a change of rotation for such solutions of (14.40) (0.007) (7) = 0.69°, or over half a degree, but Meyer did not find any appreciable difference at the two temperatures. With this error of half a degree plainly visible in his published work it is impossible to agree with him that such readings as 40.45° and 40.41° differ beyond his experimental error; and yet the deviation from the unimolecular order which he found the inversion of cane sugar by acids to show, depends on the reality of the difference between such measurements.[1]

The rates of the inversion of cane sugar and the mutarotation of glucose at different temperatures and acid strengths have been measured by various investigators, and it is possible to calculate from them the deviation which is to be expected from the unimolecular order due to the mutarotation of the glucose. The author has made such a calculation and finds the deviation to be, under the most favorable conditions of temperature and acidity, a very small quantity only about a tenth of 1 per cent. It agrees in magnitude and sign with the deviation which Armstrong and Caldwell found and it is quite possible that the mutarotation reaction is responsible for a portion of their deviation, but the change in the specific rotation of fructose which has been mentioned, causes a deviation in the same direction and the two possible causes of the deviation leave the matter still in doubt as to whether Armstrong and Caldwell's deviation is due to mutarotation, change of rotation of fructose, or a true exception to the law of mass-action, which latter view is the one that Armstrong and Caldwell hold. But there can be no reasonable further doubt regarding the cause of Meyer's deviation—it was due to experimental errors alone, and is opposite in sign to the deviation predicted by theory.

A REVIEW OF DISCOVERIES ON THE MUTAROTATION OF THE SUGARS.[2]

By C. S. Hudson.

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Dubrunfaut[3] discovered in 1846 that the specific rotation of a freshly prepared cold solution of crystalline glucose decreases from an initial value of about 110° to become constant at 52°. This phenomenon he named *birotation* but later discoveries have shown the name to be inappropriate and the better term *mutarotation*, which was introduced by Lowry[4] in 1899, has generally replaced it, though the word *multirotation*

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[1] See *Z. physik. Chem.*, **62**, 59–88 (1908).

[2] Presented at the Second Decennial Celebration of Clark University, Worcester, Mass., Sept. 15, 1909.

[3] *Ann. chim. phys.*, 18, 99–107 (1846); **21**, 178–80 (1847); *Compt. rend.*, **23**, 38–44 (1846).

[4] *J. Chem. Soc.*, **75**, 212–5 (1899).

is also in use. In addition to glucose the following crystalline sugars have been found to show mutarotation: lactose,[1] galactose,[2] arabinose,[3] maltose,[4] xylose,[5] fructose,[6] fucose,[7] rhamnose,[8] mannose,[9] rhodeose,[10] gentiobiose,[11] melibiose,[12] perseulose,[13] and several rare synthetic sugars. All of these sugars reduce Fehling's solution and combine with phenylhydrazine, proving that they are aldoses or ketoses and contain the carbonyl group; on the other hand such sugars as sucrose, raffinose, gentianose, and stachyose, and the polysaccharides starch, inulin, mannan, etc., and the glucosides salicin, amygdalin, helicin, arbutin, etc., none of which show the characteristic reactions for the carbonyl group, do not exhibit mutarotation. This proves that the mutarotation is in some way dependent upon the carbonyl group.

After Dubrunfaut's great discovery the next important observation on mutarotation was made by E. O. Erdmann[14] in 1855, who noticed that lactose occurs in two crystalline modifications, one having a higher rotation (86°) than that of the stable solutions (52°), and the other a lower rotation (36°), and each form showing mutarotation towards the same final rotation (52°). Erdmann measured the rates at which each form changes in rotation to that of the stable solution, but did not notice that the rates are the same in value and that this fact is of much theoretical significance. Many years later, after the principles of chemical dynamics became better known, the author[15] showed that these equal rates prove that the two changes of rotation are not different reactions but are opposite parts of one balanced reaction. In this way the mutarotation of lactose, and what is true of this sugar is doubtless true of all which show mutarotation, was proved to belong to the great class of balanced reactions.[16]

In 1859 Anthon[17] noticed that crystalline glucose forms its saturated solutions in cold water very slowly even when the mixing is vigorous; this fact was discovered for lactose by Mills and Hogarth[18] in 1879. It is now known that this slowness of the process of solution is caused by the same slow balanced chemical reaction, involving the carbonyl group,

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[1] E. O. Erdmann, *Fortschritte Physik.*, p. 13; *Fortschritte Chemie*, p. 671 (1855).

[2] Pasteur, *Compt. rend.*, **42**, 347–51 (1856).

[3] Parcus and Tollens, *Ann.*, **257**, 160–78 (1890).

[4] Soxhlet, *J. prakt. Chem.*, **21**, 283 (1880).

[5] Koch, *Pharm. Ztg. Russland*, **25**, 619, 635, 651, 667, 683, 699, 730, 747, 763 (1886).

[6] Jungfleisch and Grimbert, *Compt. rend.*, **107**, 390–3 (1888).

[7] Guenther and Tollens, *Ber.*, **23**, 2585–6 (1890).

[8] Parcus and Tollens, *Loc. cit.*

[9] Van Ekenstein, *Rec. trav. chim.*, **15**, 221–4 (1896).

[10] *Z. Zuckerind. Böhmen*, **25**, 297 (1902).

[11] Bourquelot and Hérissey, *Ann. chim. phys.*, **27**, 397–432 (1902).

[12] *Z. Ver. d. Zuckerind.*, **53**, 1050–9 (1903).

[13] Bertrand, *Compt. rend.*, **147**, 201–3 (1908).

[14] *Loc. cit.* Also *Ber.*, **13**, 2180–4 (1880).

[15] *Z. physik. Chem.*, **44**, 487–94 (1903).

[16] Using the same method Meyer later proved this for glucose, *Z. physik. Chem.*, **62**, 74 (1908). Cf. also Roux, *Ann. chim. phys.*, **30**, 422–32 (1903).

[17] *Dingler's poly. J.*, **151**, 213–23 (1859); **155**, 386–8 (1860); **166**, 69–71 (1862).

[18] *Proc. Roy. Soc. London*, **28**, 273–9 (1879).

which causes the mutarotation, and that it is a general property of all the aldehyde and ketone sugars.[1]

The first attempt to find the physical law which governs the rate of the mutarotation was made by Mills and Hogarth[2] in 1879, but the result was only an empirical formula and must be regarded as unsatisfactory. It is to Urech[3] that we owe the first real progress in this line. He showed by a series of experiments during 1882–5 that the mutarotation follows the law of unimolecular reactions. It is interesting, and to some minds instructive, to note that this correct beginning in the physico-chemical study of the long unsolved mutarotation reaction was coincident in time with the beginning of the modern theory of solutions and chemical dynamics. There can be little doubt that Urech's experiments, which are the starting point of all exact work on mutarotation, were suggested by the advances that were being made at that time in the study of chemical dynamics by the new physico-chemical school.

In 1888 Brown and Morris[4] and Arrhenius[5] observed that the freezing temperatures of glucose solutions remain unchanged during the process of mutarotation, which proves that the reaction which causes mutarotation is not a polymerization or dissociation of the sugar. More recently Roth[6] has detected a slight change in freezing temperature of concentrated solutions of anhydrous glucose on standing but this is doubtless due to hydration and does not alter the conclusion from the work of Brown and Morris and Arrhenius, because a polymerization or dissociation would also affect the freezing point of dilute solutions, and the investigators are all agreed that such an effect is not discernible.

In 1890 O'Sullivan and Tompson[7] noticed that the invert sugar which is produced by the hydrolytic action of the enzyme invertase on sucrose shows mutarotation; this fact was later investigated by E. F. Armstrong[8] and has been precisely studied lately by the author.[9] These researches have shown that the glucose which is liberated from sucrose is α-glucose and the fructose is a hitherto unknown form of this hexose, α-fructose; these facts show that sucrose has the constitution α-glucose $< >$ α-fructose. The new form of fructose has not as yet been obtained crystalline. This method for determining the constitution of the polysaccharides by studying the mutarotation of the sugars which are formed by their enzymotic hydrolysis was first used by E. F. Armstrong[2] in his correlation of the α- and β-methylglucosides with the α- and β-glucoses. In applying the method to other substances such as cane sugar where two mutarotating sugars are formed at the same time it is necessary to extend the theoretical considerations; a mathematical theory of the modified method of Arm-

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[1] Hudson, *Z. physik. Chem.*, 44, 487–94 (1903); THIS JOURNAL, 26, 1065–82 (1904).

[2] *Loc. cit.*

[3] *Ber.*, 15, 2130–3 (1882); 16, 2270–1 (1883); 17, 1547–50 (1884); 18, 3047–60 (1885).

[4] *J. Chem. Soc.*, 53, 610–21 (1888).

[5] *Z. physik. Chem.*, 2, 491–505 (1888).

[6] *Ibid.*, 43, 539–64 (1903).

[7] *J. Chem. Soc.*, 57, 920 (1890).

[8] *Ibid.*, 83, 1305–13 (1903).

[9] THIS JOURNAL, 30, 1160–6, 1564–83 (1908); **31, 655–64** (1909).

strong and an experimental demonstration of it has recently been published by the author.[1]

In 1895 Charles Tanret[2] discovered a new form of crystalline glucose which was found to have a specific rotation lower than that of the stable solution (52°), though its value increased to this on standing. This discovery is the complement to Dubrunfaut's and the two must cause chemists the world over to be grateful to French science, because more fruitful single discoveries in the chemistry of the carbohydrates have hardly been made. Tanret found the final rotation of glucose solutions to be the same whether the solution is made from the higher or the lower initially rotating form. He interpreted his results as proving that three forms of glucose exist, one of high rotation, one of low, and the third the form to which each of these changes in aqueous solution. About the same time Tanret isolated similar new crystalline forms of rhamnose, galactose and arabinose, and obtained Erdmann's lower rotating form of lactose practically pure. Tanret's striking discoveries immediately caused new interest to be taken in the problem of mutarotation. In 1899 Lowry[1] advanced the view that the mutarotation of glucose is caused by a balanced reaction between the highest and lowest rotating forms of the sugar, a view which may be expressed by the equation α-*glucose* $\rightleftarrows$ β-*glucose*. This explanation is essentially different from any that preceded it and later investigations have proved it to be entirely correct. On the other hand, Lowry did not support this hypothesis with any direct proof and it remained without such proof for several years. In 1902[3] the author published the same view as an explanation of the mutarotation of lactose, being at that time unacquainted with the publication of Lowry. The explanation may be expressed by the equation α-lactose $\rightleftarrows$ β-lactose, and experimental evidence for the view was given by measurements on the heats of solution of the three forms of lactose, which showed that the stable form to which α- and β-lactose change in solution is not a chemical individual, as Tanret had supposed, but is a mechanical mixture of α- and β-lactoses. In 1903 the author[4] measured the slow maximum rate of solution of α-lactose and showed that the slowness of dissolving, which had been discovered by Mills and Hogarth,[1] is caused by the balanced reaction which produces the mutarotation. By quantitative measurements the hypothesis of the balanced reaction was tested and proved, and the explanation which these measurements gave of the mutarotation of lactose was immediately accepted by such an authority as Nernst.[5] In the same year Lowry[6] published similar experiments on glucose and proved the suggestion which he had advanced in 1899. These questions of priority are here stated for the reason that E. F. Armstrong[7] has recently claimed for Lowry the discovery of the balanced reaction which causes the mutarotation, a claim which in the opinion of the author is entirely too broad.

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[1] *Loc. cit.*

[2] *Bull. soc. chim.*, **15**, 195–205, 349–61; **17**, 802–5.

[3] Princeton Univ. *Bull.*, April, 1902.

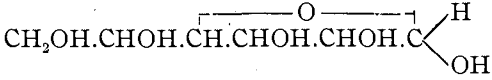
[4] *Z. physik. Chem.*, 44, 487–94 (1903).

[5] "Theoretische Chemie," ed. 1904.

[6] *Proc. Chem. Soc.*, **19**, 156–7 (1903); **20**, 108–9 (1904).

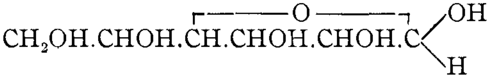
[7] "The Simple Carbohydrates and Glucosides," p. 8.

A very fruitful idea was advanced by Lippmann[1] in 1895 in the suggestion that the lactonic formula for glucose predicts two possible forms of the sugar on account of the asymmetry of the end carbon atom, the two structures being



$$\mathrm{CH_2OH.CHOH.\overbrace{CH.CHOH.CHOH.C}^{O}}\begin{matrix}\diagup H\\ \diagdown OH\end{matrix}$$

and



$$\mathrm{CH_2OH.CHOH.\overbrace{CH.CHOH.CHOH.C}^{O}}\begin{matrix}\diagup OH\\ \diagdown H\end{matrix}$$

This suggestion, after a slight development by Simon,[2] was made more probable by Armstrong's discovery,[3] that the α- and β-forms of methyl glucoside are hydrolyzed by enzymes to give methyl alcohol and the α- and β-forms of glucose respectively. As the methyl glucosides show no aldehyde reactions the lactonic formulas have always been chosen for them, the hydroxyl of the end carbon atom in the structures shown above being replaced by the group OCH_3. Armstrong's discovery indicates that similar structures probably apply to the forms of glucose. This suggestion received final proof in 1909 when the author[4] showed that certain numerical relations which can only be explained by the assumption of such lactonic structures for the two forms of the sugar, hold all through the sugar group. If the rotation of the end carbon atom is B for one structure it must be —B for the other, and if A is the rotation of the remaining asymmetric carbon atoms, which are common to both structures, the total rotation of the one structure is $A + B$, and of the other structure $A - B$, the difference between the two total rotations being then $2B$. This rotation B applies to all the aldoses because they contain the same end asymmetric carbon, therefore the difference between the molecular rotations of the α- and β-forms of all the aldose sugars should be a constant quantity if the sugars have the two isomeric lactonic structures. The molecular rotatory powers of the two forms of lactose, glucose, arabinose and galactose were found indeed to differ by the quantities 17600, 16000, 16200, and 15700, which are sufficiently alike to show that the theory is correct and that the two forms of each of the mutarotating sugars have the stereomeric lactonic structures. Certain other similar conclusions from the same theory were also found to agree with the rotatory powers of the sugars and their glucosidic derivatives.

The catalytic action of various substances on the mutarotation reaction has been investigated by various chemists.[5] These researches have shown that only acids and alkalies have a strong action. Osaka[6] made the first quantitative study of the relation between acidity or alkalinity and catalytic action and found that the catalysis is proportional to the concentration of the hydroxyl ions and proportional to the square root

[1] "Die Chemie der Zuckerarten," ed. 1895, pp. 130, 990, 992.

[2] *Compt. rend.*, **132**, 487–90 (1901).

[3] *Loc. cit.*

[4] This Journal, **31**, 66–86 (1909).

[5] Levy, *Z. physik. Chem.*, **17**, 301–24 (1895); Trey, *Ibid.*, 18, 193–218 (1895); **22**, 424–63 (1897); **46**, 620–719 (1903); Simon and Bénard, *Compt. rend.*, **132**, 564–6 (1901); Lowry, *J. Chem. Soc.*, **83**, 1314–23 (1903).

[6] *Z. physik. Chem.*, **35**, 661–706 (1898).

of that of the hydrogen ions. Later the author[1] showed that the proportionalities are somewhat different from this and that the rate of the mutarotation of glucose is related to the acidity and alkalinity of the solution by the expression $rate = A + B(H^{\cdot}) + C(OH')$, where A, B, and C are constants at constant temperature. This formula has lately been used as the basis of a new method for measuring the electrolytic dissociation of water.[2] A satisfactory explanation of the fact that acids and alkalies are enormously powerful catalysts of the mutarotation while all other substances are without comparable action is lacking.

The sugars glucose, lactose, galactose, rhamnose, melibiose, arabinose, maltose, xylose and some others occur as monohydrates and these have generally been regarded as hydrated aldehydes without lactonic structure and thus intermediate forms between the two lactonic α- and β-forms of the sugars. The freshly prepared solutions of these monohydrates are identical in properties with such solutions of one of the anhydrous lactonic forms of the sugars and it is therefore to be concluded that the equilibrium between this lactonic form, whichever it may be, and the monohydrate is established instantly. For most of the sugars the lactonic form which is thus in instantaneous equilibrium with the monohydrate is the α-form, but for one sugar at least, maltose, it is the β-form. The mutarotation reaction may then be considered to be the slow change of the monohydrate into the other lactonic form by a reversible reaction, or in the form of an equation,

$$\alpha\text{-sugar} + H_2O \underset{(1)}{\rightleftarrows} \text{monohydrate} \underset{(2)}{\rightleftarrows} \beta\text{-sugar} + H_2O.$$

For most of the sugars the reaction 1 is instantaneous in comparison with 2, which is therefore the mutarotation reaction, but for maltose the relations are reversed. Why the monohydrate should change instantly to the α-form for some sugars, but to the β-form for others is entirely unknown and is a most interesting problem.

The mutarotation reaction is general to all the aldehyde and ketone sugars. It may indeed be called the fundamental reaction of the sugar group. While its cause remained unknown during the half century following its discovery, the last decade has brought a full explanation of it. The principal facts regarding it have been accurately measured and correlated. On the other hand the application of these facts to the elucidation of the chemical and biological reactions of the sugars, in every one of which mutarotation plays a part, has just begun, but it is even now apparent that the unfolding chemistry of the polysaccharides is to be largely a development of the mutarotation reaction.

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[1] THIS JOURNAL, 29, 1571–6 (1907).

[2] *Ibid.*, 31, 1136–8 (1909).