Structure of the NMR Revolution

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Introduction
Was there an nmr revolution in chemistry, and what did it consist of? This paper will answer the first question in the affirmative. The second question is more interesting. I shall contend that, notwithstanding conventional wisdom, the nmr revolution did not add just one more analytical technique to the existing ones (UV-visible and vibrational spectroscopies, mass spectrometry) feeding run-of-the-mill, paradigmatic chemistry. Nmr caused a revolution from altogether different quarters. It ushered in many a discovery in chemistry. It opened up new avenues of research. Yet more importantly, it changed the thinking of chemists.

The title of this piece borrows deliberately from the title of Thomas S. Kuhn’s classic.

Periodization
I choose to focus on the period 1960-1975. The first date is that of the first nmr conference — known thereafter as ENC —, it is also when the first commercial spectrometers became available, devoted to proton nmr. The second date coincides with the heyday of carbon-13 nmr. It happened a couple of years after Paul Lauterbur introduced what he had named «zeugmatography», afterwards renamed imaging (MRI).

My own involvement in nmr was contemporary with its entry into chemistry. During the summer of 1960, I acquainted myself with a spectrometer in Grenoble, a 40 MHz wideband solid state machine. Applied to structural work on zeolites, it was a prized possession in the group of physicist Michel Soutif.

During the 1960-61 winter, I served an apprenticeship in high-resolution nmr at Imperial College in London, in Derek Barton’s group, under the distant supervision of Lloyd M. Jackman and the more direct supervision of J. W. Lown.

In 1961-1962, jointly with Alain Gaudemer, I worked in Pierre Grivet’s laboratory in Orsay on a Varian HR-60 spectrometer. I chose to analyze strongly-coupled three-spin systems in diterpene molecules. For which I wrote Fortran software that ran on the university’s IBM 650 mainframe computer. During that time, Alain and I attended the lectures on nuclear magnetism by Professor Anatole Abragam, at Collège de France.

In 1962-63, I served a post-doctoral stay in Paul Schleyer’s group at Princeton University.

1. A section of my article "On the self-image of chemists, 1950-2000." Hyle, 2006, 12(1), 99-130, dealt already with the nmr revolution in chemistry. Accordingly, I shall strive not to repeat it here, only to complement it by tackling issues absent from that paper, due to space restrictions.


3. Appearances to the contrary, this is not a personal memoir. The genre it belongs to is that of ego-histoire. As Pierre Nora wrote when defining it, "It serves to clarify, in historical mode the link between the history that was made and the history that made you."

The department had just acquired a Varian A-60 spectrometer. We outfitted it with a CAT device, for higher sensitivity. I applied it to carbon-13 satellites of proton resonances. Which enabled me to discover the dependence of the coupling constants between ethylenic protons upon ring size, which I reported at the 4th ENC (then known as OCEANS) in Pittsburgh in 1963. I was responsible also for a comprehensive analysis of spin-spin couplings within norbornene molecules.

My doctoral dissertation in 1964 took coupling constants as its topic. Back in Princeton as an assistant professor from 1966 to 1970, I led a research group doing organic chemical projects, with a strong emphasis on nmr as our tool of study.

At that time I was called by the University of Liège in Belgium to a full professorship, I published, together with Peter Stang, a textbook on Organic Spectroscopy, heavily slanted towards nmr. By 1975, the closing date for the period I have chosen to emphasize here, with my group in Liège we were pioneering sodium-23 nmr, with applications ranging from inorganic chemistry to biophysics. The advent of Fourier transform nmr came with a major switch in supplier of spectrometers. The German Bruker bumped the Californian Varian from the first rank. This advent, with much easier access to a whole bunch of nuclei, opened the gates for a flourishing of organometallic chemistry — a major subdiscipline that came into being, predominantly because of nmr. But this is outside my self-imposed periodization.

Carsten Reinhardt has provided useful accounts of the history of applications of nmr to chemistry. There is an abundance of historical accounts of the beginnings of nmr. Most emanate from physicists. The vast majority deal with methodological advances their authors pioneered.

The present paper strives to sketch out the influence of nmr upon chemistry and why it turned out to be profound.

12. He has sensibly focused on contributions by a few outstanding individuals. In this area, as in others, historians ought to cover the early scouting of a new field by a few — a handful usually — daring explorers, and not to delve on the later Gold Rush by ‘me-too’ exploiters.
Context

The historical context for nmr bursting upon chemistry was the end of the Fifties-beginning of the Sixties, in the aftermath of WWII and recourse of the military to radar. A key element of this context was conversion of physicists to peacetime physics. Advances in electronics vastly helped, the transistor was invented in 1947. The location was the United States, first and foremost. It was at that time and by far the dominant economic power in the world.

From the combination of Vannevar Bush’s report to the President, "Science the Endless Frontier," and the Sputnik launch in 1957, American research universities were undergoing unprecedented growth, with generous allocation of federal funding. Some of these grants were allocated to the purchase of mainframe computers. At Princeton, I thus had access during the Sixties to an IBM 7040, housed in the Engineering Department building.

Industrial laboratories, during this 1960-1975 period, led by Bell Telephone Laboratories, did not lag behind academic laboratories in the excellence of fundamental scientific studies. In particular, Varian Associates, in Palo Alto, California, had recruited an outstanding team of physicists working on nmr applications: Weston A. Anderson, Richard R. Ernst, Ray Freeman, Jim Hyde, Martin Packard, and Harry Weaver. To cite only a single other industrial laboratory, DuPont de Nemours then had William D. Phillips, D. R. Eaton, Earl Muetterties doing brilliant pioneering work on chemical applications of nmr.

Lastly, this context included two outstanding books. One was a magnificent exposition by Anatole Abragam of the principles of nuclear magnetism, published in 1961. The other, nicknamed The Bible from a pun on the senior author’s name, was by John A. Pople, William G. Schneider and Harold J. Bernstein, with a timely publication in 1959.

Just another analytical technique?

According to this widespread thesis, applications of nmr to chemistry did not differ in kind from earlier devised techniques. Mi Gyung Kim conveys this viewpoint in a nutshell in a recent article:

14. Could the interaction between industrial scientists and academic scientists, over nmr, during the Sixties, be described as a galisonian trading zone? In spite of the lone but shining example of Varian Associates, it was much more a case of all those scientists sharing in the goals and values of pure science. Bell Labs provided the beacon around which other industrial and government laboratories set themselves: Argonne - IBM - JPL - DuPont - NIH - Xerox - Syntex, to name but a few. A joint zone rather than a trading zone. Which is substantiated by individuals — Fred W. McLafferty, Earl Muetterties, George Olah, Ed Wasserman — shuttling between the two spheres.

15. An industrial scientist, James N. Shoolery, played a major role in providing nmr to chemists in a form they could assimilate. After joining Varian Associates in 1952, he became that company’s chief scientist-propagandist for nmr. He was responsible for publication of catalogs of spectra, for organization of workshops educating chemists in the basics of nmr and, arguably most important, for providing them with the user-friendly A-60 spectrometer. See his paper «NMR spectroscopy in the beginning,» Anal. Chem., 1993, 65 (17), 731A–741A.


«A sudden advancement in chemical practice is more often caused by a radical innovation in analytic method than by a new theory. One can also make a similar argument about the introduction of NMR as a method of identifying organic compounds.» 19

This is not an isolated view, to the contrary it reflects a consensus. If we look at the overall picture, at the ordinary, routine uses of nmr by run-of-the-mill chemists, nmr appears indeed as just another analytical tool.

Its introduction, during the late Fifties and early Sixties, made it into a sister technique to, basically, infrared spectroscopy (IR) and mass spectrometry (MS). All three were applied to determination of molecular structure.

The methodology of nmr as a molecular spectroscopy of that type was indeed analytical, there is no doubt about it. Chemists identified groups of atoms from the positions of characteristic absorptions. Nmr improved upon both IR and MS because it provided information on interactions between hydrogens on neighboring atoms: one could follow this coupling pattern, in simple linear logic, and establish gradually the connectivity matrix for the whole molecule studied.

In other applications, that typically monitored chemical transformations in real time, seeing intermediates appear and then disappear, looking at the progressive build-up of reaction products, nmr was also just another analytical tool.

Is that all? Is such an assessment sufficient to describe the input of nmr to chemical science? Absolutely not.

In order to make my point, allow me first to jump forward in time by a couple of decades, to the time when the Nobel prizewinner and Swiss physicist Richard R. Ernst was able to rest from his pioneering contributions to nmr methodology and to turn his remarkable abilities to mainstream nmr-in-chemistry studies. 20

A New World

A small group of signpost publications 21 by Richard R. Ernst will serve us as a guide into the New Territories, opened up by the nmr revolution. After he had done most of the R&D

21. Signpost publications deserve special attention from historians of science. They reveal, at a particular time and place, a trend, not only worthy of study, but deserving particular attention. It may be an origin or a closure, but other types also present themselves. New departures belong in this category. Typically, an overachiever feels a need to display his mastery with a topic in another field than his major discovery. An example is Svante Arrhenius’s announcement of CO2-induced climate warming in 1896, quite a few years after his ionic theory (1884).

Another, more recent example, also from a Nobel prizewinner in chemistry, is Richard R. Ernst’s work on the antamanide antibiotic, ca. 1990, a number of years after he had completed most of his work on 2D nmr, centered around 1976. His publications on antamanide are noteworthy for being totally outside the norm of Richard R. Ernst earlier output, in which he provided new tools to the toolbox of nmr spectroscopists. When he started publishing these antamanide papers, he knew not only that he had been nominated for a Nobel prize, that it was only a matter of time before he was awarded one. What then do these antamanide papers signal? That Ernst could have been, had he wished, a member of the club too, with work typical of organic chemists doubling up as nmr spectroscopists. These signpost papers are precious because, as the minor masterpiece they represent, they also pinpoints the areas of study that the NMR Revolution had opened up.
work on 2D nmr that secured him a Nobel prize, he turned to other directions. He interested himself in antibiotics, of the cyclic peptide family. After a false start with lasalocid, he latched on to antamanide, as his molecule of choice. He devoted several papers to an nmr study of this cyclic decapeptide. There are basically two interpretations of what might be termed, by analogy to an artist’s oeuvre, Ernst’s Last Period. These two readings of the evidence are complementary rather than mutually exclusive. It can be seen as a return to the fold, as joining the mainstream of nmr in chemistry. It can be seen also as exploratory, a pioneering move to explore novel productive uses of nmr. I submit that this late work by Richard Ernst in and by itself defines what the nmr revolution in chemistry consisted of: a focus on the brand-new molecular reality of stereochemistry and intramolecular dynamics, viz. internal motions within molecules that interconvert various conformations, i.e., instantaneous arrangements of their atoms. Ernst’s antamanide work thus studied the backbone of that molecule. He showed that it fluctuated between different states. He and his group identified two pairs, syn and anti, of hydrogen bond exchanging systems, located at residues $^{1}$Val and $^{6}$Phe. He went on to study the motion of the phenylalanine sidechains.

New Territories Found by Nmr

As Richard Ernst’s work on antamanide illustrates, a cardinal virtue of nmr was its ability to characterize a molecule, not only by its structure, i.e., the precise arrangement of its atoms in space, but also by its dynamics. Nmr gave to chemists the tools to anchor a molecule in both space and time. Given the novelty of conformational analysis at the turn of the 1960s, ring inversions became an early application of nmr for their full, accurate characterization. As a keynote episode, I would single out the bond shift of the ethylenic bonds in cyclo-octatetraene: as this eight-membered ring undergoes inversion, it goes through a planar transition state which, more than incidentally, is anti-aromatic.

Fluxional molecules were such a major new territory opened by nmr. A key episode, in nmr impacting chemistry, was the bullvalene story, originating in 1961 and developing from 1963

26. Since I mentioned Frank Anet, an Australian by birth, I should add that, if the US was the birthplace of nmr in chemistry, a number of immigrants, some only temporary, had a major impact: Richard R. Ernst from Switzerland, Ray Freeman and John A. Pople from England, Gerhard Closs from Germany, others too.
on. Its importance stems from nmr having been crucial, first to establishing the molecular structure unambiguously, second and most importantly to enable measurement of the rate of internal rearrangement.

Bullvalene is a $\text{C}_{10}\text{H}_{10}$ hydrocarbon. It was designed by William von Eggers Doering (1917-2011). Bullvalene undergoes multiple Cope rearrangements, each of which returns the molecule to itself — a so-called degenerate rearrangement. However, this is a permutational exchange process, interchanging the four different carbon types. Bullvalene, when it started being studied, was the prototypical fluxional molecule, i.e., an entity uniquely suited to determination by nmr of its dynamics.

Doering had a junior colleague at Yale, Martin Saunders (1931-2011) who did the nmr work on bullvalene. In addition, he wrote the software that accounted for the nmr lineshape as a function of temperature, thus enabling extraction of the rate constant.

Nmr was the tool of choice to measure the kinetics of other degenerate rearrangements. A whole class is that of pentacoordinate molecules, of which phosphorus pentafluoride PF$_5$ is the prototype. During the very early years of nmr, an interesting discrepancy showed between the vibrational spectrum, consistent with the geometry of a trigonal bipyramid, and the temperature-dependent fluorine-19 nmr spectrum. The explanation, termed pseudorotation, following the Berry mechanism, is interchange between the two axial fluorines and two of the equatorial ones, the remaining equatorial fluorine serving as the pivot in this exchange.

I can find no better example than CIDNP for a new chapter of chemistry having been opened by nmr. The acronym stands for chemically-induced nuclear polarization. What it translates into is a means to monitor free-radicals in the nascent state, as a chemical reaction is run directly in the nmr tube. The most frequent situation, as first explained by Gerhard Closs, is the radical-pair mechanism. Kaptein has pioneered application of the photo-CIDNP

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27. More than 1,200,000 structures interconvert!
experiment to proteins.  

**Grand unification: bridges to molecular biology**

A key aspect of the nmr revolution was exploration and establishment of the tight connexion between molecules of organic chemistry and those of molecular biology, proteins and nucleic acids especially. Small biomolecules, for instance the cyclic peptide ionophores (such as antamanide), bridged what had been earlier perceived as a gap, as a difference in kind — rather than just in size.

I have just mentioned CIDNP, a methodology that bridged chemistry and biochemistry, whether of proteins or nucleic acids. I will illustrate this point with another three examples.

The first is the co-called magnetic nonequivalence. Nmr spectroscopists taught their colleagues in organic chemistry that pairs of nuclei, or groups, could be diastereotopic, enantiotopic or homotopic. This characteristic hinged on molecular symmetry. For instance, a chiral molecule could have only diastereotopic protons. 34 Of course, biochemists had made such distinctions much earlier, but they had not penetrated at all the field of organic chemistry. Nmr spectra thus helped to bring closer together the two disciplines.

A second link between organic and biochemistry came about from the ability of nmr to measure rate constants for extremely fast processes, of the type exemplified by some of the side chains in antamanide, as studied by Ernst and his coworkers. Measurement of relaxation times gives access to processes in the timescale of nanoseconds to picoseconds. 35 This proved crucial in the study of the molecular dynamics of proteins, and therefore in the understanding of the binding of small drug molecules to their receptors, for instance.

My third exhibit is measurement of the nuclear Overhauser effect. Rather shortly after Frank Anet showed its operation in some crowded organic molecules which had been synthesized by Saul Winstein, 36 it became a very important tool in the nmr determination of protein structure. 37

**Other key features of the NMR Revolution.**

Chemists taught themselves how to read a spectrum, i.e., to attach meanings to features such as resonance frequency, line intensity, lineshape, relaxation time, etc. Those meanings amounted to an abundance of information about molecular characteristics such as the connectivity of atoms, their spatial nearest neighbors, electronic distribution, internal motions such as rotations of groups of atoms, ring inversions, pyramidal inversions of atoms such as nitrogen or phosphorus, tumbling times for the molecule as a whole, etc. The complete understanding of a molecule nmr allowed for and invited was truly revolutionary.

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Thus, nmr spectra provided representations of molecules in three-dimensional space, known as stereochemistry. As a fortuitous coincidence, the advent of nmr in chemistry was contemporary with conformational analysis, also synonymous with stereochemistry.

A key feature, rather unique to nmr in self-evident simplicity, was equivalence between atoms and groups of atoms in pairs, triads, etc., that specified the type of symmetry inherent in a molecule.

Chemists, whether of the organic, inorganic, organometallic or biochemical subdivision, could thus partake of what can only be termed "molecular intimacy:" a familiarity with details of molecular structure and dynamics at the microscopic scale, that of nanometers.

The nmr revolution brought about social consequences too. Since nmr illustrates quantum mechanics with impressive accuracy, chemists had to teach themselves a modicum of quantum physics. To put it another way, quantum chemistry, from being a marginal subdiscipline reserved to a tiny number of specialists, became integrated into mainstream chemistry.

Introduction in 1961 of the Varian A-60 nmr spectrometer made it possible for non-specialists to use the machine themselves. This hands-on policy ensured that graduate students could run their own spectra and, in so doing, watch molecules at play. Which led to many a discovery. It antedated and probably influenced the general move from mainframe to personal computers.

**Discussion**

The word «revolution» was part of my title. Is it accurate, or just a wild exaggeration? To examine this implicit claim, in order to either justify or refute it, will be my final point.

First, the contrarian view: the term «revolution» is poorly chosen and inadequate. During the Sixties and Seventies, chemistry did not undergo an upheaval, a refoundation comparable to, say, the revolution wrought by Lavoisier in the 1780s; nor anything like the advent of quantum mechanics in physics during the 1920s. I know that this feeling, if collective, is no proof. But another couple of arguments bolster it. The first is that chemistry was already a mature science in mid-twentieth century. Hence, pretending that it then underwent a revolution would be oxymoronic and preposterous. In any case, as the second additional argument, we are still too close to the event to be able to evaluate it.

How then should we describe the effects nmr had on chemistry? Can it qualify as a revolution, in the sense Thomas Kuhn gave memorably to this notion? If so, if indeed a mutation had occurred, what were the two paradigms, the ancient and the newer one that replaced it? The mere mention of this question suffices, one does not readily have an answer, the kuhnian description does not seem to be applicable to the event, or group of events I am discussing.

Granted that the kuhnian description does not seem to apply, how then should historians view the impact of nmr on chemistry? What jumps to mind is a contribution by Derek de Solla Price to science historiography. In his view, invention of new scientific instruments was the engine of change. Nmr thus belongs with the telescope and the microscope. Its sway over chemistry might compare with X-ray diffraction or mass spectrometry. While this view is held by many, it does not satisfy me. There was definitely more to nmr than an instrumental innovation, however powerful.

Before I state my answer to the question, allow me to mention some of the evidence one has to contend with. Maybe first, the significant number of Nobel prizes awarded because of nmr.
38 As already mentioned in connexion to Richard Ernst’s work on antamanide, nmr accelerated the ongoing unification of chemistry and biology. Nmr of proteins became a logical extension of nmr of organic molecules. Antamanide, a decapeptide, marked an intermediate point, in between the small molecules of organic chemistry and biological macromolecules.

Another piece of evidence, from a different quarter, from my intuition since there is no room here for supporting data, at least at this time, is the slow reorganization of chemistry as a university discipline. The advent of nmr, intriguingly, coincided with the wane of analytical chemistry as a powerful subdiscipline; and, as already mentioned, with the infusion of quantum chemistry instead.

Since I bring to bear, in a sociological light, departments and institutes of chemistry, a related observation is the close relationship between the power structure within a department and control over the nmr spectrometer(s). This is another point worthy of more research, for whose corroboration at this stage I can only state personal experience.

Let me not forget the obvious, how quickly nmr became a standard tool for chemists. The most important aspect though is not material, nor technological, it has to do with perception: nmr brought about molecular intimacy. Such a result was the epitome of rationality.

Going from the nmr to the underlying molecular structure is an entirely logical construct, the molecule itself identifies to an edifice obeying the laws of logic. A new mental set-up for knowledge build-up came to the fore. I submit, as a prime example of the new mentality nmr brought about, retrosynthetic analysis: E. J. Corey was not only one of the leading synthetic organic chemists, his thought processes were influenced by nmr — of which he had indeed an in-depth understanding.

Accordingly, the advent of nmr, if it influenced chemistry in numerous ways, above all advanced knowledge by algorithmic reasoning, pushing aside traditional trial-and-error. Chemists, henceforth, would achieve their goals by design rather than haphazardly.

38. The following scientists owed their award to nmr, to a small or a major degree: E. J. Corey, Donald J. Cram, Richard R. Ernst, Martin Karplus, Paul Lauterbur, Jean-Marie Lehn, George Olah, John A. Pople, Kurt A. Wüthrich. By itself, their sheer number is highly significant.