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Methylation of Cyclodextrins by Phase-Transfer Catalysis*

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Abstract. A new, simple method has been developed for the methylation of cyclodextrins. The reaction proceeds in the heterogeneous phase with dimethyl sulphate, using a solvent in which the original cyclodextrins and the bases used are poorly soluble or insoluble. However, in the presence of phase transfer catalysts, methylation proceeds with good yields. The products are mixtures of randomly methylated cyclodextrins (RAMEB), containing 60–70% of heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DIMEB), 10–15% of heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) and some monomethylated isomers. These methylated products have proved to be excellent detergents; e.g., they are able to significantly increase the water solubility of hydrocortisone, methyltesterone, etc. On repeating methylation twice, the amount of TRIMEB increases, and a pure product (28% yield) can be obtained by crystallisation.

Key words: Methylated cyclodextrins, phase-transfer catalysis.

1. Introduction

Of the partially methylated cyclodextrins, heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DIMEB) has the greatest importance. On the one hand, it has several potential fields of application in drug preparations, while on the other, it behaves as a new type of detergent for hydrophobic substances. Other partially methylated derivatives and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) also display these properties.

The methylation of some of the hydroxy groups of cyclodextrins causes solubility in water to increase to a surprisingly great extent, with simultaneous retention of their complexing abilities. The increase in solubility is, in fact, important for β-cyclodextrin only, since α- and γ-cyclodextrins have greater water solubility than the β modification. The hydroxy groups of cyclodextrins, unlike those of alcohols,

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are generally difficult to methylate. In all previous processes, cyclodextrin had to be dissolved in a solvent for it to be methylated.

The first methods were published by Irvine [1], Muskat [2] and Freudenberg [3] and coworkers. These last performed methylation in liquid ammonia using methyl iodide, but it was possible to introduce 21 methyl groups into β-cyclodextrin only after repeating the reaction 18 times.

Later, the method of Kuhn [5, 6] was applied by Casu *et al.* [4] to the methylation of α- and β-cyclodextrin: methylation with methyl iodide in dimethyl formamide medium in the presence of barium oxide or with dimethyl sulphate in a 1 : 1 mixture of DMF and DMSO in the presence of barium oxide and barium hydroxide yielded hexakis(2,6-di-*O*-methyl)-α-cyclodextrin and heptakis(1,6-di-*O*-methyl)-β-cyclodextrin (DIMEB).

Lipták [7] and then Szejtli *et al.* [8] prepared permethylated α-, β- and γ-cyclodextrins by dissolving anhydrous cyclodextrins in DMF and treating them with methyl iodide. Boger *et al.* [9] used similar methods for the selective methylation of the primary hydroxy groups of α- and β-cyclodextrin.

Since the DIMEB derivative is important in drug technology [10], attempts have been made to prepare it more simply and clearly. According to a Hungarian patent [11], methylation is performed in aqueous medium with dimethyl sulphate in the presence of sodium hydroxide, at 50–100°C. After isolation, the product is repeatedly methylated, and DIMEB is obtained after the third step. The permethylation of anhydrous β-cyclodextrin may also be performed with methyl iodide in the presence of sodium hydride in DMSO [12] or DMF [13].

The other processes for methylation or alkylation have been reviewed by Szejtli [14, 15], König [27–29] and Takeo [30].

The aim of our work was to solve the problem of methylating cyclodextrins using phase transfer catalysis. This method eliminates the need for expensive solvents (like DMF or DMSO), and a dry, homogeneous reaction medium and it enables the organic reactions to proceed under mild conditions [16–18].

2. Experimental

2.1. General Method for the Methylation of Cyclodextrins

Dimethyl sulphate (61.6–180 mmol) was added to a vigorously stirred suspension of 5.0 g (4.4 mmol) of β-cyclodextrin, 100–200 mL of solvent, 220 mmol of powdered base and 1.0 g of phase transfer catalyst. The mixture was stirred at 20°C for 2 h and at 50°C for 4 h, allowed to stand overnight, then filtered. The filtrate was treated with aq 25% NH_4OH (2–3 mL), then evaporated to dryness *in vacuo*. The catalyst (insoluble in water) was removed by dissolving the residue in 50 mL of water, and then filtering through a paper filter. The filtrate was evaporated *in vacuo*, the residue was dissolved in 60 mL of chloroform and evaporated to dryness after repeated filtration steps. A white, amorphous solid product was obtained. The water solubility of the products was measured at 22°C (given as g/100 mL of water). The

methoxy content of the products was determined by Zeissel's method [26] (given as the average degree of methylation per mol of cyclodextrin). ^{1}H NMR ($CHCl_3$, TMS, 80 MHz, ppm): 5.04 (d, J = 4 Hz. 7H, anomeric H); 3.61 (s, OCH_3, C-2); 3.38 (s, OCH_3, C-6); 3.48 (s, OCH_3, C-3). The intensity ratio of the C-2, C-3 and C-6 signals is 1.4 : 1 : 1.5 in the product of the reaction performed under optimum conditions.

Dissolution studies were performed with hydrocortisone, piperonal and methyltestosterone substrates in distilled water, at room temperature, under stirring for 18 h, according to the following procedure: 50 mg of methylated cyclodextrin and 67 mg of hydrocortisone were stirred in 1 mL of distilled water at 25° for 18 h. The mixture was filtered, and the hydrocortisone content of the clear solution was determined by UV photometry at $\lambda_{max} = 248 \pm 2$ nm. The concentration of dissolved hydrocortisone was determined on the basis of prior calibration.

Chromatography: Kieselgel $60F_{254}$ on plastic foil (Merck)
Eluents: Toluene/methanol 10 : 3, benzene/methanol 8 : 2
Development: Draggendorf reagent
Abbreviations: CD: cyclodextrin, DIMEB: dimethylcyclodextrin, RAMEB: randomly methylated CD, DMSO: dimethyl sulfoxide, DMF: N,N-dimethyl-formamide, THF: tetrahydrofuran, Aliquat: Tricaprylmethylammonium chloride, TEMED: N,N,N',N'-tetramethylethylene-diamine, TEBA: benzyltriethylammonium chloride, TBAB: tetrabutylammonium bromide, BTBA: benzyltributylammonium bromide, TBAH: tetrabutylammonium hydrogensulphate.

3. Results and Discussion

3.1. Previous Results

We have discovered some reported examples of the O-alkylation of carbohydrates by phase transfer catalysis. The reactions were performed in a two-phase, liquid–liquid system by dissolving the carbohydrate in an excess of alkylating agent or solvent (CH_2Cl_2, dichloroethane, benzene, etc.) and vigorously stirring with a 50% aqueous solution of a base (NaOH, KOH, etc.) in the presence of a phase transfer catalyst (BTBA, TBAH, etc.) [19–21]. Töke *et al.* [22, 23] alkylated the hydroxy groups of benzylidene monosaccharides with tosyl esters in a two-phase THF/50% KOH system, in the preparation of chiral crown ethers. According to their assumption, the resulting crown compound plays the role of the catalyst in these reactions [22, 23].

Bessoders *et al.* [24] alkylated isopropylidene sugar derivatives with alkyl bromides, using solid KOH, in the presence of a crown ether catalyst, obtaining good yields. The main difficulty was the insolubility or poor solubility of cyclodextrins in the solvents generally used, coupled with their solubility in water, which means that, instead of aqueous alkali, only solid bases can be used. It has been found that in a system composed of an organic solvent (+dimethyl sulphate) and solid KOH,

TABLE I. Effect of solvent on the methylation of β-CD (Aliquat catalyst, KOH base).

Solvent	Me_2SO_4/CD	Yield, g/gCD	Solubility of hydrocortisone mg/mL*
Petroleum ether	49	0.16	2200
1,2-dichloroethane	27.2	0.71	2100
Benzene	27.2	0.35	3300
Benzene, dry	16.2	0.17	3150
Dichloromethane	21.7	0.16	2900
Toluene	24.4	0.70	2500
Dioxane	49	0.82	3300
THF	49	1.18	4500

*Without RAMEB 470–510 mg/mL.

in the presence of phase transfer catalysts, even the low solubility of cyclodextrin is sufficient for the reaction to proceed (which is promoted by the fact that the methylated product is already well soluble in the organic solvent) to yield a mixture of partially methylated cyclodextrins. The amount, solubility, average degree of methylation and solubiliser potency of the product depend on the preparation conditions [25].

3.2. Optimisation of Reaction Conditions

Table I shows the results of experiments performed in various solvents with KOH in the presence of Aliquat catalyst. Regarding yield and applicability, THF has proved to be the best solvent, followed by dioxane, 1,2-dichloroethane, toluene and benzene. The desired product was not obtained in dichloromethane; however, in toluene and dioxane the main product was DIMEB, whereas the product of the reaction in THF also contained 15–20% of the trimethyl derivative.

Table II contains the results of experiments carried out with various solid bases in THF, using Aliquat as catalyst. The reaction proceeds slowly with alkali carbonates: a product could be detected only after 20 h. The reaction is much faster with sodium hydroxide. The mixture of barium oxide and barium hydroxide was tested because this base was used by Casu [4] in DMS or DMSO, respectively, for the preparations of pure DIMEB. The barium cation presumably plays a role in selective complex formation. The best result was given by KOH. The yield was superior: 1 g of starting substance yields 1.18 g of product, with a significant hydrocortisone solubiliser potency. Though the specific optical rotary power ($[\alpha]_D^{20} = 115.3$ in $CHCl_3$) is close to that of pure DIMEB, this is not characteristic, due to the inhomogeneity of the product.

TABLE II. Effect of base on the methylation of β-CD (THF solvent, Aliquat catalyst).

Base	Me_2SO_4/CD	Yield, g/gCD
$K_2CO_3 + KHCO_3$	16.2	0.05
$Na_2CO_3 + NaHCO_3$	16.2	0.14
$KOH + K_2CO_3$	49	0.68
NaOH	49	0.77
$Ba(OH)_2 \cdot 8H_2O + BaO$	49	0.46
KOH + CaO	49	1.05
KOH + BaO	27.2	0.33
KOH	49	1.18

TABLE III. Effect of the phase-transfer catalyst on the methylation of β-cyclodextrin (THF solvent, KOH base, molar ratio Me_2SO_4/CD = 49). Time: 20°C 2 h, 50°C 4 h.

Catalyst	Yield g/gCD	$[\alpha]_D^{20}$ ($CHCl_3$)	Solubility of hydrocortisone mg/mL[c]
Aliquat	1.18	115.3	4500
TEMED	0.61	125.5	3010
TEBA	0.85	115.2	4200
TBAB	0.23	117.2	3700
DB18C6[a]	1.17	131.8	3570
Sugar-crown[b]	0.91	121.1	3300

[a] Dibenzo-18-crown-6.

[b] Bisglucosido-18-crown-6. Refs. 22 and 23.

[c] Without RAMEB 470–510 mg/mL.

Table III shows a comparison of experiments in which different catalysts were used with THF as solvent together with solid KOH. Aliquat proved to be the most efficient catalyst, but dibenzo-18-crown-6 was scarcely inferior to it. The reactions catalysed by crown ethers yielded predominantly DIMEB. The optimisation of the other parameters has given the following reaction conditions: dimethyl sulphate is added to the reaction mixture at 20°C during a period of 2 h and the mixture is stirred for 4 h at 50°C.

Under these reaction conditions α- and γ-cyclodextrin were also methylated; the results are given in Table IV.

When β-cyclodextrin was methylated three times using the optimised method (without isolating the intermediate product), by adding fresh reagents after each step, pure TRIMEB was obtained with a yield of 28% after crystallisation.

TABLE IV. Methylation of cyclodextrins (THF solvent, Aliquat catalyst, KOH base).

Substrate	Me_2SO_4/CD	Yield, g/gCD	Solubility of hydrocortisone mg/mL*
α-CD	34	1.16	3400
β-CD	49	1.18	4500
γ-CD	48	0.86	3700

*Without RAMEB 470–510 mg/mL.

3.3. The Composition of the Product

The product (RAMEB) prepared in heterogeneous medium in the presence of a phase transfer catalyst has a heterogeneous composition. The ^{1}H-NMR spectra show that the product may also contain mono- and/or trimethylated components. TLC studies detect TRIMEB and the 3-6 monomethyl derivatives in addition to DIMEB as the main product.

Specific rotatory power is also insufficient to characterise the product. Values of $[\alpha]_D^{20}$ for TRIMEB and DIMEB are 159.6° and 122°, respectively, whereas those of the products of heterogeneous reactions vary between 114 and 136°.

The products have also been characterised by their methoxy numbers. The calculated methoxy number of TRIMEB is 45.3%, that of DIMEB is 32.6% and that of the pure industrial product is 31.7–32.8%. The methoxy content of our products varies between 29.1 and 30.9% (mean degree of methylation: 12.4 to 13.2), close to the value corresponding to two methoxy groups. Of course, these values are averages only; the fact that 21 hydroxy groups can be methylated leads to an enormous number of positional isomers, unless the product is fully methylated.

3.4. The Solubiliser Potency of the Products

There are some applications in which the homogeneity of methylated cyclodextrin is irrelevant. When they are used to solubilise certain hydrophobic substances, a mixture of isomers is sufficient in many cases, similar to the detergents in common use, for example. They can be characterised by average degrees of methylation: their most important property, however, is their ability to make certain hydrophobic substances hydrophilic.

The solubility enhancing effect of the heterogeneous mixtures of methylated β-cyclodextrins prepared by phase transfer catalysis was investigated on hydrocortisone, methyltestosterone (Figure 1) and piperonal substrates. A significant solubility enhancement could be observed in all cases: the water solubility of hydrocortisone, for example, was increased 5–9 times by the RAMEB product (the

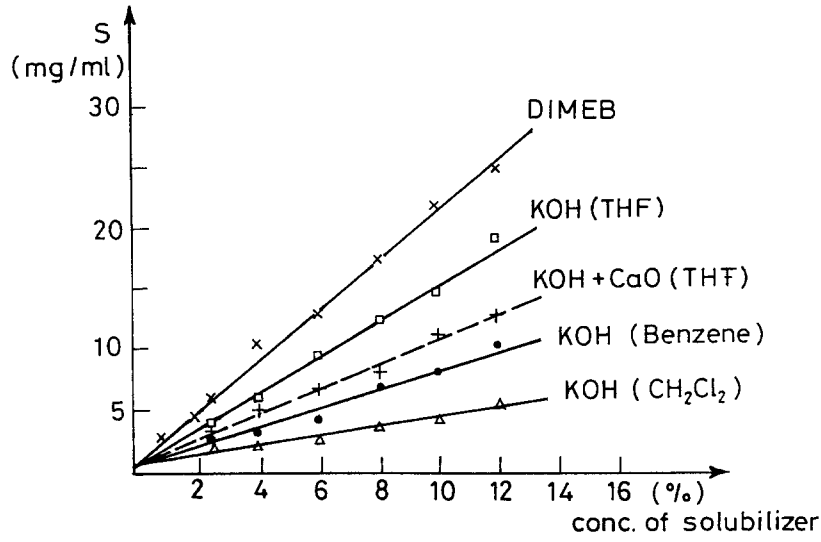

Fig. 1. Solubility isotherms of methyltestosterone with randomly methylated β-cyclodextrins (made by Aliquat catalyst) and with pure DIMEB at 25°C in water. The reaction conditions (base, solvents) are presented on the isotherms.

effect of pure DIMEB is 17 times). With all substrates, RAMEB prepared in the presence of Aliquat catalyst (KOH–THF in Figure 1) proved to be the most effective. Therefore, it appears that for certain technical purposes, like the conversion of hydrocortisone into prednisolone, methylated cyclodextrin mixtures can be used with advantage. The mixtures are heterogeneous but well defined in composition, their preparation is relatively simple and inexpensive by means of phase transfer catalysis.

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