Emil Fischer and the “Art of Chemical Experimentation”

1 Introduction

What did nineteenth century organic chemists do? And what did they know?

These questions motivated my previous essays analyzing the work of chemists including Justus Liebig, August Hofmann, and Albert Ladenburg. In each case, my work revealed aspects of the labor, practices, and materials chemists used to build the new science of organic chemistry. I showed, for example, how Hofmann used what he called “synthetical experiments” to develop type theory around 1850; and that his choice of aniline as a model compound was essential to his success. In Ladenburg’s landmark (1886) synthesis of the hemlock alkaloid coniine, only a new method of melting point measurement, implemented in standard glassware, enabled Ladenburg to prove the identity of his synthetic product with natural coniine.[1]

Taking a classic study – Emil Fischer’s analysis and synthesis of the sugars in 1880s and 90s Germany – as its example, the present essay builds on themes of practice, pedagogy, and material culture to extend these arguments. It shows that chemists’ experimental reliance on model compounds and their introduction of new reagents were integral to the development of chemistry. Organic chemists’ knowledge was neither exclusively theoretical nor what the great experimentalist Michael Faraday termed “mere manipulation.”[2] Chemical practice was inextricable from its cognitive component. When Fischer’s teacher Adolf Baeyer encapsulated chemical skill as the ability “to think in phenomena,” he highlighted exactly this seamless integration of experiment with theory through reason.[3] This study of Fischer’s sugar work makes clear that such reasoning remained constitutive of synthetic organic chemists’ accomplishment and capability as their discipline attained maturity. By revealing the nature of what Fischer called the “art of chemical experimentation,” this essay transforms our understanding of what a chemist like Fischer knew, producing a series of new insights into what it meant to do organic chemistry while theories of chemical structure and stereochemistry were being made into useful heuristic tools.[4]

Previous scholars, most notably Joseph Fruton, have characterized Fischer’s remarkable accomplishment as the application of the stereochemical theory proposed in 1874 by Jacobus

Henricus van't Hoff and Joseph Achille Le Bel to the problem of sugar synthesis. It seemed obvious to Fruton both why Fischer selected this problem, and how he solved it – with the result that neither step required explanation.[5] More recently, Peter Ramberg's history of stereochemistry drew useful attention to the multifaceted nature of Fischer's approach to the problem of sugar synthesis. Ramberg also noted taxonomic reasoning played a part in Fischer's thinking about the sugars. But because Ramberg perpetuated Fruton's basic assumption regarding the role of theory in enabling Fischer's synthetic work, these valuable insights remained ungrounded in the practices that I shall argue gave them stability.[6]

This essay, by contrast, explains when and why Fischer became interested in the synthesis of sugars and how, during a period of almost two decades, he developed a series of methods and techniques with which to solve this supremely difficult problem. Most important among these methods was Fischer's new reagent, phenylhydrazine. First prepared in 1875, in Fischer's hands phenylhydrazine emerged around 1884 as a potential solution to the sugars' legendary experimental intractability, and it ultimately became an essential component of Fischer's chemical toolkit. In fact, so great was phenylhydrazine's usefulness that its importance in the sphere of sugar chemistry later became entirely self-evident. Writing in 1919, Fischer's obituarist, the English chemist Martin Onslow Forster, openly wondered why it had taken Fischer almost a decade to apply phenylhydrazine to the sugars, while simultaneously celebrating Fischer's unique chemical genius.[7] Subsequent historians have continued to see things from essentially the same vantage point. As a result, the present study is the first to explain why and how Fischer developed phenylhydrazine into "an instrument and a tool" for the investigation of sugars and exactly how this powerful new reagent functioned in his research.[8]

Fischer used phenylhydrazine to purify, identify, and characterize sugars. My work reveals Fischer's ability to say with absolute confidence which sugars were the same and which were different as the absolutely crucial factor in enabling Fischer – rather than any other contemporary sugar chemist – to solve the problem of the sugars. It is therefore a central argument of this essay that the problem of sugar chemistry was essentially an extreme problem of chemical identity, whose solution Fischer accomplished using the particular material culture of nineteenth-century organic chemistry.[9] As organic chemistry developed, chemists experienced increasing difficulty in purifying and identifying what was in their test tubes and flasks, a situation I have called a "chemical identity crisis." Chemists responded to this crisis by using glass apparatus to develop melting and boiling points into reliable criteria of chemical identity and purity. In a world without access to three-dimensional molecular structure, melting and boiling points were by far the best tools available for the identification of substance.[10]

Understanding how Fischer used phenylhydrazine to solve the problem of the sugars takes us to the heart of what I shall call laboratory reasoning, the process by which chemists are able to translate wet, laboratory chemistry into the formulae that encode their understanding of molecular constitution and structure. It is certainly not true that phenylhydrazine, once made, could be straightforwardly applied to sugars. On the contrary, Fischer was pressed at each stage in his investigation of the sugars to introduce new techniques, new reactions, and even entirely new classes of organic compound in order that phenylhydrazine continued to produce reliable chemical evidence. This was difficult, demanding, and time-consuming work. And this is why it took Fischer the best part of a decade to get to grips with the sugars.

The approach developed in this essay provides the first practice-based explanation of both Fischer's accomplishment and its subsequent exemplary status, and it therefore makes a significant contribution to studies of science as practice.[11] In so doing, it revises our understanding of the theory/experiment relationship in Fischer's work. Fischer did not solve the problem of the sugars by applying the Le Bel – van't Hoff theory. On the contrary, Fischer's success resulted from mastery of the *art of chemical experimentation* - something many of the most eminent nineteenth-century chemists, including Hofmann and Baeyer as well as Fischer, regarded as the absolute core of their expertise.[12] This was what they worked so hard to learn, teach, and practice. And it is by using the methods of history to uncover this *art* that we shall learn how it was possible for laboratory work to stabilize a productive molecular world in three dimensions.

1.1 A Chemist in Training: What Fischer learned in Baeyer's laboratory

Emil Fischer learned to be a chemist in Adolf Baeyer's Strasbourg laboratory in the mid-1870s. Analyzing Fischer's training reveals what Fischer learned from Baeyer, and how this knowledge equipped him for research in organic chemistry. More generally, this analysis clarifies what nineteenth century chemists knew and, crucially, what they did not. Aspects of chemical knowledge that have long been assumed to be stable and powerful in this period are shown to have remained riddled with uncertainty. Chemical knowledge did not reside in formula and structure but rather in laboratory reasoning, the process by which chemists connected the minutiae of laboratory work with major advances in chemistry. An example from Fischer's PhD research allows me to illustrate how this reasoning process worked and it provides the foundation for the explanation of Fischer's mastery of the sugars that follows.

Right from the start, laboratory training in chemistry emphasized minute attention to precise manipulation and the production of reliably replicable results. The famous "alphabet" in use in Liebig's Giessen laboratory in the 1830s and 40s, presented would-be chemists with a series of graded exercises in inorganic analysis, arranged in order of increasing difficulty. In order to progress, students were required to complete each exercise successfully before moving on to the next. Only when the *alphabet* was complete could they make the transition to organic chemistry, beginning with the analysis of organic substances.[13]

Historians have highlighted the factory-like qualities of the system of laboratory training pioneered by Liebig in Giessen.[14] This approach identified chemistry as a practical science only to be learned in the laboratory, and it provided a useful corrective to histories that present chemistry as a primarily cognitive pursuit. The factory analogy is nevertheless of limited applicability. In part, this is because of changes in chemical training following the mid-century introduction of synthesis as a key method of investigating organic nature.[15] Significantly less amenable to being made routine, training in organic synthesis remained far from systematic until around 1890, Fischer playing a leading role in this development.[16]

Even more important, the factory analogy was never appropriate for all students. Liebig was always on the look out for students who showed exceptional aptitude, bringing the chosen into the intimate circle of his research and supporting these protégés as they forged independent careers. This was how Liebig launched many of the most successful chemists of the next generation including August Hofmann.[17] Hofmann likewise formed an "inner ring" in his research school at London's Royal College of Chemistry in the 1840s and 50s.[18] As we shall see, Baeyer stood in exactly this relationship to Fischer, actively cultivating the young chemist as his chosen successor.

This raises the question of what differentiated Fischer from his peers. In this case, the comparison between Emil Fischer and his cousin Otto Fischer provides compelling evidence of tangible distinctions between Fischer and his peers. It shows that, although the Fischer cousins shared a similar background in chemistry when they entered Baeyer's laboratory at the University of Strasbourg in October 1872, Baeyer soon singled Emil out for training on a very different level. Both Fischers received a PhD degree in 1874 but, whereas Otto made a minor contribution to Baeyer's larger research project, Emil's dissertation reported a self-contained and largely independent study, whose execution equipped him with first-hand experience of key methods in chemical research.[19] Here is the kernel of a plausible explanation for the two cousins' very different futures: both went on to become full professors in the German university system but while Emil ranks as one of the greatest chemists of all time, Otto remains in relative obscurity.

By the time they arrived in Strasbourg, both Fischers had completed a year of university chemistry. Emil had spent a year at the University of Bonn, where he attended August Kekulé's lectures on organic chemistry and took an introductory course in inorganic analysis.[20] Otto, meanwhile, began his studies in Berlin before joining his cousin in Bonn. Both cousins experienced difficulties with the chemical instruction offered in Bonn but Emil struggled badly with the exercises in inorganic analysis that constituted Liebig's *alphabet*. Nothing in his previous exposure to chemistry had prepared Fischer for the difficulty of this work, and he felt himself distinctly disadvantaged alongside his fellow students, many of whom already had significant laboratory experience. Deeply frustrated, Emil contemplated giving up chemistry for physics, and was only persuaded to give chemistry another try by his cousins Ernst and Otto. In summer 1872, Emil and Otto agreed it was time to move on and, after visiting several possibilities, they selected Baeyer's laboratory in Strasbourg.[21]

This move changed the course of Emil Fischer's life. Once settled in Strasbourg, he continued to study the analytical *alphabet*. His teacher was Friedrich Rose, fresh from four semesters in Heidelberg as assistant to the "grandmaster" of inorganic chemistry, Robert Bunsen.[22] Training with Rose effected a remarkable transformation: learning Bunsen's "rapid and convenient" methods felt like a "deliverance" to Fischer, and he emerged from Rose's course as a committed chemist for whom inorganic analysis would always remain a positive pleasure.[23]

In the summer of 1873, his basic training in inorganic chemistry complete, Emil Fischer (hereafter, Fischer) transferred into the organic division, where he came into contact with Baeyer for the first time. His encounter with organic chemistry was far from easy. Organic analysis *circa* 1870 remained a challenging manipulative process whose results were frequently difficult to interpret.[24] Synthetic organic chemistry was worse. As Fischer recalled, training in this new field was largely unstructured at this time, and no manuals of preparative organic chemistry existed. Baeyer's emphasis on comradely cooperation rather than scholarly instruction lends credence to Fischer's claim that he began doctoral research unable to perform the most basic operations in organic chemistry.[25]

This inauspicious start was followed by a catalog of "foolishness and accidents" that culminated in Fischer dropping his entire supply of an essential intermediate all over the laboratory floor. Baeyer saved the day by proposing a completely new project: this was how Fischer's PhD research came to focus on the fluorescent dye fluorescein, one of the new phthalein dyes Baeyer had first prepared in 1871. It also began Fischer's training as a dye chemist.[26]

That training ranged widely but ultimately entailed total immersion in the collegial surroundings of Baeyer's laboratory.[27] At first, Fischer pursued studies in physics and mineralogy. These provided fine examples of laboratory instruction and lecture demonstration but were curtailed when Baeyer complained Fischer was neglecting his chemical studies.[28] For Fischer and his contemporaries, long days in the laboratory were followed by evenings in the pub, talking chemistry. The coherence of this chemical community was also important within the laboratory. Baeyer took little interest in beginners' routine training, leaving Fischer and his fellow students to seek guidance elsewhere. Fischer recalled that one especially important source of help was Julijan Grabowski, whom Baeyer's students followed to the pub at lunchtimes "to seek his advice on chemical matters."[29] In fact, Baeyer's "talented and experienced" private assistant Grabowski had yet to receive his PhD, suggesting his contribution to Fischer's training focused more heavily on manipulative skill than the laboratory reasoning highlighted by this essay.[30]

It was nevertheless vital that Fischer learned a range of essential manipulative skills during his PhD, including how to use standard reagents, how to coax products to crystallize, how to measure reliable melting points, and how to perform accurate quantitative analyses. He was alert to the unusual, and capable of responding skillfully to common laboratory problems. Fischer knew how to minimize unwanted secondary reactions, what to do when reactions that ought to work did not, and – above all – how to make things crystallize. This is a supremely important point. A chemist like Fischer relied absolutely on being able to produce crystalline products. Despite advances in techniques such as distillation, crystallization remained by far the best method of purifying organic substances. Measuring the melting point of a crystalline solid, moreover, was chemists' only reliable method of characterizing and identifying what they had made.[31]

My previous work revealed not only the general constraints imposed by nineteenth-century chemists' reliance on crystallization and melting point, but also some of the strategies chemists used to overcome these limitations. I showed how Hofmann used aniline as a model for natural alkaloids.[32] Because aniline contained a phenyl group its derivatives were almost invariably crystalline, a crucial factor in Hofmann's development of the ammonia type. The general principle was not lost on other chemists: the presence of one or more phenyl groups, a characteristic component of aromatic compounds, was a reliable indicator of crystallinity. When reactions produced intractable, non-crystalline products, chemists like Hofmann, Baeyer, and Fischer knew shifting to an aromatic model compound was likely to solve the problem.[33]

Analogy was another fundamental principle underlying Hofmann's synthetic approach, and this mode of reasoning remained central to both Fischer cousins' research.[34] My previous work explained how Hofmann applied known reactions to new starting materials, in the expectation these would react in the same way as similar substances subjected to identical conditions.[35] This was how Hofmann reasoned by analogy from knowledge of starting materials to new understanding of products, an approach that also provided an explicit framework for much work in Baeyer's laboratory.

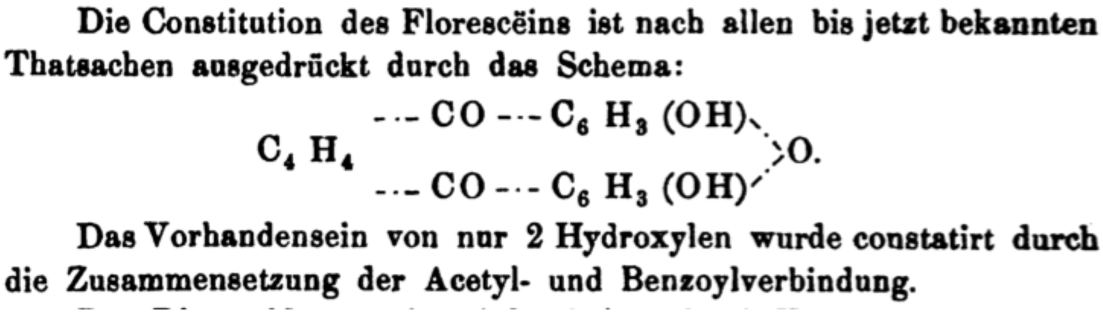
As he prosecuted his PhD research, Fischer's practical skills therefore developed far beyond the merely manipulative to encompass a series of strategies for finding experimentally tractable solutions to interesting chemical problems. Using forms of reasoning that owed a great deal to Hofmann, he could make reliable inferences from the behavior of substances in glass vessels to their chemical nature and identity. This was how Fischer learned to connect work at the laboratory bench to provisional notions of formula and structure.

Fischer's experience of reacting fluorescein with the chlorinating agent phosphorus pentachloride (PCl_5) will help clarify this important point, while also introducing a central concept in organic chemistry: the reagent. Reagents have a prior history in inorganic analysis, where they functioned as methods for identifying particular elements and groups of elements, usually by provoking a visually characteristic reaction.[36] Organic chemists began to use the term reagent around 1860 to refer to substances known to have a similarly reliable and identifiable effect on particular families of organic compound.[37]

Phosphorus pentachloride was one of the earliest and most important of these reagents. First prepared by the French chemist Auguste Cahours in 1848, phosphorus pentachloride was quickly established as a reliable method of substituting the reactive hydroxyl group of atoms (OH) by chlorine (Cl) in many kinds of organic substance.[38] From the mid-century onwards it also became a widely used test for the presence of hydroxyl groups in organic compounds.[39] This function of organic test reagents, however, was far from theoretically neutral, implying at least a heuristic acceptance that organic molecules were composed of groups of atoms arranged according to the recently introduced theories of valence and chemical structure.[40] It is a significant claim of this essay that chemists' use of reagents such as phosphorus pentachloride went hand in hand with their increasingly structural conception of organic substance. As Fischer's study of fluorescein perfectly illustrates, and his later work with phenylhydrazine confirms, organic reagents served to elucidate structural components of organic molecules as well as being aids to the identification of specific organic substances.

When Fischer reacted phosphorus pentachloride with fluorescein, he isolated a pure, crystalline product that he characterized by its melting point. Quantitative analysis revealed only two of fluorescein's five oxygen atoms had been replaced by chlorine. Fischer inferred from this outcome that two hydroxyl (OH) groups known to exist in fluorescein had reacted, while three further oxygen atoms remained unaffected. Chemical knowledge concerning these three oxygen atoms in fluorescein was limited. Two were believed to exist as carbonyl (CO) groups derived from the starting materials. Similar reasoning suggested the third formed a bridge between two aromatic phenyl groups, but this largely speculative view lacked a solid experimental foundation. This was the problem Fischer tackled using phosphorus pentachloride. He tried repeatedly to substitute this oxygen by chlorine but could not. Such inertness to phosphorus pentachloride was very unusual but shared by diphenyl ether, a compound in which two phenyl groups were linked by oxygen to form a group called an aromatic ether. Fischer reasoned from this observation to the constitutional conclusion that fluorescein must also contain an aromatic ether, then used experiment to elevate inference to the status of established knowledge.

Throughout, Fischer's PhD showed a firm grasp of what was known with some certainty and what remained relatively uncertain. Fischer stated laboratory procedure and experimental outcomes with precision. His melting points were sharp and he detailed observations of color, crystal form, and chemical behavior. He reported the results of quantitative organic analysis alongside values calculated from the assigned molecular formula, clearly displaying the fit between experimental and expected theoretical values.



Die Constitution des Florescëins ist nach allen bis jetzt bekannten Thatsachen ausgedrückt durch das Schema:

$$C_4H_4 \begin{matrix} \text{---}\,CO\,\text{---}\,C_6H_3(OH) \\ \text{---}\,CO\,\text{---}\,C_6H_3(OH) \end{matrix} \rangle O.$$

Das Vorhandensein von nur 2 Hydroxylen wurde constatirt durch die Zusammensetzung der Acetyl- und Benzoylverbindung.

Figure 1: It is tempting to invest this this schematic representation of fluorescein's constitution with present day structural meaning. But this is to assume knowledge Fischer did not have, and that this formula did not imply to his peers. This constitution was not a driver of Fischer's investigation. Neither did it indicate phenyl groups should be considered benzene rings. In fact, their nature was so irrelevant to Fischer's chemistry that he incorrectly represented one of them as containing only four carbon atoms.[41] *More than a decade after its introduction, in the laboratory of one of its earliest proponents, Baeyer, Kekulé's theory of benzene's structure did not provide a universally useful basis for experiment.*[42]
Emil Fischer. 1874. "Ueber Fluorescëin und das Phtalëin des Orcins" Berichte *7:1211-16, 1212.*

When it came to constitution – chemists' term for the arrangement of atoms within a molecule, often expressed using a graphic formula, and usually thought of as a forerunner of chemical structure – Fischer drew upon a very different vocabulary. Fischer's constitution for fluorescein was based on previous work by Baeyer and Grabowski and it accorded with "all the facts known to date" [Figure 1].[43] But, as we have seen, this formula initially incorporated just two items of stable knowledge derived from experiment. The presence of two hydroxyl groups had been "determined" by preparing and fixing the composition of fluorescein's acetyl- and benzoyl-derivatives.[44] And quantitative analysis showed loss of water accompanied the formation of fluorescein from the starting materials. Fluorescein's constitution was otherwise purely inferential and therefore did not provide a secure basis for experiment.[45] Fluorescein's constitution was not a driver of Fischer's investigation.

I have explained how Fischer showed that fluorescein contained an aromatic ether group. It may surprise the reader to learn this was the most significant outcome of Fischer's PhD. It should not. At a conservative estimate, it took many weeks to establish this single fact. Once proved, moreover, this was secure knowledge. Chemists have long since discarded the constitution Fischer illustrated in 1874. But they still believe fluorescein contains an aromatic ether and two hydroxyl groups [compare Figure 1 and Figure 2]. This example from Fischer's early work indicates that established reactive groups – and not constitution, structure, or formula – provided nineteenth century chemists with a secure foundation for experiment and laboratory reasoning. Similarly, it shows how chemists could secure knowledge of great value to organic synthesis without comprehensive structural knowledge.

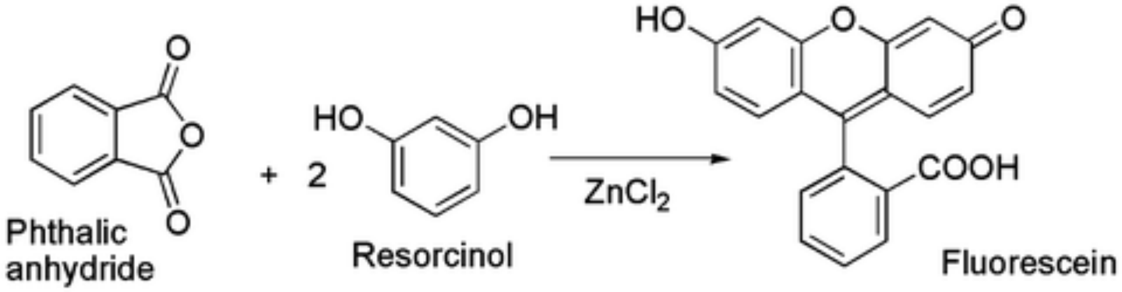


Figure 2: This modern representation of Baeyer's route to fluorescein illustrates a deep-seated problem for historians of chemistry. Conceptualizing substances according to their present-day structural formulae makes it all but impossible to avoid projecting this understanding onto historical actors. When Baeyer made fluorescein in 1871, he fixed its composition but did not speculate on its constitution or structure. And, as comparison with Figure 1 shows, the constitution proposed later that year by his assistant Grabowski, bears almost no resemblance to the modern structure.
Image courtesy of https://en.wikipedia.org/wiki/Fluorescein. Last accessed May 17 2016.

Briefly revisiting my earlier comparison between Emil and Otto Fischer's PhD research confirms this important revision in our understanding of chemical practice. It also emphasizes that, although both cousins learned essential manipulative techniques and became well versed in principle in laboratory reasoning during their PhDs, there was a perceptible gap in their personal experience of applying such methods. Otto's work contributed to Baeyer's larger study of the condensation reactions of carbonyl compounds.[46] Otto's dissertation largely consisted of a review of other chemists' studies of condensation reactions of aromatic compounds. This review exposed him to the principles of laboratory reasoning, but did not give him the opportunity to develop his own skill in this area. Otto's original experimental work was significantly more limited in its scope than his cousin's, and it provides no evidence that he developed the command of laboratory reasoning Emil Fischer's independent investigation of fluorescein so clearly displayed.

In summer 1874, Emil Fischer became the first student from Baeyer's Strasbourg laboratory to be awarded a PhD. Fischer was emerging as Baeyer's chosen protégé and a highly skilled chemist in his own right. Investigating fluorescein had exposed him to all aspects of the *art of chemical experimentation*. Importantly, it had also introduced Fischer to dye chemistry, preparing him for the study of dyes as both objects of academic research and potentially lucrative industrial products.

2 Dye Chemistry and Fischer's Discovery of Phenylhydrazine

Most nineteenth-century dyes were artificial products of laboratory chemistry. The vast majority were also crystalline aromatic compounds, and thus susceptible to the laboratory methods described above. William Perkin's 1856 preparation of mauve had launched a lucrative new industry in England. By 1874, however, Germany had taken a clear lead. Many chemists in many laboratories were engaged in the pursuit of new dyes and the search for improved understanding of dyes and the chemistry of color. But the world-leading site of academic dye research in 1874 was Baeyer's Strasbourg laboratory.

By the time Baeyer moved from Berlin's Trade Academy to the University of Strasbourg in 1871 he already had an impressive track record as a dye chemist. In 1869, two chemists in his Berlin laboratory, Carl Graebe and Carl Liebermann, prepared the natural red madder dye, alizarin, a significant milestone in dye chemistry. Baeyer had also developed an extremely productive collaboration aimed at dye manufacture with Heinrich Caro, research director of the recently founded firm BASF. Baeyer is justly famous for his 1878 laboratory synthesis of the natural dye, indigo. It is rather less well known that Baeyer accomplished this feat in association with Caro, and that the subsequent development of an industrially viable route for the production of this widely used blue dye was also a product of this early academic-industrial collaboration.[47]

This was the context for Fischer's discovery of phenylhydrazine. Fischer's PhD research, as we have already seen, extended Baeyer's earlier work on phthalein dyes. Shortly after its completion, Baeyer appointed Fischer as his assistant. In this role, Fischer was entrusted with the supervision of younger chemists. One important research focus of Baeyer's laboratory at this time was a reaction called diazotization.[48] First introduced in the 1850s, by the mid 1870s diazotization was becoming an important step in the manufacture of azo dyes, a new family of artificial dyes that greatly expanded the color spectrum available using existing aniline dyes. The diazotization reaction was of great commercial significance. It usually produced reliable results – at least in terms of color - but the course of the reaction was poorly understood in structural terms, a situation many chemists including Baeyer were keen to remedy.[49]

Sometime between the fall of 1874 and the spring of 1875, Fischer set a student to perform what he anticipated would be a routine diazotization (conversion of benzidine [4,4' – diaminobiphenyl] into biphenol [4,4' – dihydroxybiphenol]).[50] The student's reaction failed, producing "dirty, intractable products." Fischer's initial assumption was that the student's failure was due to manipulative error but, on repeating the procedure, he obtained exactly the same result. Despite phenylhydrazine's significance, we know remarkably little about these events. We do not know the student's name, nor do we have an account of how Fischer ultimately rationalized what had gone wrong. In particular, the available sources provide no indication that Fischer himself succeeded in accomplishing the originally desired transformation.[51]

Such an unusual outcome of diazotization evidently piqued Baeyer's interest. Proceeding with Baeyer's support, Fischer responded to problematic aspects of the student's experiment. *Intractable, dirty products* suggested unwanted oxidation; it also indicated the reaction product could not be crystallized. Fischer suppressed the former by introducing a standard reducing agent (potassium sulfite). The modified reaction produced a yellow precipitate, a far more attractive outcome for a chemist in Baeyer's dye-focused laboratory. Next, Fischer simplified the starting material while retaining its aromatic core, a rational strategy intended simultaneously to minimize possible side reactions and capitalize on the tendency of aromatic starting materials to form crystalline products. Where the student had begun with benzidine, Fischer substituted diazobenzene.[52] This time, the reaction produced a yellow substance Fischer could purify because it was crystalline. This was phenylhydrazine.

Previous accounts have emphasized the serendipitous nature of Fischer's discovery. This study by contrast shows Fischer was led to phenylhydrazine by learned processes of laboratory reasoning. From the moment he confirmed the student's experimental outcome was not the result of manipulative error, Fischer began to deploy a series of standard strategies mastered during his PhD. The discovery of phenylhydrazine exemplified the systematic empirical approach by means of which most new dyes were produced in this period. It also brought Fischer to the cutting edge of dye chemistry.[53]

3 From Dye Chemistry to Sugars

Placing Fischer's discovery firmly in the context of dye chemistry prompts us to consider how he came to develop phenylhydrazine as a reagent. Fischer initially pursued phenylhydrazine as a route to improved understanding of the azo dyes and a potential starting point for the production of new dyes. This section explains why Fischer abandoned attempts to produce a new dye from phenylhydrazine and how he recognized phenylhydrazine's potential as a reagent. Fischer's decision to tackle the problem of sugar chemistry using phenylhydrazine emerges from this new analysis as the response to circumstances including a prior interest in sugar chemistry. It was not initially an obvious route to success.

Fischer spent the spring of 1875 in an intensive study of phenylhydrazine, entering the contentious ongoing debate concerning the chemical nature of diazo compounds and azo dyes. Following Baeyer to Munich that fall, Fischer arrived convinced – and had persuaded his father – it made sense for him to pursue his "pretty discovery."[54] Fischer soon began exploring phenylhydrazine's potential for the production of new dyes.[55] Performed with cousin Otto, an early attempt involved reacting phenylhydrazine with rosaniline, itself a hugely important dye. Unfortunately, the reaction produced "abnormal" results rather than a useful dye. These attempts bore a different kind of fruit. This work led the Fischers to propose a new constitution for rosaniline in early 1876.[56]

It was also in their joint paper on rosaniline that the Fischer cousins first referred to phenylhydrazine as a reagent. This marked a significant change of status: no longer the object of study, phenylhydrazine was becoming a tool with which to investigate other substances.[57] Fischer now had extensive knowledge of phenylhydrazine, including its reactions with the simple carbonyl compounds acetaldehyde and benzaldehyde.[58] His investigations also encompassed an entire family of hydrazines related to phenylhydrazine. There is nothing at this time, however, to suggest Fischer actively pursued phenylhydrazine's potential as a reagent. In 1876, Fischer still anticipated phenylhydrazine's most interesting applications related to dye chemistry.

Three things changed that situation. First, as Fischer concluded his research on the hydrazines in 1879, phenylhydrazine had still failed to produce any useful dye. Second, inspired by chemists' longstanding desire to produce sugars in the laboratory and almost certainly seeking a new project of commercial significance, Fischer in the same year turned his attention to the sugars. As Baeyer's protégé, Fischer was well placed to see the advantages of such a project. Baeyer's career was a model of academic-industrial collaboration in the field of dye chemistry, and it showed how an academic chemist could build a lucrative and economically significant career. Sugars offered similar opportunities, if only someone could master the chemistry. Fischer first attempted to prepare a sugar in 1879. He produced a sugar-like syrup but was forced to abandon his experiments because he was unable to crystallize, and therefore could not purify, characterize, or identify, his product. As Fischer later explained, without a pure crystalline product, he had nothing to work with, and nothing to publish. [59]

The third development concerns work in Victor Meyer's Zurich laboratory during the early 1880s to establish hydroxylamine as a reagent for carbonyl compounds, an important family of organic compounds containing the carbonyl (CO) group of atoms. I have already mentioned Baeyer's research into condensation reactions.[60] Many condensation reactions involved carbonyl compounds, and they were of enormous importance to both chemistry and physiology from the 1860s onwards. In 1870, Baeyer proposed sugars were carbonyl compounds.[61] Around 1875 Meyer – whose interest in organic chemistry dated from time (1868-1871) spent as Baeyer's assistant in Berlin – began to study hydroxylamine, a new compound that reacted with carbonyl compounds.[62] By 1882, Meyer focused on the condensation between hydroxylamine and the simple carbonyl compound, acetone.[63] Baeyer's world-leading expertise in carbonyl chemistry combined with Meyer's study of hydroxylamine provided both stimulus and unique context for Fischer's next move.

Fischer followed Meyer's work on hydroxylamine throughout. In 1875, he considered hydroxylamine as a starting material for the synthesis of phenylhydrazine.[64] The following year, Fischer used the "fairly close analogy" between the hydrazine family and hydroxylamine to explain some unexpected results in his constitutional analysis of the hydrazines.[65] As early as 1876, Fischer recognized important chemical similarities between hydroxylamine and phenylhydrazine. That knowledge acquired new significance in February 1883, when Meyer's student Ernst Nägeli proposed hydroxylamine as a useful reagent for carbonyl compounds.[66] Work in Meyer's laboratory showed simple carbonyl compounds (aldehydes and ketones) reacted with hydroxylamine to form products called oximes that, if crystalline, could be purified by recrystallization and characterized by their melting points. Each carbonyl compound produced a different oxime, and every oxime had a different melting point.

This finding had three important consequences. First, it meant chemists could show by reaction with hydroxylamine whether or not any substance was a carbonyl compound. Second, they could characterize this specific compound by measuring the melting point of its purified oxime, provided this was crystalline. Finally, comparing this melting point with those obtained for existing oximes showed whether the substance under test was identical to any known compound. In this way, reagents in organic chemistry enormously transcended their much more limited use in inorganic chemistry. Not only did reagents provide a method for investigating the reactive groups composing organic substances, reagent plus standardized melting point also constituted nineteenth-century chemists' only reliable method of individuating and identifying substance.

The established chemical similarity between phenylhydrazine and hydroxylamine led Fischer – now full professor at the University of Erlangen – immediately to suspect phenylhydrazine might react like hydroxylamine. He was right. Within weeks of Nägeli's paper being read before the German Chemical Society, Fischer's student Hermann Reisenegger submitted a paper showing phenylhydrazine reacted predictably with complex ketones, i.e. phenylhydrazine was capable of identifying the carbonyl (CO) group within molecules containing other reactive groups.[67] Phenylhydrazine had another enormous advantage over hydroxylamine: its aromatic nature meant it had a much greater tendency to form crystalline products. Fischer therefore anticipated phenylhydrazine would show superior laboratory handling as well as wider applicability, qualities he soon confirmed with the help of his assistant Friedrich Jourdan.[68] His assertion that phenylhydrazine was a "more easily available" alternative to hydroxylamine for the "detection and separation" of ketones completed Fischer's argument for the superiority of his reagent over Meyer's.[69]

Detection and separation are key words here, alerting us to the continuing significance of organic chemistry's *chemical identity crisis*. Fischer explained it very well: "As the number of organic compounds increases, so it becomes ever harder to … recognize them again. All the more valuable are methods which make possible the analytical detection of a greater number of compounds in a simple manner."[70] Meyer's hydroxylamine was "such a reagent" but phenylhydrazine was easier to prepare and reliably produced crystalline products with a variety of more complicated carbonyl compounds. By March 1884, Fischer was convinced phenylhydrazine would "soon be widely adopted as an analytical reagent."[71]

As soon as he recognized phenylhydrazine's potential as a reagent for carbonyl compounds, Fischer applied his new reagent to sugars, producing pure, crystalline sugar derivatives.[72] Almost a decade after his serendipitous discovery of phenylhydrazine, Fischer had "laid the foundation for [his] future sugar work."[73] While existing historical accounts assume Fischer was first led to the sugars in 1884 by phenylhydrazine, this crucial step now emerges as the consequence of three inter-related developments. Looking for a new and commercially significant project, Fischer had made an excursion into sugar chemistry as early as 1879. Only organic chemists' expanding conception of what a reagent could and should do, combined with Meyer's work with hydroxylamine, alerted Fischer to the possibility that phenylhydrazine might transform sugar chemistry into an experimentally tractable research problem.

4 The State of Sugar Chemistry in the 1880s

In order to appreciate exactly what Fischer accomplished with the aid of phenylhydrazine, it will be helpful to outline the state of sugar chemistry in the mid-1880s, when Fischer entered the field. Natural sugars were of enormous commercial, medical, and industrial importance, essential in brewing and already implicated in the diagnosis of diabetes. They were also produced for both domestic consumption and the manufacture of alcohol by a global sugar industry of rapidly growing economic significance. In addition, chemists recognized the sugars as important constituents of living nature, whose chemistry was therefore a legitimate object of academic study. The development of organic chemistry, meanwhile, had crystallized these interests into a pair of interconnected and increasingly urgent goals: chemists wanted to understand the structure of the sugars and they wanted to make them in the laboratory by synthesis. As in other areas of organic chemistry, there was a very large discrepancy between these goals and chemists' actual capabilities.[74] Despite many decades spent trying, late nineteenth-century chemists still struggled to produce accurate analytical results for many sugars and they had yet to make any sugar by synthesis.[75]

By 1884 chemists had produced a stable formula for glucose ($C_6H_{12}O_6$). This formula was shared by several other sugars including galactose. Chemists also knew sugars contained oxygen in the form of hydroxyl (OH) and carbonyl (CO) groups but the manner in which these groups were arranged within sugar molecules was far from certain.[76] Even in the case of glucose, the most available and hence most studied sugar, such an arrangement or constitution had yet to be definitively established. According to Heinrich Kiliani – whom Fischer regarded as one of the most significant contributors to the field – most experts accepted the formula proposed by Baeyer and Fittig around 1870: $CH_2OH.(CHOH)_4.CHO$.[77]

The key feature of the Baeyer-Fittig formula for glucose was the terminal position of the carbonyl group. This meant glucose contained an aldehyde (CHO, carbonyl carbon at the end of the chain) and not a ketone group (CO, carbonyl carbon in the middle of the chain). In the developing language of sugar chemistry, this made glucose an aldehyde-alcohol or aldose rather than a ketone-alcohol or ketose.[78] But in 1886, when Kiliani was writing, the chemical evidence remained sufficiently equivocal for some chemists – including Meyer – to maintain glucose was a ketose and not an aldose. Another leading sugar chemist Bernhard Tollens had attempted to resolve this dispute in 1883, without producing definitive results.[79] And this was the question Kiliani now settled using a novel method based on reaction with hydrocyanic acid. Kiliani's method, in 1886, represented the state of the art in sugar analysis. It attracted Fischer's attention and admiration, and later became an important component of Fischer's experimental toolkit.[80]

As Fischer entered the field, Kiliani was in the process of establishing the constitution of glucose. But this exceptional case should not blind us to the more general fact that even the best chemists of this period struggled with the enormous practical difficulties of sugar chemistry. Many sugars and sugar-like substances had been isolated from natural sources and laboratory preparations but their tendency to form syrupy mixtures made them notoriously difficulty to purify, and hence all but impossible to individuate, characterize and identify.[81] As one indicator of this difficulty, consider the names given to sugars. Some were named after their natural origin – lactose from milk, for example – while others such as laevulose (fructose) were named for their optical rotatory ability (to the left, in this case). In several instances, chemists used a range of names to refer to the same substance. Glucose, most notably, was also known as dextrose (optical rotation, to the right) and grape sugar (because it had originally been obtained from raisins).[82]

This practical difficulty had extremely important consequences for chemists' ability to understand and study the sugars. It meant they frequently treated as single, pure substances what subsequent work – much of it Fischer's – would reveal to be complex mixtures. And, as we shall see below, they also identified several distinct sugars Fischer would later show were one and the same chemical compound. Much sugar chemistry prior to Fischer's work was performed without chemists having a clear idea of exactly what their sugar samples contained. This was the absolutely fundamental practical difficulty that Fischer – using phenylhydrazine – was eventually able to overcome.

5 Fischer's Solution to the Problem of the Sugars

In 1885, newly established as professor of chemistry in Würzburg, Fischer resumed work on the sugars.[83] This work led to Fischer's sugar syntheses, including the landmark synthesis of glucose in 1890. In total, it took Fischer almost a decade to understand and control the sugars. The following sections reveal the enormous body of work, much of it performed by junior chemists in his laboratory, by means of which Fischer imposed order on sugar chemistry. As he proceeded from a re-definition of sugars to new understanding of the sugars' chemical nature, Fischer relied on exactly the approaches highlighted earlier in this essay: model compound, melting point, and reagent. Fischer's resolution of critical questions of chemical identity emerges as constitutive of his solution to the problem of the sugars. Fischer tackled these questions using phenylhydrazine and it was in mastering this practice – and not by merely applying any theory – that Fischer ultimately mastered the sugars. Laboratory reasoning – that seamless melding of experiment and theory – led Fischer to the sugars' three-dimensional nature, simultaneously equipping Fischer with the methods of sugar synthesis. While the synthesis of glucose is usually viewed as Fischer's great breakthrough, this study explains why Fischer himself identified quite different events as the crux of his sugar work.

5.1 Fischer's Hydrazine Test: Melting Points and Laboratory Standardization

Already in 1884, Fischer had shown phenylhydrazine reacted with simple sugars to produce products he later called "osazones."[84] Because osazones were invariably crystalline, Fischer could purify and analyze them, and he was therefore able to determine the first consistent, reliable molecular formulae for sugars. In what would prove to be a particularly important move, Fischer also used the characteristic reaction between a sugar and phenylhydrazine as the basis for what he called the "hydrazine test."[85] Indeed, Fischer subsequently used the *hydrazine test* as the basis for a new definition of a sugar. Because it converted sugars into crystalline osazones, the *hydrazine test* also suggested individual sugars could be characterized and differentiated by the melting point of their osazones. But, as the following episode shows, realizing this possibility required Fischer to specify standard laboratory procedures and establish these throughout the chemical community.

In summer 1886 Friedrich Beilstein's *Handbook of Organic Chemistry* reported new melting point data for the osazones of two sugars, galactose and arabinose. This data, obtained the previous year by the sugar chemist Carl Scheibler, was the first application of Fischer's *hydrazine test* by another chemist.[86] From Fischer's point of view, however, Scheibler's results were not good news, and their dissemination through Beilstein's *Handbook* was a disaster.[87] Scheibler's melting point for phenylgalactosazone (171 °C) was much lower than Fischer had previously obtained for the same compound, a clear indication to Fischer that Scheibler's compound was impure. If such an inaccurate value were to remain unchallenged, it would fatally undermine the *hydrazine test*.[88] For the melting points of osazones to serve as useful characteristics, they had to be replicable.

Fischer repeated Scheibler's work. He found phenylgalactosazone began to discolor around 188 °C and did not melt completely until 193-4 °C. Discoloration indicated the osazone tended to decompose during heating, greatly increasing the practical difficulty of measuring a reliable melting point. A chemist like Fischer knew that sample purity affected melting point. He now learned the measured melting point of osazones also depended on how fast the sample was heated. In this case, slow heating minimizing decomposition. In March 1887 Fischer described in minute detail how the melting points of osazones should be measured.

Within and beyond his laboratory, Fischer began to impose his values on sugar chemistry. He trained students in standard methods of purification and melting point measurement.[89] Fischer approached these essential techniques using standard, commercially available items of chemical glassware, a material basis that made them significantly easier for chemists elsewhere to replicate.[90] Fischer also detailed both methods and apparatus in the book that made his rigorous system of training available to others: *Introduction to the Preparation of Organic Compounds*. First published in Würzburg in 1887, this textbook became a durable model for instruction in organic synthesis, carrying Fischer's practical approach across Europe and North America in a multitude of editions, translations, and adaptations.[91] Fischer used the *hydrazine test* to control the sugars but making this test useful entailed standardizing laboratory practice throughout the chemical community.

5.2 Benzoyl Carbinol: Fischer's Model Compound, Analogy, and the Definition of a Sugar

Measuring reliable melting points for osazones did not require understanding what these sugar derivatives were and how they formed. But in order to advance his knowledge of sugar chemistry, Fischer needed to know how sugars reacted with phenylhydrazine to form osazones.[92] He tackled this problem using a carefully selected compound as a model for sugars – much as Hofmann had used aniline in his investigations of alkaloids in the 1840s.[93]

Fischer's model compound was benzoyl carbinol (2-hydroxyacetophenone). He chose it because it incorporated the same reactive groups as sugars: a carbonyl (CO) group and a neighboring hydroxyl (COH) group.[94] Importantly, it was also an aromatic compound, one Fischer had worked with before and knew readily formed crystalline compounds.[95] The reaction between benzoyl carbinol and phenylhydrazine was therefore significantly easier to study than the analogous reaction with sugars. Benzoyl carbinol's chemical similarity to the sugars, meanwhile, allowed

Fischer to reason by analogy from the behavior of his model compound to knowledge of the sugars.

This was how Fischer showed osazones were produced in a two-stage reaction in which first one, and then a second, molecule of phenylhydrazine combined with the sugar. This indicated an intermediate product, later called a phenylhydraz***one***,[96] formed when a sugar reacted with a single molecule of phenylhydrazine. Fischer learned to prepare sugar phenylhydrazones, and he characterized these crystalline derivatives by their melting points. Thus Fischer gained a detailed picture of how sugars reacted with phenylhydrazine, establishing the chemical nature of both phenylhydrazones and osazones.

Equipped with this knowledge, Fischer began using phenylhydrazine to reveal and begin solving problems of chemical identity. His first case concerned mannitose, a sugar produced by oxidizing the sugar alcohol mannitol. In January 1884 the sugar chemist Franz Wilhelm Dafert suggested mannitose was identical to fructose.[97] Fischer used the *hydrazine test* to confirm this result. When he converted mannitose to its osazone, Fischer found this melted at exactly the same temperature as the osazone derived from fructose. Using phenylhydrazine also enabled Fischer to identify another, previously unknown sugar among the oxidation products of mannitol: this was the sugar Fischer later called mannose.

Fischer was quick to see the significance of phenylhydrazine's potential to identify new sugars.[98] Not only could he make the formulae and melting points of osazones into the basis of a new taxonomy of sugars,[99] Fischer now used the *hydrazine test* to *re-define* what it meant for a substance to be a sugar. Until this point, sugars had been identified by their sweet taste and ability to support fermentation. This broad, functional definition related to chemists' longstanding practice of identifying a substance by its source and observable characteristics.[100] Using phenylhydrazine, Fischer now argued "true sugars are aldehyde- and ketone-alcohols. They reduce Fehling's solution and produce osazones with phenylhydrazine."[101]

This was a significant shift in chemists' understanding of the sugars. Beilstein's recently published *Handbook*, for example, listed among the sugars "Scyllitol and 8 other compounds whose individuality is doubtful."[102] Fischer's definition implicitly imposed new standards of identity and purity on sugar chemistry. By re-defining sugar chemistry terms of his *hydrazine test*, Fischer positioned himself as uniquely qualified to decide whether or not any particular substance was a pure sugar, or, indeed, a sugar at all.

5.3 Synthetical Experiments on the Sugars: Fischer and the Synthesis of the Acroses

Fischer's new definition had an immediate impact on one particular aspect of sugar chemistry: sugar synthesis. Attracted by the sugars' commercial importance, many nineteenth-century chemists attempted to prepare sugars in the laboratory, including the Russian chemist Alexander Butlerov. In 1861, Butlerov produced a sweet-tasting substance by condensation of formaldehyde and claimed the first synthesis of a sugar.[103]

Butlerov's work sparked a controversy involving Oscar Löw and Bernhard Tollens, and a putative sugar Löw named "formose."[104] Löw believed he – and not Butlerov – had synthesized the first sugar but Tollens questioned whether formose was a true sugar. Prior to Fischer's work, such claims were unresolvable. Synthesis implied the production of a single, pure sugar. But chemists like Butlerov, Löw, and Tollens had no way of unequivocally demonstrating the purity and identity of their synthetic products. Fischer's *hydrazine test* provided the first means of adjudicating these claims, and in 1888 Fischer used phenylhydrazine to show formose was actually a complex mixture and not a single, pure sugar as Löw supposed.[105] No chemist had yet produced a sugar by synthesis.

Establishing this fact was essential for Fischer as he began a synthetic investigation of the sugars. Fischer's initial goal was not the production of natural sugars by target-oriented, constructive synthesis. Instead, he began a series of synthetical experiments, an approach modeled on Hofmann's extension of the taxonomy of amines thirty years earlier. Fischer knew that oxidizing the sugar alcohol mannitol produced the sugar mannose. He therefore attempted the same reaction on a number of other similar alcohols including glycerol, erythritol, and dulcitol. Aided by his assistant Julius Tafel, Fischer began this study in 1887, starting work that culminated in the synthesis of the first artificial six-carbon sugars, α– and β–acrose.[106]

When they first made α–acrose in 1887, Fischer and Tafel identified this new compound as a sugar by isolating its osazone, and they characterized this osazone by measuring its melting point.[107] This was secure practical knowledge but it did not correspond to stable constitutional knowledge. Fischer and Tafel soon isolated a second sugar whose osazone had the same composition as the osazone derived from α–acrose but melted at a different temperature (148 °C cf. 205 °C). This indicated the two sugars were isomers, leading Fischer and Tafel to name the second sugar β–acrose. But although Fischer and Tafel were able to make, identify, and differentiate α– and β–acrose, they could not draw a formula that represented either constitution.[108] Fischer and Tafel made only one constitutional inference: β–acrose's unusually low melting point indicated "an abnormal carbon chain" compared with natural sugars.[109]

The experiments that enabled Fischer and Tafel to reason from laboratory results to the constitution and structure of the acroses proved among "the most arduous labors of organic chemistry."[110] Some of the preparative chemistry was so demanding that Tafel invented a new piece of laborsaving laboratory apparatus.[111] Fischer and Tafel also developed several new reactions that later equipped Fischer with a repertoire of transformations he used in synthesizing natural sugars.[112] One part of this work allows me to illustrate two important points. First, it highlights the extreme laboriousness, physical unpleasantness, and danger of this work. Second, it shows why problems of chemical identity were the key to sugar chemistry, and what it took for Fischer to solve these problems using phenylhydrazine.

Ready access to the acroses was essential to further study, but Fischer and Tafel's original preparation from bromacrolein was difficult and messy. In an attempt to improve things, Fischer and Tafel adopted a new starting material, glycerol. By late December 1887 they succeeded in isolating both osazones from this new preparation. The behavior of these osazones matched the originals in every respect except one. Fischer and Tafel found that α- and β-acrosazone prepared from glycerol melted at significantly higher temperatures than the originals prepared from bromacrolein (217 °C and 158-9 °C respectively).[113] This raised a very serious problem for Fischer. Everything except their melting points indicated these new acrosazones were the same as those previously produced from bromoacrolein. Yet Fischer was committed to melting point as an organic compound's most important identifying characteristic.[114] The matter demanded resolution. As Fischer explained, "we cannot delude ourselves that a more precise comparison is required as proof of the true identity of both osazones [from glycerol and bromoacrolein]."[115]

Seeking this proof, Fischer and Tafel undertook a large-scale preparation of α- and β-acrosazone from bromacrolein using the facilities of the Hoechst chemical company. They eventually obtained pure α- and β-acrosazone, confirming by melting point measurement that the same osazones were produced from both glycerol and acrolein. But this was no easy task. Because the synthesis of acrose required multiple steps, many of which produced extremely low yields of pure product, Fischer and Tafel had to begin with kilograms of glycerol. They converted 20 kg glycerol to 1700 g acrolein, then to bromoacrolein, and finally to α- and β-acrosazone. Purifying the osazones proved extremely difficult. Recrystallization did not work: Fischer and Tafel recrystallized α-acrosazone eight times from ethanol without detecting any increase in the melting point (over 205 °C). Only a "stratagem" involving a series of tedious operations in boiling ethanol enabled them to isolate reasonably pure α- and β-acrosazone.[116]

This tortuous process produced a mere 200 g α-acrosazone. Final purification resulted in "considerable" further losses, reducing the overall yield to well under 10%. This must have been awful work. As Fischer and Tafel explained, acrolein is "terrible stuff," and this preparation involved the largest quantity they had ever handled. The key reaction (converting acrolein to 2-bromoacrolein) was so noxious it could only safely be performed outside on a windy day. Fischer and Tafel worked hard to show by measuring identical melting points that the same osazone formed from both glycerol and bromoacrolein.[117]

Fischer and Tafel's study of the acroses also exemplifies a frequently overlooked issue underpinning the development of organic chemistry in general, and sugar chemistry in particular. I argued in an earlier essay that the histories of purification and identification are intertwined.[118] As we have seen, it was not the case that Fischer – having learnt to prepare crystalline osazones and believing these could be differentiated by their melting points – could straightforwardly apply this technique to the sugars. On the contrary, establishing this as a reliable method of identifying sugars required Fischer simultaneously to develop appropriate, standardized techniques of preparation and purification.

Finally, Fischer's preparation of the acroses revealed a key distinction between artificial sugars and their natural counterparts. α-Acrose displayed many characteristic properties of a sugar: it tasted sweet, fermented brewer's yeast and, crucially for Fischer, formed crystalline phenylhydrazine derivatives he could purify and characterize. But where natural sugars – and all the compounds they formed with phenylhydrazine – were optically active, α-acrose and its derivatives were not. Despite meeting Fischer's definition of a sugar, α-acrose was not identical to any natural sugar.

This outcome revealed a vital omission from Fischer's definition of a sugar, simultaneously raising important doubts about the status of α-acrose as a pure substance. Fischer now knew optical activity – the ability to rotate light – was an essential defining characteristic of natural sugars, a characteristic property any sugar synthesis would have to replicate. This also suggested optically inactive α-acrose was a mixture of optically active components. Although Fischer at this stage did not relate optical properties to three-dimensional molecular structure, he now began investigating methods for separating optically inactive synthetic sugars and sugar derivatives into their optically active components.[119]

5.4 Unraveling the Puzzle of Mannose and Glucose: Fischer's Paradox

Meanwhile, Fischer also continued to study mannose, produced by oxidizing the sugar alcohol mannitol. By February 1889, this work confronted Fischer with a crucial paradox. In response, he invoked the Le Bel – van't Hoff theory for the very first time. Understanding how Fischer reached this impasse and how he resolved it offers an invaluable opportunity to lay out Fischer's reasoning and provides unique insight into how laboratory work with reagents, reactions, melting points, and glassware were linked to abstract notions of purity, identity, reactive group, formula, structure, and stereochemistry in Fischer's work.

Before continuing, it will be helpful to recap the meaning of some important terms. This essay has already introduced ideas of composition and constitution: the former reflected in a molecular formula giving the number of atoms of each kind contained in a single molecule (e.g. $C_6H_{12}O_6$ for glucose); the latter referring to the arrangement of atoms within the molecule (e.g. $CH_2OH.(CHOH)_4.CHO$, displayed glucose's six-carbon backbone and the position of reactive groups on this chain). It is also essential to appreciate that nineteenth-century ideas of chemical structure were strictly two-dimensional, expressing knowledge of how atoms were linked and grouped but nothing more. Stereochemistry, not structure, is chemists' term for the three-dimensional spatial arrangement of atoms, the concept independently theorized in 1874 by Le Bel and van't Hoff.

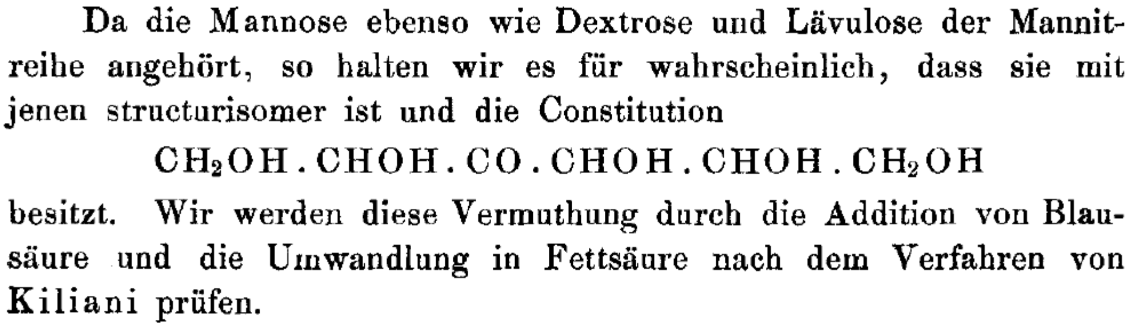
Fischer first isolated mannose in 1884 as its phenylhydrazone, formed when mannose reacted with one equivalent of phenylhydrazine. Analysis showed the molecular formula of this compound was the same as the phenylhydrazone derived from glucose. This indicated mannose and glucose were isomers: different compounds with the same molecular formula ($C_6H_{12}O_6$). Two results enabled Fischer to confirm this important finding. First, he compared the melting points of the phenylhydrazones formed from each sugar: where glucose phenylhydrazone melted at 144-5 °C, Fischer recorded a melting point of 188 °C for mannose phenylhydrazone.[120] Second, he found that where glucose phenylhydrazone dissolved easily in water, mannose phenylhydrazone was almost insoluble. In fact, Fischer observed such great differences between the two phenylhydrazones as to suggest mannose was very differently constituted from glucose.[121]

Fischer sought to elucidate the relationship between mannose and glucose. Working with his assistant Josef Hirschberger, Fischer obtained mannose from its phenylhydrazone but the sugar would not crystallize and was therefore impossible to purify. Fischer and Hirschberger produced insufficient mannose to test all its properties.[122] The results they did obtain, however, were intriguing. Mannose behaved very like glucose: it tasted sweet and dissolved easily in water and alcohol; it burned with a caramel odor, reduced Fehling's solution and fermented with brewers' yeast; it was easily converted into mannitol; and, like glucose, it rotated light to the right. Mannose appeared "so closely related to glucose that it could easily be confused with it." Yet Fischer could easily differentiate mannose from glucose by its "highly characteristic phenylhydrazone."[123]

As in Fischer's earlier study of phenylgalactosazone (section 5.1), Fischer and Hirschberger experienced enormous difficulties in stabilizing the melting point of mannose phenylhydrazone. Depending on how fast it was heated, they recorded values between 195 and 200 °C, significantly higher than Fischer's previous value (188°C).[124] They also found it very difficult to prepare an osazone from mannose, Fischer's essential definition of a true sugar. Mannose phenylhydrazone's "limited solubility" in water meant the usual reaction did not work but Fischer and Hirschberger eventually succeeded by heating mannose phenylhydrazone with excess phenylhydrazine in sealed tubes for 4-5 hours. Purified by recrystallization from alcohol, mannose's osazone formed as "fine yellow needles" that melted "about 210 °C."[125]

These results led Fischer and Hirschberger to propose a constitution for mannose [Figure 3]. In May 1888, guided by melting point data, Fischer and Hirschberger believed mannose and glucose were structural isomers, i.e. compounds with the same composition but different two-dimensional chemical structures.[126] By the following spring they knew they were wrong. Mannose and glucose were certainly different but they shared the same two-dimensional structure. This was the paradox at the heart of Fischer's sugar work, the first result he was unable to explain using two-dimensional structural theory. It was this finding that prompted Fischer to invoke Le Bel – van't Hoff theory, and it rested on a single piece of experimental evidence: a revised melting point for mannose's osazone. Explaining how Fischer reasoned from melting point to stereochemical conclusions illustrates how Fischer navigated from experimental results to significant new chemical knowledge, and it shows clearly exactly what role theory played in this work.

In May 1888, Fischer and Hirschberger classified mannose in the same group of six-carbon sugars as glucose and fructose because all three shared the same molecular formula ($C_6H_{12}O_6$). But because the hydrazones formed from mannose and glucose melted at different temperatures (195-200 °C and 144-5 °C, resp.) Fischer and Hirschberger knew mannose and glucose were distinct sugars. They also believed mannose and glucose formed different osazones, again on the basis of melting point measurements (210 °C cf. 205 °C).



Da die Mannose ebenso wie Dextrose und Lävulose der Mannitreihe angehört, so halten wir es für wahrscheinlich, dass sie mit jenen structurisomer ist und die Constitution

$$CH_2OH.CHOH.CO.CHOH.CHOH.CH_2OH$$

besitzt. Wir werden diese Vermuthung durch die Addition von Blausäure und die Umwandlung in Fettsäure nach dem Verfahren von Kiliani prüfen.

Figure 3. In May 1888, Fischer and Hirschberger situated the carbonyl group in mannose at C3. This reflected their conviction that mannose, glucose, and fructose shared the same composition but differed in the position of the carbonyl group on the carbon backbone. Experimental work indicated the carbonyl group was at C1 (the head of the chain) in glucose and C2 (next door) in fructose. Fischer and Hirschberger therefore reasoned the carbonyl group in mannose was at C3. Emil Fischer and Josef Hirschberger. 1888. "Ueber Mannose. I." Berichte *21: 1805-9, 1809.*

Fischer and Hirschberger's interpretation of these results drew on the established constitution of six-carbon sugars in which six carbon atoms were arranged in a single chain. Prior experimental work on glucose and fructose also indicated these were structural isomers that differed in the position of the carbonyl group on the carbon chain. Glucose was an aldose with the carbonyl carbon at the head of the chain (C1) whereas fructose was a ketose. Because osazones formed in a reaction involving the carbonyl carbon and its immediate neighbor, Fischer's demonstration that glucose and fructose formed identical osazones implied the carbonyl carbon in fructose must be immediately next to the head of the chain, i.e. at C2. If mannose and glucose formed different osazones as well as different hydrazones, Fischer and Hirschberger reasoned, then it was "probable" the carbonyl carbon in mannose was at C3 [Figure 3].

As in their study of the acroses (section 5.3) Fischer and Hirschberger continued by preparing mannose on a large-scale (starting from 3kg of mannitol). Despite repeated attempts, they failed to produce pure, crystalline mannose, instead obtaining a colorless, waxy mass that absorbed moisture so rapidly it soon became fluid in moist air.[127] They also struggled to determine a reliable melting point for the osazone from mannose. Fischer and Hirschberger had previously reported this as "about 210 °C," some 5 °C higher than the melting point of phenylglucosazone. They now admitted this value was "not correct."[128] As they improved the purity of mannose's osazone, Fischer and Hirschberger found its melting point approached that of phenylglucosazone.

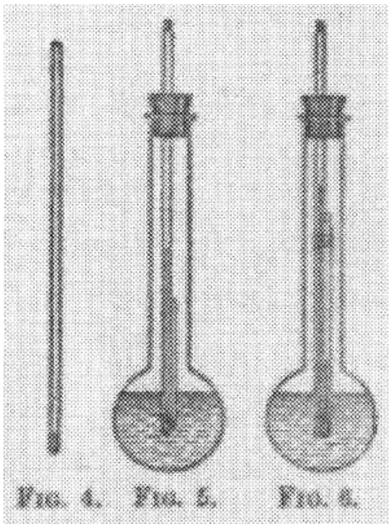
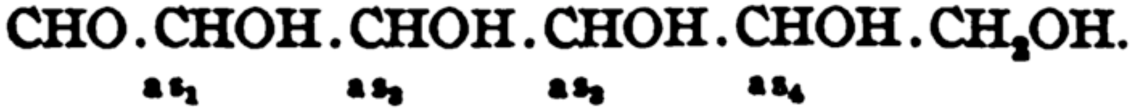


*Figure 4. Fischer's melting point apparatus consisted of a capillary tube containing the sample attached to a thermometer, all immersed in concentrated sulfuric acid enclosed in a standard round-bottomed flask. FIscher carefully explained the importance of using a standardized thermometer (*Normalthermometer*) and how "uncorrected" melting points obtained using this apparatus should be corrected to "true" values.*
Emil Fischer. 1909. Introduction to the Preparation of Organic Compounds Transl. from the 8th German edition by R. V. Stanford (London: Williams and Norgate), 10.
Image courtesy of the Science Museum Library/Science and Society Picture Library.

This raising the disturbing possibility the osazones produced from mannose and glucose were in fact the same. If proved, this chemical identity would falsify Fischer and Hirschberger's notion that the carbonyl carbon in mannose was at C3. In light of additional experimental work showing that mannose, like glucose, was an aldehyde sugar, with the carbonyl carbon at C1, it would also indicate that mannose and glucose had identical two-dimensional chemical structures.[129] In other words, if mannose and glucose formed the same osazone, then the difference between the two sugars could not be explained within established structural theory. The question of whether the two osazones were identical or not therefore became the crux of Fischer's sugar work.

In seeking to answer this crucial question, Fischer and Hirschberger used an innovative technique of melting point measurement. Fischer's usual method involved attaching a capillary tube containing the sample to a thermometer and heating both together in concentrated sulfuric acid until the sample melted [Figure 4]. The recorded melting point was then compared with existing values to determine whether the sample was a known compound. The reliability of this comparison depended critically on several factors. Impurities were known to lower the melting point, and different thermometers frequently recorded different temperatures in the same environment. Fischer also knew even perfectly pure samples of sugars and their derivatives melted at different temperatures depending on how quickly they were heated.

In order to avoid these sources of error, Fischer and Hirschberger made an ingenious modification that allowed them simultaneously to measure the melting points of both osazones. They attached two capillary tubes – one containing each osazone – to the same thermometer. Heating samples and thermometer together, Fischer and Hirschberger found both osazones melted "at exactly the same temperature, in fact at 205-6 °C." This established beyond all doubt that the two samples were not two distinct compounds but a single osazone, afterwards called phenylglucosazone.[130]



$$\mathrm{CHO.\underset{as_1}{CHOH}.\underset{as_2}{CHOH}.\underset{as_3}{CHOH}.\underset{as_4}{CHOH}.CH_2OH.}$$

Figure 5. Fischer and Hirschberger explained both mannose and glucose shared this two-dimensional structure. Because the osazones were identical but the hydrazones were different, they reasoned the difference between mannose and glucose must relate to the arrangement of the four substituent groups around carbon C2 (CHO, H, OH, CHOH.CHOH.CHOH.CH_2OH). In explaining this finding, Fischer drew on the Le Bel – van't Hoff theory for the first time, denoting C2 as as_1 to identify this as the first asymmetric carbon in the carbon chain forming the backbone of the sugar.
Emil Fischer and Josef Hirschberger. 1887. "Ueber Mannose. II." Berichte 22: 367-76, 375.

Fischer and Hirschberger now had what they regarded as absolutely reliable evidence for two findings that could not be reconciled within two-dimensional structural theory. They knew mannose and glucose were six-carbon aldehyde sugars that formed distinct phenylhydrazones but the same osazone. This meant mannose and glucose were indeed distinct compounds with identical two-dimensional structure. This experimental paradox prompted Fischer to seek an explanation in the theory of atoms in three-dimensional space. Because Fischer knew mannose and glucose produced distinct phenylhydrazones by reaction at the carbonyl carbon only (C1) while osazone formation required reaction at both C1 and C2, he inferred mannose and glucose must differ in the spatial arrangement of atoms around C2 [labeled as1 in Figure 5]. This was how Fischer concluded from melting point measurements that mannose and glucose were not structural isomers that differed in their two-dimensional chemical structure. Fischer's laboratory reasoning revealed the difference between mannose and glucose as stereochemical, making the two sugars what the Le Bel – van't Hoff theory termed "geometrical isomers."[131]

5.5 Three-Dimensional Sugars: Fischer's Key Step and Sugar Synthesis

This was a remarkable moment in the history of chemistry, as Fischer himself recognized.[132] Fischer's command of sugar chemistry – and especially reactions between sugars and phenylhydrazine – allowed him to make this claim with complete confidence. It was only when confronted by a paradox produced by his own reasoning and experimentation that Fischer drew upon the Le Bel – van't Hoff theory. Fischer and Hirschberger introduced the sugars as three-dimensional entities, and they demonstrated the possibility of investigating stereochemistry (*Asymmetrie*) by experiment, just as chemists had developed reagents into powerful tools for studying chemical structure.[133] In accounting for the relationship between mannose and glucose, the Le Bel – van't Hoff theory provided its first useful explanation of the chemistry of natural products, helping to elevate stereochemistry from its previously speculative status.

Fischer's experimental work on the sugars continued to elucidate stereochemical concepts. Around the end of 1889, Fischer and Hirschberger identified the first pair of optical isomers in sugar chemistry. Optical isomers (also called enantiomers) were a special case of Le Bel and van't Hoff's *geometrical isomers*, paired compounds with mirror-image three-dimensional structures that melted at the same temperature but rotated light in opposite directions. When Fischer and Hirschberger prepared mannonic acid lactone from mannose, they noted its very great similarity to arabinose carbonic acid lactone, previously produced by Kiliani from the sugar arabinose.[134] Further investigation confirmed the two lactones were optical isomers that, when mixed in equal amounts, formed a third, optically inactive lactone. This was how Fischer linked the natural sugars' optical activity to their three-dimensional structures.

This result provided Fischer with "the key" to understanding mannose because it allowed him to connect his analysis of natural sugars to his earlier synthesis of the artificial sugar, α-acrose.[135] By converting each lactone into its related sugar, Fischer showed mannonic acid lactone produced natural, dextrorotatory mannose, while arabinose carbonic acid lactone formed laevorotatory mannose. The optically inactive lactone formed an optically inactive sugar Fischer showed was identical to α-acrose. Fischer now identified α-acrose as the optically inactive sugar produced by mixing equal amounts of dextrorotatory- and laevorotatory-mannose.[136]

Having established this relationship, Fischer was able to apply reactions and methods developed during the preparation of α-acrose to the synthesis of natural, dextrorotatory mannose. An essential step in this work involved separating α-acrose into its optically active components, a task Fischer had begun to tackle in 1887, when he realized the products of his synthetical experiments did not share the optical activity of natural sugars. Fischer accomplished this optical resolution using fungi and strychnine salts and he published the synthesis of mannose within a few weeks, in February 1890.[137] This was the first synthesis of a natural sugar.

In elucidating the connection between the sugars' optical activity and three-dimensional structure, Fischer clarified the structural and stereochemical relationship between mannose, glucose, fructose, and their parent sugar alcohol, mannitol. This work equipped Fischer with methods of chemical transformation, purification, and identification he later used to make other members of the mannitol series including glucose. Fischer published the synthesis of glucose in early March

1890.[138] From this point, it took just over a year to establish the three-dimensional structure of glucose.[139]

6 Conclusion

My introduction highlighted the somewhat awkward relationship between Fischer's status as lone genius and existing assessments of his achievements. Fruton's classic study is a noteworthy example. Fruton simultaneously celebrated Fischer's genius and condemned his autocratic management style. The present study indicates both judgments are flawed.[140] Solving the problem of the sugars depended crucially on Fischer's ability "to follow phenomena empirically and to search for unexpected occurrences."[141] Fischer constantly judged which results were trustworthy and which remained, or had become, uncertain. Appreciating this expertise explains why Fischer was such a stickler for the minutiae of laboratory technique, and why he maintained such tight control over chemists in his laboratory. Junior chemists produced essential evidence for Fischer's sugar work but this essay shows there was nothing arbitrary about Fischer's managerial practices. Rather, these were a necessary component of Fischer's ability to solve one of the most difficult chemical problems of his day. This essay therefore contributes to our understanding of the interaction between collective labor and individual creative oversight in cutting edge research.

It is also noteworthy that Fischer's laboratory was situated in the economic and industrial powerhouse of late nineteenth-century Germany, and not in any ivory tower.[142] Although earlier accounts have given the impression that Fischer's work was performed in academic isolation, the present study places Fischer's sugar work firmly in its industrial and commercial context. Not only did Fischer make frequent reference to industrial and commercial benefits that might follow from his work,[143] this essay has revealed Fischer's sugar chemistry as responding to, correcting, using, and developing the work of sugar chemists in technological as well as academic laboratories – Heinrich Kiliani, Victor Meyer, Carl Scheibler, and Bernhard Tollens among them. Despite its huge significance for the development of academic chemistry, Fischer's solution to the problem of the sugars was also intimately connected with the sugar industry.

Many of Fischer's most significant breakthroughs were equivalent to his ability to decide whether two substances were identical, or merely similar. Fischer accomplished this by using phenylhydrazine to convert sugars into crystalline compounds he could purify and differentiate by their melting points. Fischer developed phenylhydrazine into a powerful tool of chemical investigation, and he used it to define a new taxonomy of sugars. As he explored sugar chemistry using phenylhydrazine, Fischer developed a vast suite of reactions by means of which he was able to navigate and expand that taxonomy. What Fischer elsewhere termed "genetical relationships" were central to his sugar chemistry, and nowhere more so than in his classification of sugars in relation to their parent sugar alcohol.[144] Organizing mannose, glucose, and fructose into what Fischer called "the mannitol series" took account of stereochemical as well as structural relationships between the sugars, and it connected them to secure laboratory knowledge.[145]

We have seen how Fischer's original urge to define the sugars ultimately became co-extensive with the goal of revealing the stereochemistry of natural sugars. Fischer not only adjusted his original definition of a sugar to include optical activity, he also established the sugars' three-dimensional nature. Fischer ultimately synthesized all sixteen six-carbon aldoses whose existence was predicted by the Le Bel - van't Hoff theory. It would, however, be quite wrong to assume – as so many historians have done – Fischer accomplished this by applying theory.[146] On the contrary, when Fischer's laboratory work revealed an impasse, he used the Le Bel – van't Hoff theory to offer an explanation. This theory then suggested additional synthetic targets but, crucially, did not tell Fischer how to pursue them.

This essay has revealed Fischer's *art of chemical experimentation* as the foundation of his success, and it has shown why Fischer always regarded the sugars as an "experimentally extremely difficult" problem.[147] Laboratory reasoning combined with extraordinary manipulative resources taught Fischer what the sugars were and how they might be made. In mastering the sugars, Fischer did far more than merely demonstrate the correctness of the Le Bel – van't Hoff theory. As Fischer explained, the methods he had developed not only opened up the possibility of investigating complex stereochemical relationships by experiment, they also constituted the only mechanism by which the Le Bel – van't Hoff theory could be stabilized and extended. All of the compounds produced by Fischer's sugar work "fitted the general frame of the theory." But Fischer's experimental study of the sugars also indicated stereochemical theory required modification to handle “the combination of isomeric substances containing asymmetric carbon atoms” – a central process in the synthesis of natural products.[148]

This was the very first time the methods of organic chemistry had been successfully applied to elucidate the chemistry of an entire group of natural products. This was why Fischer’s study of the sugars was quickly recognized as *the* paradigm of experimental organic chemistry, an exemplar that assured Fischer’s status as one of the greatest organic chemists of all time. Fischer’s mastery of experimental organic chemistry remains legendary – so much so that he has been called the Einstein of organic chemistry.[149] By explaining what Fischer actually did in the laboratory this essay makes clear why subsequent generations of chemists have continued to find his work so instructive and impressive. Fischer’s study of the sugars was an important milestone: it was the first to define an entire family of natural products by their three-dimensional chemical structure, and it provided a durable model for such investigations.

Fischer’s sugar work marks a major landmark in the changing relationship between experiment and theory in late nineteenth-century organic chemistry. This essay has re-situated theory in Fischer’s work by demonstrating the intimate connection between experimental manipulation and two-dimensional structural theory in Fischer’s laboratory reasoning. It has shown how, when structural theory reached the limits of its explanatory power, Fischer re-conceptualized sugar chemistry in three dimensions, ultimately establishing a new sugar classification based on the Le Bel – van’t Hoff theory.[150] This account of Fischer’s sugar work confirms the primacy of experiment in driving and enabling the incorporation of cutting edge theoretical concepts such as stereochemistry within chemical practice. It begins to explain how Fischer made experiment and theory work together in the laboratory in a robust and reliable manner. In doing so, it lays the foundations for an account of how nineteenth-century chemists built initially unstable concepts like structure and stereochemistry into the powerful theories their successors still work with today.

This understanding of Fischer’s chemistry has important consequences for our perception of the differences between organic chemistry as practiced by an experimental organic chemist like Fischer and August Kekulé’s more theoretically oriented (and so much more widely studied) research program.[151] Where Kekulé focused on the study of the aromatic compound benzene as a theoretical object, Fischer – like his teacher Baeyer – used the laboratory methods of organic chemistry to gain productive control over Nature. By clarifying how experiment and theory were related in Fischer's chemical practice this essay indicates the two are very different ventures, suggesting why Fischer, as a young student, rejected Kekulé's laboratory in favor of Baeyer's.[152] Of even greater significance for our understanding of chemistry, it exemplifies an approach by which future studies might develop a historical account of the relationship between organic chemistry as an experimental art and a theoretical pursuit.

7 Acknowledgments

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[1] Catherine M. Jackson. 2008. "Visible Work: the Role of Students in the Creation of Justus Liebig's Giessen Research School." *Notes and Records of the Royal Society* 62: 31-49; Catherine M. Jackson. 2014. "Synthetical Experiments and Alkaloid Analysis: Liebig, Hofmann and the Origins of Organic Synthesis." *Historical Studies in the Natural Sciences* 44: 319-63; Catherine M. Jackson. 2014. "The Curious Case of Coniine: Constructive Synthesis and Aromatic Structure Theory." In Ursula Klein and Carsten Reinhardt, eds. *Objects of Chemical Inquiry* (Sagamore Beach, MA: Science History Publications), 61-101.

[2] Michael Faraday. 1827. *Chemical Manipulation; being Instructions to Students in Chemistry, on the Methods of performing Experiments of Demonstration or of Research, with Accuracy and Success* (London: Phillips), iii.

[3] Hans Rupe. 1932. *Adolf Baeyer als Lehrer und Forscher: Erinnerungen aus seinem Privatlaboratorium* (Stuttgart: Enke), 15 (*in Erscheinungen denken*).

[4] Emil Fischer. 1922. *Aus meinem Leben* (Berlin: Springer), 52 (*chemische Experimentierkunst*).

This study has been greatly assisted by existing accounts of Fischer's life and work, in particular his autobiography (*Leben*) and Emil Fischer. 1905. "Erinnerungen aus der Strassburger Studienzeit. 1872 bis 1875." In Adolf Baeyer. *Erinnerungen aus meinem Leben. 1835 bis 1905*. (Braunschweig: Vieweg), xxi-xxxi. Martin Onslow Forster. 1920. "Emil Fischer's Contribution

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to Organic Chemistry." *Nature* 106: 326-7 (abbreviated from Martin O. Forster. 1920. "Emil Fischer Memorial Lecture." *J. Chem. Soc., Trans.* 117: 1157- 1201); Carl D. Harries. 1919. "Emil Fischer's wissenschaftliche Arbeiten." *Naturwissenschaften* 7: 843-80; and Lewis Lewin. 1919. "Eine toxicologische Erinnerung an Emil Fischer." *Naturwissenschaften* 7: 878-882; Kurt Hoesch. 1921. *Emil Fischer: Sein Leben und sein Werk* (Berlin: Chemie Verlag); Karl Freudenberg. 1966. "Emil Fischer and his Contribution to Carbohydrate Chemistry." *Advances in Carbohydrate Chemistry* 21: 1-38, are among many accounts written by chemists and biochemists.

Joseph S. Fruton. 1985. "Contrasts in Scientific Style: Emil Fischer and Franz Hofmeister, their Research Groups and their Theory of Protein Structure." *Proceedings of the American Philosophical Society* 129: 313—370, developed into a major book comparing the research groups of Fischer, Liebig, Baeyer, and Hofmeister: Joseph S. Fruton. 1990. *Contrasts in Scientific Style: Research Groups in the Chemical and Biochemical Sciences* (Philadelphia: American Philosophical Society). Fischer also featured in several recent studies focused on other aspects of chemistry's history. Of particular relevance are: Peter J. Ramberg. 2003. *Chemistry in Space: the Early History of Stereochemistry, 1874-1913* (Aldershot: Ashgate); Carsten Reinhardt and Tony Travis. 2000. *Heinrich Caro and the Creation of Modern Chemical Industry* (Berlin: Springer); Jeffrey A. Johnson. 1990. *The Kaiser's Chemists: Science and Modernization in Imperial Germany* (Duke, N.C.: North Carolina University Press).

[5] Fruton *Contrasts* (ref. 4) remains the classic study of Fischer's work.

[6] Ramberg *Chemical Structure* (ref. 4), Chapter 8, gave an account of Fischer's sugar work intended to elucidate the stereochemical reasoning by which Fischer proposed the absolute configuration of glucose, an emphasis that perhaps reinforced Ramberg's interpretation of much of Fischer's work as applying theory (see especially 272-3).

[7] Forster "Memorial Lecture" (ref. 4), 1163.

[8] Hoesch *Emil Fischer* (ref. 4), 206.

[9] On the general significance of material culture in producing new knowledge, see Pamela H. Smith, Amy W. Meyers, and Harold J. Cook, eds. *Ways of Making and Knowing: The Material Culture of Empirical Knowledge* (Ann Arbor: University of Michigan Press, 2014). On the specific material culture of nineteenth-century organic chemistry, see Catherine M. Jackson. 2011. "Chemistry as the Defining Science: Discipline and Training in Nineteenth-century Chemical Laboratories." *Endeavour*, 35: 55-62; and Catherine M. Jackson. 2015. "The 'Wonderful Properties of Glass': Liebig's *Kaliapparat* and the Practice of Chemistry in Glass," *Isis* 106: 43-69.

[10] Catherine M. Jackson. 2015. "Chemical Identity Crisis: Glass and Glassblowing in the Identification of Organic Compounds," *Annals of Science* 72: 187-205.

[11] For a recent discussion of the historical turn to practice, and its relationship to the field of laboratory studies, see Catherine M. Jackson, "The Laboratory," in *Companion to the History of Science*, ed. Bernard Lightman (Oxford: Blackwell-Wiley, 2016), 296-309, esp. 302-5.

[12] August W. Hofmann. 1871. "A Page of Scientific History." *Quarterly Journal of Science* 8: 145- 153, 146.

[13] William H. Brock. 1997. *Justus Liebig: The Chemical Gatekeeper* (Cambridge: Cambridge University Press), 45-6; Catherine M. Jackson. 2006. "Re-examining the Research School: August Wilhelm Hofmann and the Re-creation of a Liebigian Research School in London." *History of Science* 44: 281-319.

[14] Jack B. Morrell. 1972. "The Chemist Breeders: The Research Schools of Liebig and Thomas Thomson." *Ambix* 19**:** 1-46.

[15] Jackson "Synthetical Experiments" (ref. 1) argued organic synthesis began in early 1840s Giessen.

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[16] Emil Fischer. 1887. *Anleitung zur Darstellung organischer Präparate* 2nd edition (Würzburg: Stahel) became the classic laboratory textbook of organic synthesis.

[17] Jackson "Re-examining" (ref. 13) studied the relationship between Liebig and Hofmann.

[18] Michael N. Keas. 1992. *The Structure and Philosophy of Group Research: August Wilhelm Hofmann's research program in London (1845-1865)* (PhD Dissertation, University of Oklahoma), 216-34.

[19] Emil Fischer. 1874. *Ueber Fluorescein und Phtalein-Orcin* (Bonn: Neussar); Otto Fischer. 1874. *Ueber Verbindungen von Chloral und Aldehyd mit Toluol unter Austritt von Wasser* (Bonn: F. Wolff).

[20] The course followed Heinrich Will's introductory textbook, first published for use in Liebig's laboratory. Heinrich Will, *Anleitung zur qualitativen chemischen Analyse zum Gebrauche im chemischen Laboratorium zu Giessen.* Erste Auflage. (Heidelberg: Winter, 1846).

[21] Fischer *Leben* (ref. 4), 45-6, 50-2.

[22] Christine Nawa. 2014. "A Refuge for Inorganic Chemistry: Bunsen's Heidelberg Laboratory." *Ambix* 61: 115-140.

[23] Fischer "Studienzeit" (ref. 4), xxii.

[24] Jackson "Visible Work" (ref. 1) revealed the ongoing difficulty of mid nineteenth-century organic analysis.

[25] Baeyer *Leben* (ref. 4), xix. Fischer "Studienzeit" (ref. 4), xxiii, claimed Fischer could neither distil ether, nor perform a quantitative organic analysis.

[26] Fischer "Studienzeit" (ref. 4), xxiii. Adolf Baeyer, "Ueber eine neue Klasse von Farbstoffen," *Berichte* (1871) 4: 555-8; and Adolf Baeyer, "Ueber die Phenolfarbstoffe," *Berichte* (1871) 4: 658-65, confirm Baeyer conceived this project within the sphere of dye chemistry.

[27] Jackson "Visible Work" (ref. 1), 33.

[28] Fischer "Studienzeit" (ref. 4), xxiv.

[29] Fischer "Studienzeit" (ref. 4), xxiii

[30] Julijan Grabowski. 1874. *Ein Beitrag zur Kenntniss der Wasserentziehungsprocesse (in der Naphthalingruppe).* (Strassburg: Wolff).

[31] Jackson "Chemical Identity Crisis" (ref. 10).

[32] Jackson "Chemical Identity Crisis" (ref. 10); Jackson "Synthetical Experiments" (ref. 1).

[33] Fischer *Fluorescein* (ref. 19), 6.

[34] E.g. Otto Fischer *Toluidin* (ref. 19), 1. Michael N. Keas, "The Nature of Organic Bases and the Ammonia Type," in Christoph Meinel and Hartmut Scholz, eds., *Die Allianz von Wissenschaft und Industrie August Wilhelm Hofmann (1818-1892): Zeit, Werk, Wirkung* (Weinheim: VCH, 1992), 101-118, highlighted Hofmann's use of analogy.

[35] Jackson "Synthetical Experiments" (ref. 1), 347-51.

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[36] E.g. Georgette N. L. Taylor. 2006. *Variations on a Theme: Patterns of congruence and divergence among 18th century chemical affinity theories* (PhD Dissertation, University College London), 121, described Joseph Black's characterization of fixed air (carbon dioxide) using limewater (calcium hydroxide solution).

[37] While earlier editions referred only to inorganic reagents, George Fownes. 1861. *A Manual of Elementary Chemistry, Practical and Theoretical*, 8th ed., edited by August W. Hofmann and Henry Bence Jones (London: Churchill), 600, also used the term in the context of organic chemistry.

[38] Auguste Cahours. 1848. "Action du Perchlorure de Phosphore sur les Acides et les Aldéhydes du Groups Benzoïque." *Ann. Chem. Phys.* 23[3]: 327-357.

[39] According to Baeyer *Leben* (ref. 4), xi-xii, phosphorus pentachloride was "fashionable" by the late 1850s.

[40] Colin A. Russell. 1971. *The History of Valency* (Leicester: Leicester University Press).

[41] cf. Fischer *Fluorescein* (ref. 19), 7ff., which illustrated C_6 units.

[42] Baeyer *Leben* (ref. 4), xv, was quick to adopt aromatic structural theory but subsequently recognized this as insufficiently stable to be useful.

[43] Adolf Baeyer. 1871. "Ueber Phenolfarbstoffe." *Berichte* 4: 658-65, 659, 661.

[44] Emil Fischer. 1874. "Ueber Fluorescëin und das Phtalëin des Orcins" *Berichte* 7: 1211-16, 1212; Fischer *Fluorescein* (ref. 17), 10-13.

[45] Fischer *Fluorescein* (ref. 19), 7.

[46] Condensation reactions join two starting materials with consequent elimination of a small molecule, usually water. This category of reaction was identified in Baeyer's Berlin laboratory in the 1860s, ultimately attaining enormous synthetic significance.

[47] Reinhardt and Travis *Heinrich Caro* (ref. 4), Chapter 7.

[48] Adolf Baeyer and Carl Jaeger. 1875. "Ueber die Amide des Diazobenzols." *Berichte* 8: 148-50; and 893-4.

[49] According to Reinhardt and Travis *Heinrich Caro* (ref. 4), 60, aniline yellow was the first commercial azo dye, developed by Martius and Caro in 1863/4. K. H. Saunders. 1949. *The Aromatic Diazo-Compounds and their Technical Applications* 2nd edition (Bungay: Clay), 44-49, considered understanding of diazotization remained incomplete into the mid twentieth century.

[50] George B. Kauffman and Richard P. Ciula. 1977. "Emil Fischer's Discovery of Pheynylhydrazine." *J. Chem. Ed.* 54: 295, referred to the intended product as bisphenol.

[51] Fischer "Studienzeit" (ref. 4), xxv-vi, is the most comprehensive source concerning this episode.

[52] Fischer's choice simultaneously simplified the starting material's hydrocarbon component and confined the reaction to its second, crucial phase: reduction of the intermediate diazonium salt.

[53] Reinhardt and Travis *Heinrich Caro* (ref. 4), 165-6, described Kekulé's work (with Caro) on the development of azo dyes. Anthony Travis. 1993. *The Rainbow Makers: The Origins of the Synthetic Dyestuffs Industry in Western Europe* (Bethlehem, PA: Lehigh University Press), provides an account of the development of azo dyes.

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[54] Fischer *Leben* (ref. 4), 60. This marked a significant change of heart on the part of Fischer's father. According to Fischer, his father was frustrated when he rejected a career in business and somewhat grudgingly supported undergraduate study in chemistry, presumably because he believed his son's education should equip him to earn a living. It seems reasonable to infer Fischer and his father anticipated phenylhydrazine would prove important to industrial dye chemistry.

[55] Harries "Arbeiten" (ref. 4), 845; and Kauffmann and Ciula "Discovery" (ref. 50) are unusual in recognizing phenylhydrazine's significance as a driver of Fischer's chemistry. Forster "Memorial Lecture" (ref. 4), 1163, by contrast, characterized rosaniline as "a distraction" from Fischer's pursuit of phenylhydrazine.

[56] Emil Fischer and Otto Fischer. 1876. "Zur Kenntniss des Rosanilins." *Berichte* 9: 891-900, 892.

[57] Fischer and Fischer "Zur Kenntniss" (ref. 56), 891.

[58] Emil Fischer. 1877. "Ueber aromatische Hydrazinverbindungen. IV." *Berichte* 9: 880-91, 888.

[59] Fischer related this story to the German Chemical Society on June 23 1890. See Emil Fischer. 1890. "Synthesen in der Zuckergruppe. I." *Berichte* 23: 2114-2141, 2117.

[60] Adolf Baeyer. 1867. "Ueber Condensation und Polymerie." *Ann. Chem. Pharm.* Suppl. Vol. 5: 79-95, was an early contribution to Baeyer's work in this area, which remained active throughout his time in Strasbourg.

[61] Adolf Baeyer. 1870. "Ueber die Wasserentziehung und Ihre Bedeutung fur das Pflanzenleben und die Gährung." *Berichte* 3: 63-75.

[62] Wilhelm Lossen. 1865. "Ueber das Hydroxylamin." *Zeitschrift fuer Chemie* 8: 551-3, described the first preparation of hydroxylamine. Victor Meyer. 1875. "Notiz zur Geschichte des Hydroxylamins." *Annalen* 175: 141-42. See also Victor Meyer and J. Lochner. 1875. "Ueber neue Bildungsweisen des Hydroxylamins." *Berichte* 8: 215-19.

[63] Victor Meyer and Alois Janny. 1882. "Ueber die Einwirkung von Hydroxylamin auf Aceton." *Berichte* 15: 1324-26, first proposed "Acetoxim" as the name for the condensation product formed by acetone and hydroxylamine. On the reaction of hydroxylamine with aldehydes, see J. Petraczek. 1882. "Ueber die Aldoxime." *Berichte* 15: 2783-86. The name of the condensation products of both aldehydes and ketones with hydroxylamine was later generalized to "oxime."

[64] Emil Fischer. 1875. "Ueber aromatische Hydrazinverbindungen. II." *Berichte* 8: 1005-11, 1011.

[65] These inconsistencies arose when Fischer compared the reactions of diphenylhydrazine and its better-known isomer, hydrazobenzene. Emil Fischer. 1877. "Ueber aromatische Hydrazinverbindungen. V." *Berichte* 9: 1840-45, 1845. Explaining this result took Fischer more than six months. Emil Fischer. 1877. "Ueber aromatische Hydrazinverbindungen. VI." *Berichte* 10: 1331-38, 1334-35.

[66] Ernst Nägeli. 1883. "Zur Kenntniss der Hydroxylaminreaktionen." *Berichte* 16: 494-500), 494, used the unusual term "Reaktiv" rather than the more widespread "Reagens."

[67] Hermann Reisenegger. 1883. "Ueber die Verbindungen der Hydrazine mit Ketonen." *Berichte* 16: 661-64.

[68] Emil Fischer and Friedrich Jourdan. 1883. "Ueber die Hydrazine der Brenztraubensäure.*"* *Berichte* 16**:** 2241–2245, studied the reaction between phenylhydrazine and pyruvic acid, containing both carboxylic acid and ketone.

[69] Fischer fn. to Reisenegger "Hydrazine mit Ketonen" (ref. 67), 661.

[70] Emil Fischer. 1884. "Phenylhydrazin als Reagens auf Aldehyde und Ketone." *Berichte* 17: 572-78, 572.

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[71] Fischer "Reagens auf Aldehyde und Ketone" (ref. 70), 573

[72] Emil Fischer. 1884. "Phenylhydrazin als Reagens auf Zuckerarten." *Berichte* 17: 579-84.

[73] Fischer *Leben* (ref. 4), 94.

[74] Jackson "Synthetical Experiments" (ref. 1), 331-8.

[75] Fischer "Zuckergruppe I" (ref. 57), 2126-27, described Butlerov's claimed sugar synthesis: Alexander Butlerov. 1861. "Bildung einer zuckerartigen Substanz durch Synthese." *Annalen* 120: 295-8. See also Emil Fischer. 1888. "Ueber die Verbindungen des Phenylhydrazins mit den Zuckerarten. III." *Berichte* 21, 988-91 (received March 15 1888), 991, for Fischer's refutation of Butlerov's claim.

[76] E.g, Bernhard Tollens. 1883. "Ueber das Verhalten der Dextrose zu ammonalkalischer Silberlösung." *Berichte* 16: 921-4, 923.

[77] Heinrich Kiliani. 1886. "Ueber die Einwirkung von Blausäure auf Dextrose." *Berichte* 19: 767-72, 767.

[78] These terms, coined by Fischer's student Henry Armstrong, were introduced into the chemical lexicon by Fischer "Zuckergruppe I" (ref. 59), 2136.

[79] Tollens "Verhalten" (ref. 76).

[80] Fischer "Zuckergruppe I" (ref. 59), 2116, referred to Heinrich Kiliani. 1885. "Ueber das Cyanhydrin der Lävulose." *Berichte* 18: 3066-72.

[81] Fischer "Zuckergruppe I" (ref. 59), 2117**.**

[82] Sigismund Marggraf. 1747. "Experiences chimiques faites dans le dessein de tirer un veritable sucre de diverses plantes, qui croissent dans nos contrées." *Histoire de l'académie royale des sciences et belles-lettres de Berlin*: 79-90, 90.

[83] Fischer *Leben* (ref. 4), 110.

[84] Emil Fischer and Julius Tafel. 1887. "Oxidation der mehrwertigen Alkohole." *Berichte* 20: 1088-94, 1089, introduced the term "osazone" but for the sake of convenience I have used this term throughout.

[85] Fischer "Reagens auf Aldehyde und Ketone" (ref. 70), 573 (*Hydrazinprobe*).

[86] Emil Fischer. 1887. "Ueber die Verbindungen des Phenylhydrazins mit der Zuckerarten. II." *Berichte* 20: 821-34, 821, cited Carl Scheibler. 1884. "Ueber die Nichtidentität von Arabinose und Lactose." *Berichte* 17: 1729-32, 1732.

[87] Friedrich Beilstein. 1886. *Handbuch der organischen Chemie* Vol. I, 2nd ed. (Hamburg and Leipzig: Voss), 831, also cited Scheibler "Nichtidentität" (ref. 75), 1732. For more on Beilstein and his *Handbook*, see Michael D. Gordin. 2005. "Beilstein Unbound: The Pedagogical Unravelling of a Man and his *Handbuch*." pp. 11-40 in David Kaiser ed. 2005. *Pedagogy and the Practice of Science: Historical and Contemporary Perspectives* (Cambridge, MA: MIT Press).

[88] Emil Fischer. 1888. "Ueber die Hydrazone." *Berichte* 21: 984-88, responded similarly to other chemists' inaccurate melting points for hydrazones.

[89] Jackson "Chemistry as the Defining Science" (ref. 9).

[90] Jackson "Chemical Identity Crisis" (ref. 10). See also Jackson "Wonderful Properties" (ref. 9).

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[91] Fischer *Anleitung* (ref. 16). Emil Fischer. 1909. *Introduction to the Preparation of Organic Compounds* Transl. from the 8th German edition by R. V. Stanford (London: Williams and Norgate) illustrates the temporal and geographical dispersal of Fischer's textbook.

[92] Fischer "Zuckerarten II" (ref. 86).

[93] Jackson "Synthetical Experiments" (ref. 1), 339-47.

[94] This move may also have been inspired by Adolf Emmerling's suggestion that glucose was a ketone alcohol. Adolf Emmerling. 1880. "Ueber Acetol und Traubenzucker." *Tageblatt der Naturforscherversammlung zu Danzig*, was abstracted in the 1880 *Chemisches Zentralblatt* 51: 807-8. Benzoyl carbinol was also an appropriate choice because it was about the same molecular size as simple sugars like glucose.

[95] Emil Fischer. 1882. "Ueber das Furfurol." *Annalen* 211: 214-32, see esp. fn. 214-15.

[96] The term phenylhydrazone first appeared in Heinrich Laubmann. 1888. "Ueber die Verbindungen des Phenylhydrazins mit einigen Ketonalkoholen." *Annalen* 243: 244-46, and was formally introduced in March 1888 by Fischer "Hydrazone" (ref. 86).

[97] Franz Wilhelm Dafert. 1884. "Ueber die Bildung des Mannits aus Laevulose und Dextrose." *Berichte* 17: 227-30, was a preliminary report later published in full as Franz Wilhelm Dafert. 1884. "Ueber Mannit." *Zeitschrift des Vereins der Deutschen Zucker-Industrie* 34: 574–603.

[98] Fischer "Zuckergruppe I" (ref. 59), 2122, drew attention to exactly this aspect of phenylhydrazine's usefulness.

[99] Fischer, "Zuckerarten II" (ref. 86), 830, explained this classification for phenylglucosazone, phenylgalactosazone, and phenylsorbosazone. All three shared molecular formula $C_{18}H_{22}N_4O_4$ but were easily differentiated by their melting points (203-4 °C, 193-4 °C, and 162-4 °C, respectively).

[100] Jackson "Chemical Identity Crisis" (ref. 10), 190.

[101] Fischer, "Zuckerarten II" (ref. 86), 833.

[102] Fischer, "Zuckerarten II" (ref. 86), 833.

[103] See ref. 75.

[104] Oscar Löw, "Ueber Formaldehyd und dessen Condensation." *Journ. für prakt. Chem.* 33: 321-51, 328, coined the name "formose."

[105] Oscar Löw. 1889. "Nachträgliche Bemerkungen über Formose." *Berichte* 22: 478-82**,** disputed Fischer's results. Löw continued to defend his priority in various aspects of his sugar work until 1915.

[106] Fischer and Tafel "Oxidation" (ref. 84).

[107] Fischer and Tafel "Oxidation" (ref. 84).

[108] Emil Fischer and Julius Tafel. 1887. "Synthetische Versuche in der Zuckergruppe. I." *Berichte* 20: 2566-75, 2568-69, 2566.

[109] Fischer and Tafel "Synthetische Versuche I" (ref. 108), 2574.

[110] Fischer and Tafel "Synthetische Versuche I" (ref. 108), 2568.

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[111] Julius Tafel. 1889. "Ein Schüttelapparat für das Laboratorium." *Berichte* 22: 1868-70.

[112] Fischer and Tafel "Synthetische Versuche I" (ref. 108), 2572, described the development of a particularly important reaction: the interconversion of glucose and laevulose (fructose) via phenylglucosazone. Emil Fischer. 1890. "Synthese der Mannose und Lävulose." *Berichte* 23: 370-94 (received February 8 1890), 372, applied this reaction to the synthesis of laevulose (fructose). The reaction proceeded via isoglucosamin. See Emil Fischer. 1886. "Ueber Isoglucosamin." *Berichte* 19: 1920-24.

[113] Emil Fischer and Julius Tafel. 1887. "Synthetische Versuche in der Zuckergruppe. II." *Berichte* 20: 3384-90, 3387.

[114] Jackson "Chemical Identity Crisis" (ref. 10), 196, discussed Hofmann's resolution of a similar problem.

[115] Fischer and Tafel "Synthetische Versuche II" (ref. 113), 3387-8 (direct quotation from 3388).

[116] Fischer and Tafel "Synthetische Versuche II" (ref. 113), 3388-89, 3389 (*Kunstgriff*).

[117] Fischer and Tafel "Synthetische Versuche II" (ref. 113), 3388 (*fürchtbaren Stoffe*); 3389 (*beträchtlichem Verluste*).

[118] Jackson "Chemical Identity Crisis" (ref. 10).

[119] Fischer and Tafel "Synthetische Versuche I" (ref. 108), 2568-69.

[120] Fischer "Zuckerarten II" (ref. 86), 824, reported the melting point of glucose phenylhydrazone.

[121] Fischer "Zuckerarten. II" (ref. 86), 832.

[122] Emil Fischer and Josef Hirschberger. 1888. "Ueber Mannose. I." *Berichte* 21: 1805-9 (received May 30 1889).

[123] Fischer and Hirschberger "Mannose I" (ref. 122), 1807.

[124] Fischer and Hirschberger "Mannose I" (ref. 122), 1806.

[125] Fischer and Hirschberger "Mannose I" (ref. 122), 1808-9, cf. Fischer, "Zuckerarten II" (ref. 86), 831.

[126] Fischer and Hirschberger, "Mannose I" (ref. 122), 1809.

[127] Fischer and Hirschberger therefore still lacked accurate results for some important quantitative tests – most notably measurement of mannose's optical rotatory power, later estimated by Emil Fischer and Josef Hirschberger. 1889. "Ueber Mannose. II." *Berichte* 22: 365-76, 368.

[128] Fischer and Hirschberger "Mannose II" (ref. 127), 374.

[129] This result also depended on Kiliani's method for chain extending sugars from their carbonyl group. When Fischer and Hirschberger applied Kiliani's method to mannose they produced a carboxylic acid that could be reduced to normal heptyl alcohol (heptan–1–ol). This meant the carbonyl group in mannose must occupy the terminal position. See Fischer and Hirschberger "Mannose II" (ref. 127), 374-5.

[130] Fischer and Hirschberger "Mannose II" (ref. 127), 374.

[131] Fischer and Hirschberger "Mannose II" (ref. 127), 375.

[132] Fischer "Zuckergruppe I" (ref. 59), 2123.

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[133] Fischer and Hirschberger "Mannose II" (ref. 127), 376.

[134] Fischer "Mannose und Lävulose" (ref. 112), 370.

[135] Fischer "Zuckergruppe I" (ref. 59), 2123.

[136] This was also how Fischer learnt that sugars and all their derivatives (osazones, hydrazones, alcohols, acids, and lactones) could exist in enantiomeric forms that, when mixed in equal amounts, gave rise to a related series of optically inactive compounds.

[137] Fischer "Mannose und Lävulose" (ref. 112), 379.

[138] Fischer "Mannose und Lävulose" (ref. 112); Emil Fischer. 1890, "Synthese des Traubenzuckers." *Berichte* 23: 799-805.

[139] Emil Fischer. 1891. "Ueber die Configuration des Traubenzuckers and seiner Isomeren. I." *Berichte* 24: 1836-45.

[140] Fruton "Contrasts" (ref. 4), 330-41, suggested Fischer's laboratory offered a less than ideal environment for young chemists, and that Fischer was ungenerous in recognizing the contributions of others in publication. Freudenberg "Emil Fischer's Contribution" (ref. 4), 3, provides a useful, first-hand corrective: Carl Freudenberg found it "magnificent to work under [Fischer's] direction."

[141] Fischer *Leben* (ref. 4), 112.

[142] For more on this point, see Johnson *Kaiser's Chemists* (ref. 4); and Reinhardt and Travis *Heinrich Caro* (ref. 4).

[143] Fischer "Zuckergruppe I" (ref. 59), 2114. Fischer's citations indicate he was a regular reader of journals concerned with the industrial and economic significance of sugar chemistry. Fischer's sugar work was also reprinted in such venues, reflecting the editors' belief in its industrial importance.

[144] Fischer "aromatische Hydrazinverbindungen. VI" (ref. 65), 1331, used the term (*genetische Beziehungen*), as did Fischer's *Habilitationschrift*: Emil Fischer. 1877. *Ueber die Hydrazinverbindungen* (Munich), 23. Jackson "Synthetical Experiments" (ref. 1), 338, explained the origins of the term "genetical chemistry." Ramberg *Chemical Structure* (ref. 4), 265, noted what he called "genetic relationships" in Fischer's sugar work – though he found no instance where Fischer used this term.

[145] Fischer "Zuckergruppe I" (ref. 59), 2131.

[146] Emil Fischer. 1966 [1902]. "Syntheses in the Purine and Sugar Group." (Nobel Lecture delivered December 12, 1902.) In *Nobel Lectures, Chemistry 1901-1921* (Amsterdam: Elsevier), 21-35, 31, reported 12 of 16 already known, with the remaining 4 sure to be found by the same methods.

[147] Fischer *Leben* (ref. 4), 113

[148] Fischer "Zuckergruppe I" (ref. 59), 2134 (direct quotations). Fischer "Purine and Sugar Group" (ref. 146), 31, also emphasized the important role of sugar chemistry in establishing stereochemical theory.

[149] "Emil Fischer and the Structure of Grape Sugar and Its Isomers." Last accessed May 17 2016.
< http://www.chem.yale.edu/~chem220/STUDYAIDS/history/Fischer/fischer.html>
Chem 220 is an introduction to the general principles of organic chemistry.

[150] Fischer "Configuration" (ref. 139), 1836.

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[151] The most recent study of Kekulé’s work is Alan J. Rocke. 2010. *Image and Reality: Kekulé, Kopp, and the Scientific Imagination* (Chicago: Chicago University Press).

[152] Fischer *Leben* (ref. 4), 51.