The Hudson Memorial Lecture.

CLAUDE SILBERT HUDSON.

DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON JUNE 3RD, 1954.

By E. L. HIRST, D.SC., LL.D., F.R.S.

CLAUDE SILBERT HUDSON (1881—1952) will take his place along with Sir James Irvine (1877—1952) and Sir Norman Haworth (1883—1950) as one of the pioneers of modern carbohydrate chemistry. For more than 40 years he was regarded as a leading authority in a field which had become transformed out of all recognition since the time when in 1901 he began his classical investigations into the mutarotation of lactose. Indeed, for so long had Hudson and his work been known to a wide circle of friends and colleagues that he might almost be said to have achieved the rare distinction of becoming a legendary figure during his own lifetime. Quite apart from his work Hudson's rich colourful personality contributed to this and to those whose privilege it was to know him his warm friendliness, his keen interest and original mind, and his extraordinary patience and skill in laboratory work rendered him unique and evoked from all both respect and regard. In the foreword to the volumes containing his collected papers which were published in his honour in 1946, Hudson wrote that at first he resisted a request for an autobiographical notice but was later persuaded by H. O. L. Fischer that future readers might " desire to know what sort of a person this man Hudson was and how it came about that he carried out these chemical researches." This is certainly true and in his case it is singularly difficult to separate his personality from the record of his scientific achievements, so before any attempt can be made to assess the latter it is essential to consider briefly something of his history and upbringing.

The story is one of quite unusual interest. Claude Silbert Hudson was born in Atlanta, Georgia, on January 26th, 1881, the second child of William James Hudson (1851—1931) and his wife Maude Celestia Wilson (1854—1932). Through his father he could trace his ancestry back to Joseph Gregg, a member of a Scottish family which migrated to Londonderry, Ulster, in the late 17th century and from there to South Carolina about 1752. In 1812 Joseph Gregg's daughter Margaret married Robert Hudson, a wealthy plantation owner in Williamsburg County and their eldest son was C. S. Hudson's grandfather. His mother's ancestry was a mixture of English, Scots, and Huguenot French, and on this side both his grandfather and greatgrandfather were physicians. The early portion of William Hudson's life had been spent in South Carolina, but in the troubled period after the Civil War he left his father's estate and entered business in Georgia. Soon after the birth of Claude Silbert Hudson his parents moved to Greenville, Alabama, and then, when he was three years old, to Mobile where his father was occupied in the fertiliser business, ultimately becoming President of the Mobile Fertilizer Company.

It was therefore in this pleasantly situated and small but active southern town with its unusual community of families with cultures stemming from a wide group of European countries that C. S. Hudson passed the impressionable years of his boyhood. In later times he recorded his memories of those early days, the festivities and processions, the quiet dignified home with its trees and gardens, the pleasant outdoor life of swimming, fishing, and sailing which could be enjoyed in the warm climate. He recalled too encouragement he received from his parents during his school days at the Barton Academy in Mobile and at the University Military School supervised by Julius T. Wright, a man who exercised a deep influence over Hudson in his dual capacity of headmaster and Sunday School Teacher at Government St. Presbyterian Church. During this period Hudson came to know the Rev. A. C. Harte, secretary of the Mobile Y.M.C.A. and like J. T. Wright a man of high culture and saintliness of character.

C. S. Hudson as a boy had early displayed a seriousness of outlook which was manifested in his interest in various church activities. It is not altogether surprising therefore to find that when he was ready to enter college at the early age of 16 it was with the fixed intention of training for the Presbyterian Ministry. So in 1897 he entered Princeton where he knew nobody and as a southerner found the northern speech and customs of his classmates very strange. Perhaps even stranger still was the fact that here he was established in Princeton studying to enter the Presbyterian ministry but enrolled nevertheless in the course leading to the B.Sc. degree. His idea was, apparently, that he would prepare for his prospective duties by learning as much science as

Claude S. Hudson

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possible and during his freshman year he attended Professor L. W. McCay's chemistry class where he was profoundly impressed by the brilliant lectures and the excellence of the demonstrations. So much was this the case that when he returned to Princeton in the autumn of 1898, after a summer spent as assistant to the Rev. A. C. Harte in Y.M.C.A. work for the second Alabama Regiment mobilised for service in the Spanish American war, he came to realise that he possessed but little aptitude for ministerial work and decided to aim for a scientific career. The interest he found in the courses in physics (Professor E. H. Loomis), astronomy (Professor C. A. Young), geology (Professor W. B. Scott), and mathematics (Professor C. G. Rockwood, Jr.) confirmed this decision and after a highly successful 4 years at Princeton he graduated in 1901.

At this period he was much worried about his future. He wished to continue in academic work but his father could no longer support him and he had made arrangements to join his former headmaster J. T. Wright as an assistant teacher at the University Military School at Mobile when, quite unexpectedly, the whole course of his career was changed. It so happened that in 1901 a Princeton Fellowship in experimental science was due to be awarded to a chemistry graduate and in May 1901 it was offered to Hudson. Wright, considerate and friendly as always, released Hudson from his engagement and in the autumn of that year he was fairly launched on a career in chemistry. His leanings were towards physical chemistry which was then taught by Professor Loomis in the Physics Department. Before the new Fellow had decided upon a problem for investigation Professor Magie of the Physics Department asked Hudson to crystallise a sample of lactose which was needed for some specific-heat measurements—a fateful request the consequences of which are best told in Hudson's own words.

" During a measurement of the rotation of the sugar as a control of purity, I noticed its mutarotation, a phenomenon of which I had never heard, and asked Dr. Magie for its explanation. He found Erdman's measurements of it in the *Berichte* (1880, **13**, 2180), but none of the current general treatises gave any real explanation of mutarotation. I promptly requested that my research problem be a physico-chemical study of the mutarotation of milk sugar. The result from my request was an unexpected one. Dr. Magie consulted Professor Neher, who told him that it would be unfair to a student to let him select a subject in sugar chemistry because the chemistry of sugars had recently been thoroughly explored by Emil Fischer. But Dr. Magie over-ruled Neher when the latter could not show that Fischer had disclosed the cause of mutarotation; the final decision was that the Chemistry Department would be relieved of all responsibility toward me beyond the supplying of a laboratory bench and chemicals, and that during my research on the mutarotation of milk sugar I would report to Dr. Magie. This decision delighted me and I went ahead with enthusiasm; my first scientific paper was on the forms of milk sugar, published near the end of the fellowship year, at the age of twenty-one."

In this unexpected way and almost accidentally, Hudson began his long series of investigations in the sugar group. The work on lactose brought him the M.Sc. degree in 1902 and he now decided to gain further experience by postgraduate study in Germany. The state of the family finances at this time was such that it appeared to be just possible for him to stay in Europe for 3 years. It was arranged that he should go to Nernst's laboratory at Göttingen, where he continued his investigations on the mutarotation of milk sugar and had numerous discussions with Tollens in the laboratory of Agricultural Chemistry. He learned much but records that he was teacher as well as pupil in that one of his very successful activities was to interest Nernst in the game of poker.

Once again, however, difficulties arose which threatened Hudson's whole career. Financial troubles at home made it imperative for him to give up the idea of 3 years' study in Europe and to return to the U.S.A. at the end of one session. Characteristically he made the utmost use of the time he had. Before leaving Göttingen he spent some weeks in Tammann's laboratory testing experimentally the idea which had come to him while reading Landolt's book on optical activity, that the temperature–solubility curve for the nicotine–water system would take the form of a closed ring. He spent the summer semester in van't Hoff's laboratory in Charlottenberg working on the aqueous vapour pressure of lactose monohydrate, receiving much inspiration from personal contact with so striking a character as van't Hoff. Before returning to the States he had an opportunity to meet Emil Fischer whom he always regarded as the greatest organic chemist of his age.

At the International Chemical Congress in Berlin in the summer of 1903 Hudson met A. A. Noyes who offered him a place in the new research laboratory for physical chemistry at the Massachusetts Institute of Technology in Boston. Here work on the inter-relationship between the various forms of lactose was continued and proposals were made for an extension of the programme to include mannose. Attempts to secure funds for this work were unsuccessful and

Hudson, greatly discouraged, applied unsuccessfully for a vacant professorship in one of the colleges in the State of Washington. He then returned to Princeton for a year as an instructor in physics, following this in 1905 by taking a similar post in the University of Illinois. These positions were nevertheless only stop-gaps since it was by now abundantly clear that Hudson's talents lay in the chemical field rather than in physics. His efforts to secure a teaching or research post in chemistry met with nothing but failure and almost in despair he asked his father to take him into the family mining business at Twomey. He was prevailed upon to wait a little longer before taking the final decision and shortly afterwards the crisis passed when in 1907 he was unexpectedly offered the post of Assistant Physicist in the Technologic Branch of the U.S. Geological Survey.

The short period in Germany had not permitted him to take the Ph.D. degree which was the passport to so many chemical posts, but this handicap was removed when he gained, *magna cum laude*, the Ph.D. of Princeton in 1907. It is interesting to note that the diploma was signed by Woodrow Wilson who was then President of Princeton. A striking illustration of Hudson's single-minded devotion to research occurred during the short visit he made to his old University to obtain the degree. He took the opportunity to spend a few days in experimental work on sugar chemistry in Professor Hulett's laboratory, and in the course of this he measured the rate of mutarotation of glucose at differing pH values and put forward the equation for the reaction which came to be generally accepted.

Hudson was now nearly 27. He knew the work he wanted to undertake but he still had no settled post in which he could pursue it. The work of the Technologic Branch served only to divert his attention from his true field and in any case its activities were soon curtailed and he moved to a post in the New York Testing Laboratory at the plant of the Barber Asphalt Company, New Jersey. The year 1908 marked the beginning of a new era in Hudson's research activities but once again the circumstances were so unusual that they are well worth recounting as illustrating both the personality of Hudson and the extraordinary series of vicissitudes which had to be surmounted before his real work could be begun. In March 1908 he became Chemist Aid in the Bureau of Chemistry at Washington where his duties were to assist Frederick Weber in routine analyses. These were so well organised by Hudson that, his work completed, he was allowed to spend two hours a day in the library. His reading, chiefly it is to be noted in sugar chemistry, was to such good effect that it led in a short time to his paper of January 1910 on " The Significance of Certain Numerical Relations in the Sugar Group." The suspension of the analytical work owing to political difficulties enabled Hudson to give his whole attention to research for the time being and, still interested in mutarotation, he sought and obtained permission to study the rotational changes observable during the hydrolysis of sucrose by invertase. This was the beginning of a notable series of investigations on the enzyme invertase carried out over a period of years, many of them in collaboration with C. B. Purves. Hudson's position was now secure. He soon became head of a section of Physical Chemistry in the Bureau and was given leave of absence for the session 1911 to return to Princeton as Acting Professor of Physical Chemistry. On his return to the Bureau of Chemistry in 1912 he was given charge of the newly established Carbohydrate Laboratory. He now had the opportunities he had so long wished for and he took the fullest advantage of them publishing year by year a large number of papers on carbohydrate chemistry characterised throughout by the precision and accuracy of the experimental work and the clarity of the writing and argument.

By 1914 Hudson's work had earned for him an international reputation as an authority on rare sugars and an interesting side-light on this is to be found in the request made to him at the beginning of the 1914—18 war for details of the methods of preparation he had devised for several sugars and sugar derivatives which were urgently required by the British Health services.

It was not long, however, before Hudson himself became involved in war-time activities on behalf of the U.S. Government. As a sugar chemist he had been interested in active carbon for decolorising solutions and when in May 1917 the problem of protection against poison gas became urgent he was asked by Dr. Alsberg to undertake work on the large-scale production of active carbon. Although Hudson's part of this project was soon completed and he returned to the Bureau of Chemistry in October 1917 his experience had a strange and unexpected sequel. At the end of the war he decided to resign from the Bureau and try his luck as a consulting chemist in Trenton, New Jersey, in the fields of active carbons, yeasts, and malt syrups. This period lasted for 4 years (1919—1923) and came to an end when F. J. Bates, Chief of the Polarimetry Section of the National Bureau of Standards, offered him a research post in which he would be free to carry out fundamental studies in the field of sugar chemistry—an offer which he tells us he accepted with delight. A period of five years devoted to brilliant and fruitful investigation then followed, broken only by a period of leave of absence spent in scientific work in Honolulu. He now was in a position to attract mature collaborators to his laboratory and in much of the work carried out at the National Bureau of Standards during the five years 1923—28 he was assisted by researchers who came to hold high positions in the world of science. Amongst them, for example, were to be found A. Kunz, C. B. Purves, E. Pacsu, W. C. Austin, M. L. Wolfrom, together with H. S. Isbell, Miss O. Hartley, and Miss E. Montgomery who were at that period regular employees of the Bureau.

Another important change came in 1929 when Hudson was offered the Professorship of Chemistry in the United States Public Health Service. He hesitated over acceptance since conditions at the Bureau offered him ample opportunity for the work he was most interested in, and he was less certain whether the Public Health Service would give him equal freedom. In the end he decided to make the change, swayed by the belief that the importance of the carbohydrate group in problems of nutrition would always call for fundamental research in that field. In this he was fully justified and the years from 1929 to 1951 which he spent at the National Institutes of Health were amongst the happiest and most fruitful of his career. He found that ample funds were provided for fundamental research and, writing many years later, he paid a warm tribute to the generous and friendly encouragement he received both in Washington and in Bethesda, Maryland, where the N.I.H. laboratories were situated from May 1941. "My experience," he states, and his remarks are of general import, "of about thirty years in research under three Departments of the Federal Government (Agriculture, Commerce and Federal Security Agency) has convinced me that those offices of the Government which are primarily concerned with matters of science can best render a high grade of public service if the spirit of fundamental research is encouraged among the personnel. Moreover I believe that in the choice of personnel for such government offices an innate and studious interest in fundamental research should be a major criterion of selection."

In the year after his appointment to the professorship Hudson travelled to Europe to attend the meetings of the International Union of Chemistry at Liége. The occasion was an important one for him since a conference on carbohydrate chemistry had been arranged and Hudson was taking the opportunity to present a complete system of ring structures for the simple sugars and their glycosides based on optical rotatory data interpreted in terms of the rules of isorotation. In many important instances, for example, methyl α-mannoside, the ring structures so deduced were at variance with those put forward by Haworth and Hirst on the basis of evidence obtained by the methylation procedure. So sure was Hudson of the accuracy of the principle of optical superposition that he claimed to have proved the inaccuracy of the methylation method. The outcome of the conference was in many ways a severe disappointment to Hudson. At an early stage of the meetings Haworth arranged a private discussion at which Hudson, C. B. Purves, Haworth, and the writer took part. The whole question was considered in detail and Hudson was told of the latest experiments of the Birmingham School from which it emerged that the rotational anomalies of the mannose group of sugars were not connected with ring structure, but involved departures from the isorotation rules which necessitated the abandonment of Hudson's scheme of structural proof. It is a measure of the real greatness of the two men that a situation which might have led to much friction was in fact the occasion for cementing a firm bond of friendship which was broken only by Sir Norman Haworth's death twenty years later.

The meetings at Liége had lasting effects in other respects also. In Hudson's later years he stressed the need for obtaining complete and often repeated proofs of structure, and his interest in theoretical matters was less pronounced. Another, and a highly important result of these controversies with Haworth, was the application to the sugar group of the periodate method of oxidation. In Hudson's own account of this development he writes "The new experimental results from methylation data which Haworth and Hirst presented at that Conference led me to return home with grave doubts of the validity of the views that I had advanced on the basis of my interpretation of rotatory relations. Therefore I sought to find some way by which evidence on this question could be obtained that would be independent of both methylation data and relations. The result is well known to organic chemists. By applying the periodate oxidation reaction of Malaprade to carbohydrates of many types, the workers in our laboratory were able to obtain the desired independent evidence. It confirmed the views of Haworth and Hirst in all respects. I look back on this conflict of views between Haworth and myself, which aroused much interest and discussion among organic chemists at the time, without a feeling of regret; the difference of opinion at least hastened the application of Malaprade's beautiful reaction to the study of carbohydrate structures and thereby gave to all a new tool of great usefulness, the value of which is evident from its extensive and increasing use in present carbohydrate researches in many laboratories."

The years spent at the National Institutes of Health saw the publication of much of Hudson's best work. He attracted to his laboratory many workers who have subsequently come to occupy important positions of leadership in chemical research both in the U.S.A. and in other countries. As time went on there appeared to be no sign of slackening in interest or in his astonishing powers of concentrated work and to all who knew him it came as a great surprise that in 1951 he had reached the age of 70 and was due to retire. Nevertheless retirement to him meant little in the way of relaxation. It gave him more time to devote to editorial work for the series of volumes of " Advances in Carbohydrate Chemistry " in the inauguration of which he had played a large part. He continued to be interested also in drawing up rules of nomenclature for the carbohydrate group and played a prominent part in the discussions which resulted in the set of rules which in all essentials have now been jointly agreed upon by both American and British carbohydrate workers.

Another activity in which he maintained great interest was the " Starch Round Table " which he, Norman F. Kennedy, and William B. Newkirk started in 1939 as an annual conference at which chemists, mainly from the United States and Canada but with invited guests from other countries, could meet to discuss problems in the chemistry and technology of starch and related carbohydrates. The number of those attending is kept small and the discussions, which are usually held in some pleasant country resort, are informal and extraordinarily successful.

Hudson had little time to enjoy such leisure as his official retirement brought him. While still busily engaged in preparing for publication reports of work which had been completed before he left the National Institutes of Health, and in editing a new volume of the " Advances in Carbohydrate Chemistry " he died suddenly on December 27th, 1952, at the age of 71. By his death the world lost one of its leading exponents of organic chemistry whose long period of activity covered a decisive phase in the development of our knowledge of the carbohydrates. He was an inspiring leader and his influence is spread far beyond his own laboratory and is seen in many flourishing schools of research established by his pupils and associates. Friendly and informal in manner he nevertheless inspired in those he met a wholesome respect and admiration, and the essential bigness of his character could not be hidden by his outward informality. He demanded much of himself and expected it of those collaborating with him. Generally patient and sympathetic as a supervisor of research and in discussions there was nevertheless one thing which moved him to wrath—pretentiousness and glib argument based on what he considered to be insufficient experimental evidence. His own standards in this were extraordinarily high and one of his major contributions to knowledge lies in the innumerable exact descriptions he has given for the preparation of sugars and sugar derivatives of the highest degree of purity It may be said of him more truly than of most to whom the remark is applied that he lived for his work. He had a fund of stories of life in his beloved southern states and was most entertaining in conversation, but his heart lay really in carbohydrate chemistry and in matters closely related to it such as the growing of plants which contained rare sugars. Many tales are told of the intense concentration he invariably brought to bear on problems of the moment. In his laboratory everything, no matter how urgent, had to wait when Hudson was crystallising some intractable syrup. More awkward still was the predicament in which he and many others found themselves when Hudson, driving his motor car, went into an apparent trance while waiting for traffic lights to change, having just then had an inspiration concerning a possible proof of the structure of turanose.

Hudson was married four times. By his first wife he had a son and two daughters. The son, William Abbott, born in 1907, served as a corporal in the Eighth Air Force and died in England early in 1945 while on active service.

Despite the difficulties Hudson encountered in early life before he found a post in which his special qualities could reveal themselves, the novelty and importance of his work was quickly recognised. As early as 1912 Emil Fischer spoke of Hudson's Rule for lactones of the sugar group, and in 1916 he was awarded the Nichols Medal of the New York Section of the American Chemical Society. Election to membership in the National Academy of Sciences came in 1927. The Chicago Section of the American Chemical Society gave him the Willard Gibbs Medal in 1929, the Washington Section the Hillebrand Prize (1931), and the Northeastern Section the Richards Medal (1940). The American Chemical Society awarded him the Borden Medal in 1941 and he received the Cresson Medal of the Franklin Institute in 1942. He was a member also of the Kaiserlich Deutsche Akademie der Naturforscher (Halle). In May 1949 he was elected to the Honorary Fellowship of the Chemical Society, and in the following year he received the first Federal Security Agency Award and the Grand Prize of the Sugar Research Foundation.

Hudson derived very special satisfaction from the award of the Honorary degree of Doctor of Science given him by Princeton University at their Bicentennial Convocation on 22nd February 1947. Another of his great joys was the possession of a gold watch and chain which had belonged to Emil Fischer. After his death these were returned to H. O. L. Fischer. The originals of all his medals he gave to Princeton.

In 1946 his friends in industry and in academic circles combined to honour his 65th birthday by holding a symposium and publishing in book form the 247 original papers which had come from Hudson's laboratories up to the end of June 1945. The occasion was marked by a banquet under the auspices of the Division of Sugar Chemistry and Technology of the American Chemical Society at which one of the appreciatory addresses was given by Sir Norman Haworth. Five years later, on January 25th, 1951, another banquet was held in his honour to celebrate his 70th birthday. This was attended by members of the various divisions of the National Institutes of Health, and by representatives from many other government departments, Universities, and Research Institutes. Congratulatory messages were received from friends and admirers on both sides of the Atlantic and many speakers paid tribute to the contributions made by Hudson to the cause of science during the previous half-century. It was, however, particularly appropriate that one of the speakers should be Nelson K. Richtmyer who had been a colleague of Hudson's at Bethesda since 1934, and spoke as a representative of the "Undergraduates of Hudson University." For great as Hudson's own contributions had been both in theory and in experimental work, he has an even greater claim to fame in the inspiration which he gave to so many who came under his influence and are now actively engaged in carbohydrate chemistry in centres to be found all over the world.

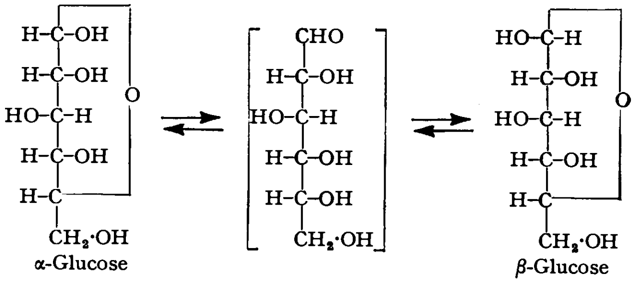
Hudson's first researches were concerned with problems of mutarotation and much of his later work can be regarded as a logical development of his early discoveries. When he began work extensive information was available about the physical properties of the monosaccharides and thanks mainly to the insight of Emil Fischer the configurations of many of them were known. But the detailed structures were in every case obscure and little was known with certainty concerning the phenomenon of mutarotation. Many suggestions had been made, including a change from an anhydrous to a hydrated form by analogy with the hydration of lactones. Alternatively a change from a supermolecular aggregation to a unimolecular form, or from open-chain aldehydic to cyclic hemiacetal forms of the type then accepted for the two methyl glucosides, had been postulated. The case of lactose which Hudson chose to study was particularly complicated for no less than two anhydrous and two hydrated forms were known. In the first instance he regarded the problem as one of the physical chemistry of hydration and by quantitative measurements of the heats of solution and other observations he showed that one of the supposed forms of lactose was not a chemical individual but a mechanical mixture of two of the other forms. In 1903 he demonstrated that this mutarotation involved a reversible unimolecular reaction in which two of the forms came into equilibrium. Proof of this came from kinetic studies which involved for the first time the use of the powerful technique by which the rate of solution of a single pure form of the sugar was studied. For example, the concentration of α-lactose hydrate was maintained constant by continuous shaking of the solution at 0° in the presence of an excess of the powdered solid, whilst the increase of solubility with time and the accompanying rotation changes were studied. By an extension of this device it subsequently became possible, given one form of a sugar in a pure condition and a knowledge of the mutarotation data, to calculate the rotation of the anomer. In this early work on lactose it became clear that hydration of the α-form was a very rapid reaction independent of the mutarotation reaction, which could be regarded as α-lactose $\rightleftharpoons$ β-lactose. In 1908 he summarised the results obtained with lactose by the accompanying equation in which the second balanced reaction is the one involving

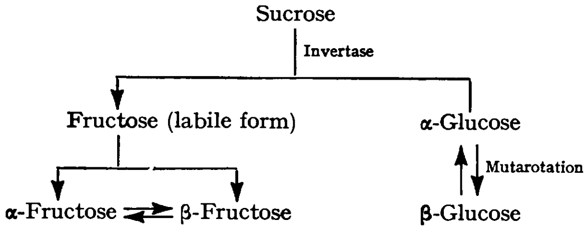
Mutarotation of lactose

$$\alpha\text{-Form} + H_2O \underset{\text{(Fast)}}{\rightleftharpoons} \text{hydrated form} \rightleftharpoons H_2O + \beta\text{-form}$$

mutarotation. The way was prepared therefore for the modern concept that mutarotation involves the interconversion of cyclic forms of a reducing sugar. This had in fact been suggested by von Lippmann in 1895, but no detailed mechanism could then be put forward. That mutarotation involved a reversible reaction was in fact first suggested by T. M. Lowry (1899), but Hudson's independent work provided the first experimental proof. Arising out of these studies came his investigation into the effects of hydrogen and hydroxyl ions on the rate of mutarotation of glucose, during which he established the relations generally accepted, and incidentally provided yet another method for determining the dissociation constant of water. The formula for the rate of mutarotation of glucose at 25° in aqueous solution was expressed as $k = 0{\cdot}0096 + 0{\cdot}258[\mathrm{H}^{\cdot}] + 9750[\mathrm{OH}']$.

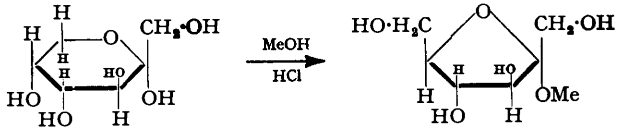
It was perhaps fortunate that the mutarotation phenomena shown by lactose were essentially straightforward in character despite the complications introduced by the existence of crystalline hydrates, and involved only the reversible transformation of two forms possessing the same ring structure. In other instances which have been studied more recently much greater complexities arise owing to the interplay of the α- and the β-varieties of both furanose and pyranose ring structure, with the additional possibility of the presence also of the open-chain aldehydic or ketonic form. Hudson's early work paved the way for investigations in these more difficult regions and he applied the new ideas himself in an examination of the changes which occur during the inversion of cane sugar by the yeast-enzyme invertase. As far back as 1890 O'Sullivan and Thomson had claimed that the inversion of sucrose by invertase was a unimolecular reaction, but the position had become confused as the result of later work which could not be satisfactorily interpreted until the nature of mutarotation had been ascertained. Hudson's work on lactose led him naturally to this more complicated problem. In a long series of articles he confirmed and extended the original work of O'Sullivan and Thomson, developing the physicochemical theory of rates of reaction to cover the new complications. One of the key experiments of this series involved the rapid hydrolysis of a quantity of cane sugar by use of a large excess of enzyme, when it appeared that the optical changes could be accounted for almost entirely by the mutarotation of the liberated reducing sugars. Shortly before this (1903), E. F. Armstrong had described his classical experiments on the correlation by enzymic methods of α- and β-glucose with the corresponding methyl α- and β-glucosides. This idea was then applied by Hudson in interpreting the detailed kinetic measurements made during the experiments on the hydrolysis of sucrose with invertase. It followed that the glucose residue in cane sugar was present as the α-glucoside. The fructose portion could not be identified and indeed the extremely labile β-fructofuranose which is now known to be the form in which the fructose first makes its appearance has never yet been isolated.





The results of this work were far-reaching, going much beyond the structural chemistry of sucrose. In the first place Hudson's pioneering researches did a great deal to establish a sound conception of enzyme action. He was the first to demonstrate the possibility of preparing invertase from yeast by rapid autolysis in the presence of water saturated with toluene. Salkowski had previously used toluene to prevent the putrefaction of the yeast during the autolysis, but Hudson employed it not merely as a bacteriostatic agent but as a chemical which induces a rapid autolytic reaction when there is sufficient of it present to saturate the mixture of yeast and water. His work in this field led also to the use of invertase in the exact analytical determination of sucrose by the Clerget procedure, and by suitable modifications of the enzymic method it is possible to determine sucrose and raffinose in admixture. More important still, it must be remembered that general ideas on the mode of action of enzymes were uncertain, to say the least, at the beginning of the century and Hudson's work did much to discredit finally the view that the chemical activity of enzymes was governed by some unknown and obscure force. Writing in 1908 he said: "May it not be that other enzymic reactions are, after all, quite similar to the usual types of chemical catalysis and do not constitute a group that has unique laws of catalytic action as is now generally believed." So different is the present day outlook that it seems hardly credible that such words were considered necessary less than 50 years ago.

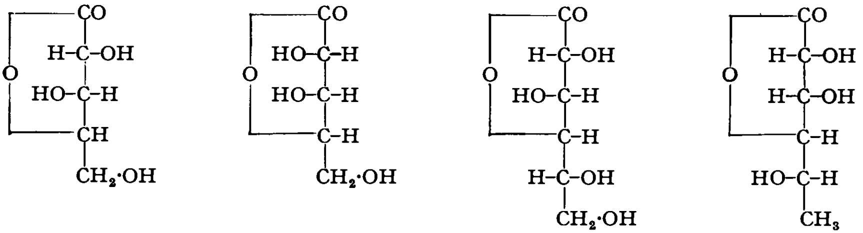
Hudson and his collaborators continued their interest in enzyme studies, particularly with regard to the fractionation and purification of the enzymic systems present in yeasts, and the mode of action of the purified enzymes on various substrates, Mildred Adams and N. K. Richtmyer being closely associated with much of this work. Similar problems relating to the action of the starch-splitting amylases were also investigated. One of the most spectacular results of the work on invertase came when Hudson and C. B. Purves showed that by the use of invertase it was possible to separate from the so-called "γ"-methyl fructoside, obtained by the controlled reaction of cold methanolic hydrogen chloride with fructose (I), a pure crystalline methyl fructoside having $[\alpha]_D$ +93° in aqueous solution. This was a typical "γ"-glucoside and was subsequently shown to be methyl α-D-fructofuranoside (II).



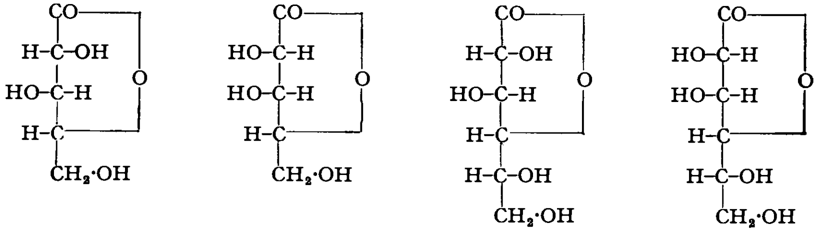
(I) (II)

One very important feature of this discovery was that it provided an accurate rotation of a member of the fructofuranoside group for use in connection with the isorotation rules which occupied Hudson's attention so markedly throughout his career. This aspect of his work once again followed directly and naturally from his early investigations on the mutarotation of lactose. In 1908 he began to collect from the chemical literature all the known specific rotations of the sugars and their derivatives. For the most part these numerical values constitute a chaos in which no signs of order have been detected, the exceptions to this statement being comprised in Hudson's Rules of Isorotation. The regularities he discovered are indeed most remarkable and when used with due caution they provide sugar chemists with a valuable means of elucidating structure, but perhaps the most astonishing thing about them is that they should be valid at all, since there is no sure ground in physical theory for the underlying principle of optical super-

Rotations of γ-lactones.



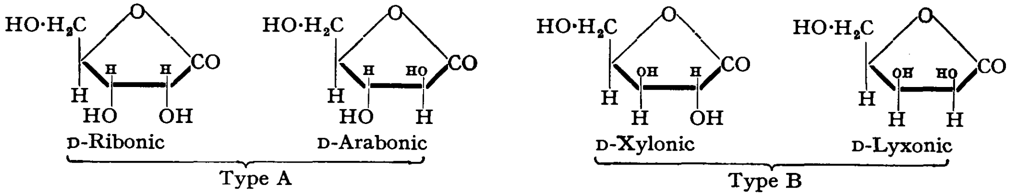
L-Arabonic (−74°) L-Ribonic (−18°) D-Galactonic (−78°) L-Rhamnonic (−39°)



D-Xylonic (+83°) D-Lyxonic (+82°) D-Gluconic (+68°) D-Mannonic (+54°)

position first enunciated by van't Hoff. Some idea of the problems involved may be gained from a consideration of the first of these rules which dealt with the sign of rotation of the lactones of the sugar acids. The rule was enunciated in 1909 (published early in 1910) in the following words : " Lactones of dextrorotation have the lactonic ring on one side of the structure, lactones of levorotation have it on the other, and the position of the ring shows the former position of the OH group on the γ-carbon atom." The rule was shown to apply to 24 different lactones which were then known and since 1910 many others have been added to the list. Some typical examples are given in the accompanying Table. This rule has been widely used by sugar chemists and in the great majority of instances it has been a reliable guide to structure, giving results which are in agreement with those ascertained by other methods. Much has been written of the high probability of the accuracy of this rule—stated to be millions to one in its favour—yet in the form in which it was first enunciated it fails in the case of D-allonic γ-lactone ($[\alpha]_D$ $-6{\cdot}8°$). This case however falls into line if the stipulation is made that when the OH is on the right in the Fischer projection formula the lactone is more dextrorotatory than the corresponding free acid. This rule is a qualitative expression and for many years Hudson believed that principles of optical superposition could not hold in the lactone group. This principle, first enunciated by van't Hoff, requires that if the partial rotation due to any one of several asymmetric carbon atoms is represented by $+A°$ then on replacement of that group by its mirror image the latter should be responsible for $-A°$ of the rotation of the new compound. In 1939 however he came to the conclusion that the isorotation and the superposition rule did apply approximately provided the lactones are divided into two types according to their known configurations. For instance, the molecular rotation differences (epimeric differences) between pairs of γ-lactones epimeric in respect of $C_{(2)}$ range between $-3400°$ to $-4000°$ in the group containing the pairs ribonic–arabonic; galactonic–talonic and pairs of lactones homomorphous with these, whereas in the other series (xylonic–lyxonic; gluconic–mannonic; etc.) small positive epimeric differences are found.

Lactones. Epimeric differences in molecular rotations.



Lactone	$[M]_D$	½ Epimeric diff.	Type
D-Ribonic	+ 2,660°	−3970°	A
D-Arabonic	+10,600		
D-Galactonic	−13,780	−3800	A
D-Talonic	− 6,170		
D-Manno-D-galaheptonic	−15,400	−3980	A
D-Manno-D-taloheptonic	− 7,430		
D-Xylonic	+13,590	+ 690	B
D-Lyxonic	+12,200		
D-Gluconic	+12,100	+1460	B
D-Mannonic	+ 9,170		

The isorotation rules cannot be applied to the free sugar acids, the rotations of which are usually small, and the greater regularities encountered in the lactone series probably have their origin in the great increase in rotation which is found in most cases to accompany ring formation. The centre at $C_{(4)}$ then becomes dominant in fixing the sign of the rotation but the complexity of the underlying physical phenomena is seen in the observation made in later studies of the anomalous optical rotatory dispersion of certain sugar lactones (Hirst and Wood, 1936) that the term $k/(\lambda^2 - \lambda^2_0)$ which really controls the sign of rotation in conformity with Hudson's rule contains a wave-length constant corresponding to absorption of light by the CO group at $C_{(1)}$. It is all the more remarkable therefore that so many useful regularities could be deduced from observations of rotations made at an arbitrary temperature and wave-length and in the one solvent (water).

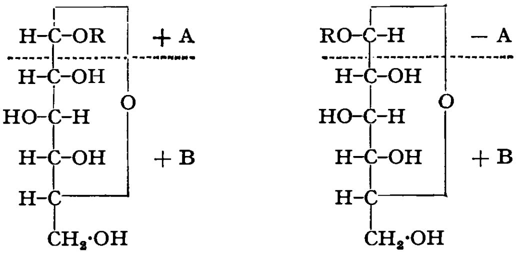
If the lactone ring is not present, then for many derivatives of the acid the centre at $C_{(2)}$ becomes dominant and several extremely useful rotation rules were developed by Hudson in this field. For example, the rotations of the phenylhydrazides of the acids conform to the rule (put forward in 1917) that the direction of rotation is to the right if the hydroxyl on the α-carbon atom is on the right in the Fischer projection formula, and its opposite.

Rotations of phenylhydrazides and amides of aldonic acids ($[\alpha]_D$ *in water*).

Acid	Rotation of phenylhydrazide	Rotation of amide	Configuration of $C_{(2)}$
D-Gluconic	+12°	+33·8°	Right
D-Gulonic	+13·7	+16·1	„
D-Galactonic	+11	+36·7	„
D-α-Glucoheptonic	+ 9·3	+10·6	„
D-α-Mannoheptonic	+21	+28	„
D-α-Galaheptonic	+ 8·5	+14·3	„
D-Mannonic	− 8	−29·9	Left
D-Arabonic	−14·5	−38	„

An exactly similar rule was found to apply in the amide group (1918) and also to the benziminazole derivatives of the aldonic acids (Richtmyer and Hudson, 1942). All of these have had a wide use in the development of sugar chemistry, their value being particularly evident in the determination of the configurations of the epimeric acids formed during the cyanohydrin synthesis of higher sugars.

Equally important results followed from Hudson's efforts to bring some order into the rotational relations exhibited by the sugars, their glycosides, and other derivatives. Starting with observations (1909) of the approximate constancy of the differences between the rotations of the known methyl α- and β-glycosides Hudson proceeded to build a vast edifice of structural relations on numerical data with the aid of two isorotation rules, which he reformulated in 1930 in the following terms. (1) " The rotation of carbon 1 in the case of many substances of the sugar group is affected in only a minor degree by changes in the structure of the remainder of the molecule." (2) " Changes in the structure of carbon 1 in the case of many substances of the sugar group affect in only a minor degree the rotation of the remainder of the molecule." It is worth mentioning that these rules go far beyond predictions which could be made from the van't Hoff theory of optical superposition. The latter assumed that the rotations contributed by a given set of asymmetric centres were additive, but in the various glycosides the centres in the bulk of the molecule are not identical and make various and very different contributions. According to the rules enunciated by Hudson the rotation of an alkyl glycoside is to be regarded as made up of two parts (1) A, contributed by $C_{(1)}$ and (2) B the sum total of the rotatory contributions of the other centres.



If these rules are valid it follows that the sum of the molecular rotation values, 2B, should have a numerical value characteristic of the sugar concerned and independent of the nature of R. On the other hand the difference of the rotation values, 2A, should be independent of the nature of the sugar, but will carry its own particular value. The value of B would be expected to vary for any one sugar according to the nature of the ring system present. For instance, the 2B value for the glucopyranose residue, calculated from the rotations of the ethyl glucosides is 24,000, whereas for the glucofuranose ring it is 2500. Now for glucose itself, when the rotation values for α- and β-glucose are used, 2B is 23,600, strong evidence being thus provided for the presence of the pyranose ring structure in α- and β-glucose.

The regularities hold over a very wide range including simple sugars, oligosaccharides, and polysaccharides and some typical examples will be found in the accompanying Tables, but no attempt can be made here to illustrate the wealth of material assembled by Hudson and his colleagues during some 40 years of work on these problems. At this point it is appropriate to make special reference to the lengthy series of investigations, with which the name of R. M. Hann is particularly associated, on syntheses of the higher-carbon sugars and their derivatives, undertaken primarily in order to obtain data for comparison of the rotations of these substances with those of the configurationally similar hexoses and pentoses. All types of derivatives were prepared and examined and the mass of information thus obtained concerning methods of preparation of sugars and their derivatives, together with the accurate determinations of the physical properties of the pure substances, must be regarded as one of Hudson's major achievements in organic chemistry.

By means of sets of coefficients derived by aid of the rules from the rotations of known substances the rotations of substances then unknown were calculated, and on synthesis of these materials excellent agreement was usually found between the observed and the predicted values. So certain did the validity of the rules appear to be that to those working in the field the failure of a new substance to conform implied impurity of the material under examination rather than an exception to the rules, and in many instances this has subsequently been found to be the correct explanation. Certain groups of substances, however, required special treatment. It is perhaps not unexpected that the rotational relations between the various substituted phenyl glucosides proved to be complicated, and, as in the case of the lactones, attempts to go to extremes by calculating coefficients for each of the carbon atoms of the hexose chain achieved little. Nevertheless the area of agreement was large and that of anomalous cases small, with the result that Hudson could write in his summarising paper of 1930 :

Substance	$[\alpha]_D$	Molecular rotation	2A	Substance	$[\alpha]_D$	Molecular rotation	2A
α-D-Glucose ...	+109°	19,600	16,000	α-D-Lyxose	+ 5·5	825	6,225
β-D-Glucose ...	+ 20	3,600		β-D-Lyxose	−36	−5400	
α-D-Galactose	+140	25,200	15,700	α-L-Rhamnose ...	− 8	−1300	10,050
β-D-Galactose	+ 53	9,500		β-L-Rhamnose ...	+54	8750	
α-D-Lactose ...	+ 86	29,400	17,400	4-β-Glucosido-α-mannose	+20	6840	7,182
β-D-Lactose ...	+ 35	12,000		4-Glucosido-β-mannose	− 1	− 342	
α-D-Mannose ...	+ 30	5,400	8,460				
β-D-Mannose ...	− 17	−3,060					

Illustrations of the first and second rules of isorotation.

Substance	$[M]_D$ (in water)	2B	2A
Methyl α-D-glucoside	+30,830°		37,460
Methyl β-D-glucoside	− 6,630		
Methyl α-D-xyloside	+25,200		35,900
Methyl β-D-xyloside	−10,700		
Methyl α-gentiobioside	+23,318		36,118
Methyl β-gentiobioside	−12,800		
Methyl α-D-glucoside	+30,830	24,200	
Methyl β-D-glucoside	− 6,630		
α-D-Glucose	+20,300	23,720	
β-D-Glucose	+ 3,420		
Glycol α-D-glucoside	+30,350	23,510	
Glycol β-D-glucoside	− 6,840		

Values of 2A *for methyl glycopyranosides.*

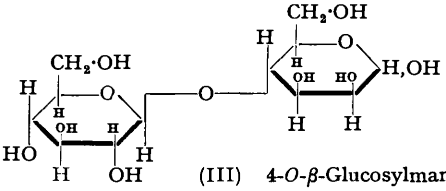
Substance	2A	Substance	2A
D-Glucose	37,500°	D-Galactose	38,220°
D-Glucose *	39,300	L-Arabinose	37,460
D-Glucofuranose *	38,300	D-Mannose	28,930
D-Gulose	39,390	L-Rhamnose	28,140

* Ethyl glucoside.

"The correlation of structures and optical rotating powers among substances of the sugar group . . . has yielded so far the following seven principal results : (1) proof that the stable lactones of the monobasic acids derived from the monosaccharides are γ-lactones, (2) a system of nomenclature for distinguishing the alpha and beta forms of the sugars and their principal derivatives, (3) determination of the hitherto unknown configurations of some of the sugars (*e.g.*, rhamnose, fucose, gluco-octose), (4) proof that amygdaloside is a glycoside of gentiobiose, (5) proof that several of the ketonic sugars (sorbose, tagatose, mannoketoheptose and glucoheptulose) exist in solution only as alpha forms and consequently do not exhibit mutarotation, (6) proof that the methylation of glycosides often involves a ring shifting, and (7) proof of the ring structure of most of the monosaccharides and compound sugars." The first five of these claims have been upheld, but (6) and (7) which had no foundation in fact require some further discussion.

Reference to the Tables of 2A values reveals that for glucose, galactose, and certain other sugars in which the OH groups on $C_{(2)}$ and $C_{(3)}$ are situated *trans* to one another, the value of 2A is approximately 38,000. On the other hand, for mannose and rhamnose and similar sugars in which these OH groups are *cis* to one another the value of 2A is only some 29,000. Hudson interpreted this as indicating a difference in ring form between the methyl α-mannoside and the methyl β-mannoside, rather than a failure of the rules. A furanose structure was arbitrarily assigned to methyl α-mannoside and on this basis a complete scheme of sugar structures was erected, consistent as regards rotation values, but opposed to the chemical evidence based on the methylation procedure which clearly demanded a pyranose structure for methyl α-mannoside. The clash was direct and admitted of no compromise. Hudson maintained his belief in the isorotation rules and was inevitably compelled to claim that methylation of methyl α-mannoside involved a change of ring from the furanose to the pyranose structure. At this stage fate played a trick on him which he scarcely deserved. The rotations of the alkyl glucofuranosides became known and by sheer coincidence the molecular-rotation difference between corresponding members of pyranose and furanose type was close to 10,000, this value being identical with the amount by which the rotation of ordinary methyl α-mannoside differed from Hudson's calculated value for the pyranose form of methyl α-mannoside. He hailed the new evidence as convincing proof of the correctness of his views and fitted it into the comprehensive scheme of structures for monosaccharides and disaccharides and their derivatives which is elaborated in the paper presented at the International Conference at Liège (1930).

It was inconceivable to organic chemists who were familiar with the Purdie reaction that such a change of ring could take place during methylation, and the Birmingham School sought a final decision by preparing from cellobiose a substance (III) (4-*O*-β-glucosylmannose) in which the occurrence of a furanose ring in the mannose residue is ruled out by the nature of the disaccharide linkage. It was found that the rotations of the α- and the β-form of this disaccharide give a value of 2A (7182) similar to that found for α- and β-mannose but very different from the larger



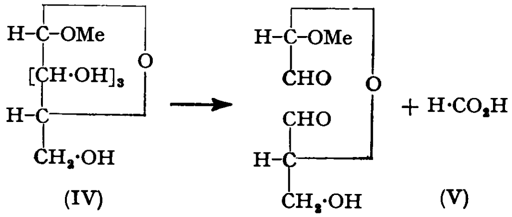
(III) 4-*O*-β-Glucosylmannose.

value (16,000) given by glucose, galactose, and other sugars of this group, all of which have *trans*-situated hydroxyl groups at $C_{(2)}$ and $C_{(3)}$. Similar results (2A = 7500) were found when the corresponding disaccharide 4-*O*-β-galactopyranosylmannose was synthesised from lactose. It was then clear that a great part of the structural use of Hudson's isorotation rules must be abandoned and it is now accepted that mannose, rhamnose, lyxose, and other sugars which possess *cis*-hydroxyl groups at $C_{(2)}$ and $C_{(3)}$ must be treated separately, their rotational behaviour being influenced by their configuration, possibly by way of variations in the conformation of the pyranose ring.

Hudson accepted, albeit with some reluctance, the evidence based on the 2A rotational values for 4-glucosyl- and 4-galactosyl-mannose, but returned to the United States determined to find a completely independent method, resting neither on isorotation rules nor on methylation processes, by which the ring structure of glycosides could be determined. In the first instance he examined exhaustively the possibility that methyl α-mannoside might be resolvable into two compounds, as he had previously demonstrated with a double crystal of methyl α- and β-xylosides. This, however, proved to be a fruitless task and it was not until some time later that observations by E. L. Jackson on the oxidation of methyl glucoside by alkaline hypobromite brought into discussion Malaprade's work (1934) on the oxidative fission of glycols, and led Hudson to realise that the very method he had been looking for was available in oxidation by periodic acid. The reaction is highly selective and in Hudson's hands it was applied with conspicuous success from 1936 onwards to a wide range of problems in carbohydrate chemistry. The main reactions are shown in the accompanying equations and it will be seen that differentiation can readily be made between furanose and pyranose rings in methyl glycosides. For example, the α-form of methyl D-hexopyranoside (IV) gives rise to a dialdehyde

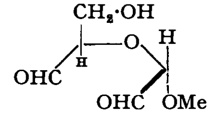
(V) containing 5 carbon atoms and one mol. of formic acid, two mols. of periodic acid being required. No formaldehyde is produced. On the other hand, the corresponding methyl α-D-furanoside would yield one mol. of formaldehyde but no formic acid, and would again consume two mols. of periodic acid during the oxidation. The consumption of periodic acid and the nature of the reaction products provide evidence of the nature of the ring system. The reaction, however, goes much further and gives important information when applied to many other problems. For instance, Hudson and Jackson used it to prove the configuration at $C_{(1)}$ of the methyl α- and β-glycosides. Inspection of the formula shown above reveals that during the oxidation of a methyl α-D-hexopyranoside the optically active centres at $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$ disappear. Now the configuration at $C_{(5)}$ determines the series, D- or L-, to which the sugar belongs, whilst the configuration at $C_{(1)}$ controls the type of glycoside. It follows that in the D-series of sugars all those methyl hexopyranosides which have the methoxyl group below the plane of the ring in the Haworth formula should give rise to one and the same dialdehyde (*A*). Similarly all those having the methoxyl group above the plane should give rise to one and the same dialdehyde (*B*) which differs from (*A*) only in the configuration at the carbon atom which was formerly $C_{(1)}$. Since the configuration at $C_{(1)}$ of the methyl α- and β-glucosides is known from other considerations the periodate oxidation procedure provides a method for determining the configuration of all the methyl D-glycopyranosides. In the pentapyranoside series the position is even simpler since $C_{(5)}$ is not an optically active centre and the two substances obtainable as reaction products (*A* and *B* with $CH_2{\cdot}OH$ replaced by H) are now mirror images. In practice the aldehydes are somewhat awkward to handle and Hudson and Jackson introduced a further stage of oxidation in which the $\cdot CHO$ groups were transformed into $\cdot CO_2H$, the final products being isolated as salts. In the hexose series it was found that the α-D-glycosides gave rise to an easily crystallisable strontium salt, whereas the barium salt was preferable for the β-glycosides.

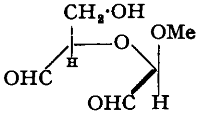
$$R'{\cdot}CH(OH){\cdot}CH(OH){\cdot}R' \longrightarrow R{\cdot}CHO + R'{\cdot}CHO$$
$$R'{\cdot}CH(OH){\cdot}CH(OH){\cdot}CH(OH){\cdot}R' \longrightarrow R{\cdot}CHO + H{\cdot}CO_2H + R'{\cdot}CHO$$
$$HO{\cdot}CH_2{\cdot}CH(OH){\cdot}R \longrightarrow H{\cdot}CHO + R{\cdot}CHO$$
$$CH_3{\cdot}CH(OH){\cdot}CH(OH){\cdot}R \longrightarrow CH_3{\cdot}CHO + R{\cdot}CHO$$



(IV) (V)

(*A*)



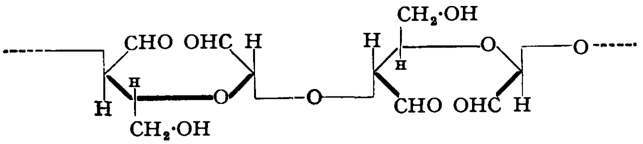


(*B*)

Evidence for the configuration at $C_{(1)}$ can be obtained even more simply by another method worked out in Hudson's laboratory. The various glycosides have different rotations but as oxidation proceeds some of the carbon atoms lose their dissymmetry and in the case of any methyl glycoside of the D-hexopyranose group the final product must be either (*A*) or (*B*). Since (*A*) and (*B*) differ markedly in their rotatory powers, observations of the rotation of the solution during the oxidation will provide evidence for assigning any given methyl hexopyranoside or methyl pentofuranoside to the α- or the β-group. Closely similar methods permit corresponding results to be achieved for the pentopyranosides.

The importance of this new approach lay in the first place in the independent proofs thus provided of the structure of the methyl glycosides and of their configuration at $C_{(1)}$. In all the instances examined the results were in complete agreement with those of the methylation method in regard to the size of ring, and the configurations of the methyl glycosides thus determined were identical with those previously allocated on the basis of the isorotation rules.

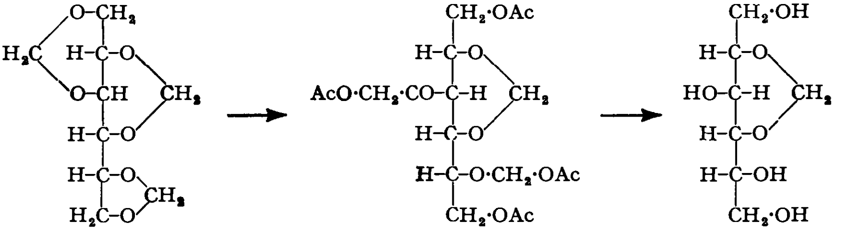
Numerous applications of this method of oxidation were soon made to sugar anhydrides, to partly substituted sugars, and to cyclic acetals, and during these developments Hudson made some of his rare incursions into the polysaccharide field. Here again he, like many who have followed him, found periodic acid to be a most versatile reagent. Applying it to cellulose and starch in 1938 Jackson and Hudson obtained evidence in support of the accepted ring structures of the glucose residues present in these polysaccharides, each 1 : 4-linked glucopyranose unit giving rise to a dialdehydic structure on consumption of one mol. of periodic acid per residue.



Oxidation of cellulose with periodate

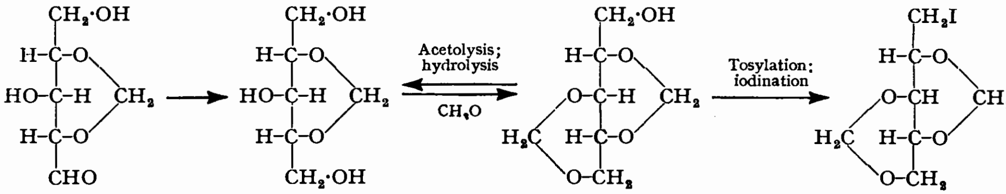
The products, which are polymers built up of residues of erythrose and glyoxal, still have a high molecular weight, but they are extremely sensitive to alkali and Hudson did not pursue the investigations.

The periodate oxidation method provided a new tool for the investigations of the chemistry of the cyclic acetals of the sugar alcohols, and much of Hudson's later work was concentrated in this field which has yielded results of great theoretical interest in addition to new and useful methods of synthesis. With its development the name of R. M. Hann is closely associated. The general scope of the problems may be illustrated by reference to the cyclic methylene acetals of D-sorbitol. When formaldehyde combines with D-sorbitol a trimethylene derivative is formed and evidence is required concerning the structure of this substance. It cannot be assumed that the six hydroxyl groups act in consecutive pairs giving three five-membered rings, leading to the structure 1 : 2-3 : 4-5 : 6-tri-*O*-methylene D-sorbitol, since it is known that 5-, 6-, and 7-membered rings can be formed in similar reactions and that the course of the reaction is much influenced by the stereochemical configuration of the hexitol. It was proved, indeed, that this particular tri-*O*-methylenesorbitol (VI) contains rings in which the methylene groups engage the hydroxyl groups at positions 1 : 3, 2 : 4, and 5 : 6, severally, two of the rings being six-membered and the other five-membered. Proof of structure was derived from the following considerations. When the trimethylene derivative was treated with acetic anhydride and acetic acid containing a little sulphuric acid two of the rings are cleaved and in earlier work it had been shown that this reagent will break only those O–C bonds in which a primary alcoholic group is involved, with formation of a tetra-acetyl derivative (VII). Methylene residues attached through secondary alcoholic positions are unaffected. Deacetylation now yielded a monomethylene derivative (VIII) in which the points of attachment of the ring were shown in the following way to be $C_{(2)}$ and $C_{(4)}$. The substance reacted with one mol. of periodic acid with formation of one mol. of formaldehyde and one mol. of a monomethylenepentose sugar (IX). It followed that the monomethylenesorbitol contained only one unsubstituted glycol unit and that this glycol unit included a primary alcoholic group. Reduction of (IX) gave a methylenepentitol (X) which was stable to periodic acid and was shown to be derived from xylitol. It followed that the methylene group in the pentitol and hence also in the monomethylenesorbitol was attached in the 2 : 4-position. If now the possible methylene acetal structures are limited to those containing 5-, 6-, or 7-members it follows that the original trimethylenesorbitol had the structure (VI). Confirmatory evidence was found in the discovery that in the reaction between D-sorbitol and formaldehyde a dimethylene derivative is also produced and this was shown independently to have the structure 1 : 3-2 : 4-di-*O*-methylene-D-sorbitol. The monomethylenexylitol (X) is internally compensated and



(VI) (VII) (VIII)

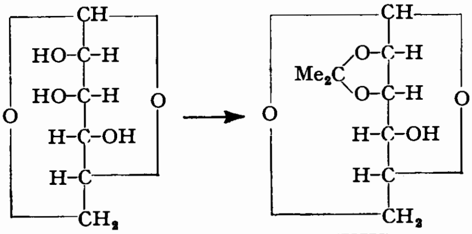
optically inactive, but when condensed with formaldehyde it gives a racemic dimethylene derivative (XI) in which the single OH group is primary alcoholic in nature, as shown by the results of the reaction with toluene-*p*-sulphonyl chloride, followed by treatment of the product with sodium iodide in acetone (to give XII). Selective acetolysis of the dimethylenexylitol followed by hydrolysis of the acetyl and acetoxymethyl groups gives back the *meso*-2 : 4-*O*-methylenexylitol (X). The structures of all these compounds in the sorbitol and xylitol series were thus established by unambiguous inter-related methods.

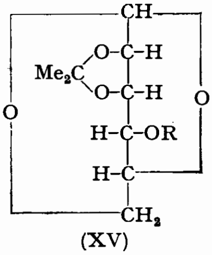


(IX) (X) (XI) (XII)

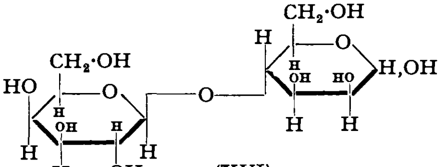
This however is merely a simple example selected to illustrate the types of methods employed by Hudson, Hann, and their collaborators in wending their way through all the intricacies of the 5-, 6-, and 7-membered acetal rings which were encountered in their detailed studies of the acetals of mannitol, sorbitol, dulcitol, adonitol, arabitol, xylitol, fucitol, iditol, rhamnitol, *epi*rhamnitol, *gluco-gulo*-heptitol, talitol, and perseitol. In this work much has been learned of the unexpected effects of *cis–trans*-isomerism, of the migration of ester groups, and of the relative reaction rates for the formation of the various types of ring systems. It appears, for instance, that the most favourable positions for methylene acetal formation involve β-situated secondary hydroxyl groups *cis* to one another in the Fischer projection formula, giving rise to a six-membered ring. The next most likely reaction would involve a 7-membered ring formed about secondary hydroxyl groups which are *trans* and γ in their relations. Next comes a 6-membered ring involving a primary alcoholic group. Formation of a five-membered ring including a primary alcoholic group is still less probable in competition with the other possibilities.

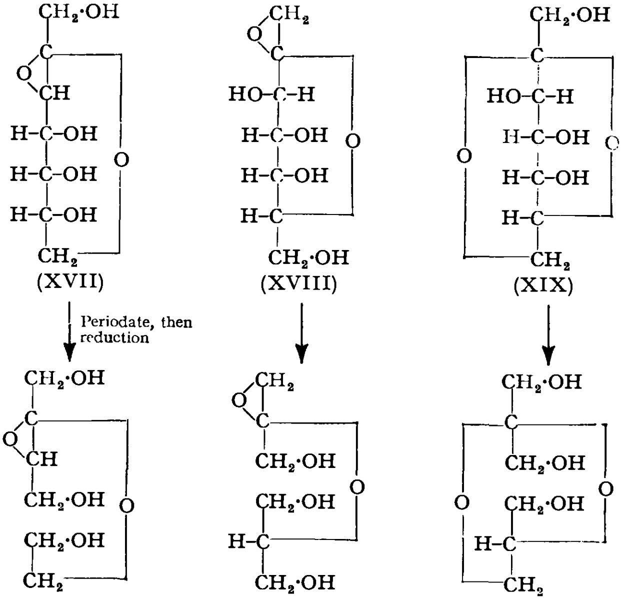
Much progress has been made also by Hudson and Hann in the use of cyclic acetals for syntheses. An important starting point in this work was the D-mannosan (XIII) which can be obtained by the dry distillation of ivory-nut mannan. It readily yielded the 2 : 3-*O*-*iso*propylidene derivative (XIV) which possesses a free hydroxyl group at $C_{(4)}$. Methylation then gave the 4-*O*-methyl derivative (XV) and, after hydrolysis and opening of the anhydro-ring, 4-*O*-methylmannose was obtained, a substance of great interest in connection with the isorotation rules. Of still greater interest is the use of (XIV) as an intermediate substance in unambiguous routes to the synthesis of disaccharides. Condensation with acetobromo-D-glucose and acetobromo-D-galactose gave (XV) in which R was tetra-*O*-acetyl-β-D-glucosyl and tetra-*O*-acetyl-β-D-galactosyl respectively. The *iso*propylidene group was removed with acetic acid and the 1 : 6-anhydro-ring was opened by controlled acetolysis, the products being respectively an acetylated 4-*O*-β-glucosidylmannose and an acetylated 4-*O*-β-galactosylmannose from which the free sugars (III) and (XVI) were obtained. By a series of known reaction steps the epimers cellobiose and lactose were then prepared. These transformations provided for the first time by synthetic methods unambiguous confirmatory evidence of the structures previously proved by degradative procedures.


(XIII) (XIV)


(XV)

It is clear, therefore, that Hudson's work in the sugar field covered a wide range of topics and that in all he entered upon he made notable contributions. It is difficult to say which of these had the greatest influence on the development of carbohydrate chemistry, but there can be no doubt of the inspiration given to other workers and of the lasting benefit to his subject provided by one of the less spectacular of his activities. He took a keen interest in the chemistry of naturally occurring substances, and he had a flair for devising methods of extraction and purification and for preparing in the purest possible state a host of derivatives, which he described in meticulous detail. When comments were made about this towards the end of his life he replied that all his early training had been in the exact measurements of physical chemistry and that his knowledge of organic chemistry was entirely self-taught. It is perhaps appropriate therefore to conclude this brief account by reference to a topic of this kind which spanned almost all his working career. In 1917 La Forge and Hudson isolated from the plant *Sedum spectabile* a new sugar which was subsequently named sedoheptulose. At that time it was merely a chemical curiosity but it has recently assumed a quite unexpected importance by reason of its occurrence at an early stage in photosynthesis (Calvin). The chemistry of sedoheptulose is unusual and its study has been actively pursued by N. K. Richtmyer in Hudson's laboratories at Bethesda. The sugar has a configuration of the altrose type and gives rise to normal derivatives of pyranose structure. It resembles altrose but differs from most sugars in its capacity to give with acids an anhydro-derivative (sedoheptulosan), the structure of which has proved unexpectedly difficult to determine. Reaction with periodate revealed the presence of 3 contiguous secondary hydroxyl groups, indicating one of the three structures (XVII—XIX). The oxidation product after reduction and hydrolysis gave glycerol which could arise from (XXI) or (XXII) but not from (XX), and from this it followed that sedoheptulosan could not be (XVII) (1951; details published posthumously in 1952). This conclusion was supported by the results obtained by methylation of the sedoheptulosan, followed by oxidative degradation. The product, contrary to earlier reports, was conclusively proved to be D-*arabo*trimethoxyglutaric acid. The final choice between (XVIII) and (XIX) rests on various pieces of evidence one of which involved a study of the rate of oxidation with periodate. A substance of structure (XVIII) would react only slowly


(XVI)



(XVII) (XVIII) (XIX)

(XX) (XXI) (XXII)

with the reagent after formation of the initial dialdehyde, whereas (XIX), the dialdehyde from which can act as a furanose sugar, would complete its uptake of periodate rapidly. The product would then be a formyl ester which would hydrolyse slowly, giving formic acid. This is precisely how sedoheptulosan reacts and the choice of (XIX) for its structure is confirmed by the failure of tetra-*O*-toluene-*p*-sulphonylsedoheptulosan to react at 100° with sodium iodide. Although this derivative contains a primary toluene-*p*-sulphonyloxy-group its behaviour is exactly similar to that of other known examples of 1-toluene-*p*-sulphonyl ketose derivatives. Other arguments in favour of (XIX) are the stability of sedoheptulosan to alkali and the fact that the dibasic acid obtained by bromine oxidation of the dialdehyde resulting from reaction with periodate is highly resistant to acid hydrolysis. The behaviour here runs parallel with that of levoglucosan (the 1 : 6-anhydride of D-glucose) and is readily understood in view of the structure of the dibasic acid which is in fact a derivative of 1 : 3-dioxolan. This brief account of sedoheptulosan serves to illustrate the ingenuity of method and argument which Hudson and his colleagues brought to bear on this complex and difficult field, but it must be remembered that this is one substance only of the many studied by them in the course of the past ten years.

Cyclic acetals and anhydro-sugars have recently acquired a new importance in carbohydrate chemistry. Their detailed structures are becoming known and the substances themselves are being used as starting materials in synthetic work. The simplicity and elegance of the methods of investigation which have been developed and the unambiguous nature of the conclusions are such that this whole chapter of work from Hudson's laboratory is likely to be regarded as a classic example of organic chemistry at its best.

While preparing this tribute to the memory of C. S. Hudson I have been privileged to have conversations with many of his friends and colleagues who joined with me in holding him in high regard as both a great man and a great chemist. To all those I express my thanks. I am particularly indebted to Professor C. B. Purves and Dr. Nelson K. Richtmyer for their kind co-operation in discussions, in the loan of manuscripts and figures, and in giving much friendly assistance in the preparation of this lecture.