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Chemospecific Monofunctionalization of α-Cyclodextrin in the Solid State†

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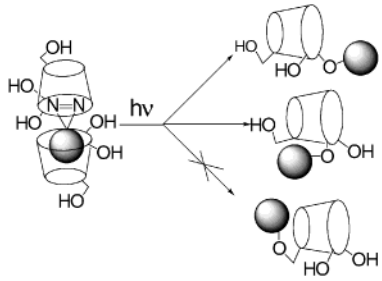
ABSTRACT

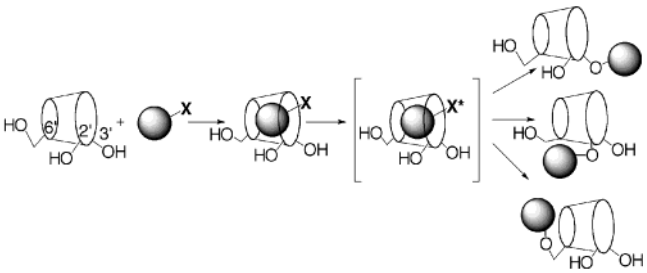


The properties of the self-assembling aziadamantane inclusion complex with two α-cyclodextrin molecules have been exploited to perform a chemospecific monofunctionalization of α-cyclodextrin. The insertion of the photochemically generated carbenes takes place chemospecifically into the cyclodextrin's C-3-OH and C-2-OH bonds in 39 and 18% yield, respectively. This model reaction surpasses conventional methods in terms of yield as well as selectivity.

The preparation of monofunctionalized cyclodextrins (Cy's) continues to attract much interest.[1] These toroidal-shaped cyclic oligosaccharides have been used in numerous instances as catalysts and enzyme mimics.[2] For such endeavors, the secondary hydroxyl groups, or their corresponding O-derivatives, on C-2 and C-3 (on the wider aperture) perform a more important role than their primary counterparts on C-6, which lie on the opposite face.[3]

While several methods have been developed to transform the C-6 positions,[4] it remains a synthetic challenge to selectively modify the hydroxyl groups on C-2, C-3, or both.[5−7] Multistep procedures are required, and direct functionalizations of the C-3 hydroxyl group suffer from very low product yields of less than 20%.[8] Often, in addition to monofunctionalized Cy's, formation of several di- and oligosubstituted compounds occurs,[9] which accounts for the low recovery no greater than 40%.[7−9] In light of these difficulties, a supramolecular approach should be much more fruitful (see Scheme 1).

Scheme 1



† Carbene Rearrangements. 52. For part 51, see: Brinker, U. H.; Miebach, T. *J. Org. Chem.* **1999**, *64*, 8000-8003.

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(1) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803−822.

(2) (a) Murakami, Y.; Kikuchi, J.-I.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721−758. (b) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997−2011.

(3) D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, *20*, 146−152.

(4) (a) Sallas, F.; Leroy, P.; Marsura, A.; Nicolas, A. *Tetrahedron Lett.* **1994**, *35*, 6079−6082. (b) Matsui, Y.; Okimoto, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3030−3034. (c) Fügedi, P.; Nanasi, P.; Szejtli, J. *Carbohydr. Res.* **1988**, *175*, 173−81. (d) Petter, R. C.; Salek, J. S.; Sikorski, C. T.; Kumaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860−3868.

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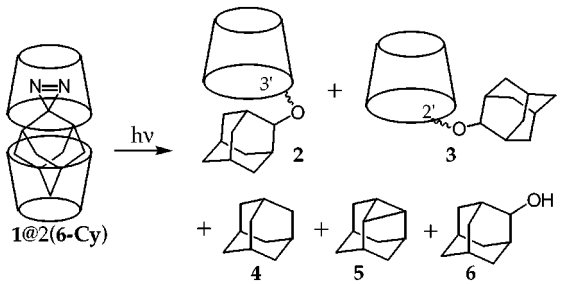
First, a stoichiometric complex is formed with a reagent bearing an appropriate trigger. A subsequent activation step initiates a reaction between the guest and Cy molecules, most likely in a selective way. Inclusion of precursor reagents into the Cy cavity prior to activation has been claimed in several cases in solution.[10] Here, however, ligand exchange can inhibit selectivity. Until now, only one functionalization by a solid-state reaction has been reported.[11] This attempt, however, suffered from very low isolated yields (4−12%) and only modest chemoselectivity.

Recently, we described the formation of a well-characterized 1:2 complex of aziadamantane (**1**) with α-cyclodextrin (**6-Cy**).[12] It was shown by UV−vis spectroscopy and circular dichroism (CD) that the sparingly soluble **1**@2(**6-Cy**) complex experienced strong noncovalent interactions between guest and host, even in dilute solution.[12] This should also be the case for the solid complex itself. Diazirines[13] are convenient and popular precursors of carbenes. Upon photochemical or thermal activation, they react readily with hydroxyl groups to form ethers.[14] Some years ago, we began to investigate the reaction behavior of these carbene precursors entrapped within the cavities of 7-Cy's and found markedly different carbene selectivities.[15] With this background, the **1**@2**(6-Cy)** system seemed very promising to test the supramolecular approach to monofunctionalization as outlined above.

Photolysis of **1**@2(**6-Cy**) in the solid state was performed at 20−30 °C under reduced pressure of argon for 6 h (Scheme 2).[16] Subsequent liquid−liquid extraction gave the product distribution shown in Table 1.

Scheme 2



Preparative reversed phase (RP) HPLC afforded three well-separated fractions. After elution of unsubstituted α-cyclodextrins, two monosubstituted isomers were collected in 34 and 11% yield (based on **1**), respectively. The total recovery of cyclodextrins amounted to ca. 90%.[16]

Table 1. Product Distributions (mol percent) Obtained After Photolysis in the Solid State and in Aqueous Solution by Quantitative GC and RP-HPLC

photolysis of **1**@2(**6-Cy**)	solid state	aqueous solution[a]
2	39	15
3	18	9
4	31	13
5	9	2
6	1	55
2-ethoxyadamantane	1	1

[a] Clear solution of **1** (7.0×10^{-4} M) and **6-Cy** (5.7×10^{-3} M) in water and 0.7% v/v ethanol; under this condition >90% of **1** is present as **1**@2(**6-Cy**) as verified by UV−vis and CD spectroscopy.

The structure of the 2-adamantyl-substituted cyclodextrins was established by homo- and heteronuclear 2D NMR spectroscopy in water-d_2. The linkage positions were determined from pulsed field gradient enhanced HMBC spectra. The major isomer shows cross-peaks over three bonds between the H-3′ of one glucose unit and the C-2 of the adamantane moiety and between the corresponding glucose C-3′ and adamantane H-2 signals, respectively. In addition,

(5) Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977−1996.

(6) Fukudome, M.; Okabe, Y.; Yuan, D.-Q.; Fujita, K. *Chem. Commun.* **1999**, 1045−1046.

(7) (a) Yuan, D.-Q.; Ohta, K.; Fujita, K. *Chem. Commun.* **1996**, 821−822. (b) van Dienst, E.; Snellink, B. H. M.; Piekartz, I. v.; Grote Gansey, M. H. B.; Venema, F.; Feiters, M. C.; Nolte, R. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6537−6545.

(8) (a) Tian, S.; Forgo, P.; D'Souza, V. T. *Tetrahedron Lett.* **1996**, *37*, 8309−8312. (b) Iwakura, Y.; Uno, K.; Toda, F.; Onozuka, S.; Hattori, K.; Bender, M. L. *J. Am. Chem. Soc.* **1975**, *97*, 4432−4434.

(9) (a) Fujita, K.; Nagamura, S.; Imoto, T.; Tahara, T.; Koga, T. *J. Am. Chem. Soc.* **1985**, *107*, 3233−3235. (b) Fujita, K.; Tahara, T.; Imoto, T.; Koga, T. *J. Am. Chem. Soc.* **1986**, *108*, 2030−2034.

(10) (a) McAlpine, S. R.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 2750−2751. (b) Onozuka, S.; Kojima, M.; Hattori, K.; Toda, F. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3221−3224. (c) Takahashi, K.; Hattori, K.; Toda, F. *Tetrahedron Lett.* **1984**, *25*, 3331−3334. (d) Komiyama, M.; Hirai, H. *J. Am. Chem. Soc.* **1983**, *105*, 2018−2021.

(11) (a) Smith, S. H.; Forrest, S. M.; Williams, D. C.; Cabell, Jr. M. F.; Acquavella, M. F.; Abelt, C. J. *Carbohydr. Res.* **1992**, *230*, 289−297. (b) Abelt, C. J.; Lokey, J. S.; Smith, S. H. *Carbohydr. Res.* **1989**, *192*, 119−130. (c) Abelt, C. J.; Pleier, J. M. *J. Org. Chem.* **1988**, *53*, 2159−2162.

(12) Krois, D.; Brinker, U. H. *J. Am. Chem. Soc.* **1998**, *120*, 11627−11632.

(13) (a) *Chemistry of Diazirines*, Volumes I and II; Liu, M. T. H., Ed.; CRC: Boca Raton, 1987. (b) Kupfer, R.; Rosenberg, M. G.; Brinker, U. H. *Tetrahedron Lett.* **1996**, *37*, 6647−6648.

(14) For reactions of carbenes with alcohols, see: Kirmse, W. In *Advances in Carbene Chemistry*, Volume I; Brinker, U. H., Ed.; JAI: Greenwich, 1994; pp 1−57.

(15) (a) Brinker, U. H.; Buchkremer, R.; Kolodziejczyk, M.; Kupfer, R.; Rosenberg, M.; Poliks, M. D.; Orlando, M.; Gross, M. L. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1344−1345. (b) Brinker, U. H.; Rosenberg, M. G. In *Advances in Carbene Chemistry*, Volume II; Brinker, U. H., Ed.; JAI: Stamford, 1998; pp 29−44.

(16) **1**@2(**6-Cy**)[12] (1.08 g, content 96%, 0.49 mmol) was photolyzed for 6 h at 20 °C under reduced pressure of argon using a medium-pressure mercury lamp (Heraeus TQ718-Z4, 700 W, doped with FeI_2). The solid was dissolved in 300 mL of water and continuously extracted with dichloromethane to remove all products of **1** which were not covalently bound to **6-Cy**. Their identification and quantification was accomplished by GC (FID) by comparison with standard samples (see Table 1). After the water was evaporated in vacuo, the residue (1.08 g) was dissolved in the minimum amount of water−methanol (7/3) (ca. 35 mL). A small aliquot (corresponding to ca. 5 mg) was diluted to give a water−methanol (6/4) mixture and was analyzed by analytical RP-HPLC [HP-1090 instrument equipped with the RI-detector HP1047 and the interface 35900E (Hewlett-Packard) using a Nucleosil 100-5C18 5 μm column (4 × 290 mm, FZ Seibersdorf)]; isocratic elution with 0.5 mL/min gave, by comparison with standards, the quantified distribution of water-soluble products (Table 1). Preparative RP-HPLC purification was accomplished [Pump AP-250−150 (Armen Instruments) equipped with a preparative differential refractometer type 98100 (Knauer) using a Lichrospher RP18 7 μm column (50 × 220 mm, Merck)]; isocratic elution with water−methanol (7/3) (30 mL/min flow at 37 bar) yielded 204 mg of **2** (34%) and 69 mg of **3** (11%). In addition, 704 mg of unsubstituted α-Cy's (0.65 mmol) (eluted as first fraction) were recovered which consisted of pure **6-Cy** and 10−15% of oxidized **6-Cy** as shown by UV−vis; total recovery of **6-Cy** was thus 89%.

NOE cross-peaks between the glucose H-3′ and adamantane H-2 protons in a 2D NOESY spectrum confirmed the structure of the major compound to be 3-*O*-(2-adamantyl)-α-cyclodextrin (**2**).[17] Furthermore, many NOE signals were observed between the 6-Cy and the pendent adamantane (Figure 1). Weak cross-peaks between adamantyl protons

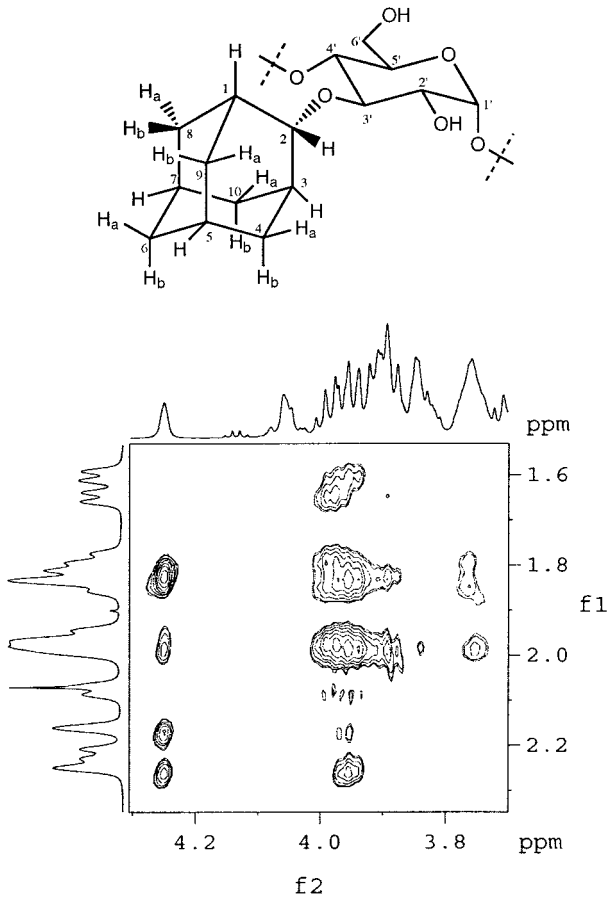


Figure 1. 2D NOESY spectrum of **2** showing strong interactions between the adamantyl moity (f1 axis) and the **6-Cy** (f2 axis).

away from the linkage position, i.e., H-6,7,8 and protons H-5 of unsubstituted glucose units were most instructive because this implies a partially submerged orientation of the adamantyl pendant in the cyclodextrin cavity. The minor isomer was characterized also by a three-bond HMBC cross-peak from a glucose H-2′ to the adamantane C-2 signal as 2-*O*-(2-adamantyl)-α-cyclodextrin. The 2D NOESY spectrum shows only a few cross-peaks between the two distinct parts, proving a relative orientation of the adamantyl moiety outside the cyclodextrin ring. This confirms the structure for 2-*O*-(2-adamantyl)-α-cyclodextrin (**3**).[17]

(17) Selected analytical data. **2**: mp = 285−288 °C (dec), $[\alpha]^{20}_{D}$ = +145°, $[\alpha]^{20}_{546}$ = +173° (*c* = 1.02, pyridine containing 5% water). FAB-MS: 1107 (M + 1$^+$). Anal. Calcd for $C_{46}H_{74}O_{30}\cdot 4H_2O$ (1179.14): C, 46.86; H, 7.01. Found: C, 44.72; H, 6.71 (corresponding to a content of 96%). **3**: no mp up to 330 °C (dec), $[\alpha]^{20}_{D}$ = +104°, $[\alpha]^{20}_{546}$ = +123° (*c* = 0.76, pyridine containing 5% water). FAB-MS: 1107 (M + 1$^+$). Anal. Calcd for $C_{46}H_{74}O_{30}\cdot 5H_2O$ (1197.16): C, 46.15; H, 7.07. Found: C, 43.85; H, 6.74 (corresponding to a content of 95%).

The conformational differences of **2** and **3** in aqueous solution account for the large differences in their retention times in RP-HPLC. Clearly, compound **2** with its adamantyl moiety partially submerged in the cyclodextrin cavity is much less lipophilic and, therefore, is eluted prior to compound **3**, which has its adamantyl pendant exposed to the solvent.

The exclusive formation of adamantyl ethers **2** and **3** resulting from an innermolecular[18] reaction of adamantanylidene with the secondary hydroxyl groups, which are all at the wider rim of the cyclodextrin, must reflect the special structure of complex **1**@2(**6-Cy**). In a previous report, we proposed four different possible arrangements[12] for this complex, based on UV−vis and CD spectra. All would account for the apparent nonpolar environment of the diazirine chromophore even in the extremly polar aqueous solution. The astounding chemospecifity of the reacting carbene intermediate with the secondary hydroxyl groups can be best explained by structure A (Figure 2). Moreover, strong

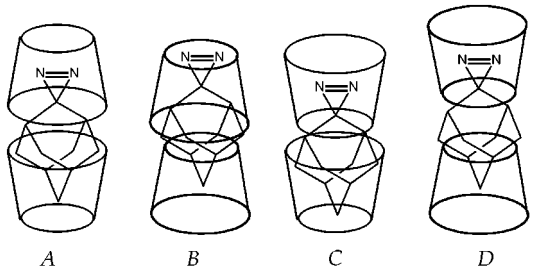


Figure 2. Arrangement for the 2:1 complex **1**@2(**6-Cy**) as proposed in ref 12.

evidence for this symmetric arrangement of guest and host molecules is presented by a 2D ROESY experiment in water-d_2 which shows only cross-peaks between the H-3 protons of **6-Cy** and all adamantyl protons. Thus, all parts of the adamantane structure are in close proximity to the 2- and 3-hydroxyl groups of the two cyclodextrin host molecules. This explains why no reaction of the carbene with the C-6-OH groups took place. Furthermore, the preferred insertion of adamantanylidene into the C-3-OH group of **6-Cy** (ratio of **2**:**3** ca. 2−3) is of great synthetic value since this position had been accessible only in reasonable yields by multistep procedures.[6,7,8a]

The superiority of the solid-state approach for monofunctionalization of cyclodextrins becomes obvious when compared with the photolysis of **1**@2(**6-Cy**) in aqueous solution. As expected, under these conditions, 2-adamantanol (**6**) is formed as the major product (see Table 1). In contrast to the solid-state reaction, however, the yields of the innermolecular insertion products **2** and **3** are reduced by a factor of more than two. Besides its main reaction with water molecules, the liberated adamantanylidene shows a reaction behavior which parallels that in the solid state. Moreover, the results in the table suggest that **1**@2(**6-Cy**)−even in

(18) Warmuth, R. *Chem. Commun.* **1998**, 59−60.

solution−exists as a complex that structurally resembles the one in the solid state.

In conclusion, the supramolecular approach to monofunctionalized cyclodextrins in the solid state described here combines chemospecificity with high yields of products, which by other methods are only difficult to obtain.

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Supporting Information Available: NMR data for compounds **2**, **3**, and **1**@2(**6-Cy**). This material is available free of charge via the Internet at http://pubs.acs.org.

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