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Foreword

The present thematic issue *Molecular Modeling of Carbohydrates* consists of 11 papers, most of which are based on lectures presented at a one-day symposium held in Grenoble on Sunday, July 6th 2003. On the occasion of this satellite meeting of Eurocarb12, 75 scientists were gathered at the CERMAV building on the picturesque campus of Joseph Fourier University surrounded by the High Alps. Considering the number of participants and the active participation of all, the workshop can be considered as a success. It illustrates the maturity that has now been reached by computational approaches in the field of carbohydrates and fully justifies a special issue of *Carbohydrate Research* devoted to this subject.

For this symposium special issue, an attempt has been made to cover very different aspects of modeling, and this is reflected in the collection of papers. The following fields are covered: (i) evaluation of methods for conformational analysis of oligosaccharides of various sizes; (ii) conformational properties of large polysaccharides; (iii) interaction of glycans with other molecules such as proteins and ions; (iv) substrate recognition and catalytic mechanism of glycosyltransferases; (v) development of web-based databases and other internet-based resources.

The methodology aspects cover both the validation of different force fields and the evaluation of various methods for exploring the conformational space of oligosaccharides. The quantitative evaluation of 20 force fields by the use of ab initio calculations has been performed on monosaccharides, pointing out the weakest and strongest points of the available molecular mechanics approaches currently used. One of the difficulties in modeling carbohydrates arises from the flexibility of the glycosidic linkages and from the presence of hydroxyl groups that are involved in intra- and intermolecular hydrogen bonds. This results in a large number of possible conformers for oligosaccharides, the equilibrium of which strongly depends on the environment. Depending on the size of molecules, different search engines can be used. The three papers that describe conformational analysis of oligosaccharides, polysaccharides and glycoconjugates perfectly illustrate the wide range of methods now available, covering molecular dynamics, Monte Carlo approach, heuristic search and filtered grid search. This latest method was applied for modeling complex branched bacterial **polysaccharides** and could predict stable helical conformations adopted by these polymers.

Interactions between carbohydrates and proteins are illustrated in two papers, one being a review with high educational value that should be useful for students and researcher embarking in the field. Interaction between carbohydrates and proteins, as well as between charged polysaccharides and cations, can be approached by new advanced NMR experiments such as transfer NOE and saturation transfer NMR. Nevertheless, the present studies clearly demonstrate that these sophisticated experimental approaches have to be combined with molecular modeling in order to construct structural models of interacting molecules.

Two articles are devoted to **glycosyltransferases**, a class of enzymes for which structural data are still sparse. From the crystal structure of a bacterial α-galactosyltransferase complexed with its substrates, DFT quantum chemical calculations give insight into the catalytic mechanism. The same structure is used as a starting point for a molecular dynamics study that visualized the loop opening correlated to substrate binding in these enzymes.

Although "glycomics" has not yet generated as much information as genomics or proteomics, a large amount of data are now available in the form of **web-based databases and tools**. An overview of the resources currently available is of general interest, and a review article covers this field. There is no doubt that more and more tools will be freely available in the future for analyzing, building and modeling oligo- and polysaccharides.

The general impression from the present collection of papers is in total agreement with the conclusions that were

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reached during the round-table discussion that closed the one-day symposium in Grenoble. Molecular modeling of carbohydrates continues towards larger and larger systems and more and more complex models including explicit solvents, interactions with proteins and reaction mechanisms in hybrid QM/MM molecular dynamics systems. Not surprisingly, this tendency can be extrapolated from the past decades of continuously and exponentially improving computer power. In the meantime, the level of theory required to perform realistic first principle calculations of carbohydrates will continuously increase as well. Today, calculations of the relaxed potential energy surfaces and a single point calculation of a disaccharide unit are approximately the practical limits for performing DFT calculations and coupled cluster calculations at a reasonably (high) theoretical level, respectively. We therefore need to continue to develop and refine more pragmatic modeling approaches such as molecular mechanics and hybrid quantum mechanics/molecular mechanics methods. They will be indispensable in the foreseeable future for modeling large systems including amorphous condensed phase systems, explicitly hydrated systems and carbohydrates interactions with proteins and enzymes.

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