A facile dialkyl ether cleavage and rearrangement under mildly basic conditions during the Williamson synthesis with β-cyclodextrin

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Alkyl (9,10-dicyanoanthracenyl-2-methyl) ethers undergo facile transetherification with a variety of alkoxides.

The ether bond is generally resistant to base cleavage.[1] Well-known exceptions occur when the alkoxide leaving group is stable, as with a phenoxide, and when cleavage relieves strain, as with an epoxide. Benzyl ethers are often used at protecting groups for alcohols.[2] These arylalkyl ethers are stable even with strong bases and are cleaved by catalytic hydrogenation or dissolving metal reduction. Thus, the ether bond should be an ideal linking group in the construction of supramolecular systems, especially when such systems will be used as reaction catalysts requiring their continued molecular integrity. In this paper we report a case involving construction of a cyclodextrin assembly wherein an arylalkyl alkyl ether bond undergoes facile cleavage under relatively mild conditions.

The Williamson ether synthesis can be applied to the regioselective alkylation of β-cyclodextrin (β-CD) at the glucose C2–OH. The regioselectivity arises from the greater acidity of the C2–OH relative to the C3 or C6–OH. The C2 alkoxide is stabilized by an intramolecular H-bond with the C3–OH of an adjacent glucose unit. D'Souza and Rong have shown that β-CD alkoxide will react by nucleophilic substitution with a variety of electrophiles to give C2 ethers.[3] We have applied this reaction to link together a 9,10-dicyanoanthracene (DCA) group with β-cyclodextrin *via* the 2-bromomethyl derivative **1**.[4] The reaction did not give rise to selective substitution at C2; in fact, a 3 : 1 ratio of C6 and C2-ethers was isolated (Scheme 1). In this communication we report the results of several experiments probing the origin of the observed regiochemistry.

In all of the following experiments the relative proportions of the DCA–β-CD ethers were determined through HPLC analysis of the reaction mixture.† The base used was β-CD alkoxide, and the base strength was controlled by the quantity of NaH used to deprotonate the β-cyclodextrin; for example, a 50% molar excess of NaH was used to generate a 1 : 1 mixture of β-CD C2-alkoxide and C2,C2′-dialkoxide. All reactions were conducted in DMF which was distilled from CaH_2 *in vacuo* before use.

The etherification reaction requires more than stoichiometric base to form ether products. The reaction with 50% excess base was monitored as a function of time. HPLC results reveal that **2** is formed initially, but disappears rapidly with concomitant formation of **3**. Ether formation is nearly complete within 30 min, but the fraction of **3** in the product mixture continues to increase well after this period. Two other unidentified species are revealed by the HPLC results.‡ These species form faster than **3**; then, like **2**, they disappear. We tentatively assign these as C3 ethers **4a,b** (*vide infra*), which are inside–outside (conformational) isomers. The faster eluting compound **4a** is assigned to the inside isomer since its hydrophobic interaction with the reverse-phase layer is less than that of the outside isomer.

Compound **2**, available from our previous work, is isomerized to **3** and **4a**,**b** by cyclodextrin alkoxide solutions. The final product distribution depends upon the initial alkoxide composition. When **2** is treated with β-CD alkoxide, the isomerization proceeds mainly to **4a**,**b**, whereas when a nearly equal mixture of β-CD alkoxide and β-CD dialkoxide is used, **3** becomes the ultimate product.

We set out to determine whether the isomerization was intra- or inter-molecular in nature. For this study we synthesized 6-*O*-per(*tert*-butyldimethylsilyl)-2-*O*-(9,10-dicyanoanthracenyl-2-methyl)-β-cyclodextrin **5**.§ The conditions for the isomerization of **2** were repeated: reaction with a stoichiometric amount of β-CD alkoxide and with 1 : 1 alkoxide/dialkoxide. The product composition at various times was probed by HPLC in two ways: (i) by direct injection of the reaction mixture and (ii) after removal of the silyl ethers with HF. Any product (**2**, **3** or **4a**,**b**) seen in the first set can arise only by an intermolecular process. The mixture from the second determination derives from a combination of both inter- and intra-molecular processes. Treatment of **5** with β-CD alkoxide gives rise to an intramolecular isomerization to the persilylated C3 ethers **6a** and **b**. However, treatment with a β-CD alkoxide/dialkoxide mixture produces **3** *via* an intermolecular process.

The assignment of **4a** and **b** as C3 ethers rests on their appearance in both the isomerization of **2** and especially of **5**. In

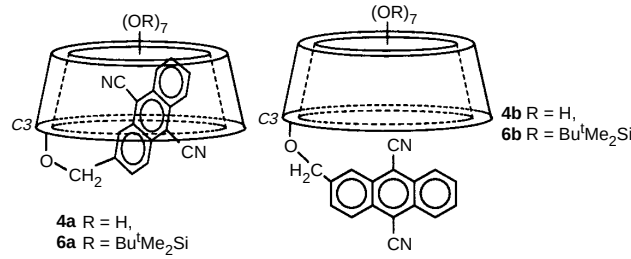
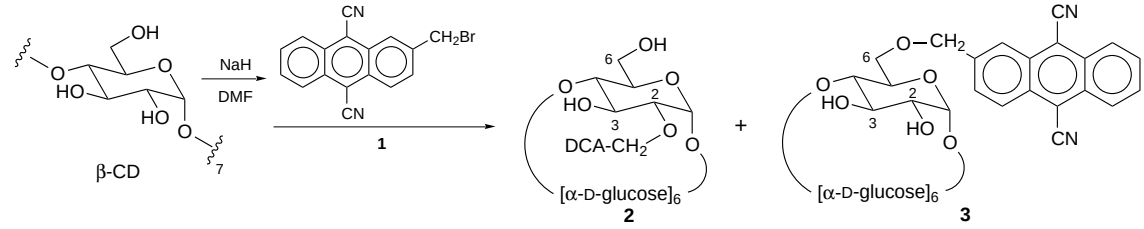


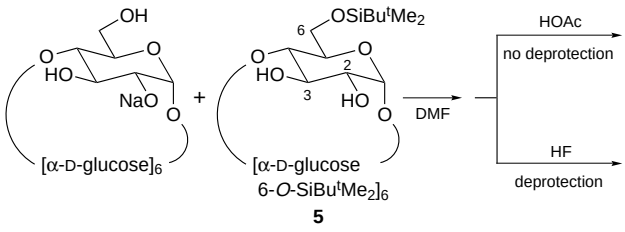
Fig. 1 9,10-dicyanoanthracenyl-2-methyl-C3-*O*-β-CD ethers **4a**,**b** and **6a**,**b**



Scheme 1 Reaction of β-cyclodextrin alkoxide with 2-bromomethyl-9,10-dicyanoanthracene **1**

the latter result, the C3 position is the only one possible for a DCA ether product since the C6 hydroxy groups are blocked and the C2 isomer is the starting material. The faster elution of C3 ethers relative to C2 and C6 ethers in reverse-phase HPLC has been documented.[6] The kinetic stability of a self-included C3 ether has been reported recently for a C3 tethered 2-naphthylmethyl group.[7] The DCA group is longer than the naphthyl group, and the C3-inside ether should be even more kinetically stable than the reported naphthyl ether.

The scope of the transetherification was probed through attempted interconversions of compounds **7**–**9** (Scheme 3).¶ The reactions were conducted in DMF using 1.5 equiv. of alkoxide to mimic the above conditions and were monitored by HPLC.‖ Table 1 shows that ether exchange is a general reaction



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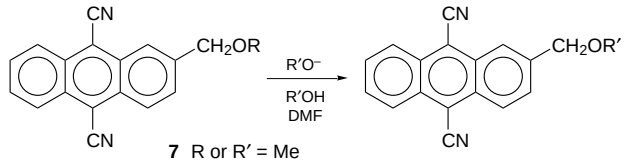
Scheme 2 Reaction of **5** with β-CD alkoxide and subsequent analysis



7 R or R′ = Me
8 R or R′ = Bn
9 R or R′ = $HOCH_2CH_2$

Scheme 3 Transetherification reactions of alkyl (9,10-dicyanoanthracenylmethyl) ethers

Table 1 Transetherification yields[a]

Ether (DCA–CH_2–OR) R=	Alkoxide (R′O^-) R′=	Yield (%)[b] (DCA–CH_2–OR′)	t/min
Me	β-CD[c]	6	360
Me	Bn	30	23
Me	$HOCH_2CH_2$	35	130
Bn	β-CD[c]	6	360
Bn	Me	27	105
Bn	$HOCH_2CH_2$	32	1320
$HOCH_2CH_2$	Me	58	105
$HOCH_2CH_2$	Bn	52	23

[a] Reaction conditions: [DCA–CH_2–OR] = *ca*. 0.01 mol dm^{-3}, [R′O^-] *ca*. 0.015 mol dm^{-3}, [R′OH] = *ca*. 10% *v/v* in DMF, 23 °C. [b] Determined by HPLC results. [c] [R′O^-] + [R′OH] = *ca*. 0.01 mol dm^{-3}.

for DCA-2-methyl ethers. In fact, both **7** and **8** can be used to prepare the DCA- tethered β-CD **3**.

The electron-withdrawing nature of the DCA group as well as the presence of H-bonding[8] should be important factors in the ether exchange process. Other CD ether tethers without such an electron-withdrawing aryl groups do not undergo isomerization.[3] While substitution of electron-withdrawing groups onto benzyl ethers renders them more reactive than benzyl ethers, usually it is the functional group which is attacked, and ether cleavage still requires forcing conditions. The reactivity of **2** is unusual in that ether bond *migrates* instead of just cleaving. The ease with which the dicyanoanthracenylmethyl group is released may render it a useful protecting group for alcohols. We are pursuing independent syntheses of **4a** and **b**, as well as the mechanism of the transetherification reaction.

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Footnotes

† Compounds **2**[4] and **3** elute at 21.8 and 22.9 min, respectively, from a 250 × 4.6 mm Whatman ODS-3 column using a linear gradient elution (80 : 20 to 50 : 50 H_2O–MeCN over 30 min) at 1.0 ml min^{-1}. The absorption at 254 nm was detected, and peak area percentages are reported as mole fractions.

‡ Compounds **4a** and **b** show retention times of 18.8 and 19.9 min, respectively.

§ Compound **5** was prepared from per-6-*O*-(*tert*-butyldimethylsilyl)-β-CD[5] by first forming the alkoxide with NaH in THF, then alkylating with **1**. It was purified by HPLC on silica gel, characterized by NMR, and gave satisfactory combustion analysis.

¶ Compounds **7**–**9** were prepared by Ag_2O-assisted alcoholysis reactions of **1**.

‖ Compounds **7** and **8** elute at 7.6 and 6.3 min, respectively, from a 250 × 4.6 mm Alltech Econosil column using an isocratic elution ($CHCl_3$) at 0.7 ml min^{-1}. Compound **9** elutes at 15.2 min using a linear gradient elution (0–20% MeOH in $CHCl_3$ over 20 min) at 1.0 ml min^{-1}. The absorption at 420 nm was detected, and an internal standard was used to determine the yields at 100% conversion.

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