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**Advances in  
Carbohydrate Chemistry and Biochemistry**

Volume 66

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## PREFACE

In this 66th volume of *Advances*, an extended tribute to the life and work of Anthony C. Richardson (Dick) is provided by Hale (Belfast). In the present day, when the successful young academic usually expects to abandon the laboratory bench and progress to become the leader of a large research group, Richardson was an anomaly in remaining an outstanding synthetic chemist who spent his entire career doing the laboratory work he loved. He had a brilliant and incisive mind coupled with a warm and nurturing personality, but he never sought the limelight or public recognition beyond the satisfaction from working with a small group and achieving a remarkable range of accomplishments in carbohydrate synthesis. These justly merit the extended documentation presented here in Hale's account. From elegantly conceived syntheses of (–)-swainsonine to Richardson's rules for predicting the outcome of sulfonate displacement by nucleophiles, to the noncaloric sucrose-derived sweetener Splenda® (trichloro-galacto-sucrose) with the Hough laboratory, and the provision of many valuable synthetic intermediates, he has enriched the carbohydrate field with a very substantial legacy.

The coordination behavior of sugars and their derivatives with inorganic cations has been largely "under the radar" of mainstream carbohydrate science in recent years, given the strong focus of many of today's researchers on glycobiology targets. However, the complexation of carbohydrate derivatives with the element chromium, in particular, has important implications in both human and animal health, and in problems of environmental damage from industrial pollutants. The toxicity and carcinogenicity of chromium is well recognized, and the use of microorganisms or plants for bioremediation of contaminated soils requires careful evaluation. The unpaired d-subshell electrons in the multiple valence states exhibited by chromium lend themselves ideally to studies of the complexes by electron paramagnetic resonance. This chapter by Sala and colleagues (Rosario, Argentina) details current knowledge gleaned from use of traditional continuous-wave EPR spectrometers and addresses the potential of newer pulsed and high-field instruments for significant advancement of our understanding.

While the pyranose and furanose ring forms of the sugars dominate the carbohydrate literature, the uncommon septanose ring forms have long intrigued sugar chemists, with particularly notable contributions by Stevens in Australia. The chapter in this volume from Saha and Peczuh (Storrs, Connecticut) provides a comprehensive overview of the subject from both the synthetic and structural viewpoints and presents a detailed analysis of the conformational behavior of these ring forms. It may be noted

that the structures of the seven-membered rings and their acyclic precursors are most conveniently depicted, respectively, by Mills-type formulas and the supposedly old-fashioned Fischer-type formulas, rather than the Haworth conformational formulas commonly favored for five- and six-membered rings. This chapter offers intriguing prospects for involvement of these ring forms in biological applications, especially with regard to antisense oligonucleotides.

A most important variant of the monosaccharide structures is the class of sugar derivatives wherein nitrogen replaces the ring-oxygen atom, namely, the imino sugars. In the comprehensive overview presented here by Stütz and Wrodnigg (Graz, Austria), they integrate the wide range of imino sugar analogues now known to occur in Nature with their remarkable functions as potent inhibitors of the glycosidase enzymes. Complementary work on numerous synthetic analogues has added important new understanding of the mode of action of glycosidases in general. The authors include a detailed structural tabulation of all such inhibitors currently known, along with the Protein Data Bank links to the enzymes that they inhibit, and offer exciting prospects for the therapeutic potential of these inhibitors in modulating essential metabolic processes.

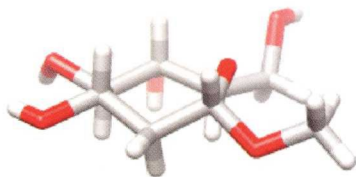
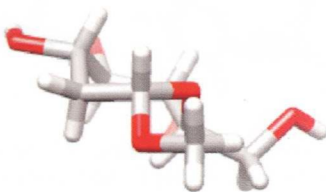
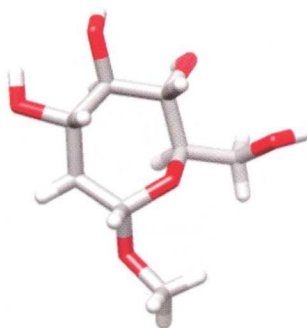
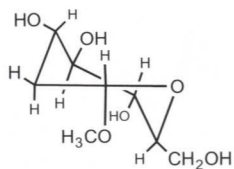
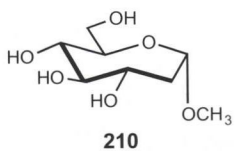
The deaths are noted with regret of two leading carbohydrate biochemists, Nathan Sharon (June 17, 2011) and Saul Roseman (July 2, 2011). Dr. Sharon served with distinction for many years as a member of the Board of Advisors of this *Advances* series, and his advice and input will be sadly missed. His work will be recognized in an upcoming volume of the series.

With this volume Professor Arnold E. Stütz is welcomed as a new member of the Board of Advisors.

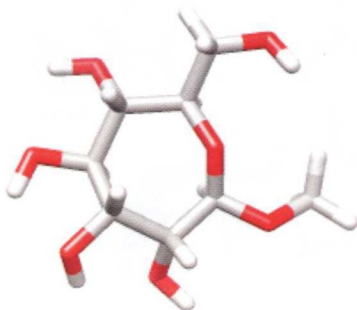
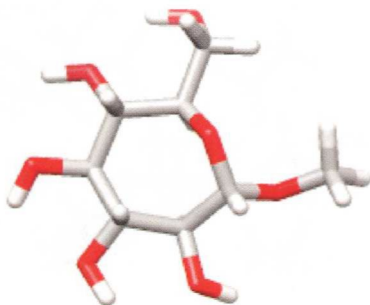
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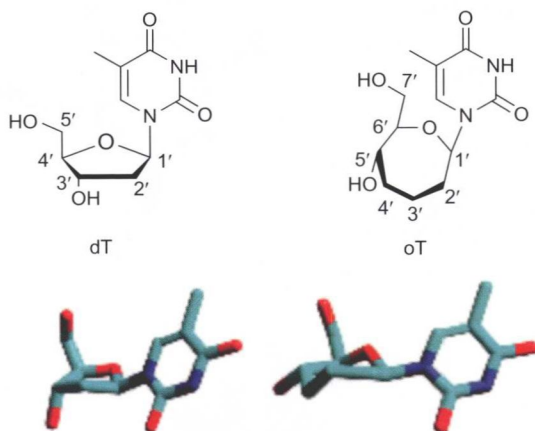


**PLATE 1** Different perspectives of the methyl 2-deoxy- $\alpha$ -D-gluco-septanoside (**210**) structure from X-ray data.

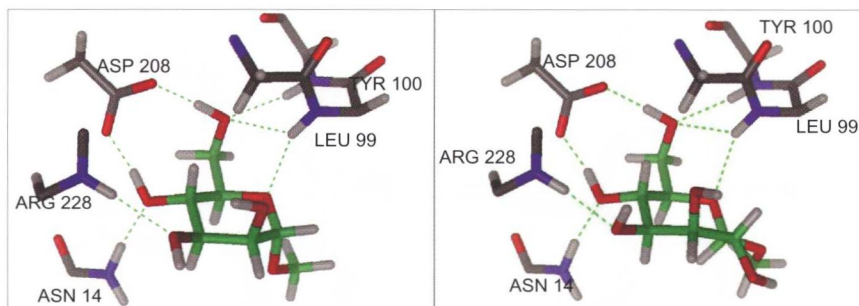


**PLATE 2** Computed low-energy conformations of methyl septanosides. Left: Methyl  $\alpha$ -D-glycero-D-ido-septanoside (conf 36); Right: Methyl  $\beta$ -D-glycero-D-gulo-septanoside (conf 1).

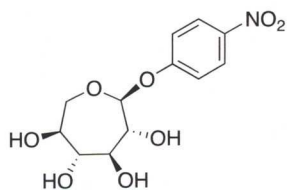




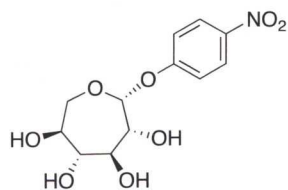
**PLATE 3** Thymidine (dT) and an oxepanyl analogue (oT). Structures on the bottom (taken from ref. 149) show minimized conformers for both dT and oT, emphasizing the similarity in the disposition of the base and the C-4/C-6 hydroxymethyl group.



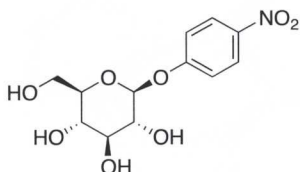
**PLATE 4** Detail of the monosaccharide binding pocket with (left) pyranoside ligand **237** and (right) septanoside ligand **208** as determined from the QM/MM computations (taken from ref. 124).



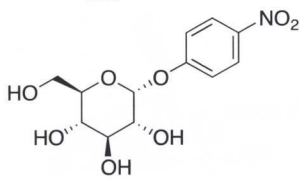
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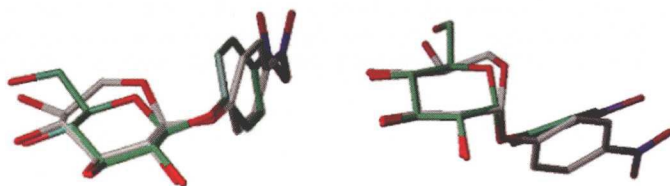
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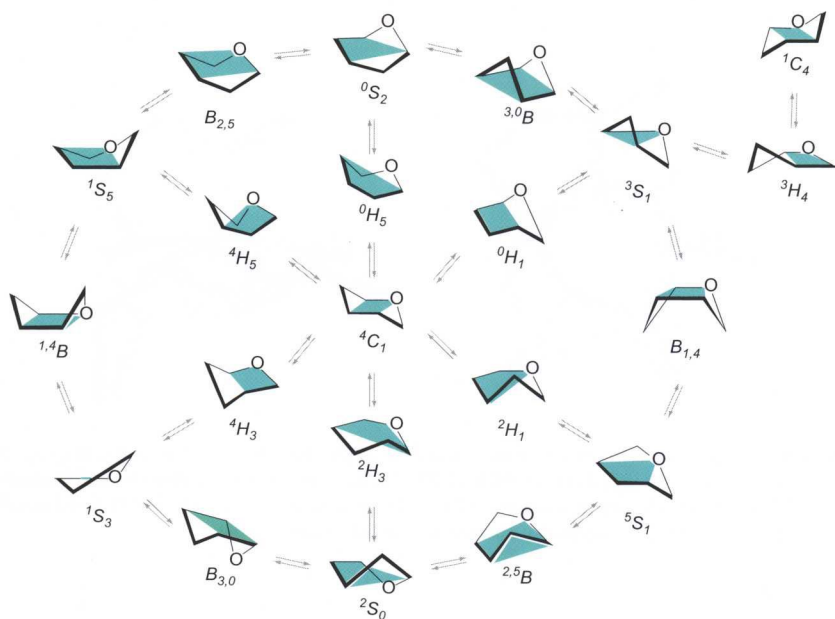
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**242**



**PLATE 5** Top: *p*-Nitrophenyl L-idoseptanosides **239** and **240** used to mimic D-glucopyranosides **241** and **242** as substrates for glycosidases. Bottom: Overlays of minimized structures. Left is the overlay of **239** with **240** and right is the overlay of **240** with **242** (taken from ref. 164).



**PLATE 6** View at “GPS,” the “Globe of Pyranoid Sugar conformations.”<sup>244</sup>



**PLATE 7** Superposition of ligands 1-deoxynojirimycin **2** (yellow, PDB 2J77) and castanospermine **8** (green, PDB 2CBU) bound to *Thermotoga maritima*  $\beta$ -glucosidase. The ring nitrogen atoms, all hydroxyl groups in the pyranoid rings, as well as O-1 (**8**) and the primary O-6 (**2**), respectively, are closely matched.



**PLATE 8** Superposition from two different viewpoints of the ligands castanospermine, **8** (gray, PDB 2PWG) and 1-deoxynojirimycin **2** (green, PDB 2PWD) bound to trehalulose synthase from *Pseudomonas mesoacidophila* MX-45. The lateral inversion of **2** relative to the pyranoid ring of **8**, with O-6 of **2** matching O-6 (corresponding to O-2 in carbohydrate numbering) of **8** is clearly visible.

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**ANTHONY CHARLES RICHARDSON**

(1935–2011)

Anthony Charles Richardson won universal respect, admiration, and distinction as a chemist for the many pioneering research contributions that he made to synthetic carbohydrate chemistry and natural product total synthesis over an illustrious 40-year career. His coauthorship, with Leslie Hough, of the now legendary treatise *Rodd's Chemistry of Carbon Compounds, 2nd Edition Vol 1F* also earned him a place in chemical history because of the highly authoritative coverage it provided of the entire field of monosaccharide chemistry, all the way back to Emil Fischer's time. Even today, more than 44 years after it was first written, the Hough–Richardson 595-page chemistry monograph remains one of the primary reference sources for all literature on monosaccharide chemistry published before 1967. It continues to be relied upon by modern generations of organic chemists for the accurate and detailed information it provides. In many ways, *Rodd's 2nd Edition Vol 1F* has become the monosaccharide chemist's Bible, because of the remarkable insights it expounds and the confidence and trust that users can place in the accuracy of its content. The integrity of judgment displayed by both authors in deciding what to omit and what to include helped to create an enduring and significant scholarly work.

The numerous excellent synthetic procedures published by A.C. Richardson also continue to be relied upon by contemporary organic chemists because of their great practicality and reproducibility. Indeed, a recent highly cited enantiospecific total synthesis of the antitumor agent, (–)-agelastatin A, justly testifies to this fact; it exploits the remarkably useful Hough–Richardson aziridine as a key synthetic intermediate in the eventual published route to this complex natural product.

Society has also greatly benefitted from A.C. Richardson's research, most especially from his discovery (with Les Hough, Anthony Fairclough, and Shashi Phadnis) of the noncaloric, high-intensity sweetener known as 4,1',6'-trichloro-4,1',6'-tri-deoxy-galacto-sucrose (TGS, sucralose), which is now sold globally under the commercial name of "Splenda." In a time of increasing obesity and high incidence of



dental disease, this outstanding research contribution is now helping to counteract the development, progression, and spread of several lifestyle diseases that currently contribute significantly to morbidity in the modern world.

Richardson also devised many novel reagents and chromogenic substances that are now used in various diagnostic kits of value for the rapid and accurate visual detection of human disease, as well as for the identification of pathogenic organisms associated with disease. For chemical posterity, it is therefore considered important to present a detailed account of Richardson's numerous research contributions.

A.C. Richardson (more commonly known as "Dick" Richardson in carbohydrate chemistry circles, or just plain "Tony" to his family and friends) was born in Catford, southeast London, on April 21, 1935. His father, Charles Richardson, was a mechanical engineer who worked at a nearby aeronautical factory, having diverged from the long-standing family tradition of working as London chimneysweeps to adopt a profession that was far less hazardous and which offered greater opportunities for originality of thought and personal creativity. His mother, Doris Richardson (née Doris White), worked as a milliner. Although Richardson's parents were working class and did not themselves benefit from a University education, they did still appreciate the career opportunities that such an education could offer. They therefore went to great lengths to encourage their young son, Anthony, and his elder sister, June, to work industriously and excel academically to achieve eminence in whatever field/discipline they ultimately chose to pursue. In Richardson's case, he entered the world of synthetic carbohydrate chemistry, and what a major turning point that proved to be for the development of this branch of the subject!

A.C. Richardson's early childhood was like that of many other young boys who grew up in southeast London as World War II began. The sustained aerial "Blitz" against the city led to many of the nation's children being evacuated to more-rural parts of the country having lesser commercial and military significance. In young Richardson's case, it led to separation of him at the tender age of 4, along with his sister, June, from their parents, and they were evacuated to Exeter, in the southwest of England. Despite the upheaval, trauma, and worry that this undoubtedly must have caused, young Richardson still managed to excel academically at school. By the time he left Exeter in 1945, his teachers lamented to his rather stunned parents over the great loss to the school of its "star pupil"!

Not long after he returned to London, Richardson passed the all-important 11-plus examination with flying colors to win a much sought-after place at Brockley County Grammar School, where he remained until he was 18. He left Brockley Grammar in 1953 to take up an undergraduate place at the University of Bristol, where he read Chemistry. It was there that he met his future mentor and lifelong colleague, Professor