



# A Perspective on Chemistry and Society

A Column on the Occasion of the 75<sup>th</sup> Anniversary of CHIMIA

ETH Zurich

## Chemie versus Chemie

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the Swiss Nationalfonds 2011–2015, serving in the Executive Board as President of Division IV 2013–2015. He was also a member of the Board of Directors of Clariant, a leading specialty chemical company 2006–2018. Among his numerous honors, Prof. Chen is most proud of winning the ‘Golden Owl’ twice, in 2005 and 2015, which is awarded for the best teaching in each department.

The title of this essay in the 75<sup>th</sup> volume of *Chimia* is intentionally the same as that for the antecedent essay written by Jakob Nüesch for the 50<sup>th</sup> volume in 1996,<sup>[1]</sup> because the fundamental issue remains the same: the Chemistry of tomorrow against the Chemistry of yesterday. We represent a field with a long and glorious history, and it is incumbent on the leaders today to seek the path forward so that we do not dwell too long in places where we could simply stagnate, and then decline. While it is easy to quote statistics on how useful Chemistry is, and Chemistry is indeed useful if one simply pauses to consider all of the materials around us, all of the active pharmaceutical ingredients, all of the components in our electronics, the catalysts, and so forth, the statistics themselves do not tell us where we need to go. Moreover, Chemistry has become an indispensable part of Life Sciences, for example, delivering, among other things, tools and methods for Biology, upon which Jakob Nüesch elegantly commented. It would be a mistake, however, and I think Jakob Nüesch would agree, to reduce Chemistry to its utility, either in commercial applications, or to other scientific fields. We are grateful that Chemistry is useful – we appreciate the generous support from State and Industry – but when Chemistry becomes merely useful (bloss nützlich), a ‘Department of Chemistry’ becomes, in the words of my late Doktorgrossvater, Bill Doering, just a ‘Department of Chemicals,’<sup>[2]</sup> which is an altogether different beast. Every vital, growing intellectual endeavor needs its own internal logic, and its own internal motivation (motivator?), or else it ceases to attract the best and most ambitious minds. What from the past applies still, and what needs to change? How can we conceptualize where Chemistry needs to go, and how do we need to educate the next generation of Chemists?

At the risk of being accused of dwelling on the past, I do want to use one particular episode from the history of Organic

Chemistry to exemplify the unique way in which Chemistry had worked and continues to work, even today; it gives us a certain intellectual continuity. While the chemical problem in the particular episode is closed, the narrative nevertheless points to where Chemistry can and will make unique contributions to the solution of new problems. Let’s look at August Kekulé (1829–1896), Jacobus Henricus van’t Hoff (1852–1911), Victor Meyer (1848–1897), and Emil Fischer (1852–1919), and the classical theory of chemical structure. Marcellin Berthelot, a French chemist, wrote about Chemistry in 1860, ‘La chimie crée son objet,’<sup>[3]</sup> emphasizing the central role of synthesis of new entities. Richard Feynman expressed (curiously in the present context of a discussion of Chemistry because he was a physicist) a similar sentiment in 1988, “What I cannot create, I do not understand.”<sup>[4]</sup> With due respect to analytical chemistry, theory, and even my own area of reaction mechanisms, I would postulate that the hard core of Chemistry is synthesis; we understand something by making it. There is a curious, and curiously deep, logic to the claim. At the most superficial level, one sees why Chemistry is so useful. We always make new things. Our society needs things, and industry sells things. We will always need chemists. But what shall we make? What does this logic imply about the areas into which the Chemistry of the future must go?

Flipping back to the particular episode I would highlight, I would point to a remarkable publication that Don Hilvert brought to my attention. In an illuminating study of Emil Fischer’s progression to the structural proof of glucose by synthesis, for which Fischer received the Nobel Prize in 1902, Catherine Jackson, a science historian, highlights the role of chemical experimentation in 19<sup>th</sup> century organic chemistry.<sup>[5]</sup> A bit under-emphasized in the narrative, however, is the oddly ambiguous relationship of this landmark achievement in organic chemistry with the theory of chemical bonding. Today, we teach chemical bonding at the very beginning of the Chemistry curriculum, with the electron pair bond, and even molecular orbitals providing a physics-based explanation for the forces holding molecules together, and, furthermore, the ultimate rationale for the three-dimensional structures that the molecules take. Structure, with lines and wedges, Fischer projections, Neumann projections, and even stereochemistry, is taught as the classical representation of the underlying quantum mechanics. It is perhaps sobering to consider that Thomson’s identification of electrons as the negative charge carrier in cathode rays came only in 1897,<sup>[6]</sup> Rutherford’s experiment indicating a dense, positively charged atomic nucleus in 1911,<sup>[7]</sup> and even Lewis’ proposal of the electron pair bond only in 1916.<sup>[8]</sup> The Heitler-London valence bond picture of covalent bonding in H<sub>2</sub> was published in 1927;<sup>[9]</sup> the molecular orbital model by Mulliken<sup>[10]</sup> and Hund<sup>[11]</sup> followed shortly thereafter. Classical structure theory, usually considered to begin with work by August Kekulé, starting in 1857,<sup>[12]</sup> and A. S. Couper in 1858,<sup>[13]</sup> preceded any physical model by which one could describe a chemical bond. While Kekulé reportedly fabricated molecular models with tetrahedral carbon atoms as lecture aids, as early as 1867, he referred to the models as heuristics rather than representations of actual physical structure, given the absence of any consistent physical theory. Van’t Hoff and LeBel pointed out that the model explained the otherwise

unexplainable phenomenon of optical activity,<sup>[14]</sup> and the pictures of tetrahedra sharing vertices, edges, or faces as representations of single, double, and triple bonds appear in van't Hoff's 1874 publication even though the models are most often ascribed to G. N. Lewis a half-century later. By 1877, Kekulé was attributing the structural models with more physical reality, even talking about vibrations of the atoms along the bonds, but the viewpoint was fiercely opposed by some, for example, Hermann Kolbe,<sup>[15]</sup> who criticized structural theory, in the words of Alan Rocke,<sup>[16]</sup> as simultaneously "too empirical and too speculative," there having been no physical basis for the chemical bond beyond vague attributions of affinities. Nevertheless, Victor Meyer postulated what we now call stereoisomerism in 1888,<sup>[17]</sup> and used the new theory as a framework for the assignment of structure to a wide range of natural products.<sup>[18]</sup> Fischer, originally no great proponent of a structure theory that lacked a solid basis in physics, nevertheless combined consistently the speculative, even fanciful, ideas of structure theory, with the solidly established tradition of chemical experimentation, in work done between 1884<sup>[19]</sup> and 1890,<sup>[20]</sup> to produce a rigorously executed and logically flawless structure elucidation and rational synthesis of glucose. Even against our infinitely better tools and theory, Fischer's proof of the structure of glucose stands today as a landmark of classical structure determination. Turning Kolbe's criticism around, a certain "speculative empiricism" seems, in retrospect, to characterize some of the greatest achievements of 19<sup>th</sup> century chemistry.

The episode, overlaid with the chronology, illustrates a key characteristic of Chemistry that proved historically so important in the evolution of the science. Not only did chemists rationally produce complex structures in a systematic, step-by-step manner prior to the development of rigorous physical theory, *e.g.* quantum mechanics, they did so even prior to the experimental proof that electrons and nuclei, or indeed, atoms, exist. Chemists have dealt with complexity by making ever more complicated molecular entities and objects before they could be 'derived' from first principles. I do not mean to imply that theory was absent, but rather that fruitful chemical practice could be done with speculative, incomplete, and even fanciful or not-completely-consistent theoretical concepts. The synthesis of these molecules was intertwined with the development of the analytical tools to detect, characterize, and quantify them, which should not be underestimated – see Jackson's description of the historical importance of oximes and hydrazones<sup>[5]</sup> – as well as the ultimate elaboration of theory which transforms initially murky heuristics into respectable physics. The successes of the heuristic approaches imply deeper, physical regularities of varying obscurity, and it is a task of theory to dig those out. The latter enterprise typically follows the synthesis, though, by up to many decades.

Taking the leap from the past to the future, and considering what has made Chemistry unique, as well as uniquely useful, consider that the problem of describing and working with complexity in the material world is still with us. The challenges today are immeasurably more difficult than those faced by Kekulé, van't Hoff, Meyer, and Fischer in the 19<sup>th</sup> century, even when viewed from the standpoint of our present technical and technological capability, but I wonder whether we are bold enough to treat large interacting systems far beyond the safety net of established theory. To apply a metaphor, if molecules are like words, Chemistry has spent the last century-and-a-half working out the rules of spelling, and those who see a Department of Chemistry as nothing more than a Department of Chemicals, reduce mastery of a language to possession of a large vocabulary. Mastery of words, however, says nothing

about grammar, and even mastery of grammar means that one could, for example, write an understandable, information-rich, and most certainly useful instruction manual for a toaster. One could also write poetry, and therein lies a difference. Within the language metaphor, this is what complexity means.

Returning from the metaphor to the more practical question of what we need to teach the Chemistry students who may be our future poets, it is clear that the education must be broad, with strong foundations in mathematics, and physics, plus the very important laboratory work which, among other things, should be structured so as to teach students to expect surprises. Experimental work in new areas is perhaps the best antidote for scientific overconfidence and intellectual complacency. While the acquisition of skills in experimental research requires students to learn to work reliably and reproducibly – and here Jackson's discourse on experimental work in Fischer's laboratory is still valid – it would be a mistake to teach students that the best experiment is one that always produces the expected result. The experiment never quite goes as predicted, and the skilled experimentalist keeps an eye open for systematic discrepancies. I shudder at suggestions made prior to, but also during, the coronavirus-mandated shutdowns, that laboratory courses might be run sensibly in virtual simulation. In terms of curriculum, too much specialization, too early, promotes the unhelpful idea that scientific work is the acquisition and application of a canon or dogma. Students also need a healthy sense of the process by which innovation arises, why new ideas come to this person, at that place, in that time? How can I be that person, in this place, in this time? Last of all, Chemistry must push forward, understanding the material world by making functional objects, not just molecules. I think of Don Hilvert's nucleocapsids, which assemble a structurally well-defined, regular object from 240 engineered and artificially evolved protein subunits that work like natural analogs even if they may be structurally quite different. They spontaneously recognize and encapsulate their coding DNA suspiciously like the way by which a virus puts itself together.<sup>[21]</sup> I think of Roeland Nolte's (Nijmegen) molecular machine that reads and writes binary information encoded stereochemically on a chiral polymer chain.<sup>[22]</sup> The functions described above may occur in Nature, but the constructs themselves are not natural. I think of hybrid organic/inorganic perovskites, whose internal motions on different time scales and different length scales, wholly unanticipated at the time of their original synthesis, and, moreover, different from those in their simpler, purely inorganic antecedents precisely because of the much larger structural diversity in the hybrids, apparently provide the physical basis for their extraordinary properties in connection to photovoltaic and other charge/hole-transport-based devices.<sup>[23]</sup> Thinking ahead, can we build, for example, a catalyst that disproportionates N<sub>2</sub> to ammonia and nitrite under mild conditions, which would be the microscopic reverse of the primary metabolic process in anammox bacteria?<sup>[24]</sup> While still a bit endothermic, the catalytic cycle would be, in principle, an energetically more efficient alternative to the Haber-Bosch reduction of N<sub>2</sub> to ammonia, followed by re-oxidation of ammonia to nitrate, but it would be primarily a most elegant case of construction of a very complicated assembly of interacting molecules. Who makes these things? Chemists make them. We do then need analytics and theory. With regard to the former, one wonders if the new imaging methods with atomic resolution,<sup>[25]</sup> for example, unimaginable just decades before, will change how we work in the coming generation as much as NMR and X-ray diffraction had done in the generation prior to ours. For the latter, the statistical mechanics of non-equilibrium systems,<sup>[26]</sup> open or dissipative systems, is still growing, as are better and faster electronic structure methods. The intuition we learn from

the present Chemistry curriculum teaches us to think about molecules at equilibrium, but, at the risk of sounding flippant to illustrate why out-of-equilibrium systems are so interesting, one could say that living things which reach a state of equilibrium can be generally described as dead. We therefore need a different intuition. We still need more and better ways to build molecules, and then hook them together. To highlight just one methodological direction among many, CLICK chemistry gives us a glimpse of what a truly universal ligation reaction could achieve, even with CLICK's (not small number of) limitations.<sup>[27]</sup> Just think of how much of Chemical Biology comes from the CLICK reaction. Where is the universal, traceless ligation reaction with which we can confidently assemble large constructs without worrying (too much) about the particulars of what we want to hook together? The only two synthetic reaction classes which even come close to the ideal of 'robust' chemistry are formation of amide bonds and the formation of phosphodiester linkages, respectively the basis for automated peptide and nucleic acid synthesizers. If we had a universal, traceless ligation making, for example, aliphatic C–C bonds, what could we build up in a modular way? How would we conceive of a search in chemical space if we had such a robust, universal ligation reaction? Consider that we prove mastery of chemical transformations by synthesis of complex molecules. This logic applies equally well for even more complex systems. Chemistry today faces issues of immense complexity, but we should embrace the complexity as the essential feature that makes Chemistry interesting rather than a hurdle to be avoided, and we will master the complexity by making the objects.

In this essay, I had hoped to review retrospectively the essay by Jakob Nüesch from 1996,<sup>[1]</sup> and turn the view to the future. After a quarter-century, much of what he wrote still applies in the larger sense. With the views expressed in the present essay, I would highlight two bits of the 1996 essay: "Die erfolgreiche Weiterentwicklung der Chemie hängt nicht zuletzt davon ab, ob es ihr gelingt, die selbst gesetzten Grenzen der eigenen Wissenschaft immer wieder zu überwinden," and "Sie verlangt nach einem fortlaufenden Überdenken des eigenen Tuns und einem verantwortungsbewussten Umgang mit ihrem Ergebnisse." Especially with regard to Nüesch's recognition that any scientific field, not just Chemistry, must constantly reinvent itself, I try in this essay to find in past successes the spirit of exploration that will set our feet on the path to future success.

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