

**POLARIZATION TRANSFER VIA LONG RANGE COUPLING
AS A SIMPLE ONE-DIMENSIONAL NMR TECHNIQUE FOR ^1H - ^{13}C CORRELATION.
APPLICATION TO THE DEFINITIVE ASSIGNMENT OF THE
SYN AND ANTI ^{13}C δ RESONANCES OF 2-SUBSTITUTED ADAMANTANES.**

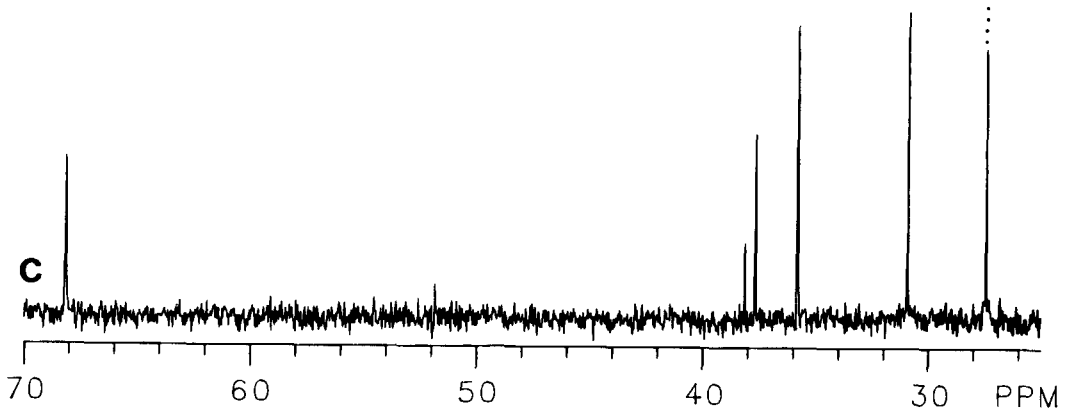
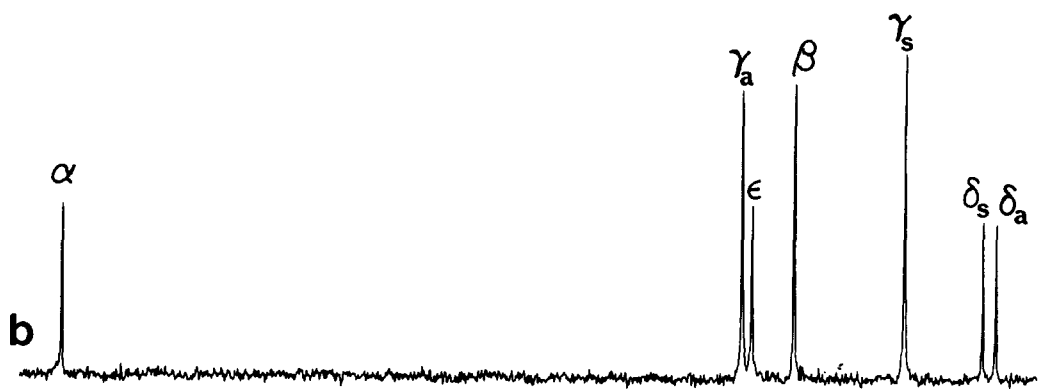
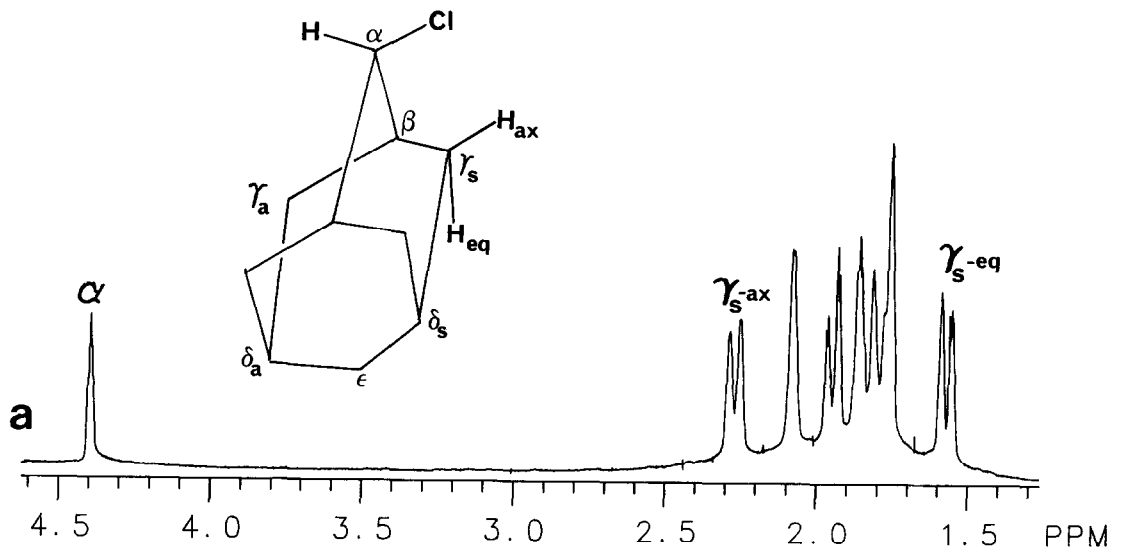
Ashraf N. Abdel-Sayed and Ludwig Bauer*
Department of Medicinal Chemistry and Pharmacognosy
University of Illinois at Chicago
P.O. Box 6998, Chicago, IL 60680

Abstract: The syn and anti δ resonances in ^{13}C NMR spectra of 2-substituted adamantanes were assigned unequivocally by means of selective polarization transfer from γ -syn protons via 2-bond carbon-proton coupling.

Two-dimensional (2-D) NMR techniques are extremely informative, but their usefulness is sometimes limited by the long time needed for spectral acquisitions. This is especially important when dealing with insensitive nuclei such as ^{13}C or ^{15}N . An understanding of the theories of 2-D NMR led to the development of several one-dimensional (1-D) methods which are considerably less time-consuming yet, in many cases, as informative as 2-D methods. Bax¹ recently described a simple 1-D NMR technique for ^1H - ^{13}C correlation by polarization transfer via long-range ^1H - ^{13}C coupling which has been successfully applied to resonance assignment of complex spectra.² We would like to report the use of this technique as a simple and quick method for solving a rather long-standing problem in the adamantane field.

The assignment of syn and anti ^{13}C δ -resonances of 2-substituted adamantanes remained debatable³ since it was reported first in 1974.⁴ Although Duddeck suggested the correct assignment of these resonances in 1975⁵, it was not until this year that his conclusion had been proven unequivocally by le Noble *et al.*⁶ and by us.⁷ le Noble and co-workers⁶ based their conclusion on analysis of the ^{13}C spectra of 2-adamantanol which has been deuterated specifically at the δ -syn and δ -anti positions. Our assignment⁷ was based on the 2-D INADEQUATE⁸⁻¹⁰ spectra of 2-bromo and 2-phenyladamantane. Although our method did not require the synthesis of specifically labeled compounds, it still suffered from the inherently low sensitivity of the 2-D INADEQUATE technique which involves the detection of ^{13}C - ^{13}C coupling in natural abundance. Large amounts of samples (2-4 g in 12 mm tubes) had to be used to obtain reasonable signal-to-noise ratios in overnight runs.

In this report we demonstrate the use of a simple and rapid 1-D NMR technique^{1,2} to assign unequivocally the δ resonances of several 2-substituted adamantanes. Only about 50 mg of sample is required to achieve good signal-to-noise ratios in an acquisition time of less than 15 minutes.



The technique is a modification of the well-known INEPT¹¹⁻¹⁴ experiment. Frequency-selective ('soft') proton pulses are used to affect polarization transfer from a selected proton(s) to those carbons that are long-range coupled to this particular proton(s). The spectra obtained by this technique reveal which carbons are 2- or 3-bonds removed from the selected proton(s). To illustrate this technique, the assignment of the δ -resonances of 2-chloroadamantane is discussed.

Figure 1a shows the 360 MHz ¹H NMR spectrum of 2-chloroadamantane. Both the axial and the equatorial¹⁵ γ -syn protons¹⁶ are free from overlap with other signals and are suitable for the application of selective pulses.¹⁷ The polarization transfer spectrum from the equatorial γ -syn protons is shown in Figure 1c.¹⁸ Only those carbons that are 2- or 3-bond away from the γ -syn protons show signals in this spectrum. In contrast to the δ -syn carbon signal, the δ -anti signal is absent. Thus, these two signals can be distinguished definitively. The same result could be obtained by selecting the axial γ -syn protons for polarization transfer. For comparison, the conventional broad-band decoupled ¹³C spectrum of the same sample is shown in Figure 1b.

We applied this technique to differentiate unequivocally between the two δ resonances in 2-amino, 2-bromo, 2-iodo, 2-acetamido, 2-phenyl, 2-acetoxy and 2-cyanoadamantane. In all the compounds examined, the δ -anti resonance was found to be upfield compared to the δ -syn resonance.¹⁹ This confirms unequivocally Duddeck's assignment² of δ -syn and δ -anti substituent effects in 2-substituted adamantanes. These effects are opposite to the well-known γ -effects of which the γ -syn is shielding compared to the γ -anti effect.

In conclusion, polarization transfer via long-range ¹H-¹³C coupling is a simple, yet powerful 1-D NMR technique which was used to definitively assign syn and anti δ -resonances in 2-substituted adamantanes.

Acknowledgements: We gratefully acknowledge the U.S. Army Research and Development Command for financial support (Contract DAMD17-79-C-9146) and the NMR Laboratory of the Research Resources Center of the University of Illinois at Chicago for providing the Nicolet spectrometer used in this study.

References and Notes

1. Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.
2. For application of this technique see: Bax, A.; Ferretti, J.A.; Nashed, N.; Jerina, D.M. *J. Org. Chem.* **1985**, *50*, 3029 and Bax, A.; Egan, W.; Kovac, P. *J. Carbohydrate Chem.* **1984**, *3*, 593.
3. For detailed history of the controversy see Ref. 6 and references quoted therein.
4. Maciel, G.E.; Dorn, H.C.; Greene, R.L.; Kleschick, W.A.; Peterson, M.R. Jr.; Wahl, G.H. Jr. *Org. Magn. Reson.* **1974**, *6*, 178.
5. Duddeck, H. *Org. Magn. Reson.* **1975**, *7*, 151.

Figure 1. (pictured left): a) 360 MHz ¹H NMR spectrum of 2-chloroadamantane (CDCl₃). b) Conventional broad-band decoupled ¹³C NMR spectrum of the same sample. c) ¹³C NMR spectrum obtained by selective polarization transfer via long range ¹H-¹³C coupling from the equatorial γ -syn protons.

6. Srivastava, S.; Cheung, C.K.; le Noble, W.J. Magn. Reson. Chem. **1985**, 23, 232.
7. Abdel-Sayed, A.N.; Bauer, L. Tetrahedron Lett. **1985**, 26, 2841.
8. Bax, A.; Freeman, R.; Frenkiel, T.A. J. Am. Chem. Soc. **1981**, 103, 2102.
9. Mareci, T.H.; Freeman, R. J. Magn. Reson. **1982**, 48, 158.
10. Bax, A.; Mareci, T.H. J. Magn. Reson. **1983**, 53, 360.
11. Morris, G.A.; Freeman, R. J. Am. Chem. Soc. **1979**, 101, 760.
12. Burrum, D.P.; Ernst, R.R. J. Magn. Reson. **1980**, 39, 163.
13. Morris, G.A. J. Am. Chem. Soc. **1980**, 102, 428.
14. Bolton, P.H. J. Magn. Reson. **1980**, 41, 287.
15. 'Axial' and 'equatorial' are used with reference to the cyclohexane ring containing the substituent at C-2.
16. The assignments of the γ -syn proton signals are in agreement with those reported in literature [Deursen, F.W.; Korver, P.K. Tetrahedron Lett. **1967**, 3923]. They were also simply confirmed by correlation with the γ -syn carbon signal using selective population transfer (SPT) experiment [Sarkar, S.K.; Bax, A. J. Magn. Reson. **1985**, 62, 109].
17. Low decoupler power ($\gamma H_2 = 25$ Hz) was used to achieve frequency selectivity. The 90° soft pulse duration (10 ms) was calibrated using a sample of acetic acid as described [Bax, A. J. Magn. Reson. **1983**, 52, 76].
18. The spectrum was obtained on a Nicolet NIC-360 spectrometer using the pulse sequence:

| | | | | | |
|-------------------|------------------------------|-------------------------------|-----------------------|-----------------------|--------------|
| ^1H : | 90(x) - (4J) ⁻¹ - | 180(y) - (4J) ⁻¹ - | 90(+y) - $\Delta/2$ - | 180(x) - $\Delta/2$ - | Decouple |
| ^{13}C : | - 180(x)- | - 90(x)- | - 180(x)- | - 180(x)- | - Acquire(+) |

An estimated value of 5 Hz for the long-range ^{13}C - ^1H couplings was used to calculate the delays. The optimal values for the delay Δ is $1/2J$ and $1/4J$ for AX and AX₂ spin systems respectively. Due to the symmetry of the molecule, the α , δ -syn, and ϵ carbons behave as an AX₂ spin system, while the β , γ -syn and γ -anti behave as an AX system in this experiment. A delay Δ of $0.3/J$ (60 ms; J=5 Hz) was used to detect both systems.

19. Carbon-13 chemical shifts (in ppm (δ) downfield from internal tetramethylsilane) are listed below in this order: α , β , γ -syn, γ -anti, δ -syn, δ -anti, ϵ , other resonances: 2-Adm-Cl: 68.15, 35.79, 30.95, 38.12, 27.45, 26.86, 37.68; 2-Adm-NH₂: 55.43, 35.12, 30.78, 37.75, 27.82, 27.34, 37.99; 2-Adm-Br: 63.18, 36.49, 31.68, 38.73, 27.73, 27.08, 37.94; 2-Adm-I: 46.69, 37.55, 32.99, 38.81, 27.73, 27.07, 38.15; 2-Adm-NHAc: 53.40, 31.92, 31.78, 37.16, 27.23, 27.12, 37.54, 169.41 (CO), 23.54 (Me); 2-Adm-Ph: 46.81, 31.08, 31.99, 39.21, 28.15, 27.91, 37.95; 144.22, 128.11, 126.77, 125.13 (Ph); 2-Adm-OAc: 76.69, 32.21, 32.00, 36.51, 27.68, 27.42, 37.63; 169.28 (CO), 20.99 (Me); 2-Adm-CN: 36.88, 30.79, 33.26, 36.53, 27.39, 27.17, 36.88; 121.84 (CN). All solutions were in deuteriochloroform except for 2-Adm-OAc and 2-Adm-CN (deuterobenzene).

(Received in USA 29 October 1985)