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Carbohydrates—A Hostile Scientific Frontier Becomes Friendlier

I believe it was George Bernard Shaw who was asked if he knew that "sugar" was the only word in the English language where "su" was pronounced "sh". He replied, "Sure". Sugars remain ubiquitous yet enigmatic, combining the simple with the complex. Carbohydrates are everywhere, from bulk sucrose in the kitchen to cross-linked peptidoglycans that comprise cell walls, from microdiverse, post-transcriptionally modified cell-surface receptors to the paper that this issue is printed on. Carbohydrates have often been relegated to the sidelines of chemistry, one example being the complete omission of essential and challenging sugar portions from many papers on "natural product synthesis". One can almost hear the collective sigh, "Difficult chemistry, difficult biology, difficult analysis, I don't want to see another protecting group, let's leave the sugar off".

In sharp contrast to the lack of attention that carbohydrates receive among the broader community, the fundamental scientific and medical importance of glycochemistry/glycobiology has lead to a dedicated and concerted attack on the field by an increasing number of pioneering research groups. Their work has lead to major advances in such diverse subjects as chemical synthesis, analytical chemistry, structural biology, and cell-surface recognition. At a time when carbohydrates should be embraced by the scientific community with ever increasing vigor, I am delighted to present reviews from some of the leading carbohydrate research groups in this thematic issue. Of course, these reviews build on decades of previous pioneering work, as cited in the introductions to each paper. The purpose of this issue is to bring together a wide range of state-of-the art reviews of synthetic, analytical, physical, and biological studies of carbohydrates in a single volume. A second thematic issue is planned in which more emphasis will be placed on biochemical/biological studies. I provide brief synopses of most of the articles here to set the stage.

We have often depended on amino acids and certain key sugars for a pool of chiral chemical reagents. Hollingsworth and Wang review how we can increasingly exploit the utility of carbohydrates as a highly diverse source of chirons (chiral synthons) for general asymmetric synthesis. Steinborn and Junicke review the diversity of structures formed when platinum-group metals are bound to carbohydrates.

The basic building blocks of polypeptides and polynucleotides have long been available for routine and advanced studies, as have elegant solution and solid-phase methods for preparing specific peptide or nucleotide sequences. Furthermore, synthetic analogs of natural amino acids, peptides, and nucleic acids have been invaluable in medicinal chemistry and biochemistry, while biotechnology and chemistry require ever more complex nucleotide derivatives. Hence, Ferrero and Gotor review biocatalytic modifications of nucleosides, carbocyclic nucleosides, and *C*-nucleosides. Solid-phase methods for oligosaccharide synthesis and combinatorial libraries are described by Seeberger and Haase. Synthetic approaches to artificial glycopeptides are described by Dondoni and Marra.

Since the proper linkage of carbohydrate subunits is of critical importance to structure and function, we have a number of contributions in this area. Jung, Müller, and Schmidt describe intramolecular *O*-glycoside bond formation, which offers the opportunity to control the regio- and stereochemistry of glycosylation. Hanessian and Lou report on "Stereocontrolled Glycosyl Transfer Reactions with Unprotected Glycosyl Donors". As anyone who has done carbohydrate synthesis will immediately recognize, the ability to use unprotected building blocks eliminates many of the time- and yield-consuming steps that plague traditional methods.

Nature certainly constructs carbohydrates as needed, no matter how complex, using a mixture of elongation, branching, and selective digestion steps. The ability to prepare specific glycopeptide constructs with recognition motifs in both the peptide and carbohydrate portions will allow many biologically important questions to be probed at the molecular level. Koeller and Wong describe enzyme-based strategies for the synthesis of both carbohydrates and glycoconjugates, and they offer an attractive set of programmable, "one-pot" strategies. Herzner, Reipen, Schultz, and Kunz provide a complementary, comprehensive review of general glycoconjugate synthesis. Sialic acids are a particular yet diverse class of 2-keto acids that includes neuraminic acid, which is

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found in oligosaccharides, glycoproteins, and glycolipids. Boons and Demchenko provide a detailed review of recent advances in synthetic methods of *O*-sialylation.

Molecular modeling of carbohydrates is a complex field, given the challenges of their polydimensional conformational space. The links between solution and crystal structures of oligosaccharides can be clarified by modeling using methods reviewed by Imberty and Pérez.

NMR is a powerful and direct experimental method of examining carbohydrate structures in solution. Modern methods and their limitations are reviewed by Duus, Gotfredsen, and Bock. Their report includes a technical discussion of how to handle small amounts of complex samples.

The metabolism of carbohydrates is not a new subject by any means, forming as it does part of what we consider to be basic biology and chemistry. Yet, as described by He, Agnihotri, and Liu, many novel enzyme mechanisms for carbohydrate metabolism have been recently determined.

The complex molecules known as polyglycosylceramides (PGCs) are highly glycosylated sphingolipids that participate in cell-surface binding, including the polyvalent binding interactions whose importance is being increasingly recognized. The properties, structures, preparation, and analyses of PGCs are described by H. Miller-Podraza. In a related article, Butters, Dwek, and Platt review the inhibition of glycosphingolipid biosynthesis and its relationship to lysosomal storage disorders.

Protein folding is often assisted by chaperones and controlled by post-transcriptional modifications. *N*-Glycosylation is a co-translational process that can occur during translocation of a protein into the endoplasmic reticulum. *N*-Glycosylation appears to assist chaperones with protein folding. Branza-Nichita, Petrescu, Negroiu, Dwek, and Petrescu review this exciting glycobiology, with emphasis on tyrosinases, which are important glycoproteins found in melanoma and other cancer cells.

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