Editorial

Glycochemistry Today

Carbohydrates (or saccharides) with the empirical formula $C_m(H_2O)_n$ are hydrates of carbon that can be divided into several chemical groupings including the monosaccharides, the disaccharides, the oligosaccharides and the polysaccharides. The word saccharide comes from the Greek word 'sákkharon' meaning 'sugar'. Monosaccharides are in fact polyhydroxyaldehydes or polyhydroxyketones. Formally formaldehyde (CH_2O) and hydroxyacetaldehyde ($HOCH_2CHO$) can be seen as the smallest monosaccharides; then the trioses D- and L-glyceraldehyde ($HOCH_2$-CH(OH)-CHO) and dihydroxyacetone ($HOCH_2COCH_2OH$), the tetroses L- and D-erythose and -threose, the pentoses such as D- and L-arabinose, -lyxose, -xylose and -ribose, the hexoses, *etc.* … The most abundant saccharides are D- and L-arabinose, D-ribose, D-fructose, D-glucose, D-galactose, D-mannose, D-glucosamine and L-rhamnose which constitute biomass. These sugars represent a sustainable source of energy and carbon-containing materials.[1] After the pioneering and fundamental work of Emil Fisher on carbohydrates[2] synthetic chemists had a hard time with carbohydrate chemistry because of the multifunctional character of carbohydrates, their complicated stereochemistry and the difficulty to obtain crystalline derivatives. When it became obvious that drugs and crop protection chemicals could not be applied as racemic mixtures, sugars became an obvious source of starting materials for asymmetric synthesis (the 'chiron approach'[3]). For a long time carbohydrate roles in living species were considered to be just the energy source (starch, glycogen) and structural components (cellulose in plants, chitin in arthropods). D-Ribose is in fact the backbone of RNA and a component of coenzymes such as ATP, FAD and NAD, essential for life. The related 2-deoxyribose is a component of DNA. For the last 30 years biologists have realized that oligosaccharides and glycans (polysaccharides) are major cellular macromolecules associated with a variety of important biological phenomena, including antigen-antibody interaction (immunization[4]), fertilization,[5] blood clotting,[6] organ development,[7] cancer development and inflammation.[8] Thus carbohydrates and their conjugates with protein and lipids (glyco-conjugates) are the next frontier in pharmaceutical research.[9]

The complexity of oligosaccharides (the 'sugar code') is much higher than that of the other major cellular macromolecules like DNA, RNA and proteins because a monosaccharide can connect to another monosaccharide forming α- or β-1→1, 1→2, 1→3, *etc*. acetal linkages for pyranosides and furanosides. For example, the most common sugars D-glucose and D-mannose can link to form 80 different disaccharides, whereas two different amino acids generate only two different peptides.[10] Furthermore, two or more monosaccharides can glycosylate a single monosaccharide generating branch-shaped extensions. In a computer science sense, glycans can be trees, consisting of nodes and edges. The current number of structurally different determined oligosaccharides and glycans surpasses 10'000. This special issue of CHIMIA starts with an article by ***Mamitsuka*** showing how glycoinformatics[11] has become a computer science in itself.

For a long time, heparin and low molecular weight heparins have been the drugs of choice to treat thromboses, but not without serious and dangerous side effects. The fully synthetic pentasaccharide Fondaparinux™ that selectively targets blood coagulant factor Xa has been used with success and thus has demonstrated the fantastic potential of glyco-drugs. This was followed by heparin analogues mimicking oligosaccharides with no unwanted side effects as described in the article of ***El Hadri and Petitou***. Chemists have developed original hybrid molecules that target specific immune cell receptors. This has led to the first example of a commercial vaccine entirely prepared from synthetic oligosaccharide antigens against infections caused by *Haemophilus influenza* type b responsible for pneumonia and acute bacterial meningitis in children, as reported by ***Roy and Shiao***. Tumor cells exhibit at their surface glyco-proteins with aberrant glycosylation patterns[12] and are thus recognized by the immune system in healthy patients. To stimulate the immune system to combat cancer cells better carbohydrate vaccines are being developed for the active immunotherapy of cancer[13] as illustrated by the article of ***Westerlind and Kunz***. The galectin family of β-galactoside-binding proteins play important roles in several biological mechanisms including inflammation and cancer progression. ***Öberg, Leffler and Nilsson*** have discovered small-molecule galectin inhibitors with low nM affinities: this opens opportunities for the development of new drugs to treat cancer.

Glycosylation and deglycosylation of a nascent protein contribute to generate its final conformation, and thus its ultimate function in cellular life. These reactions are catalyzed by enzymes called glycosyltransferases and glycosidases. Inhibitors of glycosidases are potential drugs to treat a number of human disorders. Iminosugars (1,n-dideoxy-1,n-iminoalditols such as polyhydroxypyrrolidines, polyhydroxypiperidines and analogues) are good and specific inhibitors of glycosidases. They are potential drugs to treat diseases such as liposomal disorders, diabetes, cystic fibrosis, viral pathogenesis and cancer as illustrated by the article of ***Alonzi and Butters***. An account by ***Moreno-Clavijo et al.*** describes the role of α-L-fucosidases and the syntheses of inhibitors of these enzymes.

Carbohydrates and glycomimetics are not only potential drugs for human diseases but can be useful and more sustainable agents for crop protection and growth boosters. This is shown by an article by ***Beau*** for lipo-chitooligosaccharidic modulation factors and by an account by ***Behr*** on the recent advances on the search for inhibitors of chitin synthase, a fungal glycosyltransferase. Most pharmaceutical companies have not given priority to the glyco-drugs because of the too complicated chemistry they imply for their preparation, especially since the construction of oligosaccharides has long been impeded by two major challenges: i) the regioselective semi-protection of the polyol moiety of monosaccharides to generate suitable glycosyl acceptors and ii) the stereoselectivity of the glycosidation step by an adequately protected and activated glycosyl donor. On this front substantial progress is being realized, especially by the invention of new, one-pot regioselective protection and protection-glycosidation protocols, as illustrated by the account of ***Hung and coworkers***. In the case of difficult β-glycosidation with L-rhamnose new and elegant solutions have been proposed by ***Picard and Crich***. Alternatively, when chemical glycosidation falls short, glycosidases and their mutants can now be used to carry out high yielding glycosidations with unprotected glycosyl donors as illustrated by ***Bojarová and Křen***.

Abundant monosaccharides such as D-glucose, D-mannose and D-galactose are useful synthetic intermediates for the preparation of bioactive compounds. This is illustrated by the review of ***Jenkinson and Fleet*** for the synthesis of oxetane nucleosides, oxetane aminoacids and peptidomimetics. New chiral and enantiomerically pure ionic liquids have been derived from inexpensive sugars as illustrated in an article by ***Marra et al***. With the urgent necessity to save oil and coal reserves, inexpensive polysaccharides such as alginates, carrageenans and chitosan extracted from seaweeds are becoming valuable supports for sensors, absorbents and catalysts, as described by ***Robitzer and Quignard***.
Since the discovery of the 'formose reaction' (n $CH_2O \rightarrow C_nH_{2n}O_n$) by Butlerow[14] in 1861, total synthesis of carbohydrates and analogues has made substantial progress. Nowadays any natural and non-natural monosaccharide can be prepared in both its enantiomerically pure forms starting from inexpensive starting materials. The methods apply chemical as well as biochemical catalysis as summarized in an article by ***Robina et al.*** The total asymmetric syntheses can start from simple achiral unsaturated compounds as highlighted by ***Moreno-Vargas et al***.
The guest editor wishes to thank the contributors to this special issue of CHIMIA dedicated to glycochemistry. They describe the state of the art and will convince the reader that carbohydrates have a fantastic future in medicine, biology and material sciences. Preparative chemistry based on carbohydrates contributes to a more sustainable world.[1]

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