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Elected F.R.S. 1967

BY DAVID R. BUNDLE

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INTRODUCTION

Raymond Lemieux was one of the outstanding chemists of the second half of the twentieth century. During the four decades from 1950 onwards he dominated the field of carbohydrate chemistry. His rare and special degree of insight into chemical problems resulted in numerous seminal discoveries and observations that influenced organic chemistry extensively, and provided the area of carbohydrate chemistry—and its associated subjects—with extremely significant conceptual and experimental tools. His work was a determining factor in converting this field from an academic specialization into one of great practical importance in chemistry, biology and medicine. His influential role was recognized when, with 21 world-renowned chemists, he was invited by the American Chemical Society to write his autobiography. The highly engaging series of books, Profiles, pathways and dreams, documents the development of modern organic chemistry through the research careers of chemists who made fundamental contributions to organic chemistry over many decades of research. Lemieux’s contribution, Explorations with sugars. How sweet it was, is an excellent account of his research from 1946 to 1990 (50)*.

His research contributions spanned a wide area that included stereochemistry, NMR (nuclear magnetic resonance)-based methods for structural and configurational assignments, synthetic methods and molecular recognition. He was widely recognized for his scientific achievements in Canada and on the international stage. Among numerous awards, some of the

* Numbers in this form refer to the bibliography at the end of the text.
most notable were the Gairdner Foundation International Award (1985), the Rhône-Poulenc Award of the Royal Society of Chemistry (1989), the King Faisal International Prize in Science (1990), and the Wolf Prize for Chemistry (1999).

Lemieux’s career spanned a period during which the Canadian academic scene grew rapidly to take its place on the world stage. This transformation depended on the development of young Canadian prospects supported by the influx of European scholars in the postwar period. He was one of these young lights and his remarkable rise from humble origins paralleled Canada’s rapid transformation from a resource-based economy to one with increasing reliance on technology.

FAMILY BACKGROUND AND EARLY LIFE

Raymond Urgel Lemieux, the seventh child of a pioneer homesteader, was born on 16 June 1920 in the small prairie community of Lac La Biche (current population ca. 2700), 200 km northeast of Edmonton, Alberta. Both his parents trace their roots to France. The family name, originally De Limeux, derived from Mieus (miel, honey). The name is found in villages of two départements: le Cher and la Somme. His father, Octave, was descended from Pierre Lemieux, who was born in Rouen, Normandy, and settled in Québec, La Nouvelle France, in 1646. Octave married Ida Saint Martin in 1904. She was a descendant of Jean Saint Martin, who came to Québec as a soldier near the beginning of the eighteenth century.

His mother died when he was only seven years of age, and his eldest sister, Alice, raised him until he was 12. Raymond’s father was an itinerant carpenter normally employed in the foothills of Alberta through the 1930s in the so-called coal branch. Consequently, Raymond saw relatively little of him, though he was nevertheless dedicated to the welfare of his large family. The family moved from Lac La Biche to Edmonton (the provincial capital with a population in 1935 of ca. 80 000), and in Lemieux’s words, ‘they lived in a basically Irish–French–Ukrainian ghetto, where the main challenge was to avoid associations that could lead to reform school’. Although he did well in school, Lemieux had a passion for hockey and played in the Edmonton Junior Hockey League, but this experience and his slight physique convinced him that he lacked the bulk to be truly successful in this pursuit. At about the same time, a graduate student in physics, John Convey, his future brother-in-law, was courting his sister Annette. He showed a real interest in Lemieux’s high-school studies and encouraged him to consider attending the University of Alberta. With his first-year tuition fees largely paid by his sister, he began his university education in the autumn of 1939.

HIGHER EDUCATION

One of his major considerations in choosing to study chemistry was that the university employed a number of second-year honours chemistry students as teaching assistants, an appointment he secured by virtue of leading his class in his freshman courses. This income ($18 per month) was of crucial importance to his finances. To remain at university during this period, he had to volunteer for active duty, and throughout his undergraduate years he was involved in the Officers’ Training Corps. However, because of his involvement with research he was never called up. At the suggestion of his favourite professor, Rubin Sandin, Lemieux

Biographical Memoirs
worked with Jack Morrison on detonators for his BSc thesis. This work did not amount to much and in the spring of 1943 he graduated but stayed on with Morrison to investigate what happened to coconut charcoal when it was activated for use in gas masks.

Later the same year Lemieux left Edmonton for Montréal (a three-day train trip) and McGill University, where he registered for graduate studies with Clifford Purves, at the Pulp and Paper Research Institute of Canada. Research at McGill continued to be related to the war effort, first on oxycellulose and then on nitrocelluloses. Although he found the work not particularly engaging, the exposure to Purves and discussions with him kindled Lemieux’s interest in stereochemistry and cemented his decision to seek a career in research, especially in the general area of carbohydrate chemistry. It was here in Purves’s office, each of them smoking hand-rolled cigarettes, that he became completely entranced by stereochemistry and fascinated by the structure and synthesis of sucrose, a topic to which he was later to return with considerable effect on more than one occasion.

POSTDOCTORAL STUDIES

By 1946 he had completed studies for his doctoral dissertation, and the possibility of postdoctoral studies attracted him. The discovery that the antibiotic streptomycin was a carbohydrate was of great interest, not least because 10 years earlier his younger brother Gerard had died of a streptococcal infection. When he discovered that research on streptomycin was going on in the laboratory of Melville Wolfrom, Lemieux sought Purves’s opinion on whether he should apply for postdoctoral studies in the famous carbohydrate group at Columbus, Ohio. The postdoctoral position he ultimately secured there was sponsored by Bristol Laboratories and set the stage for a 25-year-long research relationship between the young chemist and the pharmaceutical company. As important as this was, the move to Ohio held far greater significance, because it was at Ohio State University that Raymond met Virginia McConaghie, who was studying for her PhD in high-resolution infrared spectroscopy. Ray and Jeanne were married in New York City in 1948 and over the ensuing 12 years, from 1949 with the birth of their first child, Laura, to the birth of Janet, their youngest, in locations from Saskatoon to Ottawa and back to Edmonton, they raised five daughters and one son. Referring to his family as one of his proudest accomplishments, he also acknowledged in his autobiography (50) the dominant role that Jeanne played in this process because, as with many brilliant and driven scientists, his work made excessive demands on him and his family. Notwithstanding all these pressures he was proud to observe the considerable and diverse academic and professional achievements of all six children.

RESEARCH CAREER

Postdoctoral research

It was at Ohio State University that Lemieux became involved in the structural elucidation of streptomycin. He also became fascinated by the configurational correlation of sugars and amino acids and realized that he could address this problem by combining recent results from the Wolfrom group on the synthesis of the penta-\(O\)-acetyl-\(d\)-glucosamine diethyl thioacetal with Raney nickel desulphurizations he was then conducting. Reduction of the dithioacetal
followed by periodate oxidation provided a route to \( L \)-alanine and hence its correlation with the relative configuration of \( D \)-glyceraldehyde (figure 1). This work served as a milestone in stereochemistry by linking the stereochemical notation for these two important classes of molecules (1). Many years later Lemieux used \( D \)-glucose in a related fashion to synthesize one enantiomer of \( \alpha \)-deuterioethanol (13). This was one of the first examples of the use of a carbohydrate to provide a specific asymmetric centre of known chirality in the synthesis of an unrelated molecule.

Assistant Professor, University of Saskatchewan

In 1947 Raymond Lemieux became Assistant Professor at the University of Saskatchewan, and two years later he joined the National Research Council’s Prairie Regional Laboratory, also in Saskatchewan. During this period he attracted considerable public and scientific attention with the first rational synthesis of sucrose (2, 7). When the news broke, there was a dip in the commodities market for cane sugar, before the modest scale and yield of the reaction were properly understood. Two reactions involving oxidative cleavage of double bonds by sodium periodate and potassium permanganate (4, 5) and periodate–osmium tetroxide (6) were also published at this time and bear his name: the Lemieux–von Rudloff and the Lemieux–Johnson reactions. During this first academic appointment, he began his studies and lifelong interest in the chemistry of the anomeric centre (3, 14). Observations on neighbouring group participation, anomerizations and preferential reactions of certain anomers (3) set the stage for the synthesis of sucrose (2, 7). The recognition accompanying this achievement led to an invitation to participate in the 5th Summer Seminar on the Chemistry of Natural Products at the University of New Brunswick in 1953. His lecture, entitled ‘Reactions at the anomeric center of acetylated sugar derivatives’, in front of such leaders of the period as R.B. Woodward (F.R.S. 1956) and D.H.R. (later Sir Derek) Barton (F.R.S. 1954), gave Lemieux his first taste of contact with the leaders of the field, and also convinced him that he could hold his own in this company. It was obvious that the methods available at the time for determination of the stereochemistry at the anomeric centre were certainly laborious and left a great deal of uncertainty. It was also clear to him that there were special effects in play when it came to the...
conformational preference of certain pyranose derivatives, such that large substituents at C-1 of the pyranose ring did not occupy the expected equatorial position but rather the axial orientation. However, in 1953 there was no way to obtain direct evidence for the preferred conformations of such molecules in solution. The solution to this problem lay just around the corner and coincided with his move to Ottawa in 1954.

Vice-Dean and Chairman of the Department of Chemistry at the University of Ottawa

The President of the National Research Council of Canada, E.W.R. Steacie, F.R.S., had strongly urged the young Lemieux to consider a move to Ottawa to help in building the faculty and an ‘atmosphere of research’. Such was the hierarchy and paternalist attitudes of the time that one would have been ill-advised to swim against such strong currents. Raymond Lemieux became Professor and Chairman of the Department of Chemistry at the University of Ottawa in 1954, and served as the Vice-Dean of the Faculty of Pure and Applied Science. During his tenure he not only designed and supervised the building of a new chemistry department but, through his energy and perceptive staff appointments, established a flourishing research environment. Among early appointments to the faculty were F.A.L. Anet, B. Belleau and K.J. Laidler.

Conformational analysis by NMR spectroscopy

It was in Ottawa at the National Research Council (NRC) that Lemieux first heard a presentation on NMR. He immediately began to speculate on the steric effects that might influence the chemical shifts of the protons of the pyranose ring. After approaching W.G. Schneider (F.R.S. 1962) and H.J. Bernstein, Lemieux learnt that if he provided manpower to assist in recording the spectra (a considerable task at that time) he would be able to study the NMR of the sugar acetates. With Rudolf Kullnig, a graduate student in Lemieux’s group, and under the guidance of Bernstein (NRC), Lemieux obtained the first NMR spectra of these compounds at 40 MHz (8). The work provided the long-sought definitive assessment of the preferred conformations of the sugar acetates in solution. Expansion of the approach led to the first application of 1H NMR spectroscopy for the establishment of relative configurations of chiral centres in organic compounds (9) and thus the foundation of the Karplus relationship (57) (Karplus 1959). It is interesting to note that in 1958 Lemieux presented this work, before publication, in the Karl Folkers Lectures at the University of Illinois. In the audience was Martin Karplus, whose soon-to-be-published theoretical work provided a theoretical basis for the quantitative correlation of three-bond coupling constants with torsional angle, one of organic chemistry’s most potent stereochemical probes (40). Karplus later wrote (Karplus 1996):

Just as I finished the work on vicinal coupling constants, I heard a lecture by R.U. Lemieux on the conformations of acetylated sugars. I do not remember why I went to the talk because it was on organic chemistry. Lemieux reported results for vicinal coupling constants and noted that there appeared to be dihedral angle dependence, although the details of the behaviour were not clear. However, it was evident that these experimental results confirmed the theory even before it was published.

In the same year, Lemieux discovered the anomeric effect (26), now recognized as a fundamental stereoelectronic phenomenon and one that governs the outcome of many organic reactions.
The anomeric effect

It was during his Ottawa period that Lemieux first identified and reported his interpretation of the anomeric effect, the preference of large electronegative constituents at C-1 of the pyranose ring to adopt the axial orientation preferentially. The phenomenon extends to acetics in general and to electronegative substituents at the C-2 position of saturated heterocycles. Its implications were understood by chemists, and research on the general anomeric effects subsequently became an area of research with a life of its own. Such was his preoccupation with administrative matters that what many would regard as one of his major contributions went unpublished in the peer-reviewed literature for many years. In fact the only documented reports of this work are as abstracts of unpublished research lectures presented to the American Chemical Society (10, 11). The second of these abstracts was the first public report of the exo-anomeric effect (11) and it was not until 1971 that a formal publication was presented on this topic in a paper entitled ‘Effects of unshared pairs of electrons and their solvation on conformational equilibria’ (25).

Return to the University of Alberta

In 1961 Lemieux received an offer of a professorship from the University of Alberta. Burdened with administrative duties and barely able to find time for writing up his most successful work in Ottawa, he felt that this offer was too good to refuse. Discoveries of large conventional oil deposits had swollen the Alberta provincial treasury and the province was preparing to flex its newfound wealth through judicious investment in its main university. With carte blanche to build a strong department of chemistry, the recruitment of an established star was a cornerstone in the university’s strategy. Lemieux returned to the University of Alberta’s Chemistry Department, where he maintained an active research programme well into the 1990s. From 1966 to 1973 he was Chairman of the Division of Organic Chemistry and, aided by his influence and stature, the department grew to become one of the largest and foremost research centres for chemistry in North America.

His group in Alberta in the early 1960s undoubtedly represented one of the high points of his career. Several outstanding PhD students and postdoctoral fellows during the period 1961–73 helped him to establish an undisputed reputation as a world leader in his field. Key advances in the chemistry of orthoesters (19), glycals (15–17, 20, 21) and their nitrosyl chloride adducts (23, 24, 26–28) with Richard Morgan, Bert Fraser-Reid and T.L. (Nag) Nagabhushan represented major breakthroughs during this period. Against this backdrop of new synthetic chemistry and an increasing understanding of the anomeric effect, the exploitation of 1H NMR spectroscopy to solve conformational and configurational questions was now routinely applied in the Lemieux group. The determination of the opposite relative signs of geminal and vicinal coupling constants in the proton magnetic resonance spectra of saturated organic molecules was made in 1961 (12), and was followed in 1963 by the determination of the absolute configuration of dextrorotatory 1-deuterioethanol (13). With John Stevens, work on the NMR spectra of acetylated sugars continued (18) together with key developments in the use of NMR to determine the anomeric configurations of sugars and glycosides in D2O solution (22). During the same period, several postdoctoral fellows and students were engaged in the study of conformational equilibria in solution, using both NMR and chiroptical approaches. Such data added to the appreciation of the importance of the anomeric effects in dictating not only the anomeric preference of electronegative substituents but also the conformation of glycosides (exo-anomeric effect) (11, 25).
Methodology for the rational synthesis of complex oligosaccharides

With the increasingly sophisticated understanding of reactions at the anomeric centre and the capability of contemplating synthetic targets that few others could consider in the late 1960s, Lemieux’s attention turned to the selection of challenging targets. At this time circumstantial evidence was emerging that complex oligosaccharides, whose structures were beginning to be solved by reliable methodology, were involved in phenomena as diverse as cell–cell recognition and development, and the control of glycoprotein biosynthesis and transport. The oligosaccharide chains of glycoproteins and glycolipids could no longer be ignored, because these structures carry messages essential for the control of many crucial cellular functions. The study of these new phenomena was critically hampered by the enormous difficulties encountered in trying to obtain even milligram quantities of structurally well-characterized carbohydrates.

The most direct solution was to synthesize the required complex oligosaccharides, but this had not been attempted because of the difficulties involved. At that time, the synthesis of a disaccharide was considered a major undertaking, and the preparation of the more elaborate oligosaccharides must have seemed an unrealistic project. The successful completion of such a programme required at a minimum the development of new glycosylation methods, especially for the stereoselective synthesis of the $\alpha$-glycosidic linkage, and the development of new methods for the structural analysis of both protected oligosaccharide intermediates and of the final synthetic products.

Largely as the result of research in his group during the 1960s these essential methodologies for the stereospecific formation of the glycosidic linkage came to a climax in the early 1970s. For the first time, the synthesis of oligosaccharides of sufficient complexity to parallel in activity the naturally occurring structures could be accomplished. These new synthetic reactions included the oximino-chloride glycosylation method for the preparation of $\alpha$-linked 2-amino-2-deoxyglycosides (figure 2) (28) and the phthalimido glycosylation procedure for the preparation of $\beta$-linked 2-amino-2-deoxyglycosides (34). Most importantly, the development of the halide-ion glycosylation reaction permitted the synthesis of the hitherto elusive $\alpha$-glycosidic linkage (figure 3) (30). These achievements resulted in four publications in 1975 (30–33) on the synthesis of the trisaccharide antigenic determinants for both the B and Lewis$^a$ human blood groups, and opened the way for a host of other laboratories to join in the effort (figure 4). An efficient and practical route to a glycosyl donor that would provide ready access to $\alpha$-glycosides of 2-acetamido-2-deoxy-$\alpha$-D-galactopyranose provided the remaining key to the efficient synthesis of the human A bloodgroup antigen. Azidonitration of tri-O-acetyl-D-galactal afforded the $\beta$-halide of tri-O-acetyl-2-azido-2-deoxy-galactopyranosyl chloride (figure 5) (37).

Synthetic antigens and immunoadsorbents

In itself, the laboratory preparation of these antigenic determinants would have been a remarkable achievement. However, Lemieux’s insight into the potential utility of these compounds was of such clarity that he foresaw their use as artificial antigens. His syntheses were conducted in such a way that the completed oligosaccharides incorporated a linking arm to permit the covalent attachment to appropriate carrier molecules (33) (figures 4–6). He also recognized that attachment to solid supports would provide biospecific adsorbents that would be of exceptional value in medical research. The immunization of test animals with these artificial antigens was shown to result in the production of antibodies specific for the carbohydrate determinants. These antibodies could then be isolated by affinity chromatography on the synthetic
immunoadsorbent, thereby establishing a method for the preparation of carbohydrate-specific antibodies that was unrestricted by the scarcity and inaccessibility of the naturally occurring substances. This development permitted the production of antibodies specific for a large number of the human bloodgroup determinants that were capable of detecting the corresponding naturally occurring structures on cell and tissue surfaces, and later the selection of monoclonal antibodies with desired binding profiles. The work established that immunization with a totally synthetic bloodgroup oligosaccharide could result in the production of antibodies that were able to recognize this structure on the cell surface (35).

Several immediate effects of this work followed. A major grant initiative to capitalize on the practical applications of these results was funnelled to the Medical Research Council (MRC) by the Natural Science and Engineering Research Council (NSERC), the traditional funding agency for research in chemistry, and the subsequent grant was almost certainly the first major funding by that agency for an essentially chemical research programme. With this
Raymond Urgel Lemieux

Figure 3. The principle of the halide-ion glycosylation. The β-glycosyl halide is less stable but more reactive than the corresponding α-glycosyl halide. To achieve a rapid equilibrium between anomeric forms of a glycosyl halide, a soluble halide salt is added to the reaction mixture. The isomerization between α and β halides is fast in comparison with the glycosylation step, and because of the difference in stability between the two transition states, leading to α- and β-glycosides (requiring a boat-form transition state), the reaction can be steered to generate the α-glycoside.

Figure 4. Incorporation of two halide-ion glycosylation steps in the chemical synthesis of the human B bloodgroup trisaccharide. The first uses tri-O-benzyl-L-fucopyranosyl bromide and the second tetra-O-benzyl-D-galactopyranosyl bromide. As shown here the B-trisaccharide is synthesized with a nine-carbon spacer suitable for the covalent attachment of the final product to immunogenic proteins and inert affinity matrices. The scheme depicted here was eventually scaled to 100 g.
funding the size of the group grew rapidly. By early 1975 the MRC funding was in place and the group doubled in size; in the fall of that year, Ole Hindsgaul, who was destined to become another of Lemieux's key collaborators, joined the group as a new graduate student. Implicit in the MRC funding was the intention to commercialize the potential of synthetic carbohydrate epitopes, and ideas began to take root for the formation of what would now be called a bio-medical start-up or spin-off company. However, Lemieux's conception of a company that combined leading-edge chemistry with immunological applications was years ahead of its time, although subsequent and comparable ventures would later emerge in the much more progressive and adventurous climate of the USA. In 1979 the new company, ChemBiomed, was formed but after about 10 years in search of viable markets it ceased business and its key components were absorbed into the Alberta Research Council.

Oligosaccharide conformation determined by NMR and computer modelling

With the presence of many talented postdoctoral fellows and students in his group, significant quantities of bloodgroup oligosaccharides became available. At about the same time, high-field NMR was gaining momentum with the development of superconducting magnets that operated at field strengths above the previous limits of 220 MHz. The exploitation of NMR to answer stereochemical problems had already become a hallmark of Lemieux’s publications and with the advent of the pulsed, Fourier-transform technique, fast digital computers and cryomagnets, the compatibilities of the technique again offered unique opportunities.
In 1975 Christen Pedersen and Klaus Bock (Technical University of Denmark), who was a visiting scientist at the University of British Columbia with Professor Laurie Hall, paid a summer visit to Lemieux’s laboratory. Bock immediately impressed Lemieux with his knowledge of NMR especially as it applied to carbohydrates. It was also evident that the measurement of inter-proton distances by either $T_1$ measurements or nuclear Overhauser effect experiments was becoming much easier; in combination with the estimation of torsional angles, conformational analysis of oligosaccharides was a tangible objective. The stage was set and three years later Lemieux provided Bock with significant amounts of the bloodgroup oligosaccharides. Thus began a collaboration that laid the foundations for a large body of...
pioneering studies on the determination of oligosaccharide solution conformation by NMR methods and semi-empirical calculations, termed the HSEA (hard-sphere-exo-anomeric) algorithm. Lemieux had predicted, many years earlier, that the relative orientation of contiguous sugar residues in oligomeric structures was governed by the exo-anomeric effect (11). Confirmation of this hypothesis was achieved through the observation of near-invariant vicinal coupling constants between the anomeric hydrogen and aglyconic carbon atoms in the NMR spectra of appropriately $^{13}$C-enriched synthetic model glycosides (36). The development of the HSEA forcefield was basically an extension of this work. It was developed in Lemieux’s laboratory during the period 1973–75 (29) with help from the crystallographer Louis Delbaere. Then, thanks to the efforts of Klaus Bock and Bernd Meyer, these calculations were refined into a convenient computer program that was made widely available during the 1980s (42, 44). The initial NMR work on the bloodgroup oligosaccharides was performed at 270 MHz on an instrument in Copenhagen, but in 1979 a new 400 MHz spectrometer was installed in the Department of Chemistry at the University of Alberta. Shortly afterwards, Klaus Bock spent a sabbatical leave in Alberta consolidating the conformational investigations on the bloodgroup oligosaccharides. The initial work, which was largely completed by 1980, was written up and published in 1980 in a long paper that appeared in the *Canadian Journal of Chemistry* (41). Further related papers appeared in 1982 justifying the importance of the exo-anomeric effect and the effectiveness of the new HSEA forcefield (42). The second of the two 1982 papers dealt with the conformation of sucrose and unique experiments to detect an intramolecular hydrogen bond (43). This tremendous leap forward in the study of oligosaccharide conformation was first reported, as was much of Lemieux’s other groundbreaking work, at a scientific meeting. So it was that both ‘The Lewis antigens and secretor status’ and ‘The conformations of the Lewis blood group determinants, sucrose and kanamycin A’ were reported in Japan but subsequently appeared as published research lectures in the *Japanese Journal of Antibiotics* in 1979 (38, 39).

**Molecular recognition in sugar–protein complexes**

Knowledge of the three-dimensional shapes of oligosaccharides was a prerequisite for an understanding of their biological activities, and the availability of these oligosaccharides in quantities sufficient for systematic study was an essential component in the successful research programme that evolved during the decade 1980–90. These developments allowed Lemieux to apply his discoveries to the human bloodgroup-specific oligosaccharide determinants, including those with specificities designated serologically as A, B, O(H), X, Y, Lewis$^a$ and Lewis$^b$, and related antigens (figure 6). With knowledge of the three-dimensional shapes and flexibility of these important biologically active oligosaccharides, their binding to antibodies, lectins and enzymes could, for the first time, be examined at the molecular level.

A strategy based on functional-group replacement was developed to dissect the contribution of individual hydroxyl groups to the free energy of binding. Synthesis of monodeoxy and methoxy derivatives as well as deoxynhalo derivatives permitted the discrimination of hydroxyl groups that could be hydrogen-bond donors and/or hydrogen acceptors (53). Consideration was also given to topographical features whose existence could not be foreseen by simple consideration of the constituent monosaccharide residues. To explain the characteristics of the oligosaccharide binding that rendered possible their highly specific recognition by protein receptors, Lemieux initiated a vigorous synthetic programme that produced more than 100 trisaccharide and tetrasaccharide structures (35, 45–49, 54, 56). These synthetic oligosaccha-
rides were all analogues of the natural blood group determinants, which had been modified either through the removal of hydroxyl groups or by the replacement of hydroxyls with other substituents. During this period two research associates had vital and leading roles in the molecular recognition studies. First, in late 1981, on his return from a postdoctoral fellowship at Berkley, Ole Hindsgaul helped to lead Lemieux’s group until 1986 in studies on the *Ulex europaeus* and *Griffonia simplicifolia* IV lectins, as well as Lewisb and blood group B monoclonal antibodies. Ulrike Spohr, who had joined Lemieux’s group as a postdoctoral fellow in 1982, was his research associate from 1985 until he closed his research laboratory in 1995 and led in-depth studies of *Griffonia simplicifolia* IV and other lectins that recognized the Lewis or H-type antigens.

Through a systematic study of the binding of these analogues with their respective protein receptors, antibodies and lectins, Lemieux was able to define the precise molecular features required for the specific recognition of complex carbohydrate determinants. An account of this work summarizes the development of his thinking during the period 1975–96, beginning with the ‘hydrated polar-group gate effect’ as the key to the specificity in the recognition of complex carbohydrates, through to the idea of water reorganization as a major driving force for complexation (58).

The work culminated in the high-resolution crystal structure of the *Griffonia simplicifolia* lectin complexed with the human Lewisb tetrasaccharide (52), 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 or 3 out of some 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.

**Role of water in sugar–protein complexes**

The results of Monte Carlo calculations on the hydration of oligosaccharide surfaces led Lemieux to conclude that the principal 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 (51, 55). 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 and arose from binding studies of about 100 synthetic tetrasaccharide congeners. It was gratifying that at about the time that he was winding down his group, supporting evidence for this interpretation appeared from Eric Toone’s calorimetric studies showing that 25–100% of the observed enthalpy of binding could arise from solvent reorganization (Chervenak & Toone 1994).

**Summary of research contributions**

Lemieux’s profound influence on organic chemistry derived in large part from his enduring interest in the basic physical characteristics of molecules. An early understanding of the implications of reaction mechanisms for carbohydrate chemistry (3) was clearly demonstrated in the chemical synthesis of sucrose (2, 7). The extensive research on the mechanism of substitution at the anomeric centre, which lay behind this success, soon led to the recognition of the anomeric effect and, perhaps most important, the exo-anomeric effect. Theoretical support for...
these concepts followed many years after their recognition and acceptance as general stereo-
electronic effects in organic chemistry. This fundamental understanding of the chemistry of
the anomeric centre paved the way for new methods of 1,2-cis-glycoside synthesis, a career-
long interest. These major creative steps first generated methods for the assignment of struc-
tural details, then provided tools for the assembly of complex structures, and finally placed
him in a position to explore the subtleties of carbohydrate recognition phenomena.

INDUSTRIAL ACTIVITIES

Professor Lemieux founded three companies, R&L Molecular Research, Raylo Chemicals and
ChemBiomed Ltd, which sought to apply the creativity of university-based research that
occurred in his own research programme on antibiotics and complex carbohydrates. Several
practical applications arose from this work. The most significant of these was the development
of immunoadsorbents to remove ABO iso-antibodies, thereby permitting organ transplant
across the ABO histocompatibility barrier. The current shortage of organs for transplant and
the increasing attention being given to xenotransplants suggests that this Lemieux technology,
or its subsequent embodiments, might find expanded application. It should also be noted that
much of the current activity in the search for carbohydrate-based therapeutics, such as sialyl
Leα anti-adhesion molecules, has its origin in his pioneering work.

AWARDS

Lemieux’s academic and research accomplishments were recognized in Canada, the USA and
Europe through numerous awards and honorary degrees. He received the American Chemical
Society’s Claude S. Hudson Award in 1966, was elected a Fellow of The Royal Society in
1967, and was awarded the Haworth Memorial Medal of the Chemical Society in 1978. In
Canada he was appointed an Officer of the Order of Canada in 1968, and in 1996 he was ele-
vated to the highest level of recognition when he was made a Companion of the Order of
Canada. He was the first recipient of the Izaak Walton Killam Memorial Prize and of the
Science and Engineering Research Council’s Canada Gold Medal for Science and
Engineering. Among other prestigious awards he received the University of Toronto Gairdner
Foundation International Award (1985), the Royal Society of Chemistry Rhône-Poulenc
Award (1989), the King Faisal International Prize in Science (1990), the ‘Albert Einstein’
World Award of Science (1992) and most recently the Wolf Prize for Chemistry (1999).

THE MAN

Much of Lemieux’s science, certainly from the late 1960s onwards, was an evolution of his
intuition, especially with regard to his foray into molecular modelling and sugar–protein inter-
actions. He had a great gift in this regard and did not spend hours studying and piecing
together the extensive literature on immunochemistry, crystallography and biophysical data of
ligand–protein complexes. Nevertheless, his ideas drew heavily on his keen sense of the prin-
ciples of physical organic chemistry and he always insisted on a huge body of thorough experi-
mental work to support his theories.
It is fair to say that Lemieux did not enjoy the process of writing manuscripts, and his breakthroughs in the rational synthesis of oligosaccharides appeared in several remarkable bursts of consecutive publications. Thus, the reaction of oximino chlorides and related papers appeared in the *Canadian Journal of Chemistry* as four consecutive publications in 1968, followed by eight in 1973. This extensive body of work would not have been achieved without the drive and commitment of Lemieux’s close collaborator T.L. Nagabhushan, who had a major role in helping Lemieux run his group during the period from the mid-1960s to 1973. An even more remarkable burst of publications followed in 1975, with the appearance of four papers in the *Journal of the American Chemical Society* announcing the halide method, the first syntheses of the human bloodgroup determinants and the use of a tether to make artificial antigens, and the production of several bloodgroup-specific polyclonal antisera.

Lemieux strongly believed that ‘the best part of a scientific career is to talk about what you have discovered when it is hot’, which for him always preceded formal publication. In fact, publication as full papers was not infrequently put off for long periods. The best example is the anomeric effect, which for at least 10 years appeared only as abstracts of unpublished research lectures (10, 25) or in review articles that dealt mainly with other topics.

Lemieux was fiercely Canadian and, in his own words, pathologically Albertan. The vast majority of his publications appeared in the *Canadian Journal of Chemistry*, and he would often berate colleagues for not supporting this journal or for joining the American Chemical Society in preference to the Chemical Institute of Canada. Among his many awards, he was especially proud of his highest Canadian honours, the Companion of the Order of Canada and the Canada Gold Medal for Science and Engineering. He was also especially honoured by the decision of the Canadian Society for Chemistry to award a prize for organic chemistry bearing his name. To perpetuate and nurture the research he began, the University of Alberta established an endowed chair in his name, to which he and Mrs Lemieux were major benefactors.

Shortly after his retirement, Lemieux fought a major battle with prostate cancer. During his hospitalization and convalescence, his group was most ably run by Ulrike Spohr. Although ‘formally retired’, he maintained his research group well into the 1990s, and despite a continuing battle with failing eyesight caused by macular degeneration he maintained his interest in carbohydrate–protein recognition. So, in spite of these substantial obstacles he continued to tussle with the topic of molecular recognition, and right up to his 80th birthday in June 2000 he continued to work on his last manuscript. This involved considerable amounts of time peering at the screen of a molecular graphics work station, notwithstanding the fact that he had become legally blind and was by early 2000 confronted by the diagnosis of lung cancer and a sudden and markedly curtailed life expectancy.

In his early years Lemieux had a reputation as a demanding, tough supervisor and lecturer. He had intense drive, did not tolerate nonsense and always came to the point quickly, even at times brusquely. He was committed to excellence in himself and from those around him and he did not hesitate to let his co-workers know if they were wrong about something. However, criticism was also given without rancour or harshness. Although his outward demeanour mellowed in the second half of his career, his drive was as intense as ever, as witnessed by the activity and productivity of his group from 1975 to his official retirement and beyond.

Notwithstanding his intense ambition and thrill of discovery, Raymond Lemieux was an unassuming individual who was devoid of pretensions. He was regarded by colleagues from around the world as good-humoured and fun to be around, especially when he was relaxing at the pub or bar. His smile and infectious enjoyment of games are remembered by many. Indeed,
many fortunate colleagues and visitors to the Department of Chemistry in Edmonton were delighted to be invited to spend time with him and his family at their cottage on Lake Edith, in the heart of the Canadian Rockies, close to the Jasper town site. The ‘cottage’ was one of his great loves, and visitors through the 1960s and 1970s did not escape scot-free when they visited him there. This was no simple respite in the wilds, but a ‘work in progress’, and the standing joke in his group was that if heavy jobs were pending, an invitation could mean cement mixing under his close, demanding supervision and direction. Such were Lemieux’s diverse talents that he greatly enjoyed working with his hands and it was only in later years, with the good fortune of the prizes from prestigious awards, that he actually relinquished hands-on involvement in these projects to professional tradesmen.

On 20 June 2000 Ray and Jeanne celebrated their birthdays in the company of their 6 children and 17 grandchildren, as well as relatives, friends, collaborators and colleagues. Sadly, Ray died a month later.

He was rigorous and demanding in research; in an unobtrusive manner he challenged his co-workers to realize their full potential. He was without doubt one of the most outstanding Canadian chemists of the twentieth century, whose contributions to organic chemistry profoundly influenced the development of the discipline in the second half of the century.

HONOURS AND AWARDS

1954 First Award of the Division of Organic Chemistry, Chemical Institute of Canada
1961 Louis Pariseau Medal, Association canadienne-française pour l’avancement des sciences
1964 Palladium Medal, Chemical Institute of Canada
1966 Claude S. Hudson Award, American Chemical Society
1978 Haworth Medal, The Chemical Society, UK
1981 Izaak Walton Killam Award, The Canada Council
1982 University of Alberta Research Prize
Sir Frederick Haultain Prize, Government of Alberta
1983 Tishler Award Lecture, Harvard University
1985 Medal of Honour, Canadian Medical Association
Gairdner Foundation International Award
1989 Rhône-Poulenc Award, Royal Society of Chemistry
1990 King Faisal International Prize in Science
1991 Canada Gold Medal for Science and Engineering (first recipient)
1992 1992 E.C. Manning National Award of Distinction
PMAC Health Research Foundation Medal of Honour
‘Albert Einstein’ World Award of Science
1999 Wolf Prize in Chemistry

Distinctions

1954 Fellow of the Chemical Institute of Canada
1955 Fellow of the Royal Society of Canada
1967 Fellow of The Royal Society of London
1968 Centennial of Canada Medal
Raymond Urgel Lemieux

1968 Officer of the Order of Canada
1980 Award of Achievement, Province of Alberta
Dedicated Issue of the Canadian Journal of Chemistry, vol. 58, 1 December
1986 Honorary Fellow of the Canadian Society for Chemistry
1989 Le Sueur Award of The Society of Chemical Industry
1990 Alberta Order of Excellence
1992 Honorary Fellow of the Chemical Institute of Canada
1993 Great Canadian Award
Special Alberta Science and Technology Foundation Award—‘Alberta Pioneer’
1994 Induction to University of Alberta Alumni Wall of Recognition
Companion of the Order of Canada

Honorary degrees

Canadian universities
1967 Doctor of Science, University of New Brunswick, Fredericton
1970 Doctor of Science, Laval University, Québec
1975 Doctor of Science, University of Ottawa, Ontario
1979 Doctor of Law, University of Calgary, Alberta
1980 Doctor of Science, University of Waterloo, Ontario
1981 Doctor of Science, Memorial University, St John’s, Newfoundland
1982 Doctor of Science, Université du Québec, Montréal
1983 Doctor of Science, Queen’s University, Kingston, Ontario
1984 Doctor of Science, McGill University, Montreal, Québec
1986 Doctor of Science, Université de Sherbrooke, Québec
Doctor of Science, McMaster University, Hamilton, Ontario
1991 Doctor of Science, University of Alberta, Edmonton
1993 Doctor of Law, University of Saskatchewan, Saskatoon, Saskatchewan

Foreign universities
1972 Docteur, Université de Provence, France
1988 Doctor of Philosophy, University of Stockholm, Sweden

Distinguished lectures

In Canada
1969 C.B. Purves Lectures, McGill University
1977 J.W.T. Spinks Lecturer, University of Saskatchewan
1979 Armes Lectures, University of Manitoba
1980 W.I. Chute Memorial Lecturer, Dalhousie University
C.I.L. Distinguished Lecturer, Acadia University
1982 A.R. Gordon Distinguished Lecturer, University of Toronto
J.K.N. Jones Memorial Lecturer, Queen’s University
1983 C.I.L. Distinguished Lectureship, Simon Fraser University
Conferencier Barré, University of Montréal
1990 1990 University Lecturer in Chemistry, University of Ottawa

Other countries
1958 Karl Folkers Lecturer, University of Illinois
1968 Karl Pfister Lecturer, Massachusetts Institute of Technology
1978 Fred Smith Lectures, University of Minnesota
1980 Distinguished Visiting Lecturer, University of California at Los Angeles
1981 Karl Pfister Lecturer, Massachusetts Institute of Technology
      Plenary Lecture, 28th IUPAC Congress, Vancouver, BC
1983 Distinguished Visiting Lecturer, James Cook University, Australia
1984 Plenary Lecture, VIIIth International Symposium on Medicinal Chemistry, Uppsala, Sweden
1987 Leopold Ruzicka Centennial Symposium, Swiss Chemical Society, Zurich, Switzerland
      Plenary Lecture, 4th European Carbohydrate Symposium, Darmstadt, Germany
1989 Seville Academy of Science, Spain
1990 Alfred Burger Lecturer for 1990–91, University of Virginia
1992 First Cytel Lecture, Scripps Research Institute, La Jolla, California
      1st Decennium Symposium, King Faisal International Prizes in Medicine and Science, London, UK
1993 Merck Lecturer, University of Wisconsin, Madison, Wisconsin
      Nieuwland Lecturer, University of Notre Dame, Notre Dame, Indiana
      Korea Lectureship in Organic Chemistry, Korea

Named lectures
1972 Inauguration of The Lemieux Lectures, University of Ottawa
1987 Inauguration of The Raymond U. Lemieux Lectures on Biotechnology, University of Alberta
1992 Inauguration of the R.U. Lemieux Award for Organic Chemistry, Canadian Society for Chemistry

ACKNOWLEDGEMENTS

Much of the material used to prepare this memoir was taken from Professor Lemieux’s autobiography, Explorations with sugars. How sweet it was (50). I am also indebted to Mrs Lemieux, who provided access to private papers and correspondence. Colleagues in the Department of Chemistry, University of Alberta, made other material available.

The frontispiece photograph was taken by the Edmonton photographer, Con Boland, in about 1985, and is reproduced with permission. © ConBoland.com

REFERENCES TO OTHER AUTHORS


The following publications are those referred to directly in the text. A full bibliography appears on the accompanying microfiche, numbered as in the second column. A photocopy is available from The Royal Society’s Library at cost.

Biographical Memoirs


