

Roberts J D, Weigert F J, Kroschwitz J I & Reich H J. Nuclear magnetic resonance spectroscopy. Carbon-13 chemical shifts in acyclic and alicyclic alcohols.

J. Amer. Chem. Soc. 92:1338-47, 1970.

[Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, CA]

We measured the nuclear magnetic resonance chemical shifts of carbon-13 at the natural-abundance level of a variety of alcohols, and we showed that these shifts correlated well with those of correspondingly constituted hydrocarbons. Valuable conformational information could be inferred from the shifts of cyclic alcohols, but not acyclic alcohols, because their conformational possibilities are not well understood. [The SCI[®] indicates that this paper has been cited in over 430 publications.]

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We had been working since 1955 at the California Institute of Technology (Caltech) on the applications of nuclear magnetic resonance (NMR) to problems in organic chemistry. We observed the resonance signals of hydrogen and fluorine but were frustrated by our inability to observe the signals from carbon, which, of course, is the element of central interest in organic chemistry. Many organic compounds do not contain hydrogen or fluorine, but all contain carbon. The only isotope of carbon suitable for NMR studies is carbon-13. Unfortunately, it is present in small quantities at the natural-abundance level, and its magnetic moment is much less than that of hydrogen. One can easily take the NMR spectra of compounds enriched in carbon-13, but synthetically this is both difficult and expensive. Routine NMR at the natural-abundance level was therefore sorely needed.

In 1957 P.C. Lauterbur¹ (later to be famous for his work on the use of NMR as an imaging modality) demonstrated that it was possible to take carbon-13 NMR at the natural-abundance level. However, his procedure was difficult to apply (a compliment to his experimental skill), and it did not provide a high degree of resolution. The problem was poor signal-to-noise (S/N) ratios in the radio frequency receivers. In principle, one could improve S/N by using longer scanning times, but this was extremely difficult to achieve in the early days because of instrumental instabilities.

My goal was to obtain an NMR spectrometer that would be stable over long periods of time, so that

weak signals could be enhanced by time averaging. I was able to obtain funding from the National Institutes of Health for the project, but I was hard-pressed to see how it could be done with existing equipment. Just when I had decided to try another method (that would probably have been difficult and unproductive), I saw an advertisement in *Scientific American* by Hewlett-Packard (HP) for a frequency synthesizer that could cover the range of frequencies needed for carbon-13 NMR and that also had almost unprecedented frequency stability. I tried unsuccessfully to convince Varian Associates (then the leading manufacturer of NMR equipment) to build a carbon-13 spectrometer around the HP frequency synthesizer. I then ordered an HP frequency synthesizer to try to make it work myself. At that point Varian called me and said, "If you send us your synthesizer, we will try to do the job here." I was happy to get off the hook, and Varian made a superb machine; it worked even better than we hoped.

Frank J. Weigert (now of the Central Research Department of the DuPont Company) arrived at Caltech from the Massachusetts Institute of Technology in 1966 as a new graduate student with a National Science Foundation fellowship. The new spectrometer had just become available, and he recognized the potential of getting in on the ground floor of natural-abundance carbon-13 NMR. His published output over two years and nine months of graduate work can only be described as truly heroic. He published 16 publications, covering a wide range of NMR applications, many of which involved carbon-13.

The article discussed here contained a wealth of NMR shift data on alcohols, which we hoped to correlate to allow predictions of shifts in this and other classes of organic compounds. That it is the most cited of Weigert's output does not mean it was the most significant. Much of his other work, especially that related to carbon-carbon couplings,^{2,3} is of greater theoretical interest.

Near the end of his stay at Caltech, Weigert started taking the carbon-13 spectra of some larger molecules,⁴ including that ubiquitous biochemical molecule, cholesterol, which gave, for each of its 27 carbons, a unique carbon-13 signal. Weigert was not sanguine that we would be able to tell which signal came from which carbon within a 10-year period. But a group eager to take up the challenge, sparked by postdoctoral fellow Hans J. Reich, now of the University of Wisconsin, solved that problem in less than a year.⁵ More than 90 publications relating to carbon-13 NMR resulted from the development of our new spectrometer. The field subsequently developed very rapidly and has been the subject of several books. Excellent recent examples are references 6 and 7.

1. Lauterbur P C. C¹³ nuclear magnetic resonance spectroscopy. *J. Chem. Phys.* 26:217-8, 1957. (Cited 135 times.)
2. Weigert F J & Roberts J D. Nuclear magnetic resonance spectroscopy. Carbon-carbon coupling in cyclopropane derivatives. *J. Amer. Chem. Soc.* 89:5962-3, 1967. (Cited 230 times.)
3. ———. Nuclear magnetic resonance spectroscopy. Carbon-carbon coupling. *J. Amer. Chem. Soc.* 94:6021-5, 1972. (Cited 125 times.)
4. Weigert F J, Jautelat M & Roberts J D. Natural-abundance C¹³ nuclear magnetic resonance spectra of medium-molecular weight organic compounds. *Proc. Nat. Acad. Sci. USA* 60:1152-5, 1968. (Cited 85 times.)
5. Reich H J, Jautelat M, Messe M T, Weigert F J & Roberts J D. Nuclear magnetic resonance spectroscopy. Carbon-13 spectra of steroids. *J. Amer. Chem. Soc.* 91:7445-54, 1969. (Cited 400 times.)
6. Breitmaier E & Voelter W. *Carbon-13 NMR spectroscopy*. New York: VCH, 1987. 515 p.
7. Kalinowski H-O, Berger S & Braun S. *¹³C-NMR-Spektroskopie*. New York: Thieme, 1984. 685 p.