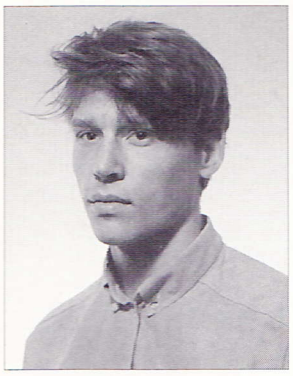
Synthesis of α,α-trehalose analogues

Tor E.C.L. Rønnow

Carlsberg Laboratory, Copenhagen, Denmark



The thesis titled 'Synthesis of α,α-trehalose analogues' describes the reaseach performed by Dr. Tor E.C.L. Rønnow at the Carlsberg Laboratory in Copenhagen under the supervision of Prof. Klaus Bock and Dr. Morten Meldal .

The goal of this project was to synthesize a variety of analogues of the sugar α,α-trehalose. α,α-Trehalose is a naturally-occurring, non-reducing disaccharide with significant biological functions. It stabilizes proteins, lipid membranes and other biomolecules in so-called anhydrobiotic organisms, which can survive almost complete desiccation for long periods of time. The molecular basis for this phenomenon is not yet known in detail. **The unique properties of α,α-trehalose may be investigated by comparison with synthetic analogues.** By creating variations in stereochemistry, oxidation level, atomic composition, and charge, one could hopefully gain some insight into the key features in the stabilization phenomena.

An introductionary chapter in the thesis provides general back-ground information about α,α-trehalose. Its natural occurrence, structure, some physico-chemical properties, and the chemical synthesis of the sugar are described. The phenomenon of anhydrobiosis is explained and an overview of various potential industrial applications of α,α-trehalose is given, emphasizing the importance of the stabilizing effect this sugar may have on biomolecules and biological material.

α,α-Trehalose analogues can be synthesized by two conceptually distinct methods: 1) by coupling of monosaccharide derivatives under suitable conditions, and 2) by chemical modification of α,α-trehalose itself. Compounds synthesized during the work using the latter method include α,α-galacto-trehalose, some deoxy-trehaloses, and α,α-trehalose 6-monophosphate and α,α-trehalose 6,6′-diphosphate. These two sugar phosphates were conveniently synthesized in gram-scale by phosphorylation of the corresponding heptakis- and hexakis-*O*-trimethylsilyl-α,α-trehalose derivatives, followed by hydrolysis. These two sugar phosphates are also of biochemical interest, because α,α-trehalose 6-monophosphate is an intermediate in the biosynthetic pathway of α,α-trehalose.

Regarding the coupling of monosaccharide units, a thorough investigation of the coupling of some glycosyl bromides with tetra-*O*-benzylated monosaccharides has been carried out. Importantly, the crude reaction mixtures have been characterized by ^{13}C-NMR spectroscopy. It has been shown that trehalose derivatives can be synthesized under strongly acidic conditions using AgOTf as the promoter. However, the *inherent* formation of dimerization by-products limits the scope of the reaction as an expedient method for obtaining larger amounts unsymmetrical trehalose derivatives.

Glycosyl trichloroacetimidates were, however, successfully used as glycosyl donors in reactions leading to unsymmetrical trehalose derivatives in high yields. These glycosylation reactions are less hampered by the formation of dimerization by-products than the silver triflate promoted reactions. Thus it should be possible to separate and isolate the individual product isomers in higher yields. Furthermore, it has been shown that by proper choice of reactants, trehalose analogues can be synthesized with significant stereoselectively. Lastly, the successful glycosylation of a hepta-benzoylated maltose hemiacetal derivative demonstrated that trichloroacetimidates can glycosylate even very unreactive glycosyl acceptors in reactions affording trehalose-containing oligosaccharide derivatives.

On the whole, a large variety of α,α-trehalose analogues were synthesized during this study, and the thesis presents the results in a professional and clear manner.