Tetrahedron Vol 44. No 7. pp 1883 to 1892, 1988
Printed in Great Britain

0040-4020/88 $3.00 + 00
Pergamon Press plc

ASSIGNMENT OF ^{13}C AND ^{1}H CHEMICAL SHIFTS OF 1,2-DISUBSTITUTED ADAMANTANES BY ONE- AND TWO-DIMENSIONAL NMR SPECTROSCOPY

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

(*Received in USA* 3 *August* 1987)

Abstract: ^{13}C and ^{1}H NMR chemical shifts of twenty-nine 1,2-disubstituted adamantanes were assigned by means of 1D and 2D NMR techniques, particularly ^{1}H-^{13}C correlations via long-range couplings using the INAPT pulse sequence. Additivity of ^{13}C substituent effects in these adamantanes was examined. Intramolecular interactions between the neighboring substituents were shown to cause considerable non-additivity effects. In particular, ^{13}C signals for C-5 and C-7 in many of the compounds were found to be opposite to the assignment of C-5 and C-7 in 2-monosubstituted adamantanes.

Adamantanes, being conformationally-rigid and minimally-strained molecules with well-defined geometry, are excellent models for studying NMR spectral parameters. Relatively little NMR spectral data has been published on 1,2-disubstituted adamantanes. This may be attributed to the complexity of their NMR spectra. The introduction of a variety of multi-pulsed one- (1D) and two-dimensional (2D) NMR techniques[2] enabled us to analyze ^{13}C and ^{1}H NMR spectra of twenty-nine 1,2-disubstituted adamantanes.

In this report, our approach to the unequivocal assignment of ^{13}C chemical shifts is discussed first. Additivity of ^{13}C substituents chemical shifts (SCS) is then examined. Finally, the ^{1}H spectra of these adamantanes are analyzed. A detailed discussion of chemical shift assignments is presented just for a few typical examples. Application of the same methodology permitted the analysis of ^{1}H and ^{13}C NMR spectra of the rest of the compounds (Tables I and III).

^{13}C NMR signal assignments in 1,2-disubstituted adamantanes

The broad-band proton decoupled ^{13}C spectrum of each of the 1,2-disubstituted adamantanes shows clearly resolved signals for each of the adamantane carbons (see, for example, the spectrum of 2-bromo-1-(hydroxymethyl)adamantane shown in Fig. 2c). Several recent NMR techniques, such as APT[3], INEPT[4], DEPT[5], and SEMUT[6], are available for distinguishing between methyl, methylene, methine and quarternary ^{13}C signals. By using any one of these techniques, we could readily assign ^{13}C signals: (a) C-1 is easily singled out since it is the only quaternary carbon in the system. (b) Of the methine carbon (C-2, C-3, C-5, and C-7) signals, the two farthest downfield are obviously attributed to C-2 and C-3, respectively, being deshielded by the substituent at C-2. At this point, however, one cannot distinguish between the two upfield methine signals, namely, C-5 and C-7. (c) Signals for the five adamantane methylene carbons (C-4, C-6, C-8, C-9, and C-10) cannot be assigned at this juncture. Further assignments are possible by using ^{1}H-^{13}C correlations, as discussed below.

^{1}H - ^{13}C correlations via long-range couplings

Bax[7] has described recently a sensitive 1D NMR experiment which correlates a selected proton with carbons that are 2 or 3 bonds removed from that proton. This technique, which was dubbed "INAPT" (insensitive nuclei assigned by polarization transfer),[8] is based on polarization transfer from ^{1}H to ^{13}C via long-range ^{1}H-^{13}C coupling. We applied the INAPT technique to ascertain chemical shifts in 1,2-disubstituted adamantanes as illustrated below using 2-bromo-1-(hydroxymethyl)adamantane (**22**) as an example.

The signal farthest downfield (δ 4.65 ppm) in the ^{1}H NMR spectrum of **22** obviously arises from H-2 (Fig. 1). When this proton is selected for polarization transfer in the INAPT experiment, the spectrum shown in Fig. 2a is obtained. This spectrum shows signals only from carbons that possess long-range coupling with H-2, such as C-1 and C-3 (coupled to H-2 over 2 bonds), and C-4, C-8, C-9, C-10, and CH_2OH (coupled to H-2 over 3 bonds). Since the ^{13}C chemical shifts of C-1, C-3 and CH_2OH, have been already identified, assignment of the remaining signals (C-4, C-8, C-9 and C-10) are addressed below. Also, absent from this spectrum are those signals due to carbons which are not coupled to H-2 by 2- or 3-bonds, namely C-6, C-5, and C-7. Of these three ^{13}C signals, C-6 can be readily identified being a methylene carbon, rather than a methine carbon. To distinguish between the chemical shifts of C-5 and C-7 needed additional experimentation.

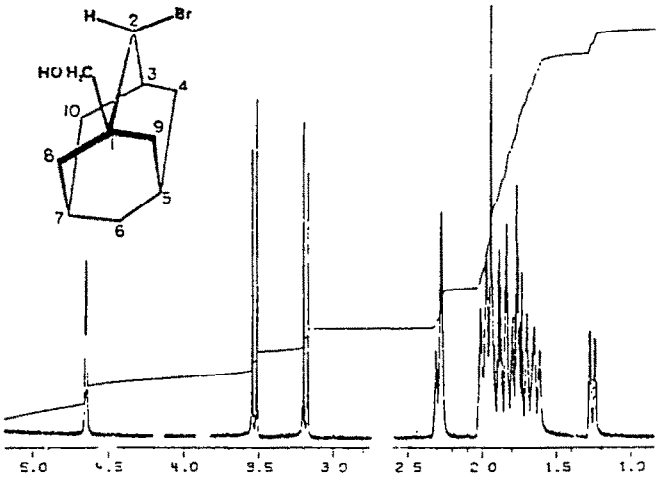


Figure 1. 360 MHz ^{1}H NMR spectrum of 2-bromo-1-(hydroxymethyl)adamantane.

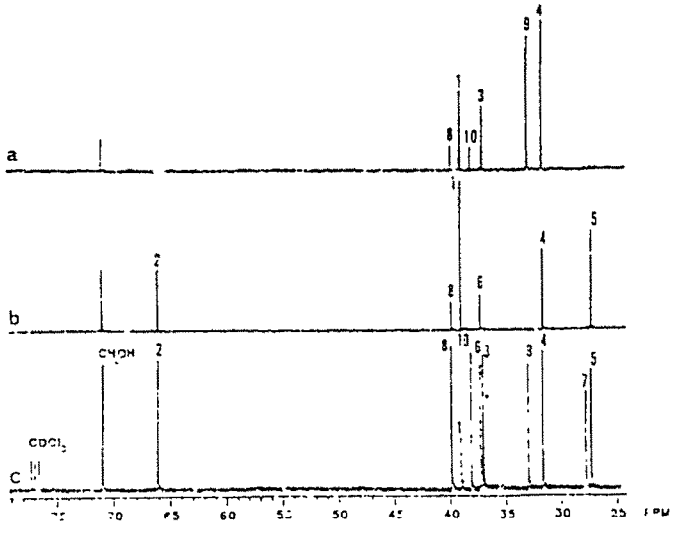


Figure 2. INAPT spectra of 2-bromo-1-(hydroxymethyl)adamantane. (a) Selective polarization transfer via long-range ^{13}C-^{1}H couplings from H-2. (b) Selective polarization transfer via long-range ^{13}C-^{1}H couplings from H-9_{eq}. (c) Broad-band decoupled spectrum.

Assignments of C-4, C-8, C-9, and C-10 signals are based on their chemical shift values. Both C-9 and C-4 are γ_{syn} relative to the substituent at C-2, while C-8 and C-10 are γ_{anti}. The γ_{syn} substituent effect is large ($\sim$5-7 ppm) and is shielding[12,13] (see, also Table II). Therefore, signals arising from C-4 and C-9 appear farther upfield than those from C-8 and C-10. Due to the β-effect of the bridgehead substituent, C-8 and C-9 are more deshielded than C-10 and C-4, respectively.

Support of the above assignments can be found in the relative intensities of the signals assigned to C-8 and C-10 vs those of C-9 and C-4 (Fig. 2a). The signal intensities in INAPT spectra are a function of the magnitude of long-range coupling constants and the fixed delays (Δ_1 and Δ_2) used in the pulse sequence.[7] For an AX system, maximum polarization transfer is obtained when $\Delta_1 = \Delta_2 = (2J)^{-1}$. In the INAPT spectrum shown in Fig. 2a, the delays used were: $\Delta_1 = \Delta_2 = 100$ ms, which gave rise to signals of maximum intensity when $J = 5$ Hz. Three-bond carbon-proton couplings, $^{3}J(C,H)$, show dihedral angle dependence related to proton-proton couplings.[9] The dihedral angle between H-2 and either C-9 or C-4 is 180°, while the dihedral angle between H-2 and either C-8 or C-10 is $\sim 60^{\circ}$. Thus, ^{3}J(H-2,C-9) and ^{3}J(H-2,C-4) are expected to be larger[10] than ^{3}J(H-2,C-8) and ^{3}J(H-2,C-10). For this reason, the signals for C-9 and C-4 are much more intense than those for C-8 and C-10 (Fig. 2a). These relative intensity characteristics of C-9/C-4 vs. C-8/C-10 confirmed their ^{13}C chemical shift assignments.

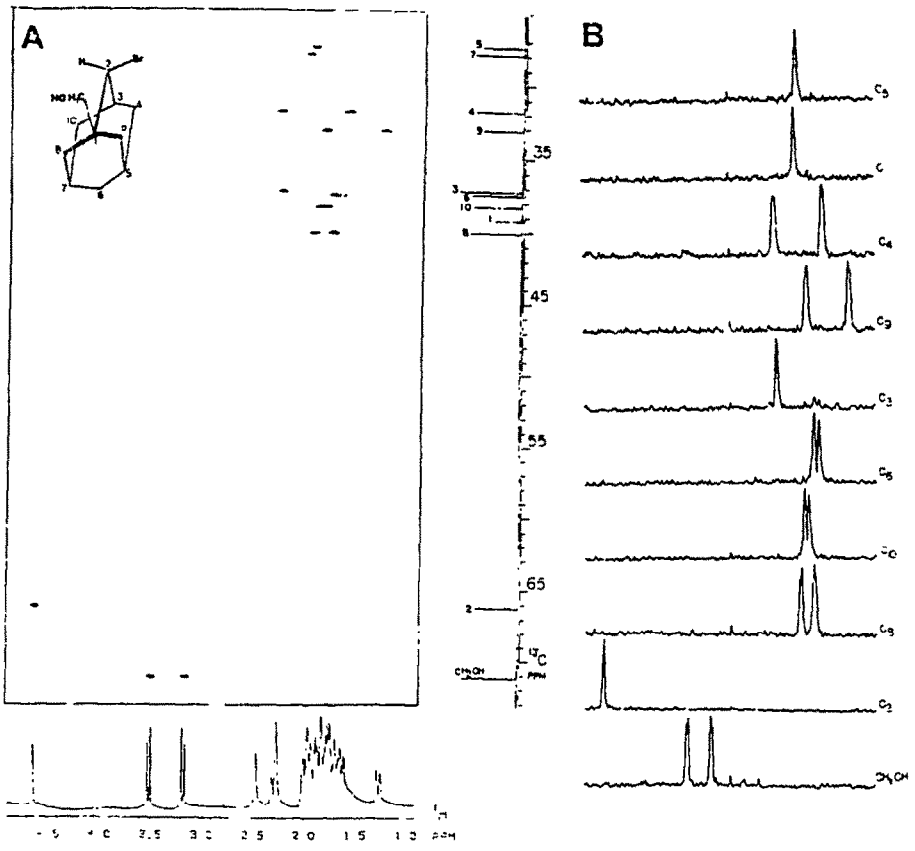


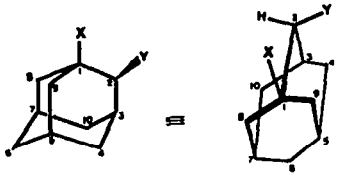
Figure 3. ^{1}H-^{13}C chemical shift correlation spectrum of 2-bromo-1-(hydroxymethyl)adamantane. **A:** Contour plot of the 2-D spectrum. **B:** Cross-sections taken parallel to the ^{1}H axis. Each trace dislays the signal of the proton(s) attached to an individual carbon.

At this point, it remains to differentiate between the chemical shifts of the two bridgehead carbons, C-5 and C-7. For this purpose we used the INAPT technique again as follows. The farthest upfield multiplet at 1.28 ppm in the ^{1}H spectrum of **22** (Fig. 1) is assigned to the equatorial proton at C-9 (see below). Figure 2b represents the INAPT spectrum obtained by polarization transfer from this proton (H-9$_{eq}$). The ^{13}C resonances in this spectrum are due to those carbons which are coupled over 2- or 3-bonds to H-9$_{eq}$, namely, C-1, C-5 (2-bonds) C-2, C-4, C-6, C-8, and CH_2OH (3-bonds). Notably, the signal from C-7 is absent thereby distinguishing between δC-5 and C-7. Furthermore, the absence of C-10 signal corroborates the assignment of δC-10 vs δC-8, made above.

Following the above approach, all ^{13}C signals of twenty-nine 1,2-disubstituted adamantanes were unequivocally assigned. The ^{13}C chemical shifts of these compounds are reported in Table I.

We previously[14] arrived at similar assignments for three of the twenty-nine 1,2-disubstituted adamantanes, namely, **22**, **21**, and **24**, by means of the 2D INADEQUATE NMR experiment.[15] Although the technique is perhaps more straightforward and more versatile than INAPT, it suffers from extremely low sensitivity. Large amounts of samples (2-4 g, in 12 mm O.D. tubes) were required in order to obtain spectra with a reasonable signal-to-noise ratio, even after long runs (12 hours). The beauty of the INAPT experiment is that it is considerably more sensitive, requiring less than a 50-mg sample in order to obtain good signal-to-noise ratios in about 15 minutes. However, one important requirement for a successful INAPT experiment is that the proton signal selected for polarization transfer (for example, H-2 and H-9$_{eq}$ in **22**) should be free from overlap with other resonances. This is because of the use of frequency-selective ('soft') proton pulses in this experiment. The above requirement is usually met by using modern high field NMR spectrometers. One can also circumvent the use of soft pulses altogether by resorting to the 2D equivalents of INAPT, for example, the COLOC pulse sequence.[16] These 2D NMR methods are, however, much more time-consuming compared to the INAPT experiment, especially if only a few essential correlations are needed.

TABLE I: ^{13}C CHEMICAL SHIFTS OF 1,2-DISUBSTITUTED ADAMANTANES[a-d]



Compd	X	Y		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1	Cl	Cl	Obsd	69.41	71.93	38.80	29.14	30.71	35.63	30.76	48.27	40.93	36.68
			Calcd	75.80	78.05	39.03	28.60	30.69	35.33	30.10	48.02	40.85	35.77
			NA	-6.39	-6.12	-0.23	0.54	0.02	0.30	0.66	0.25	0.08	0.91
2	Br	Br	Obsd	66.33	68.24	39.68	29.88	31.65	35.76	31.45	49.73	43.06	37.11
			Calcd	74.74	74.65	40.63	29.38	31.87	35.64	31.22	50.20	43.15	36.43
			NA	-8.41	-6.41	-0.95	0.50	-0.22	0.12	0.23	-0.47	-0.09	0.68
3	I	I	Obsd	52.84	56.33	40.55	31.51	32.57	36.14	32.02	51.68	47.27	37.12
			Calcd	59.54	61.14	42.02	30.67	32.20	35.83	31.54	53.26	47.44	36.49
			NA	-6.70	-4.81	-1.47	0.84	0.37	0.31	0.48	-1.58	-0.17	0.63
4[e]	$OCOCH_3$	$OCOCH_3$	Obsd	79.69	75.90	34.33	30.57	29.76	35.92	30.03	39.46	36.16	35.20
			Calcd	83.40	80.45	34.32	30.20	29.75	35.88	29.53	39.87	35.26	34.81
			NA	-3.71	-4.55	0.01	0.37	0.01	0.04	0.50	-0.41	0.90	0.39
5	OH	Cl	Obsd	69.08	73.85	37.82	29.56	29.64	36.13	29.99	43.68	39.00	37.01
			Calcd	75.57	75.71	38.12	29.27	29.78	36.00	29.19	45.64	38.47	36.44
			NA	-6.49	-1.86	-0.30	0.29	-0.14	0.13	0.80	-1.96	0.53	0.57
6	OH	Br	Obsd	68.69	71.40	38.60	30.35	29.80	36.35	30.20	43.59	39.99	37.53
			Calcd	76.27	70.74	38.82	30.00	30.06	36.26	29.41	46.25	39.20	37.05
			NA	-7.58	0.66	-0.22	0.35	-0.26	0.09	0.79	-2.66	0.79	0.48
7	OH	I	Obsd	68.29	57.75	40.02	31.77	29.94	36.57	30.46	42.67	41.45	37.47
			Calcd	77.33	54.25	39.88	31.31	30.06	36.47	29.40	46.33	40.51	37.13
			NA	-9.04	3.50	0.14	0.46	-0.12	0.10	1.06	-3.66	0.94	0.34
8[f]	$OCOCH_3$	Cl	Obsd	79.83	66.42	38.06	29.23	29.86	36.28	30.18	40.56	36.40	36.84
			Calcd	87.32	71.65	38.24	29.39	29.90	36.12	29.31	41.62	34.45	36.56
			NA	-7.49	-5.23	-0.18	-0.16	-0.04	0.16	0.87	-1.06	1.95	0.28
9[f]	$OCOCH_3$	Br	Obsd	79.24	62.06	38.57	30.69	29.90	36.41	30.22	40.49	37.21	37.27
			Calcd	88.02	66.68	38.94	30.12	30.18	36.38	29.53	42.23	35.18	37.17
			NA	-8.78	-4.62	-0.37	0.57	-0.28	0.03	0.69	-1.74	2.03	0.10
10[f]	$OCOCH_3$	I	Obsd	79.00	46.60	39.99	32.27	30.17	36.76	30.49	39.49	38.81	37.39
			Calcd	89.08	50.19	40.00	31.43	30.18	36.59	29.52	42.31	36.49	37.25
			NA	-10.08	-3.59	-0.01	0.84	-0.01	0.17	0.97	-2.82	2.32	0.14
11	Br	Cl	Obsd	66.56	72.22	38.62	28.72	31.20	35.22	30.95	49.42	41.94	36.39
			Calcd	74.04	79.62	39.93	28.65	31.59	35.38	31.00	49.59	42.42	35.82
			NA	-7.48	-7.40	-1.31	0.07	-0.39	-0.16	-0.05	-0.17	-0.48	0.57
12	I	Cl	Obsd	51.92	74.37	38.06	29.04	32.05	35.60	31.42	52.90	45.04	36.96
			Calcd	57.78	82.60	40.26	28.63	31.92	35.36	31.33	52.57	45.40	35.80
			NA	-5.86	-8.23	-2.20	0.41	0.13	0.24	0.09	0.33	-0.36	1.16
13	Cl	Br	Obsd	69.02	67.58	39.51	29.98	30.80	35.86	30.93	48.24	41.76	37.12
			Calcd	76.50	73.08	39.73	29.33	30.97	35.59	30.32	48.63	41.58	36.38
			NA	-7.48	-5.50	-0.22	0.65	-0.17	0.27	0.61	-0.39	0.18	0.74
14	I	Br	Obsd	51.65	70.65	38.89	29.96	32.32	35.91	31.69	53.09	45.88	37.43
			Calcd	58.48	77.63	40.96	29.36	32.20	35.62	31.55	53.18	46.13	36.41
			NA	-6.83	-6.98	-2.07	0.60	0.12	0.29	0.14	-0.09	-0.25	1.02
15	Cl	I	Obsd	68.94	52.21	41.05	31.46	30.97	36.06	31.22	46.84	43.28	36.92
			Calcd	77.56	56.59	40.79	30.64	30.97	35.80	30.31	48.71	42.89	36.46
			NA	-8.62	-4.38	0.26	0.82	.00	0.26	0.91	-1.87	0.39	0.46
16	Br	I	Obsd	66.73	53.13	41.35	31.46	31.90	36.04	31.82	48.36	44.61	36.92
			Calcd	75.80	58.16	41.69	30.69	31.87	35.85	31.21	50.28	44.46	36.51
			NA	-9.07	-5.03	-0.34	0.77	0.03	0.19	0.61	-1.92	0.15	0.41
17	F	Cl	Obsd	94.49	68.16	38.85	29.47	30.44	35.90	30.89	42.95	36.23	36.55
			Calcd	99.85	73.10	38.86	29.01	30.52	35.74	29.93	43.07	29.01	43.07
			NA	-5.36	-4.94	-0.01	0.46	-0.08	0.16	1.96	-0.12	7.22	-6.52
			J_{CF}	193.1	16.7	3.9	1.4	9.5	1.9	9.2	17.3	17.1	1.9

TABLE I (CONTINUED)

Compd	X	Y		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
18	F	Br	Obsd	90.64	62.72	39.52	30.30	30.66	36.21	31.11	43.14	37.22	37.17
			Calcd	100.55	68.13	39.56	29.74	30.80	36.00	30.15	43.68	29.74	43.68
			NA	-9.91	-5.41	-0.04	0.56	-0.14	0.21	0.96	-0.54	7.48	-6.51
			J_{CF}	194.4	16.2	3.9	1.0	9.3	1.7	9.4	17.8	16.6	1.4
19	F	I	Obsd	90.38	45.70	40.64	30.60	30.78	36.36	31.22	42.13	38.86	37.17
			Calcd	101.61	51.64	40.62	31.05	30.80	36.21	30.14	43.76	31.05	43.76
			NA	-11.23	-5.94	0.02	-0.45	-0.02	0.15	1.08	-1.63	7.81	-6.59
			J_{CF}	194.2	16.0	3.7	1.6	9.1	1.9	9.3	17.9	16.7	1.9
20[g]	CH_2OH	F	Obsd	38.41	96.17	32.79	31.08	27.15	36.86	27.26	37.79	33.29	35.50
			Calcd	38.96	96.75	32.70	30.91	27.11	36.67	26.77	37.02	32.77	35.16
			NA	-0.55	-0.58	0.09	0.17	0.04	0.19	0.49	0.77	0.52	0.34
			J_{CF}	16.3	179.0	18.0	1.6	0.0	0.0	1.7	6.4	0.0	9.3
21[g]	CH_2OH	Cl	Obsd	39.20	69.05	36.37	31.01	27.39	37.31	27.74	39.86	32.57	37.75
			Calcd	41.85	69.41	35.59	30.35	27.25	37.08	26.66	39.38	32.21	37.52
			NA	-2.65	-0.36	0.78	0.66	0.14	0.23	1.08	0.48	0.36	0.23
22[g]	CH_2OH	Br	Obsd	39.16	66.23	37.17	31.76	27.37	37.42	27.88	40.03	33.08	38.24
			Calcd	42.55	64.44	36.29	31.08	27.53	37.34	26.88	39.99	32.94	38.13
			NA	-3.39	1.79	0.88	0.68	-0.16	0.08	1.00	0.04	0.14	0.11
23[g]	CH_2OH	I	Obsd	38.80	51.86	38.88	33.36	27.57	37.74	28.32	38.92	34.23	38.40
			Calcd	43.61	47.95	37.35	32.39	27.53	37.55	26.87	40.07	34.25	38.21
			NA	-4.81	3.91	1.53	0.97	0.04	0.19	1.45	-1.15	-0.02	0.19
24[g,i]	CH_2OH	C_6H_5	Obsd	37.65	52.90	35.19	31.23	27.75	38.17	28.79	42.38	34.10	40.01
			Calcd	37.14	48.07	30.88	31.39	27.95	37.35	27.71	40.47	33.25	38.61
			NA	0.51	4.83	4.31	-0.16	-0.20	0.82	1.08	1.91	0.85	1.40
25[h]	CO_2H	F	Obsd	45.27	94.55	32.46	30.18	26.78	35.97	26.93	38.90	31.95	35.13
			Calcd	45.00	96.24	32.35	30.14	26.76	35.90	26.42	36.51	32.26	34.39
			NA	0.27	-1.69	0.11	0.04	0.02	0.07	0.51	2.39	-0.31	0.74
			J_{CF}	18.4	182.0	17.9	1.0	0.0	0.0	1.6	6.0	1.0	8.5
26[h]	CO_2H	Cl	Obsd	46.67	66.63	35.57	29.91	26.95	36.44	26.97	40.95	31.27	37.28
			Calcd	47.89	68.90	35.24	29.58	26.90	36.31	26.31	38.87	31.70	36.75
			NA	-1.22	-2.27	0.33	0.33	0.05	0.13	0.66	2.08	-0.43	0.53
27[h]	CO_2H	Br	Obsd	46.70	61.37	36.22	30.74	27.07	36.63	27.10	41.30	31.97	37.78
			Calcd	48.59	63.93	35.94	30.31	27.18	36.57	26.53	39.48	32.43	37.36
			NA	-1.89	-2.56	0.28	0.43	-0.11	0.06	0.57	1.82	-0.46	0.42
28[h]	CO_2H	I	Obsd	46.90	43.85	36.99	32.39	27.32	37.76	27.37	40.79	33.37	37.84
			Calcd	49.65	47.44	37.00	31.62	27.18	36.78	26.52	39.56	33.74	37.44
			NA	-2.75	-3.59	-0.01	0.77	0.14	0.98	0.85	1.23	-0.37	0.40
29[h,i]	CO_2H	C_6H_5	Obsd	43.46	50.44	35.47	30.22	27.41	36.95	27.99	43.65	33.36	39.02
			Calcd	43.18	47.56	30.53	30.62	27.60	36.58	27.36	39.96	32.74	37.84
			NA	0.28	2.88	4.94	-0.40	-0.19	0.37	0.63	3.69	0.62	1.18

[a] In parts per million (δ) downfield from internal $(CH_3)_4Si$.

[b] Obsd = observed shifts measured at 90.8 MHz in ~1.5 M solutions in $CDCl_3$.

[c] Calcd = calculated shifts, obtained by adding the respective substituent shifts to the shifts of adamantane itself (see text).

[d] NA (Non-additivity) = Obsd — Calcd.

[e] Chemical shifts of $OCOCH_3$ carbons in 4 are: 169.91 and 169.76 (2 C=O), 22.37 and 21.13 (2 CH_3).

[f] Chemical shifts of the $OCOCH_3$ carbons in compounds 8, 9, and 10, are: 169.88, 169.79, 169.85 (C=O), 22.20, 22.25, 22.47 (CH_3), respectively.

[g] Chemical shifts of the CH_2OH carbons in compounds 20-24, are: 69.19, 69.55, 71.19, 74.10, 70.33, respectively.

[h] Chemical shifts of CO_2H carbons in compounds 25-29, are: 181.94, 181.18, 180.84, 180.80, 182.92, respectively.

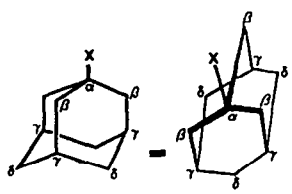
[i] Chemical shifts of the phenyl carbons in 24 are: 144.35 (C-1), 129.48 (C-o), 127.96 (C-m), 125.79 (C-p); in compound 29 are: 143.45 (C-1), 128.01, 127.96 (C-o and C-m), 125.59 (C-p).

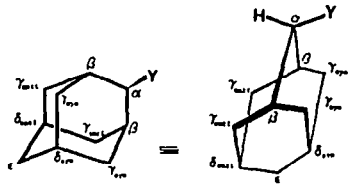
Additivity of ^{13}C substituent chemical shifts in 1,2-disubstituted adamantanes

It was of interest to examine the additivity of ^{13}C substituents chemical shifts (SCS) in 1,2-disubstituted adamantanes. ^{13}C shifts of 1,2-disubstituted adamantanes can be calculated by adding the respective SCS values to δC-1 or δC-2 of adamantane itself.[17] The SCS values reported in Table II were calculated by subtracting the chemical shifts of identical carbons in adamantane from that of the corresponding monosubstituted adamantane.

The SCS values in Table II were used to calculate the chemical shifts in 1,2-disubstituted adamantanes. It becomes obvious (Table I) that there is considerable deviation (non-additivity, NA) between some of the calculated and observed chemical shifts especially for C-1 and C-2. One might expect this non-additivity to be due to considerable intramolecular interactions between the neighboring substituents at C-1 and C-2. Non-additivities have been reported for ^{13}C chemical shifts of 2,4-disubstituted adamantanes.[18] On the other hand, good additivity was observed in 1,3-disubstituted adamantanes,[12] and in 2,6-disubstituted adamantanes[19] where the substituents are far enough apart to interact minimally.

TABLE II: ^{13}C SUBSTITUENTS CHEMICAL SHIFTS (SCS) IN MONOSUBSTITUTED ADAMANTANES





Bridgehead SCS

X	α	β	γ	δ
F	64.06	4.95	3.07	-1.94
Cl	40.01	9.90	3.24	-2.35
Br	38.25	11.47	4.14	-2.30
I	21.99	14.45	4.47	-2.32
OH	39.78	7.56	2.33	-1.68
$OCOCH_3$	51.53	3.50	2.45	-1.56
CH_2OH	6.06	1.26	-0.20	-0.60
CO_2H	12.10	0.75	-0.55	-1.37

Bridge SCS

Y	α	β	γ_{syn}	γ_{anti}	δ_{syn}	δ_{anti}	ε
F	57.70	4.50	-6.28	-2.03	-1.09	-1.43	-0.52
Cl	30.36	7.39	-6.84	0.33	-0.95	-1.54	-0.11
Br	25.39	8.09	-6.11	0.94	-0.67	-1.32	0.15
I	8.90	9.15	-4.80	1.02	-0.67	-1.33	0.36
OH	36.74	6.17	-6.75	-1.26	-0.87	-1.32	-0.19
$OCOCH_3$	39.16	3.47	-6.03	-1.42	-1.10	-1.32	-0.35
C_6H_5	9.02	2.68	-5.80	1.42	-0.25	-0.49	0.16

C-5 and C-7 Carbon-13 chemical shifts in 1,2-disubstituted adamantanes

The assignment of the δ_{syn} and δ_{anti} carbons (C-5 and C-7, respectively) in 2-monosubstituted adamantanes has been debatable for almost 15 years.[20] Although the correct assignment was suggested early by Duddeck and co-workers[18a,21] it was not until recently that it has been unequivocally proven.[22,23] The δ_{syn} signals appear downfield compared to the δ_{anti} counterparts.[23b]

An interesting set of results is reported for the chemical shifts of C-5 and C-7 in 1,2-disubstituted adamantanes. In these compounds, C-5 and C-7 are symmetrically disposed with respect to the substituent at C-1. However, they are δ_{syn} and δ_{anti}, respectively, in relation to the substituent at C-2. Close examination of the data in Table I shows that the assignments of these two δ resonances in all but six of the compounds examined are opposite to those of the corresponding 2-substituted adamantanes. This "reversal" of the δ effect of the substituent at C-2 in 1,2-disubstituted adamantanes, can be attributed to the strong interaction between the two substituents. The nature of the interaction responsible for this reversal is however not immediately apparent.

The six compounds which do not exhibit such reversal of the resonance assignments are **2, 3, 11, 12, 14,** and **16.** Interestingly, each one of these compounds has either a bromo or an iodo group at C-1. Furthermore, the observed difference between the chemical shift of C-5 and C-7 roughly increases for I > Br > Cl groups at C-2. On the contrary, these differences decrease for F < Cl < Br < I groups at C-1.

^{1}H NMR spectra of 1,2-disubstituted adamantanes

In spite of their complexity, analysis of the ^{1}H NMR spectra of 1,2-disubstituted adamantanes was possible by the use of 2D heteronuclear shift correlation techniques.[24] As an example, the 2D heteronuclear shift correlation spectrum of 22 is shown in Fig. 3a. Using cross sections parallel to the proton axis in this spectrum permitted us to extract all of the ^{1}H chemical shifts (Fig. 3b). ^{1}H chemical shifts for the other 1,2-disubstituted adamantanes were determined similarly and are reported in Table III.

To distinguish between the two geminal (axial and equatorial)[25] protons on each of the C-4, C-6, C-8, C-9, C-10, we analyzed the coupling network of the ^{1}H NMR spectra using the COSY experiment.[26] To illustrate this point, the COSY spectrum of 1,2-dibromoadamantane (2) is shown in Fig. 4. The equivalent of the conventional ^{1}H spectrum appears on the diagonal line. Off-diagonal (cross) peaks indicate J coupling between the corresponding diagonal peaks. From this COSY spectrum it is evident that the farthest downfield proton (H-2) is coupled to three protons: H-3, H-9$_{eq}$, and H-4$_{eq}$. Coupling between H-2 and each of H-9$_{eq}$ and H-4$_{eq}$ is due to a planar W arrangement between them. H-4$_{ax}$ and H-9$_{ax}$, on the other hand, do not show coupling to H-2. This coupling to the equatorial, rather than the axial, H-4 and H-9 protons permits us to distinguish immediately between these geminal protons.

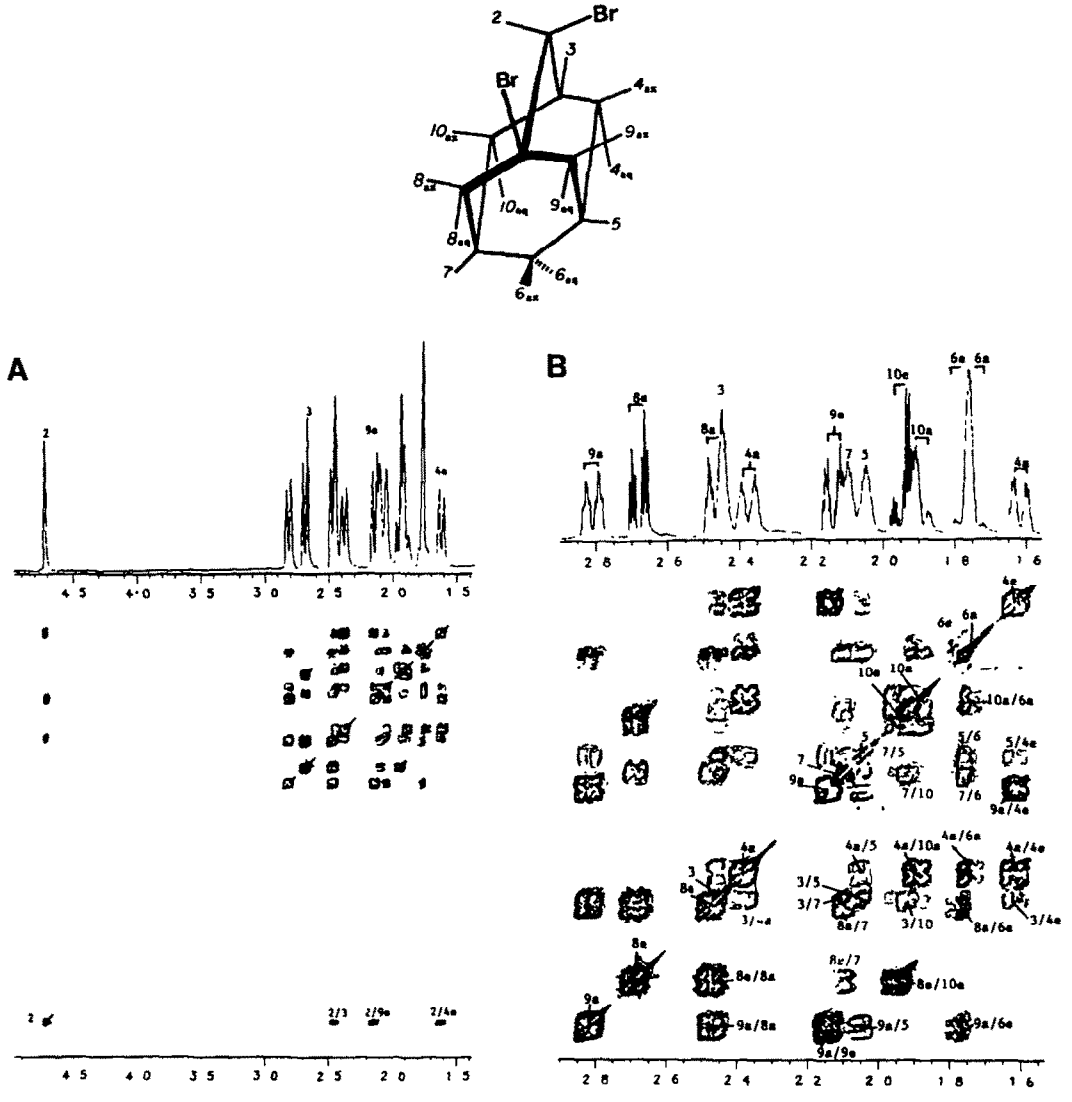
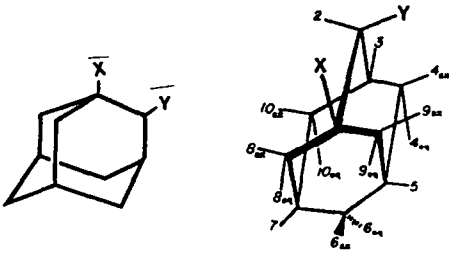


Figure 4. COSY Spectrum of 1,2-dibromoadamantane. A: Full spectrum. B: Expansion of the upfield region.

TABLE III: ^{1}H CHEMICAL SHIFTS OF 1,2-DISUBSTITUTED ADAMANTANES[a]



Compound	X	Y	H-2	H-3	H-4[b] (ax)	H-4[b] (eq)	H-5	H-6[c]	H-7	H-8[b] (eq)	H-8[b] (ax)	H-9[b] (ax)	H-9[b] (eq)	H-10[b] (eq)	H-10[b] (ax)
1	Cl	Cl	4.33	2.33	2.22	1.50	2.08	1.70, 1.70	2.11	2.35	2.17	2.57	1.88	1.83	1.80
2	Br	Br	4.72	2.46	2.39	1.63	2.06	1.78, 1.76	2.11	2.69	2.48	2.83	2.16	1.95	1.91
3	I	I	5.12	2.50	2.56	1.82	1.85	1.85, 1.85	2.01	3.13	2.88	3.04	2.49	2.00	2.00
4	$OCOCH_3$	$OCOCH_3$	5.41	2.21	1.94	1.47	2.11	1.67, 1.67	2.12	2.30	2.30	2.20	2.11	1.80	1.73
5	OH	Cl	4.23	2.29	2.09	1.46	2.07	1.67, 1.61	2.13	1.94	1.75	2.14	1.53	1.84	1.74
6	OH	Br	4.50	2.38	2.18	1.54	2.09	1.68, 1.64	2.17	2.04	1.81	2.20	1.55	1.87	1.79
7	OH	I	4.75	2.40	2.23	1.61	2.06	1.69, 1.63	2.16	2.13	1.87	2.15	1.56	1.85	1.76
8	$OCOCH_3$	Cl	5.14	2.30	2.18	1.49	2.11	1.68, 1.68	2.15	2.60	2.07	2.28	1.74	1.82	1.82
9	$OCOCH_3$	Br	5.35	2.36	2.26	1.56	2.10	1.69, 1.69	2.17	2.68	2.13	2.31	1.74	1.85	1.85
10	$OCOCH_3$	I	5.55	2.41	2.32	1.66	2.09	1.71, 1.71	2.21	2.76	2.18	2.30	1.77	1.94	1.83
11	Br	Cl	4.46	2.36	2.29	1.56	2.04	1.76, 1.74	2.06	2.59	2.41	2.78	2.11	1.94	1.84
12	I	Cl	4.54	2.36	2.36	1.65	1.92	1.83, 1.80	1.90	2.89	2.72	2.98	2.38	2.02	1.96
13	Cl	Br	4.59	2.43	2.33	1.56	2.09	1.71, 1.71	2.15	2.54	2.23	2.63	1.92	1.87	1.87
14	I	Br	4.81	2.44	2.46	1.71	1.88	1.84, 1.82	1.92	2.99	2.78	3.03	2.42	2.04	1.94
15	Cl	I	4.86	2.46	2.40	1.65	2.07	1.73, 1.73	2.20	2.55	2.31	2.61	1.96	1.92	1.81
16	Br	I	4.99	2.50	2.47	1.72	2.02	1.77, 1.77	2.17	2.80	2.55	2.80	2.19	1.96	1.87
17	F	Cl	4.28	2.34	2.15	1.48	2.19	1.67, 1.65	2.23	2.07	1.91	2.42	1.68	1.84	1.74
18	F	Br	4.46	2.41	2.25	1.53	2.19	1.67, 1.65	2.25	2.14	1.94	2.47	1.70	1.85	1.78
19	F	I	4.65	2.44	2.28	1.64	2.17	1.68, 1.66	2.30	2.16	2.01	2.46	1.71	1.85	1.79
20	CH_2OH	F	4.66	2.18	2.01	1.56	1.96	1.75, 1.65	1.92	1.63	1.53	1.89	1.30	1.85	1.65
21	CH_2OH	Cl	4.38	2.13	2.20	1.57	1.93	1.75, 1.65	1.96	1.86	1.66	1.82	1.22	1.89	1.75
22	CH_2OH	Br	4.65	2.27	2.29	1.63	1.96	1.75, 1.69	2.01	1.94	1.77	1.84	1.28	1.88	1.83
23	CH_2OH	I	4.87	2.36	2.36	1.74	1.98	1.82, 1.71	2.04	2.01	1.86	1.78	1.33	1.94	1.83
24	CH_2OH	C_6H_5	2.94	1.93	2.20	1.95	2.13	1.80, 1.76	2.09	1.85	1.61	2.12	1.42	1.90	1.90
25	CO_2H	F	4.99	2.25	2.01	1.54	2.00	1.71, 1.71	1.96	1.91	1.91	2.22	1.86	1.89	1.75
26	CO_2H	Cl	4.61	2.19	2.20	1.55	2.03	1.75, 1.69	2.01	2.05	1.99	2.34	1.84	1.93	1.89
27	CO_2H	Br	4.80	2.27	2.27	1.61	2.03	1.77, 1.69	2.04	2.11	2.03	2.38	1.87	1.95	1.93
28	CO_2H	I	4.99	2.32	2.34	1.71	2.04	1.77, 1.74	2.11	2.19	2.09	2.37	1.94	2.04	1.91
29	CO_2H	C_6H_5	2.38	2.17	1.62	1.41	2.01	1.71, 1.71	2.06	2.09	1.89	2.30	1.96	1.96	1.96

[a]Chemical shifts were determined at 360 MHz using 1.5 M solutions in $CDCl_3$ and are expressed in ppm (δ) downfield from internal $(CH_3)_4Si$.

[b]Unequivocal distinction between axial and equatorial protons was only possible for 1,2-dihaloadamantanes. For the other compounds, the chemical shift of these two protons may be interchanged (see text).

[c]Chemical shift differences between axial and equatorial H-6 are too small to permit unambiguous assignments.

Similar arguments are used to establish chemical shifts of other geminal protons. For example, in the expanded upfield portion of the COSY spectrum of 2 (Fig. 4B), the signal for H-9_{ax} (2.83 ppm), which has been assigned to H-9_{ax}, shows couplings to H-8_{ax}, H-5, H-9_{eq}, and H-6_{eq}. Again, H-8_{ax}, but not H-8_{eq}, is coupled to this proton (H-9_{ax}) *via* 4-bond W coupling. Similarly, H-9_{ax} is coupled to H-6_{eq} rather than to H-6_{ax}. The next upfield signal at 2.69 ppm, which has just been assigned to H-8_{eq}, shows couplings to H-8_{ax}, H-7, H-10_{eq}. The equatorial and not the axial H-10 has a W-relationships with H-8_{eq}. This argument can be extended to the remaining couplings which are clearly labeled in Fig. 4B.

A few comments are appropriate regards the above assignments of the ^{1}H chemical shifts of the geminal protons at C-4, C-8, C-9 and C-10. The difference in chemical shifts of the two protons attached to the γ_{syn} carbons (C-4 and C-9), is very large compared to those in protons attached to the γ_{anti} carbons (C-8 and C-10). Furthermore, the chemical shifts of the equatorial protons on C-9 and C-4 are upfield compared to those of the corresponding axial protons on these carbons. The reverse holds regarding the equatorial and axial protons on C-8 and C-10. These chemical shift characteristics were noted for corresponding protons in ^{1}H NMR spectra of 2-monosubstituted adamantanes.[27]

The above analysis was applied to other 1,2-dihaloadamantanes. The interpretation of the COSY spectra of other compounds was somewhat hampered by severe overlaps of proton signals. The distinction between H-4_{ax} *vs* H-4_{eq} and between H-9_{ax} *vs* H-9_{eq} can be made safely on the basis of large differences in their chemical shift, namely, the equatorial protons are upfield relative to the axial protons. For H-6, H-8 and H-10, chemical shift differences are too small to permit such generalizations.

Conclusions

We have applied recent 1D and 2D NMR techniques to assign ^{13}C and ^{1}H chemical shifts of some twenty-nine 1,2-disubstituted adamantanes. Particularly useful were ^{1}H-^{13}C correlations *via* long-range couplings established by means of the 1D INAPT NMR experiment. Additivities of substituent effects on ^{13}C chemical shifts in these compounds were evaluated. Intramolecular interactions between the two vicinal substituents cause interesting non-additivity effects.

Experimental Section

The synthesis of the 1,2-disubstituted adamantanes used in this study was described in the preceding paper. ^{1}H and ^{13}C NMR spectra were recorded on a Nicolet NIC-360 NB spectrometer equipped with a 293C programmable pulser and a 1180 data system and operating at 361.075 MHz for ^{1}H and 90.79 MHz for ^{13}C. Chemical shifts are reported in parts per million (δ) downfield from internal $(CH_3)_4Si$. Approximately 1.5 M solutions in $CDCl_3$ were used.

The 90° ^{13}C pulse lengths for 5 and 12 mm probes were 9 and 22 μs, respectively. The 90° ^{1}H pulse length from the decoupler channel were 40 and 85 μs. The decoupler hard pulses were calibrated as described by Bax,[28] using benzene with $Cr(acac)_3$. The decoupler soft pulses were calibrated by the same method but using a sample of acetic acid in C_6D_6. The splitting of the carbonyl signal [$^2J(CO,CH_3)$ = 6.7 Hz] was utilized for calibration.

INAPT spectra were obtained using the pulse sequence described by Bax *et al.*[7,8] The fixed delays (Δ_1 and Δ_2) used in the pulse sequence were set to 100 ms. The proton 90° soft pulse length was set to 10 ms which corresponds to $\gamma H_2/2\pi$ = 25 Hz. An 8-step phase cycle was used consisting of inversion of the last 90° proton pulse and the receiver phases, together with the conventional CYCLOPS.[29]

Heteronuclear shift correlated spectra were obtained using the pulse sequence described by Bax and Morris,[24b] with a mixing delay of 3.9 ms and a refocusing delay of 2.4 ms; the relaxation delay was 1 s. An 8-step phase cycle was employed consisting of the basic 4-step cycle,[24b] together with simultaneous inversion of the phases of the first proton pulse and the 180 carbon pulse. The initial data matrix consisted of 256 x 2048 points and was zero-filled in F_1 to 512 x 2048 points. For each t_1 increment, 32 scans were averaged. Gaussian line broadening and shifted sine-bell functions were used in the F_2 and F_1 respectively. The spectra were displayed in the absolute value mode.

Homonuclear shift-correlated (COSY) spectra were obtained using Jeener's 2-pulse sequence,[26] with a 16 step phase cycle selecting N-type cross peaks.[30] A read pulse of 90° and a relaxation delay of 1 s were used. Data matrices typically were 512 x 1024 points. Sine-bell function was used in both dimensions. The spectra were displayed in the absolute value mode and symmetrized.[31]

Acknowledgements

This paper represents contribution No. 1764 to the U.S. Army Drug Development Program. We thank the U.S. Army Research and Development Command (contract DAMD-17-79-C-9146), for generous support of this project. The use of the NMR facilities of the Research Resources Center, University of Illinois at Chicago, is gratefully acknowledged.

References and Notes

(1) Abstracted from the Ph.D. Dissertation (A.N.A.-S.), University of Illinois at Chicago, August, 1986.
(2) (a) Bax, A. In Two-Dimensional Nuclear Magnetic Resonance in Liquids; Reidel: Boston, 1982. (b) Benn, R.; Gunther, H. Angew. Chem., Int. Ed. Engl. **1983**, 22, 350. (c) Bax, A. In Topics in Carbon-13 NMR Spectroscopy; Levy, G.C., Ed.; Wiley Interscience: New York, 1984; Vol. 4, p 197. (d) Morris, G.A. In Topics in Carbon-13 NMR Spectroscopy; Levy, G.C., Ed.; Wiley Interscience: New York, 1984; Vol. 4, p 179. (e) Turner, C.J. Prog. NMR Spectrosc. **1984**, 16, 311. (f) Turner, D.L. Prog. NMR Spectrosc. **1985**, 17, 281. (g) Morris, G.A. Magn. Reson. Chem. **1986**, 24, 371. (h) Bax, A.; Lerner, L. Science **1986**, 232, 960.
(3) Patt, S.L.; Shoolery, J.N. J. Magn. Reson. **1982**, 46, 535.
(4) (a) Morris, G.A.; Freeman, R.R. J. Am. Chem. Soc. **1979**, 101, 760. (b) Doddrell, D.M.; Pegg, D.T. J. Am. Chem. Soc. **1980**, 102, 6388. (c) Burum, D.P.; Ernst, R.R. J. Magn. Reson. **1980**, 39, 163.
(5) (a) Pegg, D.T.; Doddrell, D.M.; Bendall, M.R. J. Chem. Phys. **1982**, 77, 2745. (b) Doddrell, D.M.; Pegg, D.T.; Bendall, M.R. J. Magn. Reson. **1982**, 48, 323. (c) Bendall, M.R.; Pegg, D.T. J. Magn. Reson. **1983**, 53, 272.
(6) (a) Bildose, H.; Donstrup, S.; Jakobsen, H.; Sorensen, O.W. J. Magn. Reson. **1983**, 53, 154. (b) Sorenson, O.W.; Donstrup, S.; Bildose, H.; Jakobsen, H.J. J. Magn. Reson. **1983**, 55, 347. (c) Sorensen, O.W. J. Magn. Reson. **1984**, 57, 506.
(7) Bax, A. J. Magn. Reson. **1984**, 57, 314.
(8) Bax, A.; Ferretti, J.A.; Nashed, N.; Jerina, D.M. J. Org. Chem. **1985**, 50, 3029.
(9) (a) Hansen, P.E. Prog. NMR Spectrosc. **1981**, 14, 175. (b) Marshall, J.L. In Methods in Stereochemical Analysis; Marchand, A.P., Ed.; Verlag-Chemie: New York, 1983; Vol. 2.
(10) In fact, the following coupling constants were measured using the pulse sequence described by Bax and Freeman (ref. 11): ^{3}J(H-2,C-4) = 5.6 Hz; ^{3}J(H-2,C-9) = 4.9 Hz; ^{3}J(H-2,C-8) = 1.3 Hz; ^{3}J(H-2,C-10) = 1.5 Hz.
(11) Bax, A.; Freeman, R. J. Am. Chem. Soc. **1982**, 104, 1099.
(12) Pehk, T.; Lippmaa, E.; Sevostjanova, V.V.; Krayuschkin, M.M.; Tarasova, A.I. Org. Magn. Reson. **1971**, 3, 783.
(13) Maciel, G.E.; Dorn, H.C.; Greene, R.L.; Kleschick, W.A.; Peterson, M.R.; Wahl, G.H. Org. Magn. Reson. **1974**, 6, 178.
(14) Abdel-Sayed, A.N.; Bauer, L., Presented during the 190th Annual Meeting of the American Chemical Society, Chicago, Illinois, September, 1985.
(15) (a) Bax, A.; Freeman, R.; Frenkiel, T.A. J. Am. Chem. Soc. **1981**, 103, 2102. (b) Bax, A.; Freeman, R.; Frenkiel, T.A.; Levitt, M.H. J. Magn. Reson. **1981**, 43, 478. (c) Mareci, T.H.; Freeman, R. J. Magn. Reson. **1982**, 48, 158.
(16) Kessler, H.; Griesinger, C.; Zarbock, J.; Loosli, H.R. J. Magn. Reson. **1984**, 57, 331.
(17) Adamantane shows two signals in the ^{13}C NMR spectrum (90 MHz, in $CDCl_3$ at 20 °C): the bridgehead carbons' signal (28.40 ppm), and the bridge carbons' signal (37.79 ppm).
(18) (a) Duddeck, H. Org. Magn. Reson. **1975**, 7, 151. (b) Duddeck, H.; Wolff, P. Org. Magn. Reson. **1977**, 9, 528. (c) Duddeck, H. Tetrahedron **1978**, 34, 247. (d) Duddeck, H.; Feuerhelm, H.-T. Tetrahedron **1980**, 36, 3009. (e) Duddeck, H. Tetrahedron **1983**, 39, 1365. (f) Duddeck, H.; Islam, R.M. Chem. Ber. **1984**, 117, 554.
(19) Majerski, Z.; Vinkovic, V.; Meic, Z. Org. Magn. Reson. **1981**, 17, 168.
(20) For historical background see Ref. 22 and 23.
(21) (a) Duddeck, H.; Dietrich, W. Tetrahedron Lett. **1975**, 2925. (b) Gerhards, R.; Dietrich, W.; Bergmann, G.; Duddeck, H. J. Magn. Reson. 1979, [illegible] (c) Duddeck, H.; Islma, R.M. Org. Magn. Reson. **1983**, 21, 140.
(22) (a) Abdel-Sayed, A.N.; Bauer, L. Tetrahedron Lett. **1985**, 26, 2841. (b) Abdel-Sayed, A.N.; Bauer, L. Tetrahedron Lett. **1986**, 27, 1003.
(23) (a) Srivastava, S.; Cheung, C.K.; le Noble, W.J. Magn. Reson. Chem. **1985**, 23, 232. (b) Duddeck, H.; Kaiser, M.; Rosenbaum, D. Tetrahedron Lett. **1986**, 27, 473.
(24) (a) Maudsley, A.A.; Muller, L.; Ernst, R.R. J. Magn. Reson. **1977**, 28, 463. (b) Bax, A.; Morris, G.A. J. Magn. Reson. **1981**, 42, 501.
(25) The designations, "axial" and "equatorial", are made for H-4, H-8, H-9, and H-10 with respect to the cyclohexane subunit containing the C-2 substituent. For H-6, the designations are made with respect to the cyclohexane subunit containing the C-1 substituent.
(26) (a) Bax, A.; Freeman, R. J. Magn. Reson. **1981**, 44, 542. (b) Bax, A.; Freeman, R.; Morris, G.A. J. Magn. Reson. **1981**, 42, 164.
(27) (a) Abraham, R.J.; Fisher, J. Magn. Reson. Chem. **1985**, 23, 862. (b) van Deursen, F.W.; Korver, P.K. Tetrahedron Lett. **1967**, 3923.
(28) Bax, A. J. Magn. Reson. **1983**, 52, 76.
(29) Hoult, D.I.; Richard, R.E. Proc. Roy. Soc. London, Ser. A **1975**, 344, 311.
(30) Wider, G.; Macura, S.; Kumar, A.; Ernst, R.R.; Wuthrich, K. J. Magn. Reson. **1984**, 56, 207.
(31) Baumann, R.; Wider, G.; Ernst, R.R.; Wuthrich, K. J. Magn. Reson. **1981**, 44, 402.