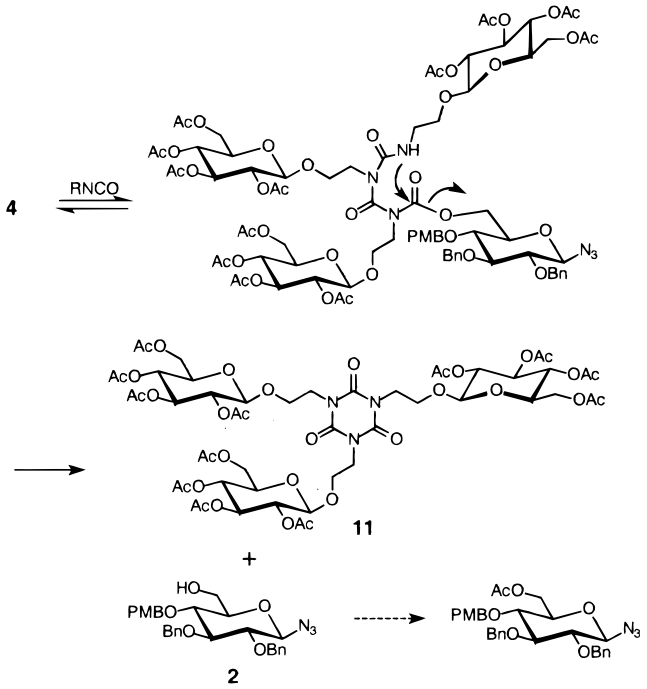
Using the observed optimal conditions for the synthesis of **4**, the corresponding allophanates **7** (73%) and **10** (75%) were obtained from alcohols **5** and **8**, respectively. The NH protons in allophanates **7** and **10** show downfield shifts similar to **4** (Table 1). These saccharide-derived allophanates (like the activated carbamate **1**) are white foams when dried in vacuo and have shown no signs of decomposition in air. They are also stable under mildly basic conditions such as

(16) The appearance of the allophanate as well as the disappearance of the carbamate was monitored by TLC during the course of the reaction. When 3.1 equiv of **1** was used, allophanate **4** was isolated in 76% yield after 1 h at 60 °C.

Et_3N in THF, however, when resubjected to the reaction conditions used for its formation (NaH, Et_3N, heat), they partially revert back to the carbamate and alcohol, verifying the reversibility of this transformation.[17]

For all of these reactions, we found that at longer reaction times (> 6 h) at 60 °C, both the corresponding carbamates and allophanates gradually become consumed, and the formation of isocyanurate **11** is observed (Scheme 2).[18] The

Scheme 2. Further Reaction of Allophanate **4**, Affording Isocyanurate **11** and Regenerating Alcohol **2**, Which Is Eventually Recovered in Its Acetylated Form



highly symmetrical isocyanurate shows one set of pyranose signals by ^1H and ^{13}C NMR while HRFAB-MS confirmed the expected molecular composition.[19] In all three cases, if heating is continued in excess of 12 h, a mixture of unidentified compounds and the corresponding acetylated alcohol is recovered. We presume that our recovery of the acetylated alcohols is the result of transacetylation of the regenerated alcohols (Scheme 2) and that the observed mixture of unidentified compounds is probably a series of partially deacetylated forms of isocyanurate **11**.

As mentioned previously, the presence of NaH was found to be essential for the progress of these reactions, due to its ability to intercept *p*-nitrophenol thereby allowing for the stoichiometric generation of the isocyanate. The use of the tertiary amine base alone with the reactants leads only to a mixture of the alcohol and the carbamate and no allophanate formation is detected. As expected, we found the relative rates of formation of the carbamate, allophanate, and eventually the acetylated alcohol to be dependent on the tertiary amine base. For example, the use of DBU/NaH for the reaction of **1** (3.1 equiv) with alcohol **2** led quickly to acetylated alcohol after 1 h at 60 °C while the same reaction (2 equiv of **1**) using DABCO/NaH afforded carbamate **3** in 82% yield after 2 h at 60 °C with no allophanate formation detected.

We note that these saccharide-derived allophanates are branched glycoforms that are not only structurally interesting but can be incorporated into the design of glycoclusters as multivalent saccharide ligands, where the rigidity imparted by the intramolecularly hydrogen bonded allophanate linkage should lead to a more ordered and well-defined ligand arrangement.[20] In conclusion, we have described the formation of saccharide-derived alkyl 2,4-dialkylallophanates from alcohols and *p*-nitrophenyl carbamates. Optimization of this process has led to the synthesis of branched glycoforms with inter-saccharide allophanate linkages.

Acknowledgment. We gratefully acknowledge NIH, PRF, American Heart Association, UIUC Research Board, and Critical Research Initiatives Program for financial support. We also extend special gratitude to Professor David Y. Gin for useful suggestions. All mass spectra were obtained by the UIUC Mass Spectrometry Lab.

Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is free of charge via the Internet at http://pubs.acs.org.

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(17) When this mixture is heated for an extended period of time, the acetylated alcohol is recovered. See following paragraph.

(18) We have been unable to prepare **11** by (a) TBAF-catalyzed trimerization of isocyanates: Nambu, Y.; Endo, T. *J. Org. Chem.* **1993**, *58*, 1932−1934; and (b) *N*-alkylation of cyanuric acid: Ghosh, M.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 1020−1026.

(19) The observed δ (^{13}C) for the isocyanurate C═O at 148.8 ppm is within the reported range for isocyanurates prepared by Miller and coworkers (see ref 18b).

(20) The issue of whether the intramolecular hydrogen bond persists in aqueous solution was raised by the referees and is an important one. Studies that address this are currently in progess.