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Study of Substituent Effects on One-Bond ^{13}C–^{13}C NMR Coupling Constants in Adamantane Derivatives

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One-bond ^{13}C–^{13}C coupling constants in a series of substituted adamantanes were measured by natural-abundance ^{13}C NMR spectroscopy using the INADEQUATE pulse sequence technique. The substituent effects on the ^{13}C–^{13}C coupling constants have been qualitatively analyzed. It is shown that the C_α–C_β and the C_β–$C_{\gamma_{anti}}$ coupling constants are sensitive to the electronegativity of the substituent while the C_β–$C_{\gamma_{syn}}$ coupling constant is dependent on the bulkiness of the heteroatom (in the substituent) containing lone-pair electrons. ^{13}C–^{13}C coupling constants together with ^{13}C–^{1}H coupling constants can be a valuable tool in ^{13}C NMR peak assignments.

Introduction

Carbon-13 nuclear magnetic resonance is now generally recognized as one of the most useful spectroscopic techniques available for stereochemical assignment and elucidation of structure of complex molecules. Application of ^{13}C NMR spectroscopy has been, in general, focused on the ^{13}C chemical shift (δ_C) or on ^{13}C–^{1}H coupling constants ($J_{C\text{-}H}$). These applications are, for the most part, based on empirical correlations of ^{13}C shieldings or $J_{C\text{-}H}$ values and molecular geometry.[1-3] Empirical correlations of substituent effects on ^{13}C chemical shifts (SCS) have also been studied in recent years.[4]

Recent advances in instrumentation and the availability of high-field NMR spectrometers have greatly increased the scope and the utility of ^{13}C–^{13}C coupling constants in structural and conformational studies. Since the Fermi contact contribution may be expected to dominate one-bond ^{13}C–^{13}C interactions,[5] in which case the coupling constants should reflect the hybridization state of the bonding orbitals, initial efforts were made in different laboratories, notably by Frei and Bernstein,[7] to obtain the necessary data using doubly labeled material.[6-8] The limited number of examples of one-bond ^{13}C–^{13}C coupling constants of each of the six combinations of hybridized carbons (sp^3–sp^3, sp^3–sp^2, sp^3–sp, sp^2–sp^2, sp^2–sp, and sp–sp) led to the conclusion that J_{CC} values are approximately correlated to the s character of the orbitals making up the bond. The major limitation of these studies was the difficulty of obtaining a wider variety of doubly labeled compounds.

The observation of carbon–carbon couplings requires the presence of two carbon-13 isotopes, and at natural abundance there is approximately one such molecule out of 10^4. Thus, the basic problem in observing ^{13}C–^{13}C coupling constants in NMR spectra of compounds with natural-abundance ^{13}C is that of identifying the appropriate weak satellite signals on the sides of strong ^{13}C lines. The limit is set not so much by the sensitivity or dynamic range of the NMR spectrometer but rather by the presence of a multitude of other weak lines from spinning sidebands, from incomplete proton decoupling, or simply from small amounts of impurities.

In order to improve the technique of observation of ^{13}C–^{13}C coupling constants at natural abundance, recently, Freeman et al[9] proposed a new approach. This enables one to investigate one-bond and long-range carbon–carbon couplings by suppressing the strong signals from molecules with a single ^{13}C nucleus. Spinning sidebands and signals due to small amounts of impurities are also eliminated. Excellent suppression ratios were achieved by momentary conversion of the magnetization from coupled spins into double quantum coherence[10,11] and then conversion into

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Table I. ^{13}C Chemical Shifts and Carbon-Hydrogen Coupling Constants in 1-Substituted Adamantanes (2)[a]

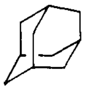
compd	δ_{C_1}	δ_{C_2}	δ_{C_3}	δ_{C_4}	other
2a	28.4 (131.6)	37.7 (126.7)	28.4 (131.6)	37.7 (126.7)	
2b	71.1	45.9 (127.6)	30.8 (130.3)	36.1 (126.6)	$\delta_{Si\text{-}CH_3}$ = 2.8 (117.8)
2c[b]	92.2	42.7 (126.0)	31.5 (136.5)	35.9 (127.5)	
2d	68.1	45.2 (127.1)	30.6 (132.1)	36.0 (125.5)	
2e[c]	52.4	40.0 (133.2)	28.9 (133.4)	35.1 (127.9)	
2f	46.6	45.5 (126.5)	29.2 (132.6)	35.7 (126.6)	
2g	68.2	47.4 (131.8)	31.5 (133.3)	35.4 (127.5)	
2h	66.4	49.2 (131.6)	32.4 (132.8)	35.4 (126.5)	
2i	50.5	52.2 (132.3)	32.8 (133.6)	35.4 (127.2)	
2j	84.5	40.6 (129.1)	29.5 (131.8)	35.3 (129.1)	
2k	29.8	44.7 (127.9)	28.9 (129.4)	37.0 (127.5)	δ_{CH_3} = 31.5 (124.8)
2l	36.1	43.1 (124.0)	29.0 (132.7)	36.8 (126.2)	δ_i = 151.1; δ_o = 124.7 (155.4) δ_m = 128.0 (158.4); δ_p = 125.4 (159.7)
2m	45.5	37.4 (128.5)	27.2 (133.3)	35.8 (126.6)	δ_{CO} = 212.1; δ_{CH_3} = 23.2 (127.1)
2n	40.4	38.4 (128.2)	27.8 (133.0)	36.3 (124.7)	δ_{COOH} = 184.7
2p	29.5	39.2 (130.6)	26.4 (135.3)	35.0 (127.7)	δ_{CN} = 124.3

[a] The chemical shifts are in ppm with respect to external Me_4Si and are accurate to ±0.1 ppm; the $J_{C\text{-}H}$ values are listed in parentheses and are in Hz with an accuracy of ±1.0 Hz; all parameters are measured in $CDCl_3$ at 20 °C unless otherwise stated. [b] $^1J_{C_1\text{-}F}$ = 183.4 Hz; $^2J_{C_2\text{-}F}$ = 17.0 Hz; $^3J_{C_3\text{-}F}$ = 9.9 Hz; $^4J_{C_4\text{-}F}$ = 2.1 Hz. [c] In D_2O.

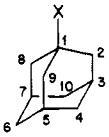
detectable transverse magnetization by means of a radiofrequency pulse. The unwanted conventional signals are filtered out by exploiting the unique phase properties of the double quantum signals.[11,12] Because of the low natural abundance of ^{13}C the spectra are always of the AB or AX type, and the theory is correspondingly simple. It has been shown that the main restriction on the generality of this technique arises from the condition for optimum transfer into double quantum coherence: $\tau = (2n + 1)/4J_{CC}$ (n = 0, 1, 2, ...), where τ is the delay in the INADEQUATE (Incredible Natural Abundance DoublE QUAntum Transfer Experiment) pulse sequence[9]–$90°(x)$–τ–$180°(\pm y)$–τ–$90°(x)$–Δ–$90°(\phi)$–acq (ψ). (See Experimental Section for details).

Although substituent effects on J_{CC} values have been studied[13-15] to some extent, mostly by using ^{13}C-labeled materials, studies of stereochemical effects on J_{CC} values[16,17] have not yet been explored.[18,19] The development of the INADEQUATE pulse sequence by Freeman et al.[9] to measure ^{13}C–^{13}C coupling constants in natural-abundance ^{13}C NMR spectra seems to open up a new avenue to study substituent and stereochemical effects on J_{CC} in a wide variety of compounds. The most suitable model compounds for such investigations are those having rigid frameworks with well-defined geometries, such as adamantane derivatives. Recently, Duddeck et al.[20] have studied the substituent effects on the ^{13}C chemical shifts of substituted adamantanes, diamantanes, and triamantanes. Interested in the study of adamantanoid hydrocarbons, we undertook a study of substituent effects on ^{13}C–^{13}C coupling constants and measured one-bond ^{13}C–^{13}C coupling constants, using the INADEQUATE pulse sequence technique, in a variety of 1- and 2-substituted adamantanes and 2,2-disubstituted adamantanes.

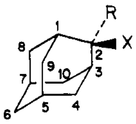
Chart I



1



2



3, R = H
4, R = CH_3
5, R = Ph

a, X = H
b, X = Me_3SiO
c, X = F
d, X = OH
e, X = NH_3^+
f, X = NH_3
g, X = Cl
h, X = Br
i, X = I
j, X = NO_2
k, X = CH_3
l, X = Ph
m, X = $COCH_3$
n, X = COOH
p, X = CN
q, X = 2-Ad (2-adamantyl)

Results and Discussion

The ^{13}C NMR parameters [^{13}C chemical shifts (δ_C), carbon–hydrogen coupling constants ($J_{C\text{-}H}$), and one-bond carbon–carbon coupling constants (J_{CC})] in a series of 1-substituted adamantanes (**2**), 2-substituted adamantanes (**3**), and 2-substituted-2-methyl- and 2-substituted-2-phenyladamantanes (**4** and **5**) were measured along with those of adamantane (**1**), the parent hydrocarbon (Chart I). The chemical shifts of most of the monosubstituted adamantanes have been published earlier.[20-26] However, for comparison, all the ^{13}C NMR chemical shifts and carbon–hydrogen coupling constants values of the adamantane derivatives studied in this work are listed in Tables I–III. All our chemical shifts values are within 1 ppm of the reported values. The assignment of the chemical shifts was straightforward and follows those already published.[20-23] However, the peak assignments of **4h** and **5h** are based on the ^{13}C–^{13}C coupling constants (vide infra).

1-Substituted Adamantanes. The one-bond ^{13}C–^{13}C coupling constant in adamantane (**1**) and the C_1–C_2, C_2–C_3, and C_3–C_4 coupling constants in 1-substituted adaman-

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Table II. ^{13}C Chemical Shifts and Carbon–Hydrogen Coupling Constants in 2-Substituted Adamantanes (3)^a

compd	$\delta_{C_1} = \delta_{C_3}$	δ_{C_2}	$\delta_{C_4} = \delta_{C_9}$	$\delta_{C_8} = \delta_{C_{10}}$	δ_{C_5}*	δ_{C_7}*	δ_{C_6}	other
3a	28.4 (131.6)	37.7 (126.7)	37.7 (126.7)	37.7 (126.7)	28.4 (131.6)	28.4 (131.6)	37.7 (126.7)	
3b	35.3 (130.5)	74.9 (141.5)	31.2 (127.8)^d	36.6 (126.0)^d	27.7 (131.4)^d	27.2 (131.4)^d	37.8 (125.3)	$\delta_{Si\text{-}CH_3}$ = 0.3 (118.0)
3c^b	32.7 (127.2)	95.3 (146.0)	31.3 (128.7)	35.6 (126.4)	27.2 (132.5)	26.8 (131.8)	37.1 (125.2)	
3d	34.7 (127.4)	74.7 (146.9)	31.2 (127.4)	36.7 (125.7)	27.8 (131.4)	27.3 (131.4)	37.8 (123.3)	
3e^c	29.9 (136.0)	54.7 (148.0)	29.5 (128.0)^d	36.2 (128.0)^d	26.4 (132.0)^d	26.3 (132.0)^d	36.9 (126.0)^d	
3f	34.8 (131.3)	55.1 (133.2)	30.4 (126.4)	37.4 (128.4)	27.4 (130.0)	27.0 (132.2)	37.6 (128.5)	
3g	35.6 (135.5)	67.6 (150.0)	30.7 (127.5)	37.8 (127.4)	27.3 (134.4)	26.7 (130.1)	37.4 (131.4)	
3h	36.1 (136.6)	62.9 (152.5)	31.3 (127.5)	38.3 (128.1)	27.3 (132.4)	26.6 (134.7)^d	37.5 (130.2)^d	
3k	33.6 (131.4)	38.9 (123.4)	31.1 (127.2)	39.3 (128.1)	28.3 (134.4)	28.0 (132.8)	38.4 (125.4)	δ_{CH_3} = 18.7 (123.1)
3l	30.9 (132.0)	46.6 (123.2)	31.8 (127.8)	39.0 (127.7)	28.0 (132.5)	27.8 (132.5)	37.8 (127.5)	δ_i = 143.9 δ_o = 126.5 (154.3) δ_m = 127.9 (158.2) δ_p = 125.0 (164.1)
3q	28.1 (127.7)	42.5 (126.5)	31.7 (125.2)	39.7 (126.7)	28.3 (132.7)^d	28.0 (132.7)^d	38.5 (123.8)	

^{a} The chemical shifts are in ppm with respect to external Me$_4$Si and are accurate to ±0.1 ppm; the $J_{C\text{-}H}$ values listed in parentheses are in Hz and are accurate to ±1.0 Hz; all parameters are measured in CDCl$_3$ at 20 °C unless otherwise stated. Parameters marked by * may be interchanged. ^{b} $^1J_{C_2\text{-}F}$ = 178.8 Hz; $^2J_{C_2\text{-}F}$ = 17.7 Hz; $^3J_{C_8\text{-}F}$ = 9.2 Hz; $^4J_{C_7\text{-}F}$ = 1.5 Hz; $^3J_{C_4\text{-}F}$, $^4J_{C_5\text{-}F}$ and $^5J_{C_6\text{-}F}$ are less than 1.0 Hz. ^{c} In Me$_2$SO-d_6. ^{d} These $J_{C\text{-}H}$ values are with only ±3 Hz accuracy due to overlap of peaks.

Table III. ^{13}C Chemical Shifts and Carbon–Hydrogen Coupling Constants in 2-Methyl-2-adamantyl (4) and 2-Phenyl-2-adamantyl (5) Derivatives^a

compd	$\delta_{C_1} = \delta_{C_3}$	δ_{C_2}	$\delta_{C_4} = \delta_{C_9}$	$\delta_{C_8} = \delta_{C_{10}}$	δ_{C_5}*	δ_{C_7}*	δ_{C_6}	δ_{CH_3} or δ_{C_i}^{b}	δ_{C_o}	δ_{C_m}	δ_{C_p}	other
4a	33.6 (131.4)	38.9	39.3 (128.1)	31.1 (127.2)	28.0 (132.8)	28.3 (134.4)	38.4 (125.4)	18.7 (123.1)				
4b	39.8 (130.3)	77.3	33.3 (129.4)	34.9 (128.0)	27.3 (132.4)	27.6 (132.4)	38.6 (126.0)^d	26.8 (124.5)				$\delta_{Si\text{-}CH_3}$ = 2.5 (117.9)
4d	38.9 (133.6)	73.7	32.8 (127.5)^d	35.0 (130.1)	26.9 (131.8)	27.4 (131.8)	38.2 (126.5)^d	29.3 (124.9)				
4g	40.7 (134.8)	79.9	34.1 (124.2)	34.7 (127.0)	26.9 (134.8)	27.1 (134.8)	38.7 (126.9)	30.3 (127.0)				
4h	41.8 (135.0)	82.1	35.7 (128.2)	34.3 (128.1)	27.0 (133.1)	27.1 (133.1)	39.1 (123.9)	32.5 (127.9)				
5a	30.9 (132.0)	46.6	39.0 (127.7)	31.8 (127.8)	27.8 (132.5)	28.0 (132.5)	37.8 (128.9)	143.9	126.5 (154.3)	127.9 (158.2)	125.0 (164.1)	
5b	36.0 (136.0)	77.9	33.1 (128.5)	34.4 (128.5)	27.0 (132.4)	27.4 (132.8)	37.8 (127.0)	143.6	126.4 (156.3)	128.1 (159.6)	126.9 (159.8)	$\delta_{Si\text{-}CH_3}$ = 2.2 (118.3)
5d	35.2 (129.8)	75.3	32.6 (128.0)	34.5 (126.7)	26.7 (131.2)	27.2 (132.7)	37.4 (127.2)^d	144.9	126.2 (156.3)	128.3 (159.7)	126.8 (160.2)	
5g	36.9 (135.5)	79.1	33.6 (128.0)	34.7 (128.9)	26.6 (133.0)	26.9 (132.8)	37.9 (124.4)	143.8	124.8 (156.7)	128.5 (160.2)	127.2 (160.6)	
5h	37.8 (135.8)	79.9	35.0 (129.9)	34.5 (128.6)	26.7 (133.4)	27.1 (131.0)	38.3 (127.7)	144.8	124.5 (157.1)	128.4 (160.7)	127.0 (161.1)	

^{a} The chemical shifts are in ppm with respect to external Me$_4$Si and are accurate to ±0.1 ppm; the J_{CH} values listed in parentheses are in Hz and are accurate to ±1.0 Hz; all parameters are measured in CDCl$_3$ at 20 °C. Parameters marked by * may be interchanged. ^{b} δ_{CH_3} for **4a,b,d,g,h**; δ_{C_i} for **5a,b,d,g,h**.

Table IV. One-Bond $^{13}C-^{13}C$ Coupling Constants in 1-Substituted Adamantanes (**2**)[a]

compd	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	other
2a	31.6	31.6	31.6	
2b	35.4	30.2	31.7	
2c	35.7	*b*	31.3	
2d	34.9	30.5	31.6	
2e[c]	33.3	31.2	31.6	
2f	33.8	30.8	31.5	
2g	33.3	29.5	31.7	
2h	32.7	28.9	31.7	
2i	32.3	28.6	31.7	
2j	33.6	30.7	31.7	
2k	31.9	31.7	31.6	$J_{C_1-CH_3} = 37.0$
2l	31.9	31.6	31.7	$J_{C_1-C_i} = 44.6; J_{C_i-C_o} = 57.6$ $J_{C_o-C_m} = 55.6; J_{C_m-C_p} = 55.3$
2m	31.5	31.6	31.7	$J_{CO-C_1} = 41.1; J_{CO-CH_3} = 39.6$
2n	31.3	31.8	31.4	$J_{CO-C_1} = 56.7$
2p	31.5	31.4	31.5	$J_{CN-C_1} = 57.3$

[a] All coupling constants are in Hz and within ±0.1 Hz in $CDCl_3$ at 20 °C unless otherwise stated. [b] Could not be measured accurately. [c] In D_2O.

Table V. Comparison of $J_{C_\alpha-C_\beta}$ Values in 1-Adamantyl and *t*-Bu Derivatives with J_{C-H} in the Corresponding Methyl Derivatives

X	$J_{1,2}$ in 1-Ad-X, Hz	J_{C-CH_3} in *t*-BuX, Hz	J_{C-H} in CH_3X,[a] Hz
H	31.6	34.7	
OH	34.9	39.2	142
NH_2	33.8	38.1	133
Cl	33.3	37.9	150
Br	32.7	37.4	152
I	32.3	37.0	152
Ph	31.9	35.4	125
CH_3	31.9	35.4	126

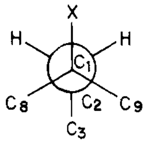
[a] References 1 and 25.

tanes (**2**) are listed in Table IV.

The C_1-C_2 ($C_\alpha-C_\beta$) coupling constant ($J_{1,2}$) decreases in the order F > Me_3SiO > OH > NH_2 > NH_3^+ > Cl > Br > I. Substitution of the C_1–H hydrogen with acetyl, carboxyl, cyano, or methyl groups does not have an appreciable effect on the $J_{1,2}$ values. The substituent effect observed on the $J_{1,2}$ values is roughly in direct correlation with the inductive electron-withdrawing ability (or electronegativity) of the substituent. For example, in 1-fluoroadamantane (**2c**), with the most electron-withdrawing substituent, the $C_\alpha-C_\beta$ coupling constant is 35.7 Hz (4.1 Hz higher than that in adamantane), whereas in 1-iodoadamantane the value is 32.3 Hz (only 0.7 Hz higher than that in adamantane).

In order to compare the observed substituent effect on the $J_{1,2}$ values with another similar system, we also measured the J_{C-CH_3} values in a series *tert*-butyl derivatives. In Table V the $C_\alpha-C_\beta$ coupling constants ($J_{1,2}$) in 1-substituted adamantanes are compared with those in the corresponding *tert*-butyl derivatives. Grant and Litchman[14] have earlier reported J_{C-CH_3} values for a set of *tert*-butyl derivatives (measured from the ^{13}C satellite in natural-abundance ^{13}C spectra) and compared these values with J_{C-H} values in the corresponding methyl derivatives. They have also shown that both of the coupling constants increase in a directly proportional manner and thus concluded that the important coupling mechanism must be similar in both instances. It must be noted that the $^{13}C-^{13}C$ coupling constant measured in our study does not compare with that of Grant and Litchman. However, the trend exhibited by the J_{C-CH_3} values in *tert*-butyl derivatives (as measured in the present study) compare very well with the trend in $J_{1,2}$ values of 1-substituted adamantanes, indicating that the substituent effects on the $C_\alpha-C_\beta$ values in both these systems are similar. Moreover, the trend in the J_{C-CH_3} values in *tert*-butyl derivatives and the $J_{1,2}$ values in 1-substituted adamantanes also compare very well with the corresponding values in 2-substituted adamantanes (vide infra). Also, a comparison of the $J_{C_\alpha-C_\beta}$ values in either 1-substituted adamantanes or *tert*-butyl derivatives with the J_{C-H} values of the corresponding methyl derivatives[1,27] (Table V) indicate that the substituent effects on the $J_{C_\alpha-H}$ and $J_{C_\alpha-C_\beta}$ values are opposite. This reverse trend between J_{CC} and J_{CH}, and the error in the J_{CC} values of Grant and Litchman, has also been pointed out by Summerhays and Maciel.[28]

The $C_\beta-C_\gamma$ (C_2-C_3) coupling constants ($J_{2,3}$) in 1-substituted adamantanes follow the trend NH_3^+ > NH_2 > NO_2 > OH > Me_3SiO > Cl > Br > I. Again, cyano, acetyl, carboxyl, and methyl substituents introduce no significant change in the $C_\beta-C_\gamma$ coupling constant. In a Newman projection formula through C_1-C_2 the bond, the substituent X is antiperiplanar to the C_2-C_3 bond. Interestingly, if the chemical shifts of the C_3 ($C_{\gamma_{anti}}$) carbon in 1-substituted adamantanes are compared with the $J_{C_2-C_3}$ values (Table VII), one observes a trend (in opposite direction) in the substituent effect on the C_γ chemical shift and on the $C_\beta-C_\gamma$ coupling constant. Several alternative explanations have been proposed[20,21,29,30] for the γ_{anti} substituent effect on the ^{13}C chemical shift. Thus, one might argue that the factors responsible for the γ_{anti} substituent effect on the chemical shift are also responsible for the substituent effect on the $C_\beta-C_{\gamma_{anti}}$ coupling constant in 1-adamantyl derivatives. However, such a comparison may be misleading. The substituent effect on $C_\beta-C_{\gamma_{anti}}$ coupling constants in 1-substituted adamantanes will be further discussed with that in 2-substituted adamantanes.



The substituents have very little effect on the $C_\gamma-C_\delta$ coupling constants ($J_{3,4}$).

2-Substituted Adamantanes. The one-bond $^{13}C-^{13}C$ coupling constants in a series of 2-substituted adamantanes (**3**) are listed in Table VI.

The C_1-C_2 coupling constants in 2-substituted adamantanes follow the same trend as those in 1-substituted adamantanes (and as those reported for isopropyl derivatives[18]), roughly in direct correlation with the inductive electron-withdrawing ability of the substituent. Moreover, a comparison of the $J_{C_1-C_2}$ values with the J_{C_2-H} values (Table VIII) also shows the reverse trend. This observation is in line with the trend observed between the $J_{C_1-C_2}$ of 1-substituted adamantanes and J_{C-H} of the corresponding methyl derivatives, showing again that the substituent effects on $J_{C_\alpha-H}$ and $J_{C_\alpha-C_\beta}$ are opposite. It must be noted that the $J_{C_1-C_2}$ (and the other one-bond $^{13}C-^{13}C$ coupling constants) in 2,2′-biadamantane (**3q**) is essentially the same as that in adamantane, indicating no apparent steric effect on the J_{CC} values.

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Table VI. One-Bond ^{13}C-^{13}C Coupling Constants in 2-Substituted Adamantanes[a]

compd	$J_{1,2}$	$J_{1,8} = J_{3,10}$	$J_{1,9} = J_{3,4}$	$J_{4,5} = J_{5,9}$	$J_{7,8} = J_{7,10}$	$J_{5,6}$*	$J_{6,7}$*	other
3a	31.6	31.6	31.6	31.6	31.6	31.6	31.6	
3b	35.5	30.5	32.3	31.6	31.7	31.4	31.4	
3c	35.4	30.3	31.8	31.5	31.6	31.7	31.6	
3d	34.5	30.6	32.0	31.6	31.7	31.4	31.4	
3e[c]	33.4	31.1	31.7	31.4	31.6	31.5	31.7	
3f	33.0	31.0	32.0	31.4	31.4	31.6	31.5	
3g	32.7	29.8	32.7	31.5	31.6	31.6	31.5	
3h	32.2	29.2	32.8	31.3	31.7	31.4	31.4	
3k	31.8	31.3	31.7	31.5	31.7	31.5	31.6	$J_{C_2,CH_3} = 35.4$
3l	32.1	31.7	31.8	31.6	31.6	31.6	31.6	$J_{2,i} = 43.1; J_{o,i} = 57.6; J_{m,p} = 55.7$
3q	31.8	31.6	31.6	31.6	31.7	31.5	31.6	

[a] All coupling constants are in Hz and within ±0.1 Hz in $CDCl_3$ at 20 °C unless otherwise stated. Parameters marked by * may be interchanged. [b] In Me_2SO-d_6.

Table VII. Comparison of $C_{\gamma_{anti}}$ Chemical Shifts and C_β-$C_{\gamma_{anti}}$ Coupling Constants in 1- and 2-Substituted Adamantanes[a]

compd	δ_{C_3}, ppm	$J_{C_2-C_3}$, Hz	compd	$\delta_{C_8} = \delta_{C_{10}}$, ppm	$J_{C_1-C_8} = J_{C_3-C_{10}}$, Hz
2a	28.4	31.6	3a	37.7	31.6
2e	28.9 (+0.4)	31.2 (−0.4)	3e	36.2 (−1.5)	31.1 (−0.5)
2f	29.2 (+0.8)	30.8 (−0.8)	3f	37.4 (−0.3)	31.0 (−0.6)
2j	29.5 (+1.1)	30.7 (−0.9)			
2d	30.6 (+2.2)	30.5 (−1.1)	3d	36.7 (−1.0)	30.6 (−1.0)
2b	30.8 (+2.4)	30.2 (−1.4)	3b	36.6 (−1.1)	30.5 (−1.1)
			3c	35.6 (−2.1)	30.3 (−1.3)
2g	31.5 (+3.1)	29.5 (−2.1)	3g	37.8 (+0.1)	29.8 (−1.8)
2h	32.4 (+4.0)	28.9 (−2.7)	3h	38.3 (+0.6)	29.2 (−2.4)

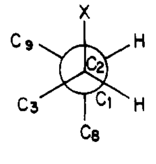
[a] Values in parentheses are the difference between the substituted adamantanes and the parent hydrocarbon.

Table VIII. Comparison of $J_{C_2-C_1}$ and J_{C_2-H} in 2-Substituted Adamantanes

compd (2-Ad-X)	X	$J_{C_2-C_1}$, Hz	J_{C_2-H}, Hz
3a	H	31.6	126.7
3b	$OSiMe_3$	35.5	141.5
3c	F	35.4	146.0
3d	OH	34.5	146.9
3e	NH_3^+	33.4	148.0
3f	NH_2	33.0	133.2
3g	Cl	32.7	150.0
3h	Br	32.2	152.5

The $J_{C_1-C_8}$ coupling constants in 2-substituted adamantanes, again, follow the same trend as the $J_{C_2-C_3}$ coupling constants (their geometrical counterpart) in 1-substituted adamantanes, indicating that the factors responsible for the substituent effect on C_β–$C_{\gamma_{anti}}$ coupling constants are the same in 1- and 2-substituted adamantanes. As has been pointed out earlier, a good correlation is observed in the substituent effects on the γ_{anti}-carbon chemical shift and the C_β–$C_{\gamma_{anti}}$ coupling constants in the 1-adamantyl system (Table VII). Almost all polar substituents cause deshielding of the γ_{anti}-carbon atom and decrease the C_β–$C_{\gamma_{anti}}$ coupling constants. However, in 2-substituted adamantanes, whereas all the polar substituents decrease the C_β–$C_{\gamma_{anti}}$ coupling constants (similar to those observed in 1-adamantyl system), only chlorine and bromine deshielded the γ_{anti} carbon. Fluorine, nitrogen, and oxygen atoms cause an upfield shift in the γ_{anti}-carbon chemical shift (Table VII). Eliel et al.[30] have indeed shown that, in general, a carbon atom situated γ_{anti} to a second-row heteroatom (F, N, or O) experiences an upfield shift and the only exception to the γ_{anti} shielding effect occurred in systems having the heteroatom attached to a bridgehead carbon.[31] Since the substituent effect on the γ_{anti}-carbon chemical shift in 2-substituted adamantanes is as expected[30] and the γ_{anti}-carbon chemical shift and C_β–$C_{\gamma_{anti}}$ coupling constant do not experience the same substituent effect, it seems that the factors responsible for the "anti" substituent effect on the C_γ chemical shift and the C_β–C_γ coupling constant are not necessarily the same. Moreover, as the C_β–$C_{\gamma_{anti}}$ coupling constants in both 1-adamantyl and 2-adamantyl derivatives follow the same trend, the seeming correlation observed between the γ_{anti}-carbon chemical shift and C_β–$C_{\gamma_{anti}}$ coupling constant in 1-substituted adamantanes is only coincidental.

The C_1–C_9 coupling constant in 2-substituted adamantanes is also of interest in that the C_1–C_9 bond is gauche to the C_2–X bond.



Whereas the C_1–C_8 (C_β–$C_{\gamma_{anti}}$) coupling constant decreases on substitution at C_2, the C_1–C_9 (C_β–$C_{\gamma_{syn}}$) coupling constant increases. It increases as the bulkiness of the heteroatom containing the lone pair increases (e.g., Br > Cl > O > F). Substituent effects are observed neither with bulky alkyl substituents (2-adamantyl or 2-methyl) nor with substituents having no lone-pair electrons (e.g., NH_3^+). It is interesting to note that the substituent effect caused by the NH_2 group on the C_1–C_9 coupling constant disappears on protonation, indicating that the gauche effect on C_β–$C_{\gamma_{syn}}$ coupling constants is due to the lone pair. This gauche effect by the lone-pair electrons on the C_β–$C_{\gamma_{syn}}$ coupling constant is also in line with that observed by Barna and Robinson[16] in the derivatives of piperidine and cyclohexanone.

As in the case of 1-substituted adamantanes, the substituents have little effect on the C_γ–C_δ or C_δ–C_ϵ coupling constants ($J_{4,5}$, $J_{5,6}$, $J_{6,7}$, and $J_{7,8}$).

2,2-Disubstituted Adamantanes. In an effort to extend our studies on ^{13}C–^{13}C coupling constants in disub-

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[31] An explanation is given for this anomaloy by: Wiseman, J. R.; Krabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 2240.

Table IX. One-Bond $^{13}C-^{13}C$ Coupling Constants in 2-Methyl- and 2-Phenyl-2-adamantyl Derivatives (4 and 5)[a]

compd	$J_{1,2}$ ($J_{2,3}$)	$J_{1,8}$ ($J_{3,10}$)	$J_{1,9}$ ($J_{3,4}$)	$J_{4,5}$ ($J_{5,9}$)	$J_{7,8}$ ($J_{7,10}$)	$J_{5,6}$*	$J_{6,7}$*	$J_{C_2-CH_3}$[c] or $J_{C_2-C_i}$	$J_{C_i-C_o}$	$J_{C_o-C_m}$	$J_{C_m-C_p}$
4a	31.8	31.7	31.3	31.7	31.5	31.6	31.5	35.4			
4b	35.9	30.9	32.5	31.4	31.7	31.6	31.7	39.8			
4d	35.2	31.1	32.1	31.6	31.5	31.4	31.4	40.7			
4g	33.2	30.2	32.6	31.5	31.5	31.5	31.6	39.6			
4h	32.4	30.2	33.0	31.7	31.5	31.4	31.6	39.2			
5a	32.1	31.8	31.7	31.6	31.6	31.6	31.6	43.2	57.2	55.7	*b*
5b	36.7	30.9	32.6	31.4	31.5	31.7	31.7	48.0	58.5	*b*	*b*
5d	36.2	*b*	32.2	31.5	31.5	31.6	31.6	48.1	58.1	56.5	*b*
5g	33.9	30.0	32.6	31.5	31.5	31.7	31.7	48.8	60.1	56.8	*b*
5h	33.2	29.5	32.9	31.7	31.3	31.5	31.5	48.2	60.3	56.9	*b*

[a] All coupling constants are in Hz and within ±0.1 Hz in $CDCl_3$ at 20 °C. Coupling Constants marked by * may be interchanged. [b] Could not be measured accurately. [c] $J_{C_2-CH_3}$ for 4a,b,d,g,h; $J_{C_2-C_i}$ for 5a,b,d,g,h.

stituted adamantanes, we also measured the one-bond $^{13}C-^{13}C$ coupling constants in a number of 2-methyl- and 2-phenyl-2-adamantyl derivatives (4 and 5), and the data are listed in Table IX.

The C_1-C_2 coupling constant ($J_{C_\alpha-C_\beta}$) follows the same trend as that in monosubstituted adamantanes, and the values are uniformly higher in the disubstituted adamantane derivatives compared to those in the corresponding monosubstituted system. Moreover, the replacement of the C_2H hydrogen with a substituent causes a larger increase of $J_{1,2}$ in 2-phenyladamantane and 2-methyladamantane than in adamantane itself. For example, while a hydroxy substituent at the 2-position in adamantane increases the C_1-C_2 coupling constant by 2.9 Hz, the same substituent at the same position in 2-phenyladamantane increases $J_{1,2}$ by 4.1 Hz (with respect to 2-phenyladamantane). This effect is observed in the case of other substituents as well as in 2-methyladamantane. This indicates that the substituent effects, although following similar trends, are not additive.

Again, the C_1-C_8 ($C_\beta-C_{\gamma_{anti}}$)[32] and C_1-C_9 ($C_\beta-C_{\gamma_{syn}}$)[32] coupling constants follow the same trend as in the monosubstituted adamantanes. Although one observes a slight deviation from additivity even in these coupling constants, they are too small for any further consideration.

The use of J_{CC} values for assignment of chemical shifts can be illustrated in the reassignment of the ^{13}C NMR resonances in 2-bromo-2-phenyladamantane (**5h**) and 2-bromo-2-methyladamantane (**4h**). In **4h** the ^{13}C resonances at $\delta_{^{13}C}$ 34.3 and 35.7 were originally assigned[20] to C_4 (or C_9) and C_8 (or C_{10}), respectively, on the basis of a comparison with the ^{13}C NMR data of 2-methyl-2-adamantanol (**4d**).[33] However, in the ^{13}C satellite spectrum, the signal at $\delta_{^{13}C}$ 34.3 appears as two doublets with coupling constants of 30.2 and 31.5 Hz and the signal at $\delta_{^{13}C}$ 35.7 appears as two doublets with coupling constants of 33.0 and 31.7 Hz. The 31.5- and 31.7-Hz couplings, respectively, can readily be assigned to $J_{7,8}$ and $J_{4,5}$. Thus, an assignment of the other two coupling constants (33.0 and 30.2 Hz) would solve the assignment of the carbon resonances at $\delta_{^{13}C}$ 34.3 and 35.7. A comparison of these coupling constants with those in the other 2-substituted-2-methyladamantanes reveals that the 33.0-Hz coupling is $J_{1,9}$ and the 30.2-Hz coupling is $J_{1,8}$. Consideration of these coupling constants thus allows unequivocal reassignment of the ^{13}C resonance at $\delta_{^{13}C}$ 35.7 to C_4 and C_9 and that at $\delta_{^{13}C}$ 34.3 to C_8 and C_{10} (reversing the original assignment). Similarly, in 2-bromo-2-phenyladamantane (**5h**), the ^{13}C resonances at $\delta_{^{13}C}$ 35.0 and 34.5 assigned tentatively earlier[20] to C_4 (or C_9) and C_8 (or C_{10}), respectively, have to be reversed on consideration of the $^{13}C-^{13}C$ coupling constants.

Conclusions

In summary, we have determined the substituent effect on one-bond $^{13}C-^{13}C$ coupling constants in a series of adamantane derivatives having rigid framework with well-defined geometries. It was qualitatively shown that the substituent effect on $C_\alpha-C_\beta$, $C_\beta-C_{\gamma_{anti}}$ and $C_\beta-C_{\gamma_{syn}}$ coupling constants follow definite trends. However, more detailed experimental and theoretical studies are needed to quantitatively evaluate these substituent effects. Moreover, it has been shown that the $^{13}C-^{13}C$ coupling constant can be used to aid the assignment of ^{13}C NMR chemical shifts in addition to the more commonly used $^{13}C-^{1}H$ coupling constants and ^{13}C chemical shift positions. We are continuing the study of substituent effects on $^{13}C-^{13}C$ coupling constants in other bicyclic and polycyclic systems and related carbocations.

Experimental Section

All the adamantane derivatives used were either commercially available or prepared by known procedures.[34] Proton noise-decoupled ^{13}C NMR, gated-decoupled ^{13}C NMR, and ^{13}C satellite spectra were recorded at 50 MHz on a Varian XL-200 superconducting NMR spectrometer equipped with a variable-temperature broad-band probe. All the spectra were recorded in $CDCl_3$ at room temperature (~20 °C) unless otherwise stated.

The pulse sequence used for the ^{13}C satellite spectra, based on Freeman et al.,[19] is $90°(x)-\tau-180°(\pm y)-\tau-90°(x)-\Delta-90°(\phi)-\mathrm{Acq}(\psi)$, where $\tau \simeq (2n + 1)/4J_{CC}$, Δ is a very short delay (~10 μs) needed to reset the radiofrequency phase, and ϕ and ψ are the phase of the last 90° "read" pulse and the receiver, respectively. Optimum setting of τ for direct coupling is when $n = 0$ and thus set a 7.0 ms (corresponding to a J_{CC} value of ~36 Hz). The repetition rate of this sequence is ~10 s, and reasonable signal to noise ratio was achieved in 6–8 h of acquisition.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No. **2a**, 281-23-2; **2b**, 36960-53-9; **2c**, 768-92-3; **2d**, 768-95-6; **2e**, 35015-52-2; **2f**, 768-94-5; **2g**, 935-56-8; **2h**, 768-90-1; **2i**, 768-93-4; **2j**, 7575-82-8; **2k**, 768-91-2; **2l**, 780-68-7; **2m**, 1660-04-4; **2n**, 828-51-3; **2p**, 23074-42-2; **3b**, 65115-51-7; **3c**, 16668-83-0; **3d**, 700-57-2; **3e**, 86846-38-0; **3f**, 13074-39-0; **3g**, 7346-41-0; **3h**, 7314-85-4; **3k**, 700-56-1; **3l**, 19066-24-1; **3q**, 29542-62-9; **4b**, 86846-39-1; **4d**, 702-98-7; **4g**, 37723-65-2; **4h**, 27852-61-5; **5b**, 86846-40-4; **5d**, 29480-18-0; **5g**, 29480-21-5; **5h**, 33831-38-8.

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[32] The "anti" or "syn" relationship is with respect to the substituent X.

[33] The peak assignment in the ^{13}C NMR of **4d** is on the basis of europium-induced shift.[20]

[34] For a survey of literature procedures for the preparation of adamantane derivatives used in the present study, see: Fort, R. C., Jr. "Adamantane–the Chemistry of Diamond Molecules"; Marcel Dekker: New York, 1976.