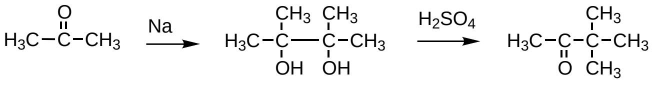
What Is a Discovery? Carbon Skeletal Rearrangements as Counter-Examples to the Rule of Minimal Structural Change

Jerome A. Berson*

Dedicated to Professor Waldemar Adam
on the occasion of his 65th birthday

The Pinacol Rearrangement

Today we know that the pinacol rearrangement is the reaction **2**→**3** shown in Scheme 1. Its emergence presaged the enormous wealth and variety of carbocationic transformations so central to modern organic chemistry. The history of how this reaction came to light records a major upheaval in chemical thought. It also raises again the vexatious question of just what we mean by the word “discovery”.



acetone (**1**) pinacol (**2**) pinacolone (**3**)

Scheme 1. From acetone to pinacolone.

Structure and Reactions

Chemists will be familiar with Kekulé’s seminal paper of 1858[1] in which he not only lays down the basis for representing the *structures* of organic compounds, but also puts forward two rules for *chemical transformations.* The first rule describes simple reactions, in which the reactant gives a product containing the same number of carbon atoms. Kekulé assumes that this will change peripheral atoms or groups but leave the structure of the carbon skeleton unchanged.

The second rule proposes that in other reactions which disrupt the carbon skeleton itself and give products with fewer numbers of carbon atoms than the reactant, the carbon atoms of the fragments have the same mutual attachments as they had in the intact reactant. Then the chemist mentally can recombine the fragments and thereby deduce the structure of the original molecule.

Both of the rules derive from the same more general idea, which came to be called the principle of minimal structural change. We recognize in the rules the foundations of two great branches of organic chemistry. The first rule really provides the source of our confidence that we can undertake a multistep synthesis of an organic compound with a strong expectation of eventually arriving at the correct structure. The second is the basis of the determination of molecular structure by degradative analysis.

Of course, Kekulé was making a bold extrapolation from his examination of the small number of organic molecules then available. Chemists today accept the possibility of violations of the rule of minimal structural change, but I think we may not be aware of how fiercely many chemists clung to it and thus delayed the recognition of a new chemical principle.

A rearrangement of the carbon skeleton is itself the definitive violation of the rule. The first such violations to be recognized were the transformations of pinacol to pinacolone, described here, and of benzil to benzilic acid.

That the pinacol rearrangement does not bear the name of a discoverer is especially puzzling, although, as we shall see, not unjust. During much of the 20th century and continuing now, most reviews that attempt to trace the development of this reaction (I have found no less than eight in this category) come to the quite definite conclusion that the discoverer was Rudolf Fittig. I quote from only one of these, written in 1938[2] where two papers of Fittig are mentioned: ref. [3] and ref. [4]. The reactions mentioned are those shown in Scheme 1, which started with acetone (**1**).

> *“In 1859 Fittig published the results of a series of experiments which he had made in a study of the reducing action of sodium on acetone. The compound pinacol was obtained. In the following year he published a paper which showed that if this substance be heated with sulfuric acid a ketone, pinacolone, is produced. Numerous examples of this reaction, now known as the pinacol rearrangement, have been found since the time of Fittig’s discovery…”*

It will become clear that the form of these statements is misleading. The literature of the time shows that Fittig’s experiments had entirely different objectives and were not

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[*] Prof. J. A. Berson
Department of Chemistry
Yale University
New Haven, CT 06520-8107 (USA)
Fax: (+1) 203-432-6144
E-mail: jerome.berson@yale.edu

knowingly directed toward “a study of the reducing action of sodium on acetone”. First of all, he did not know the structure of acetone, he did not even know its atomic composition or those of pinacol or pinacolone. Therefore, he could not have known that pinacol had been formed by a reduction. Further, he did not know that the substance pinacolone, to which pinacol was transformed by acid, was a ketone, and he certainly did not know it was formed by a rearrangement. Consequently, we must question whether the terminology “Fittig's discovery” is appropriate. Later in this paper, I argue that Fittig's work was a necessary part of the eventual full discovery but by itself fell well short of meriting that term. I propose to show that not only did Fittig not really discover the pinacol rearrangement, but in fact, he could not have done so at the time he worked on the problem.

The Early History

The discovery of the pinacol rearrangement was not a sudden event. It was a process which actually took about fifteen years, from 1859 – 1874. That was a crucial period in the history of organic chemistry, one which embodied what Alan Rocke has called a “quiet revolution”[5, 6] in the whole conceptualization of the science.

The Atomic Weight Controversy and the Rise of Structural Theory

Before the advent of the structural theory in 1858, the basic principles of organic chemistry were a turmoil of conflicting ideas expressed in several different notations. Not only were the protagonists constantly in battle over their theories, but they sometimes abandoned their positions to join the opponents on one point or another. By the middle of the 19th century, the chemical community faced a crisis over the issue of atomic weights. After several decades of dispute, many chemists had reached a consensus on the values of the atomic weights of the most common elements found in organic chemistry. These were the “conventional” weights[7] $H = 1$, $C = 6$, $O = 8$, and so on. Also in use at that time was the less popular set of weights proposed by Berzelius, and adopted with little change by a “reform” group. These are close to the modern values.

Note that the conventional atomic weights lead to molecular formulas that look strange to the present-day chemist: Methane would be CH_2 or a higher multiple instead of $(CH_4)_n$, ethanol C_2H_3O or $(C_2H_3O)_n$ instead of C_2H_6O, to name two examples. One way to think about the differences is to recognize that the modern atomic weights would require that for a given number of hydrogen atoms, the number of carbon and oxygen atoms would each have to be half the number in the conventional formulas.

Prominent among the reform group were the “structuralists,” notably Kekulé, Couper, and Butlerov.[5, 8] Their analysis of structure, as given, for example, in Kekulé's textbook,[9] depended on the assumption of the “reformed” atomic weights. How the atomic weight controversy ultimately was resolved makes a fascinating story which historians have treated extensively.[5, 6, 8] Although we cannot review all of that history here, one important theme must be stressed. In the late 1850s it became increasingly clear that no internally consistent set of structures for the known organic compounds could be devised using the conventional atomic weights. As Kekulé and his co-structuralists realized, to solve the problem of structure, it is essential to have both a set of correct weights and a set of correct valences. The “reformed” atomic weights, together with a set of valences with $C = 4$, $O = 2$, $Cl = 1$, $H = 1$, etc., led in a straightforward manner to satisfactory structural formulas for known compounds and to verifiable predictions of new structures. Thus, self-consistency now required that the reformed atomic weights be accepted.

In fact, many chemists were now quietly[10] converted to the new atomic weights perforce: If one wanted to apply the powerful new structural theory, one could hardly argue at the same time that the conventional atomic weights were correct. The early events of the pinacol rearrangement story took place in 1858 – 1860 and thus coincided with this major discontinuity in the development of organic chemistry.

The structuralists did not hesitate to point out that those chemists (and there were many) who adhered to the conventional atomic weights suffered a disabling handicap in their attempts to determine molecular structure. The first requirement of that process must be to count the number and kind of atoms. The conventional atomic weights gave a completely erroneous measure of those properties, and chemists who used those weights thus had no chance to determine the structure of any compound. It is important to know that Fittig, the putative discoverer of the pinacol rearrangement, was one of those who at that time adhered to the conventional atomic weights system. This fact prevented him from completing that problem. But who was Fittig, and how did he come to be on the wrong side of the atomic weight controversy?

Rudolf Fittig (1835 – 1910)

Fittig was born in Hamburg, Germany in 1835. He was one of many children of a private school principal and was to prove himself a brilliant student. In 1856 Fittig entered the University of Göttingen, where Friedrich Wöhler led the institute of chemistry. Fittig became associated there with Professor Heinrich Limpricht, who held the rank of extraordinary professor (roughly associate professor) and was the leader of a section of organic chemistry. Fittig carried out his early research on the sulfonation of benzamide and toluamide under Limpricht's supervision. The resulting paper appeared in the “Annalen” in 1858 with Fittig as the sole author.[11] It is significant that Limpricht was similarly generous with other students.[12] This relationship with Limpricht will become important in our subsequent discussion.

Fittig went on to a noteworthy career as a professor of organic chemistry, becoming associate professor at Göttingen, moving then to Tübingen and later to Strasbourg. He and his students published almost 400 scientific papers, among which some of the best known are those reporting a modification of the Wurtz synthesis of alkanes to permit the synthesis of alkylarenes (now called the Wurtz – Fittig reaction). There is no doubt that during his time, he was one of the major figures in German organic chemistry.

The Structure of Acetone; Uncertainty Piled on Obscurity

Fittig's work on the pinacol rearrangement was his first independent research. It grew out of an interest in a readily available substance, acetone. The first real scientific evidence on the nature of acetone had already come in 1832 from the work of Liebig,[13] who determined its elemental percentage composition by combustion analysis. These percentage composition values, derived from the Berzelius (or reformed) atomic weights, of course fit the modern empirical formula of acetone $(C_3H_6O)_n$, where n is an integer. However, with the conventional atomic weights of the mid-19th century, Liebig's results would lead to the formula $(C_3H_3O)_n$.

Pinacol and Pinacolone

During the years before and after the Liebig analysis, several chemists made attempts to determine the chemical nature of acetone. For our purposes, it will be sufficient to focus on one of them, reported in a paper by Löwig and Weidmann in 1840.[14] They were investigating the then-popular idea that acetone was an alcohol and decided to test this by treatment of it with metallic potassium, hoping to obtain a salt. Instead, they found that the main products were mesityl oxide and phorone (resulting from what we now would call an aldol condensation). These are the same products that had previously been observed from the action of potassium hydroxide on acetone.

Fittig started out with the modest objective of repeating the Löwig–Weidmann experiment with sodium instead of potassium. Superficially, one might have expected the two experiments to give similar results, but that was not to be the case.

As we have mentioned, to bring Liebig's determination of the atomic composition of acetone into harmony with the conventional system of atomic weights, Fittig had to convert Liebig's formula C_3H_6O into the incorrect conventional formula C_3H_3O. So his project was in immediate trouble.

Fittig's intention to make and alkylate a sodium salt from acetone might have been considered dubious in view of the failure of Löwig and Weidmann with the *potassium* enolate. Nevertheless, Fittig apparently was encouraged by the work of Ebersbach[15] only a year before his own. Ebersbach had reported an analogous reaction with valeraldehyde and had carried out a successful alkylation of the sodium salt with ethyl iodide. The result of Fittig's similar experiment with acetone was negative, in that he was unable to find the expected alkylation product. However, he did find an unexpected and most interesting substance, which he isolated as large, tablet-shaped crystals and which he called "paraceton." This was the substance that later would be called "pinacol". Fittig's name for this product, paraceton, came from his belief that it was a hydrate of a *dimer* of acetone. Thus, he started out trying to do an alkylation and, in his view, succeeded instead in causing a dimerization.

A rancorous and essentially inconclusive dispute then flared up between Fittig and another chemist, Städeler.[16] The argument centered around the elemental composition of pinacol, but we need not spend much time on it. It was doomed to eventual inconsequentiality, because both chemists used the incorrect conventional atomic weights. Städeler did get one thing right though: He proposed that pinacol was not a dimer of acetone, as Fittig thought, but rather a reduction product of a dimer. Eventually, others showed that Städeler's conclusion was correct. A fair historical treatment thus would be obliged to credit Städeler, not Fittig, with recognizing this.

The Transformation of Pinacol to Pinacolone

Fittig's second paper[4] on this subject, published in 1860, continued the dispute with Städeler but, more significantly, reported an observation that baffled the chemical community for years afterward. Fittig found that heating pinacol with aqueous sulfuric acid or hydrochloric acid gave rise to a new substance now known as pinacolone. The reasoning in his discussion of what the nature of this product might be was quite confusing, but in summary, he believed that pinacolone is an isomer or polymer of the anhydrous form of pinacol.

The problem of representing the *structures* of pinacol and pinacolone remained. No matter how strenuously the two investigators contested the validity of each other's conclusions, their efforts could not bring further progress as long as they adhered to their custom of using the conventional atomic weights. Apparently, they gradually recognized that they had reached an impasse. As far as I have been able to determine, neither Fittig (after 1860) nor Städeler (after 1859) ever published another word about pinacol or pinacolone.

Fittig's Atomic Weight Problem

Before we go on to later developments in this story, we must make clear Fittig's own attitude to the atomic weight issue. It is significant, and puzzling, that by 1859 Fittig had put himself into a self-contradictory position by joining the large number of chemists who were climbing onto the Kekulé bandwagon. Indeed, Rocke[17] already has called attention to a passage from Fittig's diary dated September 17, 1859, in which Fittig describes his profoundly epiphanic reaction to the appearance of the first fasicle of Kekulé's textbook:

> *" … in my opinion, all of the books on organic chemistry known to me cannot bear comparison with it. I read it page by page and with truly intense interest, and in the words said of St. Louis, 'we are all in the true sense students of Kekulé. The field that has been sown with his ideas will be cultivated everywhere and will bear unceasingly the richest harvest."'*

As we have seen, Kekulé made a major point, both in his paper on the structural theory and in his textbook, that the conventional atomic weights must now be abandoned in favor of the reformed weights. Fittig's reaction to the book in September 1859 was an emotional experience almost as intense as a religious conversion. Why then did he continue to adhere to the by then discredited conventional atomic weights in his second paper on pinacol,[4] which was submitted to the "Annalen" several months later, in December 1859?

The answer to this question must be speculative. It does not seem probable that Fittig, despite all his enthusiasm for Kekulé's book, had failed to absorb its central lesson. Fittig, after all, was a highly motivated, conscientious, thorough

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chemist. It seems to me unlikely that he would absent-mindedly overlook the contradiction between his own line of thinking on constitutional questions and that of Kekulé, which had made such a deep impression on him. I believe a more plausible conjecture is that there were forces external to the chemistry itself that kept him temporarily in thrall to the conventional atomic weights. What might these have been?

Consider that in 1859–1860, the 24-year old Fittig was still dependent on his mentor Limpricht for laboratory space. Moreover, Fittig was sensitive about his personal relationship to Limpricht. From Fittig's diary[18] we learn that he was apprehensive that Limpricht's plans for him to join a project on the sulfonation of benzoic acid derivatives would hamper Fittig's own progress. He even considered leaving Limpricht's laboratory and asking Wöhler for a place. Although the matter was smoothed over when Limpricht eventually allowed Fittig to publish his results from his thesis problem independently, one gets the impression that Fittig was wary about putting himself at cross-purposes with his mentor. We might wonder whether Fittig was being overcautious here, since Limpricht had been quite generous in granting independent publication to Fittig and to other students.[11, 12] Nevertheless, there can be no doubt that Limpricht's name and laboratory would be closely associated with these studies. Limpricht had been engaged in them for some time, and they were a centerpiece of his research program. His (necessarily incorrect) interpretation of the results employed the conventional atomic weights, as was usual for him.

Now as it happened, Kekulé had published the first part of his structural theory in 1857,[19] and in developing his arguments on the quadrivalency of carbon, he used Limpricht's immediately preceding work[12,20] on the sulfonated arenecarboxylic acids to exemplify the erroneous nature of the conventional atomic weights. In fact, in Rocke's words,[21]

> *"These two papers [of Limpricht] gave Kekulé the opportunity he had been looking for to publish his structural ideas, for Limpricht had opened himself to criticism in several ways, and such a critique provided the rhetorical launching platform for more general considerations."*

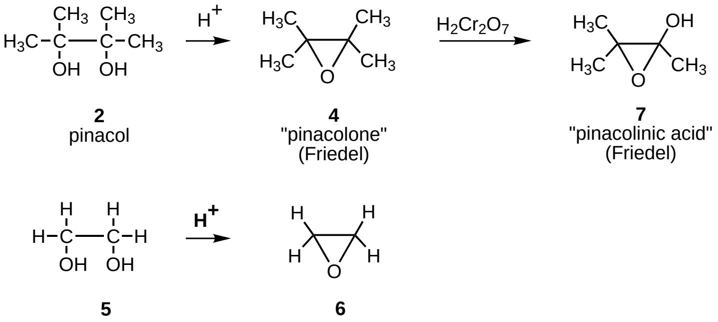
Although Limpricht published a rebuttal,[22] Kekulé soon followed with an expanded counter-rebuttal in the climactic 1858 paper[1] of his structural theory. Limpricht thus found himself battling Kekulé, in a very public arena, over the most significant question in organic chemistry.

Fittig now could not have been unaware of his own vulnerability. Although, by his own words, we know that he was strongly attracted to Kekulé's ideas, he could hardly have ignored the fact that adopting them publicly at that moment would signify a break with his mentor, one which might have been considered an act of disloyalty. For someone in his dependent position, this would have been a risky step indeed. Moreover, as an ambitious and perspicacious young chemist, he would have been wary of an association with what could well turn out to be a prominent defeat for Limpricht. One can only sympathize with his dilemma.

So is it possible that Fittig somehow rationalized and suppressed his own doubts about the conventional atomic weights when he published his 1860 paper[4] on pinacol? Did loyalty and dependency win out over science? I have no evidence on this point, but it is noteworthy that within the following year, Fittig had won laboratory space of his own. He published a paper[23] on another subject in which he once and for all abandoned the conventional atomic weights and adopted the reformed values without dissent and without even mentioning that this step represented a complete turnover in his chemical thinking. In this, he joined many other organic chemists of the time. I think we cannot ignore the possibility that Fittig's awkward personal circumstances at a crucial time may have prevented him from thinking the pinacol problem through to a satisfactory answer.

The Structures of Pinacol and Pinacolone

On the other hand, the advocates of the reformed atomic weights, including Kekulé himself, did not immediately solve the problem either. Foremost among the "pinacolists" in that group was Charles Friedel, who, like Fittig, had been a student of Wurtz. We need not outline here the various inconclusive results and the eventual insight by Friedel that pinacol was tetramethylethylene glycol (**2**, Scheme 1), the structure we recognize today. Perhaps the most important contribution of Friedel's work, summarized in an 1869 paper,[24] was the demonstration that the acid-induced transformation of pinacol to pinacolone is an overall dehydration. This became immediately apparent from the empirical molecular compositions. Friedel proposed that the two compounds are related as **2** and **4**, in the same way that ethylene glycol (**5**) is related to its dehydration product, ethylene oxide (**6**, Scheme 2).



Scheme 2. Structures postulated by Friedel in analogy to ethylene glycol and ethylene oxide.

There followed a stretch of fruitless experimentation and misguided interpretation by Friedel reported in a flurry of papers. However, these contained one important result, again misinterpreted, namely, the finding that pinacolone can be oxidized by dichromate to CO_2 and an acid isomeric with valeric acid. Friedel and Silva at first proposed[25] that this acid, "pinacolinic acid," in contrast to other known organic acids, did not have the usual carboxyl group but instead contained a hydroxyoxirane group, as in **7** (Scheme 2).

The fog surrounding all this chemistry was finally disspelled by two brilliant papers of Alexander Butlerov of St. Petersburg. In the first of these, in 1873,[26a] Butlerov accepted the pinacol structure **2** (Scheme 2) favored by Friedel, but he questioned the necessity of the special hypothesis of a unique new kind of acid structure (**7**, Scheme 2) for the oxidation product obtained from pinacolone. He proposed instead that Friedel and Silva's "pinacolinic acid" was in fact trimethylacetic acid, an assignment which he supported by direct synthesis of that compound by formation of trimethylacetonitrile from *t*-butyl iodide and mercuric cyanide followed by hydrolysis. Butlerov noted that his synthetic acid showed properties very similar to those of the pinacolinic acid obtained by Friedel and Silva from pinacolone. Later, Friedel agreed that his acid is "probably identical with trimethylacetic acid."

After having established to his own satisfaction the identity of the acid, Butlerov[26b] forged ahead boldly to suggest that the reaction of pinacol in acidic solution involves a *molecular rearrangement of the carbon skeleton* and dehydration. The product, pinacolone, is simply *t*-butyl methyl ketone (**3**, Scheme 1). He pointed out that such a reaction finds analogy in the already known transformation of ethylene glycol to acetaldehyde.

Friedel and Silva,[27] by some muddled reasoning, criticized Butlerov's analysis. However, Butlerov soon answered with a plan[26b] to confirm his proposal by the synthesis of pinacolone **3** itself from trimethylacetic acid, a task he completed the following year, 1874,[28] by the reaction of trimethylacetyl chloride with dimethylzinc. He considered the proof of the structure of pinacolone then to be complete.

One might argue that in 1874, at a time when chemists did not have reliable means for predicting when molecular rearrangements might occur, Friedel's apparent capitulation on the structure of pinacolone might have been premature. Logically, for example, it was not clear then that Butlerov's synthesis did not itself involve a rearrangement. However, the passage of time rendered such doubts less and less likely. Despite its refutation in the case of the pinacol rearrangement, Kekulé's rule that the connectivity of the carbon skeleton tends to persist throughout a chemical reaction still claimed the adherence of most chemists. For many of them, the acceptance of carbon skeletal rearrangements came only grudgingly and slowly.

Butlerov thus recognized one of the first rearrangements of the carbon skeleton and, in my opinion, deserves credit at least equal to that later assigned largely to Fittig as the discoverer of the pinacol rearrangement. Although Roscoe and Schorlemmer's textbook[29, 30] of 1881 gives a clear account of the importance of Butlerov's work, I have been unable to determine the reasons why 20th century authors slight it or overlook it entirely.

What Is a Discovery?

We now have to face the question: What is a discovery? In the context of science, there is a perception (or misperception) that a discovery takes place in a sharply defined moment of time. I believe that this idea underlies many of the frequent disputes in the scientific literature over priority. Historians of science are well acquainted with this problem and tend to take a more nuanced view. For example, Thomas Kuhn[31] wrote that it is misleading to suggest that discovering something is a simple act, directly cognizable by the senses:

> *"… That is why we so readily assume that discovering, like seeing or touching, should be unequivocally attributable to an individual and to a moment in time. But the latter attribution is always impossible, and the former often is as well … discovering a new sort of phenomenon is necessarily a complex event, one which involves recognizing both* that *something is and* what *it is."*

In the discovery of the pinacol rearrangement, fourteen years elapsed before Butlerov explained Fittig's transformation of pinacol to pinacolone. Applying Kuhn's formula, we can say Fittig found *that* a reaction of pinacol occurred in acidic medium, and it was Butlerov who recognized *what* that reaction was.

Why Worry about Proper Attribution of Credit?

If praise for a discovery is inaccurately assigned, the error has a high probability of being propagated in the literature. But why is it important to assign credit accurately? After all, there are critics of science who ascribe the scientists' obsession with this subject to our enslavement to the false gods of competition and self-promotion. A candid response would be that it is good to be first for some easily listed reasons: our grant proposals, our patent applications, our tenure resumés, and, above all, our egos. Also, simple justice and fair play demand that we try to make the right attribution. I think all of these motivations are real, although perhaps not all are admirable.

However, there is another purpose. That is the need to understand the dynamics and temporal course of the process of discovery itself. Only by this kind of analysis is it possible to apprehend the mutual influences of scientific theories and experiments. Only in this way can the effects of the scientific and cultural milieu of the time on the act of discovery be evaluated. Wrongly assigned credit for a discovery may not only offend against justice, it may distort the historical picture of the event and result in an ignorant, blunted, or superficial description. At the end of the day, we must get the assignment of credit right if we wish to understand how science works.

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