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An efficient strategy for the modification of α-cyclodextrin: direct conversion of one or two adjacent 6-OHs to phthalimides

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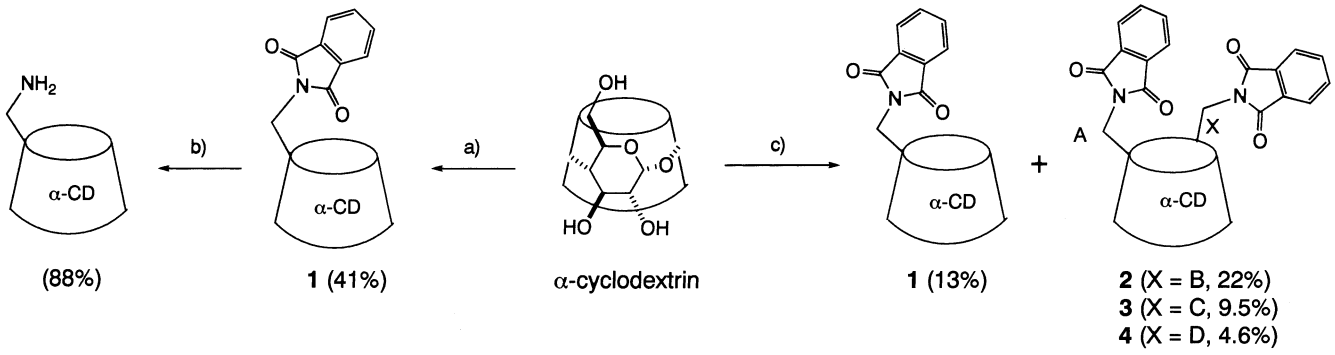
Abstract—α-Cyclodextrin was reacted with phthalimide under modified Mitsunobu conditions to give the 6^A-deoxy-6^A-phthalimido-α-cyclodextrin in 41% yield. This reaction also worked well in the modification of two methylene carbons, giving the $6^A,6^B$-, $6^A,6^C$- and $6^A,6^D$-diphthalimido-α-cyclodextrins in 22, 9.5 and 4.6% isolated yields, respectively. All the phthalimido species can be quantitatively converted to the corresponding amino cyclodextrins by hydrazinolysis.

Cyclodextrins (CDs) are widely employed as scaffolds in composing host molecules because of their ability to bind a wide range of guest molecules in aqueous solutions and to modify the physical and chemical properties of bound guest molecules. Their modifications are of particular importance for the investigation at the frontier of various research fields ranging from supramolecular chemistry to analytical techniques. The modification of particular positions represents a great challenge for chemists since the most frequently used CDs consist of 6∼8 folds of three types of hydroxyl groups, namely the primary face 6-OH groups, the secondary face 3-OH and 2-OH groups, and their competition makes the selective modification of CDs extremely difficult. During the past decades, methods for selective modification of one or two hydroxyl groups on either face have been extensively investigated.[1] However, chemists interested in modified CDs still have to contend with the problems associated with their synthesis: the multistep procedures with poor selectivity, tedious separation and low overall yields. The conventional method for the modification of the primary face follows the selective 6-OH activation–displacement protocol. Another strategy has been established for the introduction of functionalities through a nitrogen atom, in which one 6-OH is displaced by an azide group under Vilsmeier–Haack reaction conditions followed by reduction and subsequent alkylation or



Scheme 1. Reaction of α-CD with phthalimide under modified Mitsunobu condition. (a) Phthalimide/diethyl azodicarboxylate (DEAD)/Ph_3P/α-CD in a molar ratio of 3.3/1.8/2.4/1 in DMF, rt, 5 h; (b) 100 equiv. of hydrazine hydrate in water, 60°C, overnight; (c) phthalimide/DEAD/Ph_3P/α-CD in a molar ratio of 7/4.6/4/1 in DMF, rt, 4 h.

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acylation and so forth. Elimination of reaction steps is of general research interest in improving synthetic efficiency and also from the viewpoint of green chemistry principles. In this paper, we describe a new strategy to directly incorporate phthalimide functionalities onto the primary face of α-CD under modified Mitsunobu conditions (Scheme 1).[2] Reaction of phthalimide with α-CD allowed the isolation of 6^A-deoxy-6^A-phthalimido-α-CD **1** in a high 41% yield. Increasing the charged amount of phthalimide ensures the synthesis of 6^A,6^X-dideoxy-6^A,6^X-diphthalimido-α-CDs. This direct phthalimidation reaction not only gave a good total yield but also performed unprecedented interesting regioselectivity. The AB (**2**), AC (**3**) and AD (**4**) isomeric diphthalimido-α-CDs were isolated in 22, 9.5 and 4.6% yields, respectively. This represents hitherto the most efficient method to selectively modify two adjacent methylene groups of α-CD. These α-phthalimido-α-CDs can be transformed quantitatively to the corresponding CD amines by hydrazinolysis.

The reactions of α-CD and phthalimide were carried out in DMF at rt in the presence of Ph_3P, diethyl azodicarboxylate (DEAD) and 4 Å molecular sieves. In a typical run for the preparation of monophthalimide **1**, α-CD (5 g, 5.1 mmol), Ph_3P (3.2 g, 12.1 mmol) and phthalimide (2.5 g, 17 mmol) were dissolved in DMF (150 mL) and the solution was stirred at rt for 1 h. DEAD solution (40% in toluene, 4 mL, 9.2 mmol) was then added dropwise and the resultant solution was stirred at ambient temperature for another 5 h. After evaporation of the solvent, acetone (200 mL) was added to the residue and the precipitates were collected by filtration and applied to reversed-phase chromatography (Merck pre-packed RP-18 column, size C). Gradient elution from water to 27% aqueous ethanol afforded the pure product **1** (2.3 g, 41%).

The structure of **1** was characterized with FAB-MS and NMR spectroscopy. FAB-MS spectrum demonstrated pseudo molecular ion at $m/z=1124$ ($M+Na^+$). In the ^1H NMR spectrum (Fig. 1, top), two multiplets around δ 7.8 ppm were observed for the phthalimide residue and their integration area was two third that of the anomeric protons of the CD moiety, confirming the 1:1 conjugation of α-CD and phthalimide. The substitution position was assigned to C-6^A with the aid of 2D NMR techniques. One carbon resonates at a very high field (δ 40.0 ppm) in the ^{13}C NMR (Fig. 1, bottom) and it was proved to be a CH_2 carbon by DEPT measurements. In the HMBC spectra, long-range couplings were observed between the protons of this CH_2 group and the carbonyl carbons of phthalimide. Therefore this methylene carbon should be the phthalimide-attached position. In consistent with this assignment, the aromatic ring excises a very strong shielding effect on one of the unmodified sugar residue, especially on its protons located on the primary face (H-6′ at δ 2.6 and H-5′ at δ 3.05). Similar strong shielding effect was reported in the literatures.[3]

Hydrazinolysis of **1** was carried out by heating **1** and hydrazine hydrate in water at 60°C overnight. The crude product was collected by precipitation with acetone and purified via cation-exchange chromatography to give the 6^A-amino-6^A-deoxy-α-CD in 88% yield (36% based on α-CD).[4] It's NMR spectra are superimposible upon those of the same compound prepared by using the literature method which afforded this amino CD in 16% yield.[5]

Since we still lack an efficient method to selectively modify two positions on the primary face of α-CD except for the transannular 6^A,6^C-disulfonylation[6] reported recently, we are interested in expanding this direct phthalimidation method to the bifunctionalization of α-CD. In general, the substitution levels of CDs

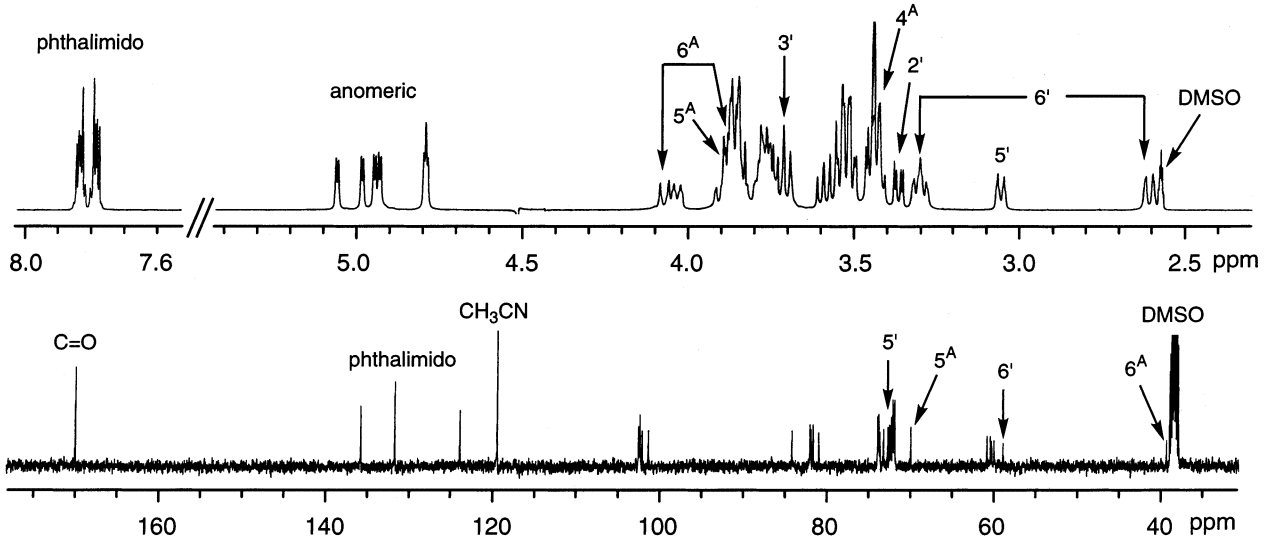

Figure 1. ^1H (top, 500 MHz) and ^{13}C (bottom, 125 MHz) NMR spectra of **1** in a mixed solvent of 40% D_2O–60% DMSO-d_6 (CH_3CN as internal standard). The numbers with a superscript 'A' indicate the protons or carbons of the substituted glucoside unit, while the primed numbers denote the protons or carbons of one of the unsubstituted units adjacent to the substituted one.

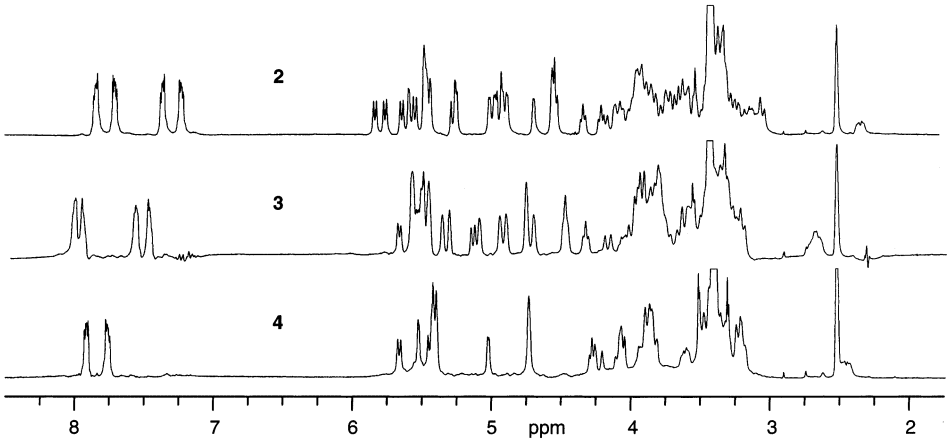

Figure 2. ^{1}H NMR spectra (300 MHz) of the diphthalimido-α-CDs **2** (top), **3** (middle) and **4** (bottom) in DMSO-d_6 (TMS as internal standard). The C_2 symmetrical feature of compound **4** is evident in the aromatic region as well as in the anomeric region from δ 4.7∼5.2 ppm.

can be increased by using more reacting reagents. The suitable conditions for the preparation of diphathalimido-α-CDs turn out to be quite similar to that used for the preparation of mono-phthalimido-α-CD **1** but with the amounts of phthalimide, DEAD and Ph_3P nearly doubled. The preparative reaction was carried out by charging phthalimide, DEAD, Ph_3P and α-CD in a molar ratio of 7/4.6/4/1 and by the same procedures described above for the synthesis of **1**. Chromatography of the reaction mixture on a reversed-phase Lobar column (RP-18, gradient elution from 10 to 40% aqueous ethanol) gave 22% **2**, 9.5% **3** and 4.6% **4** in addition to 13% **1**. FAB-MAS and NMR spectroscopic analysis[7] indicated that **2**∼**4** are all the adducts of one CD and two phthalimide moieties. Compound **4** can be reasonably assigned to the C_2 symmetrical AD isomer based on the ^{1}H NMR spectra (Fig. 2), while the determination of the regiochemistry of **2** and **3** was carried by the procedures depicted in Figure 3. Hydrazinolysis of compounds **2**, **3** and **4** under the same conditions as for **1** afforded **5** (91%), **6** (84%) and **7** (81%), respectively. Treatment of these amines with *p*-nitrobenzoic acid in the presence of DCC and 1-hydroxybenzotriazole (HOBT) gave the HPLC samples **8**, **9** and **10** which demonstrated retention times different from each other on the reversed-phase ODS column. Comparison of their HPLC retention times with those of the authentic 6^A,6^B- and 6^A,6^C-di(*p*-nitrobenzamido)-α-CDs suggested that **2** is 6^A,6^B-diphthalimido-α-CD, while **3** is the AC isomer. The authentic samples of 6^A,6^B- and 6^A,6^C-di(*p*-nitrobenzamido)-α-CDs were obtained by the selective transannular disulfonylation at the 6^A,6^B- (**11**)[8] or 6^A,6^C-positions (**12**),[9] subsequent substitution with N_3^-, reduction with Ph_3P and final acylation of the amines (Fig. 3).

The above results indicate that the present strategy ensures a direct modification of the primary face of α-CD. Two approaches have been reported hitherto to modify the 6^A,6^B-positions of α-CD. One is the consecutive disulfonylation with messitylenesulfonyl chloride,[10] which afforded the AB, AC and AD disulfonates in 7.3, 9.1 and 13.6%, respectively. Another one used 4,6-dimethoxy-1,3-benzenedisulfonyl chloride as capping reagent,[8] by taking the advantage of the 'looper's walk' strategy, to afford the 6^A,6^B-disulfonate in 2.3% yield. Obviously the present method is more efficient in modifying the two adjacent methylene carbons of α-CD.

Unusual but very interesting AB selectivity was observed in this direct diphthalimidation reaction. In the consecutive reactions on CDs, the first introduced substituent usually exercises more or less steric repulsion effect on the coming ones and thus direct them to the distant positions. This steric effect was elegantly utilized in the modifications of the ACE positions of the primary face of α-CD[11] and the secondary face of β-CD.[12] In the direct diphthalimidation reaction, however, the two phthalimide residues prefer to be closely located. The averaged relative reactivity of $6^{B(\text{or } F)}$/$6^{C(\text{or } E)}$/6^D position of the intermediate monophthalimido-α-CD can be deduced to be 2.4:1:1 based on the isolated yields of the diphthalimides. Obviously some factor other than the steric interaction predominates in locating the second molecule of phthalimide. Further work aiming at the elucidation of the phenomena is in progress.

In summary, direct substitution of the primary hydroxyl group of α-CD by phthalimide under modified Mitsunobu conditions has been effected, and the 6^A-phthalimido-α-CD can be isolated in a high 41% yield. This strategy also works well in the synthesis of disubstituted α-CDs, and demonstrated very interesting AB regioselectivity by affording 6^A,6^B-diphthalimido-α-CD in 22% yield. All the phthalimido-α-CD species can be converted quantitatively to their corresponding amino-CDs which are very important intermediates.

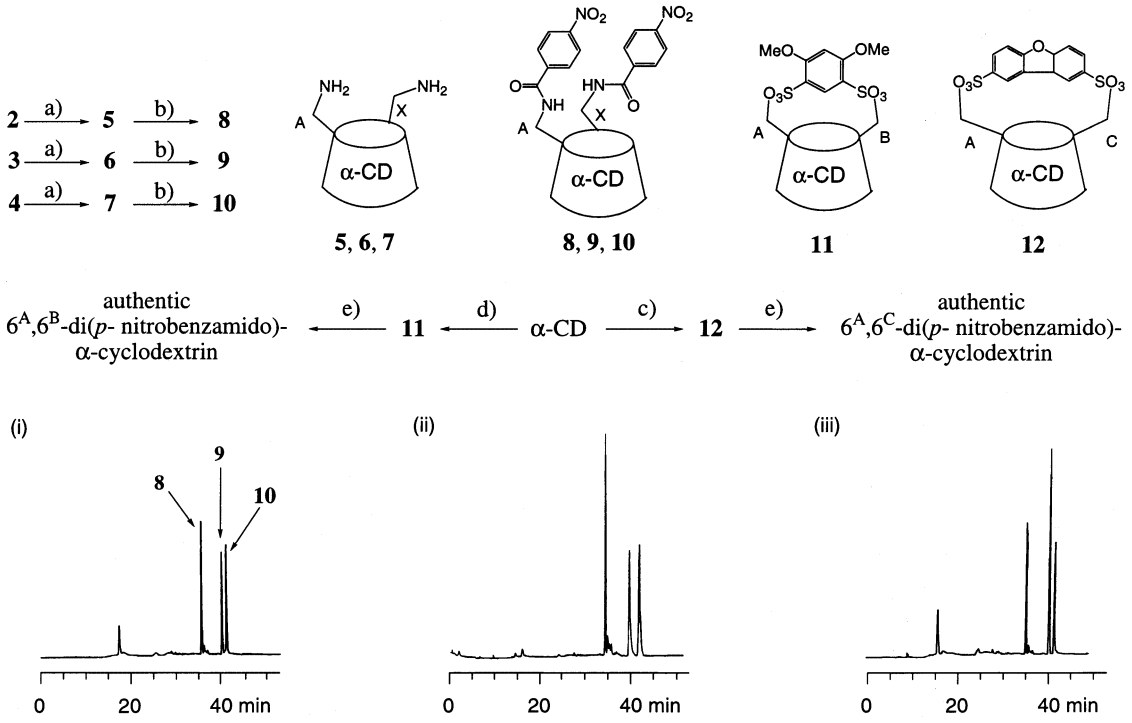

Figure 3. The procedures for the determination of the regiochemistry of the diphthalimido-α-CDs **2**, **3** and **4** based on HPLC analysis. (a) $NH_2NH_2{\cdot}H_2O$, H_2O, 60°C, overnight; (b) DMF, DCC, HOBT, *p*-nitrobenzoic acid, rt, 4 h; (c) pyridine, 4,6-dimethoxy-1,3-benzenedisulfonyl chloride, rt, 3 h; (d) pyridine, dibenzofuran-2,8-disulfonyl chloride, rt, 3 h; (e) (1) DMF, NaN_3, 80°C, 12 h; (2) DMF, Ph_3P, rt, overnight, then at rt for 24 h in the presence of aqueous NH_3; (3) DMF, DCC, HOBT, *p*-nitrobenzoic acid, rt, 4 h. The HPLC analysis was performed on a reversed-phase column (YMC ODS-AQ-313, 250×6.0 mm I.D.) eluted with a gradient from 20% aqueous CH_3CN and with the CH_3CN concentration being increased at a rate of 0.5%/min. The UV absorbance of the elutes was detected at $\lambda = 280$ nm. (i) A mixture of **8**, **9** and **10**; (ii) mixture of (i) and the authentic $6^A,6^B$-di(*p*-nitrobenzamido)-α-CD; (iii) mixture of (i) and the authentic $6^A,6^C$-di(*p*-nitrobenzamido)-α-CD.

Acknowledgements

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4. A mixture of **1** (0.1 mmol) and hydrazine hydrate (0.01 mol) in H_2O (2 mL) was stirred at 60°C overnight. After being cooled down to rt, the reaction mixture was added dropwise to acetone (50 mL). The resultant precipitates were collected by filtration and applied to ion exchange chromatography (Bio-Rad AG 50W-X2, 100–200 mesh, ϕ-SO_3H type, washed with a gradient of 0 ~ 1.5% aq. ammonia solution) to give the 6^A-amino-6^A-deoxy-α-CD (88%).
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7. Compound **2**, **3** and **4** all showed the pseudomolecular ion peak at m/z 1253($M+Na^+$) in the FAB-MS spectra. Their ^1H (Fig. 2) and ^{13}C NMR spectra are consistent with their structures. The ^{13}C NMR data (75 MHz, DMSO-d_6, CH_3CN int., $\delta_{CH_3CN} = 1.70$) are as follows. Compound **2**: δ 167.8, 167.3, 134.8, 134.7, 134.0, 130.7, 130.6, 130.4, 123.1, 122.5, 102.0, 101.2, 100.4, 100.3, 84.6, 84.0, 81.7, 81.6, 80.6, 80.0, 73.1, 72.8, 72.4, 72.1, 72.0, 71.8, 71.5, 71.4, 71.3, 71.2, 71.0, 70.7, 66.3, 59.8, 59.4, 58.1, 56.4, 39.3, 39.0. Compound **3**: δ 167.0, 134.0, 133.3, 130.1, 128.0, 127.3, 122.4, 121.7, 101.0, 100.9, 100.5, 99.7, 98.2, 83.2, 83.0, 80.3, 80.2, 79.5, 72.1, 72.0, 71.7, 71.4, 71.1, 70.9, 70.8, 70.6, 70.3, 68.8, 66.9, 58.6, 58.3, 57.3, 38.3, 38.0. Compound **4**: δ 168.2, 134.6, 131.4, 123.1, 102.1, 101.9, 101.2, 84.0, 81.4, 80.7, 73.1, 72.9, 72.4, 72.1, 71.9, 71.4, 68.8, 59.1, 57.9, 39.3.
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