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## PAPER TOOLS AND FICTIONAL WORLDS: PREDICTION, SYNTHESIS AND AUXILIARY HYPOTHESES IN CHEMISTRY

### 1. INTRODUCTION

In 1963, the chemist W. E. Dasent wrote an article for the *Journal of Chemical Education* entitled "Non-existent Compounds." In his opening sentence, he noted that

There exists a large and diverse group of compounds whose structures do not offend the simpler rules of valence, but which nevertheless are characterized by a high degree of instability; in many cases the compounds in question have never been prepared.<sup>1</sup>

The statement that there "exists a large and diverse group of compounds" that "have never been prepared" appears contradictory. How can such compounds have an existence without having been prepared? The answer, of course, is that such compounds have an existence *on paper*, in a fictional world that chemists might be capable of creating, but does not always match reality.<sup>2</sup> This fictional world of "nonexistent" compounds is created by the rules of the structure theory and its offspring, stereochemistry, and is responsible for spurring chemists to create the vast majority of chemical compounds. Such compounds are *artificial*, in the sense that they would not exist without their prediction on paper and the conscious, deliberate efforts of chemists.

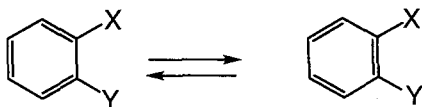
Marcelin Berthelot noted this unique aspect of chemistry when he said that "chemistry creates its own object." Chemists want to create new substances to answer a specific question, or to learn the properties it exhibits when made. Will it be of pharmaceutical value? Is tetrahedrane a stable molecule? Can we create better, longer lasting dyes and paints, or a plastic that is either completely recyclable or biodegradable? Will this sequence of reactions result in a substance that has all the properties of taxol? In formulating both these questions and answers to them, chemists display not only a unique combination of utilitarian and theoretical interests, but also an extensive use of paper tools as predictive and explanatory instruments.

In this paper, I will focus on the use of paper tools as predictive devices, and the roles that "nonexistent" compounds play in chemical practice. The subject first occurred to me while reflecting on the kinds of argument involving non-existent compounds used by Van 't Hoff in the various versions of his theory of the tetrahedral carbon atom between 1874 and 1877. Van 't Hoff's uses of non-existent compounds struck me as curious, if not contradictory, and led me to consider the

relationship between the fictional world of possible compounds on paper and the preparation of compounds in the laboratory. The more I considered the actual practice of predicting compounds on paper and comparing it to laboratory practice, the two activities did not seem to be as intimately tied together as we might think. There is, as often as not, a discord between prediction of a compound and its actual isolation, or more specifically, an *attempt* at its isolation, and the non-existence of theoretically possible compounds is often explained away by auxiliary hypotheses. To be more specific, here is the question I have posed for this paper: when do chemists decide to attempt making a compound that theoretically *could* exist, and why do they sometimes *not* make the attempt? How does work on paper relate to work in the laboratory? I will here outline an apparently confusing relationship between prediction and practice, and then offer some preliminary answers.

## 2. PREDICTION AND AUXILIARY HYPOTHESES IN CHEMISTRY

Let us begin with Kekulé's famous cyclohexatriene formula for the benzene ring and his related "oscillation hypothesis" concerning the location of the double bonds in the ring. It is well known that Kekulé's cyclohexatriene formula, although heuristically very successful, nevertheless suffered from the significant disadvantage that it predicted more isomers than was currently known. If the principles of valence and structure were followed strictly, derivatives of benzene with groups placed at positions 1 and 2 should be capable of existing in two isomeric forms with the double bonds placed at different positions (*Figure 1*). It was precisely the known experimental fact that isomers of such disubstituted benzenes were unknown that led chemists to suggest alternative structures for benzene, for example, Ladenburg's prism formula or alternate versions of the hexagonal formula that did not contain multiple bonds. Kekulé himself explained away the nonexistence of these 1,2 disubstituted isomers by assuming that the double bonds oscillated between two different positions, and any sample of a 1, 2 disubstituted benzene would therefore be a mixture of the two isomers. This is a classic example of an "auxiliary hypothesis" employed to save the phenomena, in this case the non-existence of predicted isomers.



*Figure 1. Kekulé's oscillation hypothesis*

Despite this principal weakness, Kekulé's structure was quickly adopted in the late 1860s, and has proven to be most enduring, and the cyclohexatriene structure is still used today in textbooks and research articles despite its misleading implication that the ring contains double bonds.<sup>3</sup> As Stephen Brush outlines in a recent article on the acceptance of theories of benzene, Kekulé's model was compelling enough for chemists in the 1930s to treat benzene derivatives with ozone with the hope of cleaving the "double" bonds in the 1, 2 disubstitution derivatives to isolate the

different products. The results of the experiment appeared to support Kekulé's hypothesis that a mixture of two isomers was present (Figure 2).<sup>4</sup>

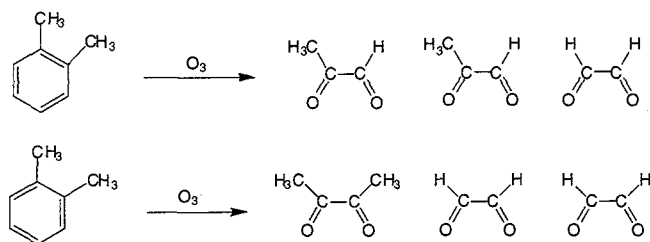


Figure 2. The ozonolysis of isomers of 1, 2 disubstituted benzene derivatives yields three glyoxals, a result that is not possible if only one of the two isomers is present. As each reaction equation shows, either of the two isomers alone would produce only two glyoxals.

Kekulé's oscillation hypothesis was also a central assumption in Guglielmo Koerner's classic experiment that established the relative positions of groups in disubstituted benzene derivatives. Koerner's proof involved the isolation of predicted products resulting from the additional substitution of 1,2 (ortho), 1,3 (meta), and 1,4 (para) disubstituted benzene isomers. The para compound would yield only one substitution product, while the ortho compound would yield two and the meta compound three (Figure 3). In what no doubt was a painstaking procedure, Koerner isolated the predicted number of substitution products in each case. Significantly, Koerner used Kekulé's formulas to make specific predictions about the existence of new compounds, but also assumed his oscillation hypothesis to reduce the number of possible isomers.

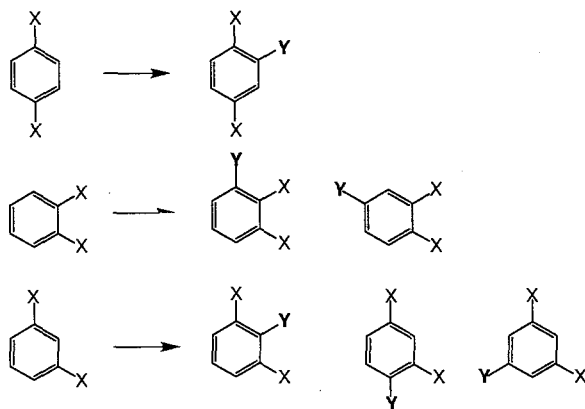


Figure 3. The compounds predicted when disubstituted benzene derivatives undergo additional substitution.

Another example comes from the anti-structural chemist, Hermann Kolbe. According to Kolbe's benzene theory (unique to him), there should be two isomers of monosubstituted benzenes. Therefore, there *must* be a second phenol and benzoic acid, and Kolbe spent a significant amount of time and effort to isolate them. Kolbe also denied that the hydrogens on the benzene ring or methane were chemically equivalent, a fact chemists had attempted to model by formulating structures (whether a hexagon, prism, or otherwise) in which the six hydrogen atoms occupied equivalent positions. According to Kolbe, however, the fact that benzene or methane could be monosubstituted at all (rather than immediately undergoing multiple substitution) indicated that the hydrogens in both were bound with different degrees of affinity. In other words, for Kolbe, random substitution of hydrogens on methane or benzene, a required condition for the assumption that all hydrogens were equivalent, was itself an unnecessary auxiliary hypothesis.<sup>5</sup> Subsequently, Kolbe was convinced for many years that eventually a second isomer of a monosubstituted benzene would be isolated.

In 1876, Victor Meyer published a short theoretical article in which he noticed that despite the success of the structure theory in ordering organic compounds and explaining isomerism, "...the nature of that what we call a valence or affinity, for the moment is still completely unclear."<sup>6</sup> In this theoretical paper, Meyer attempted to form a vague idea of the nature of valence by studying the limitations on the carbon atom's bonding ability. For example, he pointed out that all reactions in which he expected cyclopropanes (three membered rings) as the product gave only products with other structures. The fact that these compounds did not exist, coupled with the non-existence of a compound with the formula  $C_2$  (carbon with a 'quadruple' bond), even though these compounds were "easily expressable by our usual formulas," indicated specific limits on the nature of valence.<sup>7</sup> Significantly, the prediction of these compounds on paper did not prompt Meyer to attempt their synthesis. That is, although the formulas were perfectly logical on paper, there seemed no compelling reason to assume that such compounds with rings smaller than six carbon atoms could exist. As related later by W. H. Perkin, Meyer was convinced that these compounds could not exist because such a large amount of "synthetical work" had frequently led to derivatives of benzene, but never to compounds with smaller rings.<sup>8</sup>

Perkin, of course, was able to make compounds containing three, four and five membered rings during the early 1880s, in one of the earliest deliberate syntheses of an artificial compound with an unusual structure. Perkin was discouraged by Meyer and Emil Fischer when he spoke with them about his own attempt to make these compounds, and his mentor Baeyer was also discouraging, but less so. Meyer doubted their existence because none had been isolated and so little was known about them, and Fischer thought small rings would be inherently unstable. But if Meyer and Fischer were not optimistic about these compounds, why did Perkin decide an attempt was warranted? In 1929, Perkin recalled that in the early 1880s, he was working on the alkylation of acetoacetic ester derivatives, and attempting to add a second alkyl group to the carbon of the malonic ester (*Figure 4*).

I had made a quantity of the monopropyl derivative  $CH_3CH_2CH_2CH(CO_2Et)COCH_3$ , from propyl bromide by the usual process: and was proposing to introduce the second propyl group in a similar manner when it occurred to me that, if this mono-substitution derivative could be brominated at the end of the chain, the sodium derivative of the

product might decompose with elimination of sodium bromide and formation of acetyltetramethylenecarboxylic ester containing the 4-carbon ring.<sup>9</sup>

Perkin's motivation was therefore based on analogy, that is, the proposed ring compounds could be formed by a substitution reaction analogous to the reaction that added a carbon chain to the acetoacetic ester. Perkin was ultimately successful in his attempt, and he described the first synthesis of a cyclobutane derivative in July 1883, a cyclopropane derivative in January 1884, and a cyclopentane derivative in December 1885.<sup>10</sup>

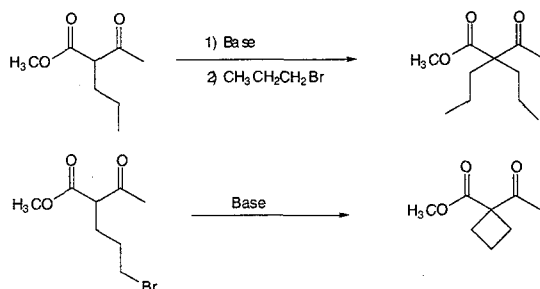


Figure 4. Perkin's proposed synthesis of cyclobutane derivatives, using the analogy of the top reaction for suggesting the success of the bottom reaction.

Let us turn now to Van 't Hoff's use of non-existent compounds in his works describing his theory of the tetrahedral carbon atom. In his initial 1874 pamphlet, Van 't Hoff introduced the tetrahedral carbon atom only after rejecting the planarity of the valences around the carbon atom. In Van 't Hoff's own words:

If one assumes that these atoms [bound to carbon] are extended in a plane, as for example in isobutyl alcohol, in which one conceives the four affinities of each carbon atom in four perpendicular coplanar directions, then, in applying this assumption to the derivatives of methane CH<sub>4</sub> (to start with the simplest case), one arrives at the following number of isomers (the different hydrogen atoms will subsequently be replaced according to the univalent groups R<sub>1</sub>, R<sub>2</sub>, etc.):

One for CH<sub>3</sub>R<sub>1</sub> and for CH(R<sub>1</sub>)<sub>3</sub>

Two for CH<sub>2</sub>(R<sub>1</sub>)<sub>2</sub> (fig. II and III in Figure 5), for CH<sub>2</sub>(R<sub>1</sub>R<sub>2</sub>) and for CH(R<sub>1</sub>)<sub>2</sub>R<sub>2</sub>

Three for CH(R<sub>1</sub>R<sub>2</sub>R<sub>3</sub>) and for C(R<sub>1</sub>R<sub>2</sub>R<sub>3</sub>R<sub>4</sub>) (fig. IV, V and VI in Figure 5)

which is evidently a much greater number than those known so far.<sup>11</sup>

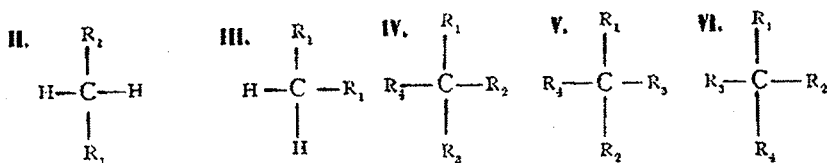


Figure 5. The isomers possible when groups are substituted around a planar carbon atom. From *Voorstel tot Uitbreiding* (1874).



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