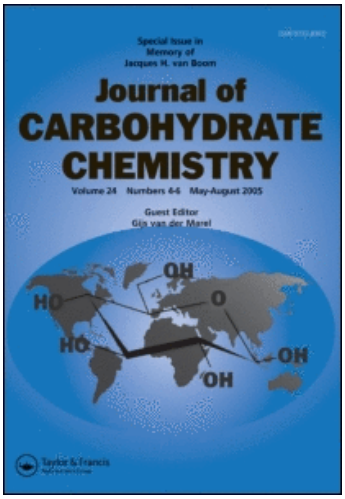

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A SONOCHEMICAL PROTOCOL FOR THE SYNTHESIS OF PERMODIFIED CYCLODEXTRINS[1]

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A SONOCHEMICAL PROTOCOL FOR THE SYNTHESIS OF PERMODIFIED CYCLODEXTRINS[1]

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ABSTRACT

A series of *O*-peralkylated β- and γ-cyclodextrins, commonly used as stationary phases in high-resolution gas chromatography or as drug carriers, has been prepared both according to the usual methods and with sonocatalysis. The sonochemical protocol, using either a common cleaning bath or sonochemical apparatus, resulted in markedly improved yields, reaction times and reproducibility.

INTRODUCTION

Selective chemical modification of β- and γ-cyclodextrins (CDs) has been widely studied.[2,3] Over the last few decades these products have spawned a host of new applications.[4] Nevertheless, an efficient regioselective modification of their three different hydroxyl groups has not been achieved to-date. Chemical and physical properties of CDs often make selective *O*-alkylation a difficult target; totally persubstituted products are usually obtained in low yields. Commercially available CD derivatives are incompletely and randomly substituted mixtures.[5] Different batches of any given modified CD show differences in composition, and chromatographic purification of these crude products is not a trivial task. It has been shown[6] that small differences of substitution degree can affect the enantiomeric se-

lectivity of alkylated CDs when used as stationary phases in high-resolution gas chromatography (HRGC).

We wish to report a marked improvement in the synthesis of permodified CDs by a particularly effective application of ultrasounds.[7]

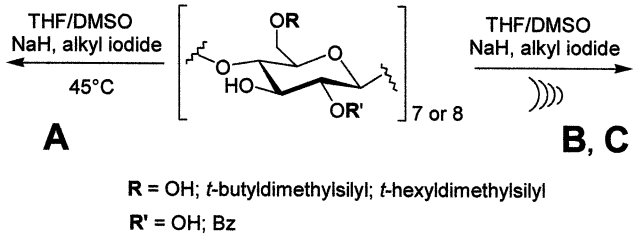
Although the influence of ultrasounds on chemical reactions was discovered 70 years ago by Richards and Loomis,[8] the field of sonochemistry lay fallow for nearly half a century. Development occurred in the '80s soon after the advent of commercial ultrasound sources for laboratory purposes, and a number of recent reviews[9] have emphasised the expanding role of sonochemistry. Sonochemical reactions of carbohydrates, both in heterogeneous and homogeneous systems, have been published: Barbier-type reactions,[10] introduction and cleavage of protecting groups, [11] *O*-glycosylation,[12] trifluoromethylation,[13] and oxidation of glucosides.[14] Surprisingly, to the best of our knowledge, applications of this technique to CD modification have not appeared in the literature.

The statement that "the reaction mixture has been sonicated" is very often found in a paper but no experimental details are given. Because sonochemical effects are dependent on several parameters, we shall report the type of equipment, frequency, power input, temperature, vessel and reaction conditions used in our experiments.

RESULTS AND DISCUSSION

We recently described[1] the preparation of a new set of selectively permodified CDs where the crucial synthetic step was carried out with the greatest ease under ultrasonic irradiation. The usual conditions (as described by Lehn and co-workers)[15] for the *O*-peralkylation of position 3 in 2,6-persubstituted CDs afforded a modest yield of the product after a week's reaction time. Our result prompted us to further investigate the effect of sonication in the synthesis of permodified CDs, focusing on *O*-alkylation under basic conditions (Scheme).

As shown in the Table, each reaction was carried out in three different ways: **A**) under stirring at 45 °C, **B**) under sonication in a common cleaning bath and **C**) in a sonochemical apparatus at higher power and intensity.



Scheme. General conditions for CDs alkylation.

Table 1. Reaction Time and Yields for Procedure **A, B,** and **C**

Entry	Starting CD	Product	A Stirring (45 °C)	B Cleaning Bath (35kHz − 160W) (20 °C)	C Sonochemical Apparatus (20kHz − 600W) (20 °C)
1	β	Et-β	72 h − 14%	7 h − 62%	3 h − 68%
2	γ	Et-γ	48 h − 41%	7 h − 71%	3 h − 81%
3	γ	Pe-γ	72 h − 32%	12 h − 63%	5 h − 64%
4	6-TB-β	6-TB-2,3-DE-β	# 72 h	8 h − 58%	4 h − 70%
5	6-TX-γ	6-TX-2,3-DE-γ	48 h − 14%	7 h − 62%	4 h − 74%
6	6-TB-2-Bz-β	6-TB-2-Bz-3-Me-β	# 72 h	8 h − 39%	4 h − 67%
7	6-TX-2-Bz-γ	6-TX-2-Bz-3-Me-γ	# 72 h	8 h − 67%	4 h − 75%
8	6-TB-2-Bz-γ	6-TB-2-Bz-3-Me-γ	# 72 h	8 h − 66%	4 h − 71%
9	6-TX-2-Bz-γ	6-TX-2-Bz-3-Et-γ	# 72 h	10 h − 42%	5 h − 53%

Pe = *n*−pentyl; TB = *t*-butyldimethylsilyl; DE = diethyl; Bz = Benzyl;
TX = *t*−hexyldimethylsilyl; # = incomplete alkylation

Heptakis-2,3-*O*-diethyl-6-*O*-*t*-butyldimethylsilyl-β-CD (**4**) is an efficient chiral stationary phase in HRGC, however small differences in alkylation degree dramatically affect the efficiency of enantiomeric separations.[16] Thanks to our sonochemical procedure, fully persubstituted **4** becomes easily available.

We used either a common cleaner bath (35 KHz / 160 W) or a sonication probe for higher power and intensity (20 KHz / 600 W). Entries **1–5** in the Table are commercially available chiral stationary phases for HRGC. Entries **6–9** were intermediates in the synthesis of persubstituted CDs that we have newly prepared and found even more efficient in enantiomeric separations.[1] *Heptakis*-2,3,6-*O*-triethyl-β-CD (**1**) plays an important role as a slow-release drug carrier.[17]

Results summarised in the Table encourage us to investigate further applications of sonocatalysis to the synthesis of modified CDs.

CONCLUSION

The sonochemical approach to the preparation of permodified CDs resulted in significant improvements in terms of yield, reaction time and reproducibility. We obtained comparable results even when working at lower power and intensity with a common ultrasonic cleaning bath, a standard piece of equipment in many laboratories.

EXPERIMENTAL

General methods. Melting points were obtained on a Büchi SMP-20 apparatus and are uncorrected. ESI-MS spectra were recorded on a TSQ-700 Finnigan-Mat spectrometer (positive mode, CH_3CN) and IR spectra with a Shimadzu

FT-IR 8001 spectrometer. All solvents and chemicals were reagent grade; anhydrous conditions were achieved (when indicated) by the flame-drying of flasks and other critical equipment; THF was dried by distillation from benzophenone-ketyl and DMSO from CaH_2. Reactions were monitored by TLC on Alufolien Fluka plates (F_{254}, 0.25 mm); spots were detected by staining with 5% H_2SO_4 in EtOH and heating. Column chromatography was performed using silica gel 60 (Merck). Sonication was performed either in a Sonic Vibra Cell 600 apparatus at 20 kHz (nominal operating frequency) and 600 W, or in an Elma TS540 cleaner bath at 35 kHz (nominal operating frequency) and 160 W.

Procedure B and **C.** All reactions were carried out on 500 mg of CD, dissolved in THF/DMSO 4:1 (20 mL), in a Carius-type pyrex tube (ACE Glassware) (100 mL) sealed with a pressure-resistant screw cap. All CDs were previously dried for 2–3 h at 105 °C in a vacuum oven. In procedure **B**, the sealed tube was placed in the ultrasonic cleaner bath together with a thermometer; during sonication the temperature was maintained below 20 °C by adding ice to the bath. In procedure **C**, the reaction tube was placed in a thermostatted bath at 20 °C (water circulation), where the sonication probe was dipped for half of its length. In either case, an excess of NaH (60–65%, 200 mg) was then added to the mixture and the tube was sonicated under a darkened aspirator hood for 20 min. Then an excess of the appropriate alkyl iodide (1 mL) was added. Reactions were monitored every two hours by TLC analysis.

Procedure A. All reactions were carried out under anhydrous conditions with the same amounts of reagents as for **B** and **C** using a 50-mL three-necked round-bottomed flask equipped with a magnetic stirrer, a condenser and a nitrogen inlet. The mixture of CD and NaH in THF/DMSO 4:1 was stirred 1 h at 45 °C under a darkened aspirator hood, then cooled to 5 °C, after which the appropriate alkyl iodide was added dropwise. Reactions were stirred at 45 °C for a maximum time of 72 h; after the first 24 h, an addition of the same amount of alkyl halide was made.

General work-up conditions. Reaction mixtures were quenched by adding MeOH (2 mL), and after 5 min were poured into ice water (20 mL), then extracted with $CHCl_3$ (15 mL × 2). The organic layer was washed with a saturated solution of NH_4Cl, a 5% solution of $Na_2S_2O_3$, and brine. After drying on $MgSO_4$ and evaporation of the solvent, the raw products were purified by column chromatography.

Structure identification. All products were examined by ^1H NMR and spectra were compared with data in the literature. *O*-alkylation was shown to be complete by IR, elemental analysis and by ESI-MS.

***Heptakis*-2,3,6-*O*-triethyl-β-CD (1)** pale yellow oil; IR (liquid film) 1462, 1377, 1113, 1032 cm^{-1}; R_f ($CHCl_3$/MeOH 98:2) 0.40. ESI-MS 1724 $[M+H]^+$, $[M+Na]^+$ 1746.6

Anal. Calcd for $C_{84}H_{154}O_{35}$ (1724.1): C, 58.52; H, 9.00. Found: C, 58.29; H, 9.12.

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***Octakis*-2,3,6-*O*-triethyl-γ-CD (2)** semisolid off-white mass; mp 33 °C; IR (liquid film) 1458, 1377, 1144, 1115, 1032 cm^{-1}; R_f ($CHCl_3$/MeOH 98:2) 0.53. ESI-MS 1970 $[M+H]^+$, $[M+Na]^+$ 1992.

Anal. Calcd for $C_{96}H_{176}O_{40}$ (1970.4): C, 58.52; H, 9.00. Found: C, 58.60; H, 8.94.

***Octakis*-2,3,6-*O*-(tri-*n*-pentyl)-γ -CD (3)** yellow viscous oil; IR (liquid film) 1464, 1377, 1111 cm^{-1}; R_f (hexane/EtOAc 1:1) 0.65. ESI-MS 2979 $[M+H]^+$, 3001 $[M+Na]^+$.

Anal. Calcd for $C_{168}H_{320}O_{40}$ (2980.3): C, 67.70; H, 10.82. Found: C, 67.66; H, 10.80.

***Heptakis*-2,3-*O*-diethyl-6-*O*-*t*-butyldimethylsilyl-β-CD (4)** white powder; mp 54 °C; IR (KBr) 1473, 1254, 1146, 1115, 1032, 835, 777 cm^{-1}; R_f (hexane/EtOAc 9:1) 0.67. ESI-MS 2326 $[M+H]^+$, 2348 $[M+Na]^+$.

Anal. Calcd for $C_{112}H_{224}O_{35}Si_7$ (2327.6): C, 57.79; H, 9.70. Found: C, 57.84; H, 9.70.

***Octakis*-2,3-*O*-diethyl-*6*-*O*-*t*-hexyldimethylsilyl-γ-CD (5)** white powder; mp 66 °C; IR (KBr) 1470, 1368, 1252, 1158, 1098, 1030, 835, 776 cm^{-1}; R_f (hexane/EtOAc 8:2) 0.42. ESI-MS 2883 $[M+H]^+$, 2905 $[M+Na]^+$.

Anal. Calcd for $C_{144}H_{288}O_{40}Si_8$ (2884.5): C, 59.96; H, 10.06. Found: C, 59.78; H, 10.22.

***Heptakis*-2-*O*-benzyl-3-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-CD (6)** white powder; mp 81 °C; IR (KBr) 1464, 1161, 1090, 1047, 835, 777, 698 cm^{-1}; R_f (hexane/ EtOAc 8:2) 0.49. ESI-MS 2662 $[M+H]^+$, 2684 $[M+Na]^+$.

Anal. Calcd for $C_{140}H_{224}O_{35}Si_7$ (2663.8): C, 63.12; H, 8.48. Found: C, 63.23; H, 8.41.

***Octakis*-2-*O*-benzyl-3-*O*-methyl-6-*O*-*t*-hexyldimethylsilyl-γ-CD (7)** viscous oil; IR (liquid film); IR (KBr) 1460, 1252, 1160, 1090, 1047, 826, 780 cm^{-1}; R_f ($CHCl_3$/MeOH 98:2) 0.84. ESI-MS 3267 $[M+H]^+$, 3289 $[M+Na]^+$.

Anal. Calcd for $C_{176}H_{288}O_{40}Si_8$ (3268.8): C, 64.67; H, 8.88. Found: C, 64.50; H, 8.94.

***Octakis*-2-*O*-benzyl-3-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-γ-CD (8)** mp 82 °C; IR (KBr) 1463, 1158, 1090, 1047, 830, 777, 698 cm^{-1}; R_f (hexane/ EtOAc 8:2) 0.50. ESI-MS 3043 $[M+H]^+$, 3065 $[M+Na]^+$.

Anal. Calcd for $C_{160}H_{256}O_{40}Si_8$ (3044.4): C, 63.12; H, 8.48. Found: C, 63.20; H, 8.37.

***Octakis*-2-*O*-benzyl-3-*O*-ethyl-6-*O*-*t*-hexyldimethylsilyl-γ-CD (9)** mp 45 °C; IR (KBr) 1465, 1256, 1160, 1090, 1045, 830, 779 cm^{-1}; R_f ($CHCl_3$) 0.42. ESI-MS 3379 (100%) 3351 $[M+H\text{-}Et]^+$ (30%), 3401 $[M+Na]^+$.

Anal. Calcd for $C_{184}H_{304}O_{40}Si_8$ (3381.04): C, 54.19; H, 8.49. Found: C, 54.02; H, 8.58.

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