Pergamon

Tetrahedron Letters, Vol. 37, No. 37, pp. 6623-6626, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01440-2

A Useful Modification of the Attached Proton Test ^{13}C NMR Experiment: Unambiguous Peak Assignments for Carbons with Large $^1J_{(CH)}$ Values

Peggy A. Radel and Stephen B. Kahl*

Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94143-0446.

Abstract: We have developed an extension of the APT ^{13}C NMR experiment which differentiates tetracoordinate methine carbons and hexacoordinate 2-carboranyl carbons in complex organic molecules bearing *o*-carboranyl functionalities, as well as discriminating between pairs of carbons such as methylenes and terminal alkynes. The differences in the $^1J(CH)$ of each carbon results in modified intensities in APT experiments using a 7.5 msec and a 10 msec delay. Comparing the spectra from these two experiments definitively assigns the peaks to the appropriate carbon, yielding information often only obtainable from 2D experiments. Copyright © 1996 Elsevier Science Ltd

As part of our work in developing new drugs containing boron for boron neutron capture therapy (BNCT), we are incorporating 1, 2 dicarbaclosodecaborane (*ortho*-carborane, a C_2B_{10} dodecahedron) into organic molecules.[1] In compounds such as **1**, the presence of the methine carbon bearing the azide group as well as the 2-carbon in the carboranyl cage yields a ^{13}C NMR spectrum with signals that can not be assigned unambiguously on the basis of chemical shift.

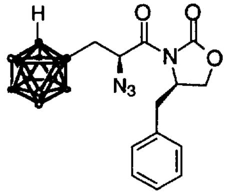


Figure 1. Compound 1

In order to definitively assign signals in the spectra of compounds bearing carboranyl functionalities, we have developed a useful extension of the Attached Proton Test ^{13}C NMR experiment.[2] It permits us to obtain connectivity information often only obtainable by 2D methods. This modification also permits differentiation of other types of carbons, methylene and terminal alkyne for example, in ^{13}C NMR spectra.

The APT experiment has been a highly useful and practical method of assigning multiplicities in ^{13}C NMR spectroscopy, and a number of related experiments and techniques have been reported since its introduction in 1982.[3] All of these methods attempt to further simplify spectral identification of complex organic molecules. However, none of them gives a readily assignable spectrum for compounds with functionalities like carboranyl and methine carbons, with similar, often nearly coincident chemical shifts.

In the APT experiment, sign and intensity of a peak are described by Equation 1 when considering only one-bond coupling. The delay time τ, during which the decoupler is turned off and the coupling evolves, can be selected for each experiment, but the ${}^{1}J_{(CH)}$ coupling is a property of each carbon in the molecule and is dependent on the hybridization of the carbon as one variable. In compounds of interest to us, a recurrent problem is assignment of the 2-carbon of the carboranyl cage and methinyl carbons in the remainder of the molecule. However, the hybridization of these two sets of carbons is vastly different and therefore the $J_{(C\text{-}H)}$ also is very distinguishable.

$$(I/I_o) = \cos^{n}(J\tau\pi) \tag{1}$$

$$\text{for } n=1 \qquad (I/I_o) = \cos(J\tau\pi) \tag{2}$$

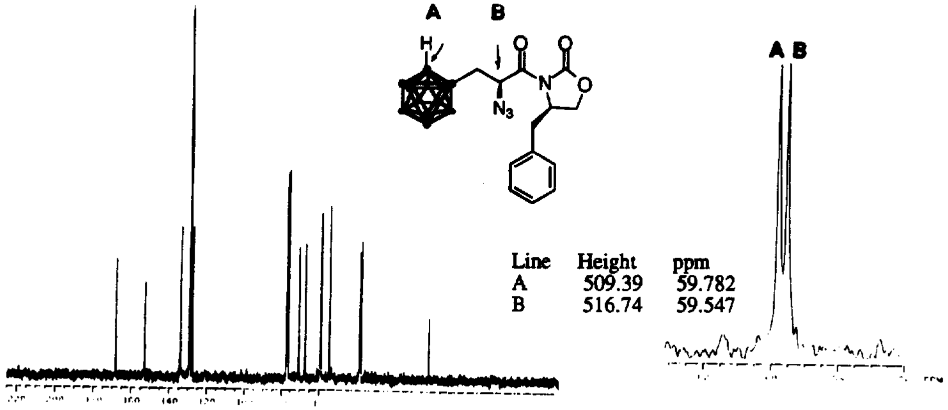
n= number of protons attached to the carbon of interest. J is the ${}^{1}J_{(C\text{-}H)}$ coupling in Hertz. τ is the spin-echo delay in seconds.

In studies by several groups, the $J_{(CH)}$'s for a number of substituted *o*-carboranes have been obtained and the hybridization calculated at $sp^{1.6}$ for these hexacoordinate carbons .[4] We can take advantage of the differences for $J_{(CH)}$ for carboranes at 190-200 Hz versus that for tetracoordinate methines with $J_{(CH)}$ from 125 to 170 Hz. [4, 5] Therefore, in the APT experiment that is usually performed to distinguish methyl and methine carbons from methylene and quaternary carbons, with a delay time of 7.5 msec, the intensity of the peak due to the 2-carboranyl carbon is diminished considerably relative to that of tetracoordinate methine carbons. Conversely, choosing a delay time of 10 msec results in decreased intensities for the tetracoordinate species and relatively enhanced intensity for the 2-carboranyl carbon. The calculated intensities of peaks in these two experiments for hexacoordinate 2-carboranyl carbons and tetracoordinate methines are shown in Table 1.

Table 1. Calculated Relative Intensities of ${}^{13}C$ NMR Peak as a Function of $J_{(C\text{-}H)}$ and Spin-echo Delay.

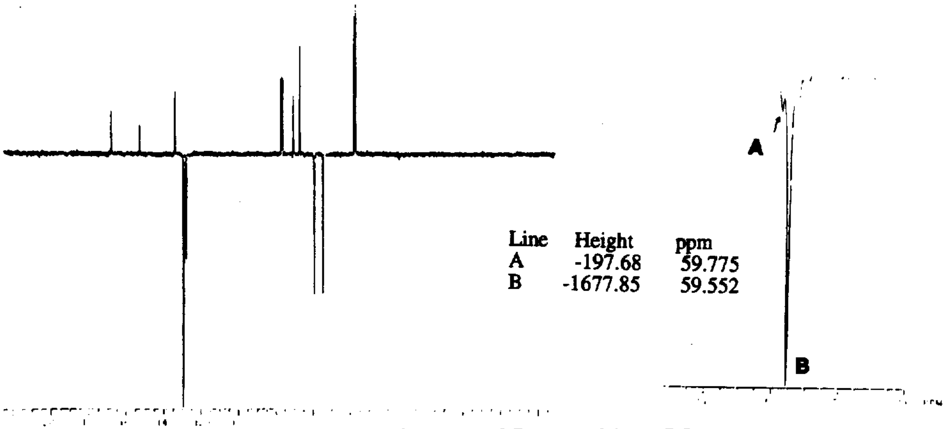
Delay time	τ= 7.5 msec	τ = 10 msec	τ = 10.43 msec
$J_{(CH)}$ = 200 Hz	$I = 0.0\ I_o$	$I = 1.0\ I_o$	
$J_{(CH)}$ = 190 Hz	$I = -0.23\ I_o$	$I = 0.96\ I_o$	
$J_{(CH)}$ = 160 Hz	$I = -0.81\ I_o$	$I = 0.33\ I_o$	
$J_{(CH)}$ = 125 Hz	$I = -0.98\ I_o$	$I = -0.71\ I_o$	
$J_{(CH)}$ = 250 Hz	$I = 0.93\ I_o$	$I = 0.0\ I_o$	$I = -0.35\ I_o$
$J_{(CH2)}$ =125 Hz	$I = 0.97\ I_o$	$I = 0.5\ I_o$	$I = 0.33\ I_o$

This approach can also be applied to compounds containing a terminal alkyne ($J_{(CH)}$= 250 Hz) along with methylene carbons ($J_{(CH2)}$= 125 Hz).[6] The currently used 7.5 msec delay experiment does not differentiate these two carbons at all (Table 1). However, adding the 10.0 msec delay experiment , one can now



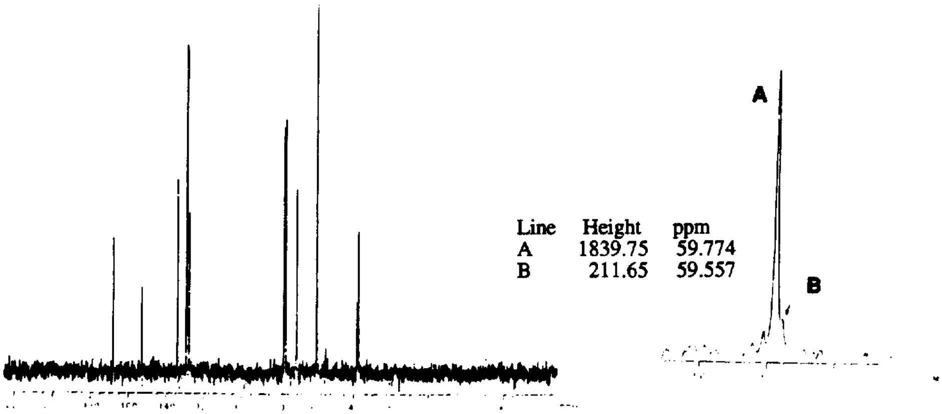
Line	Height	ppm
A	509.39	59.782
B	516.74	59.547

Figure 2 ^{13}C NMR Spectrum of Compound 1.



Line	Height	ppm
A	-197.68	59.775
B	-1677.85	59.552

Figure 3 APT Spectrum of Compound 1, $\tau = 7.5$ msec.



Line	Height	ppm
A	1839.75	59.774
B	211.65	59.557

Figure 4 APT Spectrum of Compound 1, $\tau = 10.0$ msec.

distinguish these two peaks. An ideal experiment for this set of peaks would utilize τ= 10.43 msec, permitting very simple assignment with intensities of -0.35 I_o (alkyne) and 0.33 I_o (methylene).

The spectral results for compound **1** are shown in Figures 2-4.[7] Figure 2 is the standard ^{13}C NMR experiment and shows the near coincidence of the two peaks in question and their I_o intensities. The expanded regions to the right of each of the Figures 2-4 show these peaks more clearly. Figure 3 shows the spectrum resulting from the APT experiment using a 7.5 msec delay. Figure 4 shows the spectrum using an APT experiment with a 10 msec spin-echo delay. It is seen that the two peaks due to the hexacoordinate 2-carboranyl carbon and the tetracoordinate methine are easily differentiable and assignable.

These experiments are simple to perform and interpret. A sample at 0.12- 0.16 M can provide a good spectrum in 20 minutes, thus allowing a complete set of spectra to be obtained within one hour. This provides unambiguous assignment of the entire spectrum without requiring the use of 2D experiments. We believe that this modification of the APT experiment will be a useful addition to other spectral identification methods for researchers using functionalities with large differences in $J_{(CH)}$ which may be poorly differentiable in previously reported APT and one-pulse ^{13}C NMR experiments.

Acknowledgments. We wish to thank the Department of Energy for its support of this work through grant DE-FG-03-89ER60873. We are deeply grateful to Dr. Neil E. Jacobsen, Department of Chemistry, University of Arizona, Tucson, AZ 85704, for his very helpful suggestions and comments.

References

1. Radel, P. A.; Kahl, S. B. *J. Org. Chem.*, in press.
2. Patt, S. L.; Schoolery, J. N. *J. Magn. Res.* **1982**, *46*, 535-539.
3. a. Sanders, J. K. M.; Hunter, B. K. *Modern NMR Spectroscopy, A Guide for Chemists*, Oxford University Press, Oxford, **1987**, 69-75.
   b. Mitteilung, K. *Z. phys. Chemie, Leipzig* **1984**, *265*, 1040-1045.
   c. Radeglia, R.; Porzei, A. *J. prakt. Chemie* **1984**, *326*, 524-528.
   d Crews, P.; Naylor, S.; Myers, B. L.; Loo, J.; Manes, L. V. *Magn. Res. Chem.* **1985**, *23*, 684-687.
   e. Radeglia, R. *J. prakt. Chemie* **1989**, *331*, 705-708.
   f. Torres, A. M.; Nakashima, T. T.; McClung, R. E. D. *J. Magn. Res.* **1993**, *Series A 101*, 285-294.
4. Colella, S. M.; Li, J.; Jones, Jr., M. *Organometallics* **1992**, *11*, 4346-4347.
5. a. Fedin, E. I.; Antonovich, V. A.; Rys, E. G.; Kalinin, V. N.; Zaharkin, L. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 801-805.
   b. Olah, G. A.; Surya Prakash, G. K.; Liang,G.; Henold, K. L.; Haigh, G. B. *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 5217-5221.
6. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds, Fourth Edition*, J. Wiley and Sons, New York, **1981**, 273.
7. All spectra were acquired using a GE QE300 spectrometer with a 5 mm probe at a carbon frequency of 75.5 MHz and composite pulse ^1H decoupling. 672 scans were acquired with a relaxation delay of 1.0 sec and the data were processed with a 5.0 Hz line broadening. The solvent for all experiments was $CDCl_3$.

(*Received in USA* 9 *May* 1996; *revised* 12 *July* 1996; *accepted* 18 *July* 1996)