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Profile

RAYMOND U. LEMIEUX
by O. Hindsgaul and D. R. Bundle

Raymond Urgel Lemieux was born in Lac la Biche, Alberta, Canada, on 16 June, 1920. He received his B.Sc. degree from the University of Alberta in 1943 and moved east to obtain his Ph.D. degree under the supervision of Clifford B. Purves at the Chemistry Department of McGill University in 1946. He then did a post-doctoral internship with the famous American carbohydrate chemist Melvin Wolform, at the Ohio State University, before accepting a position as Research Officer at the Prairie Regional Laboratory of the National Research Council of Canada, located in Saskatoon, Saskatchewan, in 1947. That is where he began his independent research career.

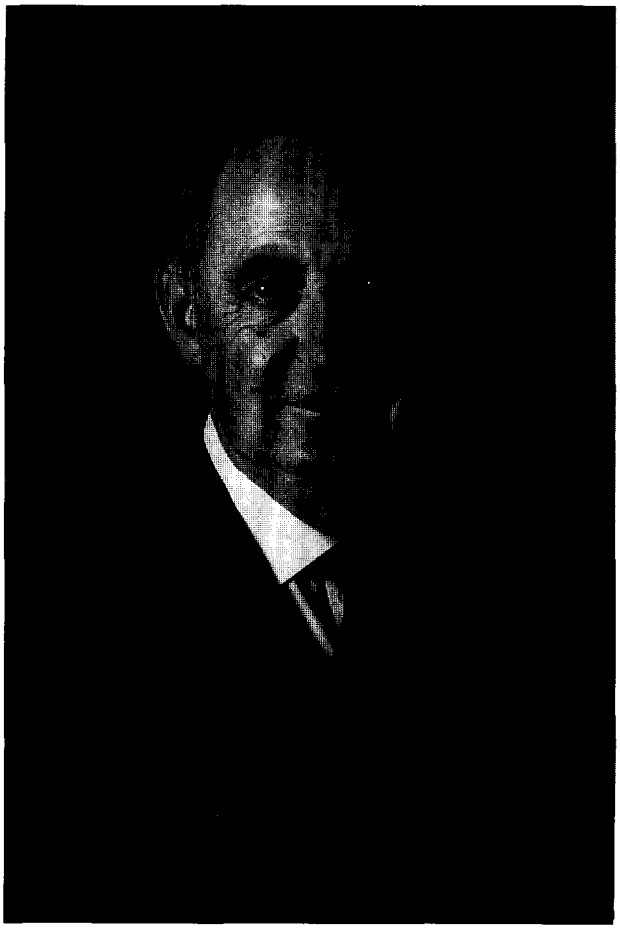
'Ray', or 'Sugar-Ray' as many of his friends have called him, eventually moved to academia in Ottawa where he was recruited in 1954 to build a new Chemistry Department at the University. He moved once more in 1961 to the Chemistry Department at the University of Alberta in Edmonton where he finally 'stayed-put'. He remained at the University but had a keen interest in the business aspects of chemistry and founded three companies during his career: R&L Molecular Research, Raylo Chemicals and Chembiomed Ltd, to attempt to capitalize on the breakthroughs occurring frequently in his own research program on antibiotics and complex carbohydrates.

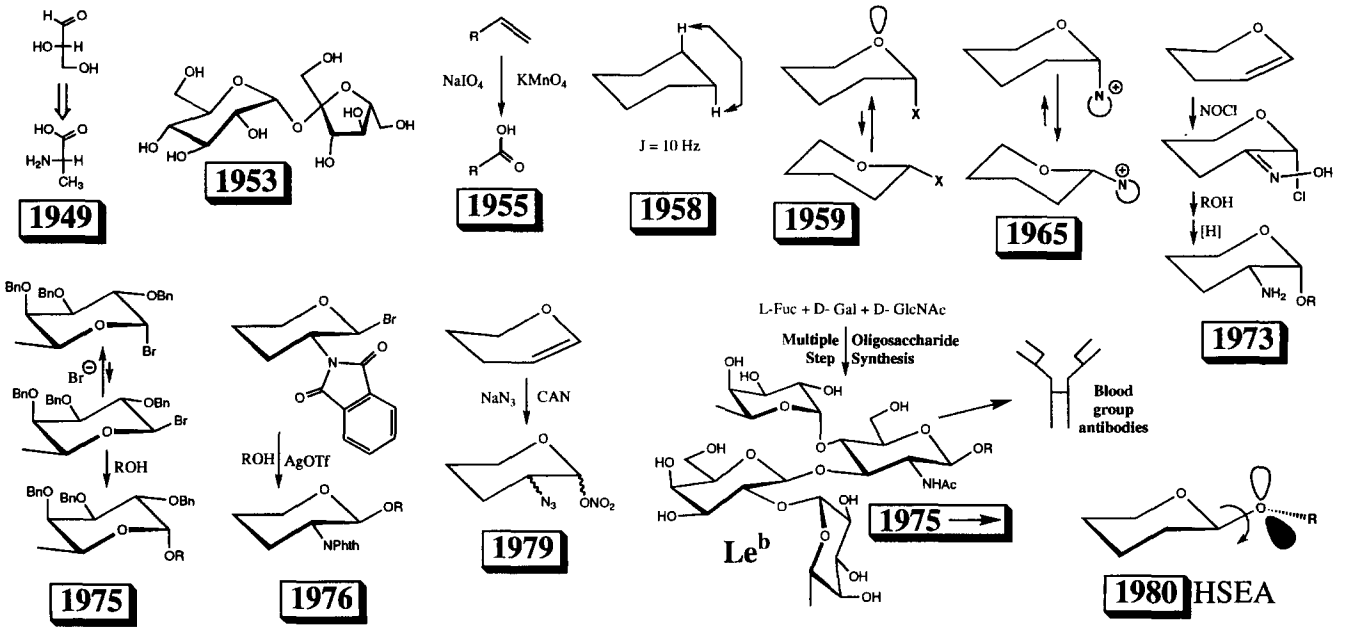
Ray is recognized as the individual who spearheaded the revolution that transformed carbohydrate chemistry from a narrow and largely empirical branch of organic chemistry into the current theoretically integrated mainstream of the discipline. His scientific accomplishments have been characterized by brilliance, originality and excellent intuition. And they have frequently been accompanied by controversy, as is the case every time a true breakthrough occurs that challenges the dogma of the time. In that regard, Ray has often advised that if you submit a truly novel piece of work a sure indicator of its importance is its initial rejection in the peer-review process.

It is natural that such an individual should receive numerous prestigious awards, and this has certainly been the case for Ray. Rather than listing his scientific accomplishments and awards in the usual manner, we chose instead to offer a 'graphical abstract' of what we see as his most significant contributions to chemistry. Ray's own account of his career may be seen in his autobiography 'Explorations with Sugars. How Sweet it Was'.[1]

Highlights of Ray's early career

1949: The configurational correlation between amino acids and sugars[2]
1953: The first chemical synthesis of sucrose[3]
1955: The Lemieux oxidation[4,5]
1958: The first correlation of vicinal coupling constants with configuration.[6,7] This paper went on to become a citation classic[8]
1959: Discovery of the anomeric effect[9]
1965: Discovery of the reverse anomeric effect[10]
1973: Synthesis of α-2-amino glycosides by the oximino-chloride method[11,12]
1975: Synthesis of α-linked disaccharides using halide-ion catalysed reactions[13]
1976: Synthesis of β-2-amino-glycosides using *N*-phthalimido glycosyl donors[14]

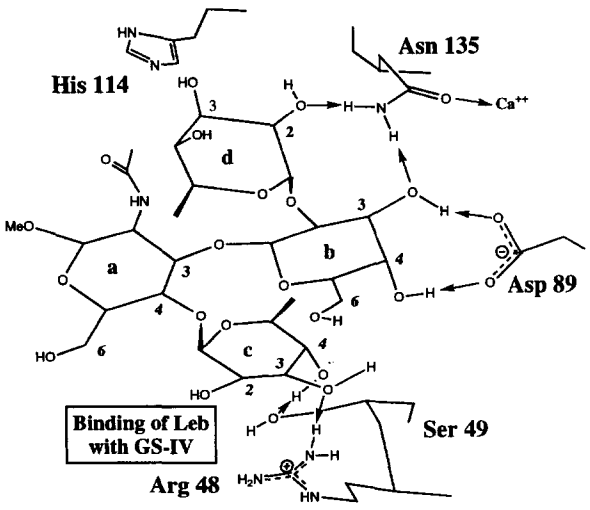




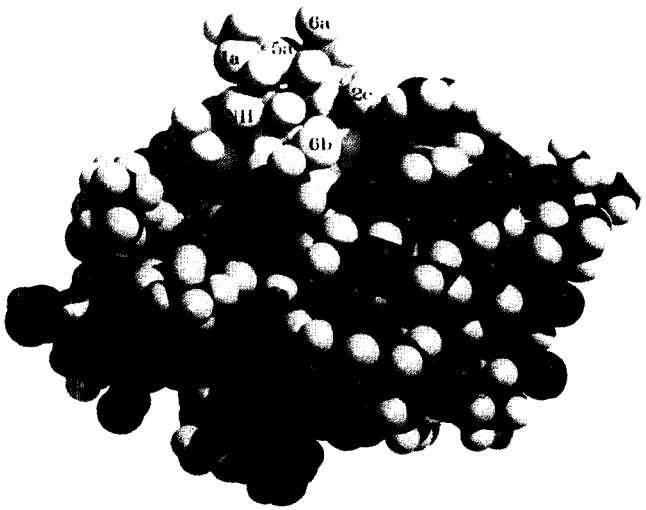
1978: Azidonitration of glycals to produce 2-azido sugars as glycosyl donors[15]

Beginning in 1975, Ray had the synthetic tools in hand to enter the area of immunochemistry and molecular recognition, specifically to gain an understanding of how oligosaccharides are recognized by the protein combining sites of antibodies, lectins and enzymes. Almost all of his papers since that time have dealt with that issue, including the classic papers[16–18] where Hard Sphere Exo-Anomeric (HSEA) calculations were developed to predict the conformational properties of glycosidic linkages in oligosaccharides. Hundreds of oligosaccharide analogues were synthesized (for representative examples see references 19–26) and used to probe the nature of carbohydrate–protein recognition. The early part of this work has been reviewed.[27] Part of the effort involved the use of well-defined synthetic oligosaccharide antigens for the production and screening of antibody specificity.[28,29]

The work culminated in the high resolution crystal structure of the lectin *Griffonia simplicifolia* complexed with the human Lewis b tetrasaccharide,[30] data that substantiated the crucial inferences that had been drawn from congener mapping of the binding site. Perhaps most dramatic was the confirmation, for this and several other systems, that only a very limited number of hydroxyl groups (often 2–3 out of some



Hydrogen bond map for the Lewis-b tetrasaccharide–*Griffonia* lectin complex. The solvent exposed GlcNAc residue makes no hydrogen bonds to the protein. Asp 89 makes crucial hydrogen bonds to Gal C-4 and C-3 hydroxyl groups and this network of hydrogen bonds is connected to those that engage Asn 135 and the C-2 hydroxyl group of the Fucose residue d.



A space filling model of the complex between the Lewis-b tetrasaccharide and the lectin *Griffonia simplicifolia*. The GlcNAc residue is solvent exposed while the Gal and each of two Fuc residues make essential contact with a shallow depression in the lectin surface.

10–12 present in an oligosaccharide epitope) are essential for acceptor recognition and biological activity. Furthermore, the bound conformation closely resembled a low energy conformer observed in solution and predicted by HSEA calculation.

The results of Monte Carlo calculations on the hydration of oligosaccharide surfaces lead Ray to conclude that the principle source of binding energy between protein receptor and oligosaccharide epitope derived not from polar interactions between solutes but from the collapse of perturbed water about the interacting, and polyamphiphilic surfaces.[31] The return of these energetically disadvantaged water molecules from the closest hydration layers to bulk water would then provide a much larger source of free energy change. These controversial ideas were refined over several years[31] and arose from binding studies of some 100 synthetic tetrasaccharide congeners. Compelling calorimetric evidence in support of these conclusions has recently been obtained by Chervenak and Toone,[32] who showed that 25–100% of the observed enthalpy of binding resulted from solvent reorganization.

Ray himself was the key to developing the tools of synthetic methodology and conformational analysis that permitted this understanding of the role of sugars in biological recognition. Despite his often stated strategy of 'putting oneself in luck's way', the remarkable insight and foresight that have characterized Ray's scientific career are clear. One is left with the impression that Ray drew the map before he traveled the route.

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