CYCLODEXTRIN DERIVATISATION: DIRECTED REACTION OF SILYLATED INTERMEDIATES

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SUMMARY

Methods for the complete or partial (selective) silylation of β-cyclodextrin are described that provide intermediates for further derivatisation. The procedure is useful in directing reaction to previously functionalised centres affording material that is soluble in organic solvents, facilitating chromatographic separations and making possible structural assignments for the product macromolecules by proton NMR spectroscopy.

The method is applied to the sequential attachment and attempted capping of β-cyclodextrin by a porphyrin template. The product conjugate was found to be hydrolytically unstable. Representative proton NMR spectra for a series of silyl derivatives and intermediates are analysed to demonstrate further the advantage of the method.

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INTRODUCTION

The host-guest capability of the cyclodextrins has resulted in their extensive employment as models for receptor binding and enzymatic catalysis, either as the parent cage molecule [1-3] or after derivatisation [4-7]. Their chemical modification for the incorporation of catalytic centres of other functionalities is complicated by the inherent physical and chemical properties of the oligosaccharide class. Thus they are hydrolytically unstable and are soluble only in relatively polar solvents [8].

Equally important is the probable lack of selectivity achievable by partial functionalisation of the cage molecule because of positional isomerism. Cage modification has to proceed at the 2,3- and 6-hydroxyl groups of the glucose molecules by derivatisation and/or displacement reactions, and in the absence of a directing influence a large (statistical) number of products can result. There have been many spectacular claims for selective modifications of the cyclodextrin molecule, and the more respectable and proven methods are summarised in Figure 1. The principal modifications to the cyclodextrin cage shown in Figure 1 can be classified as:

1. Alkylation (formation of O-C or O-Si derivatives)
2. Sulphonation or acylation (O-SO_2R or O-COR)
3. Substitution (by nucleophiles to give -NR_2, -SR, -X, -N_3 functionalities) of sulphonyl (e.g. tosylate) derivatives.

Practical problems encountered in these transformations can be summarised as being due to:

1. Use of aqueous or polar solvents (DMF, DMSO etc.) to solubilise parent or partially substituted cyclodextrins.
2. Restrictive choice in chemical functionalisation methods imposed by solvent, and cyclodextrin hydrolytic instability.
3. Comparatively few techniques to direct partial functionalisation.
4. Tidious and scale-limited chromatographic purifications on reaction product mixtures.
5. Assessing the degree of reaction and location of reacted centres on the cyclodextrin skeleton by nmr (^1H or ^13C or by mass spectrometric methods.
6. Escalating costs in sequential transformations.
7. Product instability [proximity of underivatised hydroxy groups accelerates hydrolysis of (e.g.) acyl derivatives].
8. Misleading claims in the literature of selective or efficient derivatisation.