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NMR investigation of steric effects in alkyl- and haloadamantanes†

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ABSTRACT: The use of substituent effects on ^{1}H and ^{13}C chemical shifts to probe steric interactions was applied to other monosubstituted adamantanes. Existing literature data on series of halogen and alkyl substituents confirm that NMR chemical shifts are strongly affected by steric effects. The magnitude of these effects can be associated with data that reflect the 'size' of a substituent and the direction in which it extends. For alkyl groups, conformational effects must be taken into consideration in this type of analysis. Copyright © 2004 John Wiley & Sons, Ltd.
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KEYWORDS: alkyl- and haloadamantanes; ^{1}H and ^{13}C chemical shifts; substituent effects; steric interactions; bond lengths and angles

INTRODUCTION

The adamantane framework is particularly well suited for probing steric effects by ^{1}H and ^{13}C NMR. Its rigid geometry limits the degree of molecular distortion that results from the introduction of substituents and its high degree of symmetry provides several equivalent positions that can be used to compare substituent effects.[1] Our recent work on mono- and disubstituted adamantanes revealed that substituent effects on chemical shifts could be traced to changes in molecular geometry and charge distribution. These data could also be used to separate steric contributions from those that are mainly of electronic nature and to evaluate the shape and volume of the groups that are involved in the respective interactions.[2] Changes in geometry are reflected mainly by carbon chemical shifts and hydrogen chemical shifts can be used to verify the direction in which the substituent is pointing and how far it extends.[2] The steric effects that will result from a substituent in a certain position can therefore be well established. These aspects were investigated in the series of adamantanes with alkyl (**1**–**9**) and halogen substituents (**10**–**15**) that are commonly associated with steric effects[3] and given in Fig. 1 (although experimental data for **9** have not been reported, we included calculated shifts on this system in our analysis in order to complete the series and probe the conformational aspects of its strong steric interactions).

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CALCULATIONS

Calculations are used to complement experimental data and provide insights into variations in structure and charge distribution. They are instrumental in locating effects and estimating their relative contributions. Density functional theory (DFT) methods have been successfully applied to chemical shifts of adamantyl systems and are particularly indicated for cases where the relative shieldings are of interest,[4] as in the case here. Since the basis set used for geometry optimization does not have parameters for iodine, geometries of haloadamantanes were also optimized by molecular mechanics.

Calculations were carried out with the Gaussian 98 package of molecular orbital programs.[5] Geometries were optimized fully using the B3LYP/6–31G(d,p) basis set and were also used for chemical shift calculations. Isotropic magnetic shielding tensors were calculated from optimized geometries using the GIAO method. Chemical shift values were obtained relative to isotropic shielding of TMS, as calculated at the same level. Hydrogen chemical shifts were also calculated from optimized structural data using version **6A** of the CHARGE program[6] for the purpose of comparison with chemical shifts in Ref. 2. The Chem 3D program was

	R_1	R_2
1	H	H
2	CH_3	H
3	C_2H_5	H
4	i-C_3H_7	H
5	t-C_4H_9	H
6	H	CH_3
7	H	C_2H_5
8	H	i-C_3H_7
9	H	t-C_4H_9
10	Cl	H
11	Br	H
12	I	H
13	H	Cl
14	H	Br
15	H	I

Figure 1. Substituted adamantanes

used for MM2[7] calculations. Abraham *et al.*[8] obtained geometries for the kind of molecules studied here by *ab initio* methods and by the PCModel molecular mechanics program. PCModel geometries lead to small variations in chemical shifts (<0.1 ppm). Thus halogen substituent effects on adamantane ^{1}H chemical shifts were calculated by the CHARGE 6A program from geometries optimized by the MM2 method (see Supplementary material, available in Wiley Interscience). In general, trends are similar to those of the observed data.

RESULTS AND DISCUSSION

Substituent effects on chemical shifts

Methyl adamantanes reveal that substituents on secondary and tertiary carbons lead to distinct types of effects on chemical shifts.[1] Substituents on a secondary carbon atom (as exemplified by C-2) result in considerable γ-*gauche* effects on ^{13}C chemical shifts that are normally associated with interactions between nuclei that are close in space.[1,9–12] Hydrogen chemical shifts also evidence steric interactions, nuclei under compression being deshielded relative to equivalent positions on the unsubstituted system.[2] A combination of these effects which reflects a shortening of the C—H bond, an increase in charge on the carbon nucleus and a decrease in charge on the hydrogen nucleus is referred to as bond polarization.[13] Changes in bond and dihedral angles often accompany steric effects and, in situations where the molecular framework is distorted, also may be associated with steric effects.[14]

Substituents in a tertiary position (as exemplified by C-1) do not result in γ-*gauche* effects.[1] In fact, deshielding of the γ-carbons is observed for electronegative substituents.[2] Here substituents distort molecular geometry to a lesser extent and their respective effects can be traced essentially to changes in C—C bond lengths.[1,2]

Another point that must be taken into consideration on analyzing substituent effects in adamantyl systems is the carbon–substituent bond. Although the electronegativity of the substituent makes an important contribution to the α-effect, large α-effects may also be attributed to the lengthing of the carbon–substituent bond.[2]

Before extending the substituent effect of a methyl group to other alkanes usually associated with steric effects, it is instructive to compare the effect of other halogens to that of bromine. Substituent effects on their hydrogen chemical shifts have been extensively studied[15] and their spectra for 1- and 2-substituted chloro-, bromo- and iodoadamantanes have been interpreted.[8,16] No steric effects are observed for fluorine and parameters that are important for comparison purposes, such as van der Waals radii, polarizability and electronegativity, have been quantified.[3,8] Another advantage of halogens is that conformational effects that are observed for alkyl groups (see below) do not need to be taken into consideration.

Haloadamantanes

Problems inherent in making calculations on heavy atoms such as halogens[17] are avoided here by the use of experimental chemical shifts. The extent of steric substituent effects on hydrogens in different positions is readily apparent from Table 1. For neighboring atoms, the order I > Br > Cl is observed for the magnitude of substituent effects in both positions, hence the degree of deshielding of hydrogens corresponds to the relative van der Waals radii of the substituent,[3,8,16] confirming the tendencies revealed by calculations.[2] In the case of the substituent on a tertiary carbon (structures **10**–**12**) hydrogens on β- carbon (C-2, C-8 and C-9) are deshielded in increasing order of the van der Waals radius of the substituent, C—H bonds being shortened as expected

Table 1. Substituent effects on ^{1}H chemical shifts of haloadamantanes[8,16]

	Substituent in R_1			Substituent in R_2		
	10	**11**	**12**	**13**	**14**	**15**
H-1	—	—	—	0.20	0.28	0.29
H-2a	0.39	0.62	0.88	2.65	2.92	3.25
H-2s	0.39	0.62	0.88	—	—	—
H-3	0.27	0.23	0.10	0.20	0.28	0.29
H-4a	−0.08	−0.02	0.11	−0.18	−0.13	−0.04
H-4e	−0.08	−0.02	0.11	0.52	0.59	0.63
H-5	0.27	0.23	0.10	−0.01	0.01	0.03
H-6a	−0.08	−0.02	0.11	0.01	−0.01	0.04
H-6e	−0.08	−0.02	0.11	0.01	−0.01	0.04
H-7	0.27	0.23	0.10	−0.01	0.01	0.03
H-8a	0.39	0.62	0.88	0.20	0.11	0.20
H-8s	0.39	0.62	0.88	0.05	0.22	0.20
H-9a	0.39	0.62	0.88	−0.18	−0.13	−0.04
H-9s	0.39	0.62	0.88	0.52	0.59	0.63
H-10a	−0.08	−0.02	0.11	0.20	0.11	0.20
H-10e	−0.08	−0.02	0.11	0.05	0.22	0.20

Table 2. Substituent effects on ^{13}C chemical shifts of tertiary haloadamantanes[10]

R_1	α	β	γ	δ
Cl	39.7	9.9	3.2	−2.2
Br	38.0	11.6	4.1	−2.1
I	21.7	14.5	4.4	−2.3

Table 3. Substituent effects on ^{13}C chemical shifts of secondary haloadamantanes[10]

R_2	α	β	γ_{syn}	γ_{anti}	δ_{syn}	δ_{anti}	ϵ
Cl	30.3	7.5	−6.8	0.5	−0.9	−1.5	0.1
Br	25.9	8.0	−6.1	1.0	−0.8	−1.5	0.2
I	8.6	9.1	−4.8	1.0	−0.7	−1.4	0.4

from steric effects resulting from bond polarization. In contrast, an inversion is observed in the order that hydrogens on the γ-carbon are deshielded. It would appear that, in the absence of steric effects, decreases in hydrogen chemical shifts accompany increases in carbon chemical shifts (see Table 2). For the halogen on the secondary carbon, it is the geminal hydrogens (H-2a) and the hydrogens on the γ-carbons (H-4e and H-9s) that are most strongly deshielded, their order following that of the van der Waals radius of the substituent. The steric contributions of Cl, Br and I to hydrogen substituent shifts in cyclic systems have already been firmly established.[15] They illustrate the sensitivity of NMR chemical shifts as probes for steric effects and serve as a basis for comparison with alkyl groups.

The response of carbon chemical shifts to steric effects has been widely investigated.[9–12] Although chlorine and iodine substituents (Tables 2 and 3) follow the same general trends as bromine,[2] it is noteworthy that the lengthening of the carbon–substituent bond (Table 4)

Table 4. C—R bond length for substituted adamantanes

	C—R			C—R	
R_1	B3LYP/6–31 G(d,p)	MM2	R_2	B3LYP/6–31 G(d,p)	MM2
Me	1.532	—	Me	1.534	—
Et	1.545	—	Et	1.541	—
i-Pr	1.566	—	*i*-Pr	1.555	—
t-Bu	1.592	—	*t*-Bu	1.577	—
Cl	1.852	1.812	Cl	1.845	1.805
Br	2.016	1.978	Br	2.009	1.968
I	—	2.180	I	—	2.167

and the concomitant distortions in the molecular framework can also be associated with the van der Waals radius of the halogen. For example, the large β- and γ-effects observed for **10–12** (Table 2) can be traced to the stretching of the C_β—C_γ bond (the magnitude of β- and γ-effects and the degree that the bond in question is stretched follow the order of van der Waals radii of the respective substituents).

Alkyladamantanes

In order to investigate substituent effect of alkyl groups, conformational effects must be taken into consideration. For a methyl group in a tertiary position, for example, there will be three minima, one for each of the rotamers in which the methyl hydrogens fall exactly between the two hydrogens on the β-carbons, forming a dihedral angle of around 60° with the C_α—C_β bond. Since the three are equivalent, their chemical shifts will be the same. This is not the case for 1-ethyl- and 1-isopropyladamantanes, where methyl groups will fall between the hydrogens on the β-carbons (see Fig. 2) and their respective chemical shifts will correspond to weighted averages of the rotamers that are involved. In this case, calculated chemical

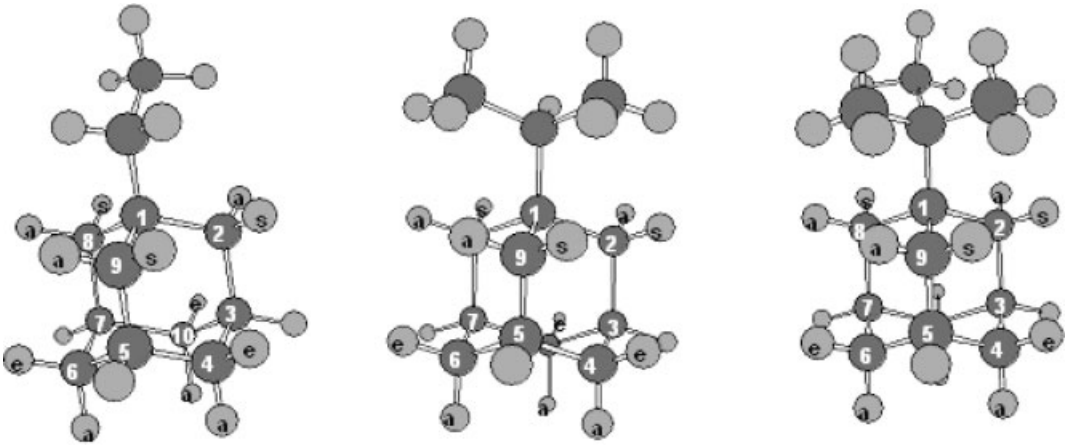

Figure 2. Final geometries of alkyladamantanes substituted in the R_1 position

shifts correspond to the lowest energy rotamers and can be used to identify their respective conformations.

Similar considerations apply to secondary alkyladamantanes. There are also three low-energy rotamers for 2-methyladamantane (**6**), for example. Each of these corresponds to a conformation in which one of the methyl hydrogens falls between H-4e and H-9s, forming a dihedral angle of 180° between H-2a—C-2—C_R—H_R. For a 2-ethyl substituent (**7**), the lowest energy rotamer will correspond to a conformation in which the substituent points in the direction of H-1 or H-3 and a dihedral angle of 170° between C-1—C-2—C_R—CH_3 is observed.

The secondary methyl derivative provides a good probe for alkyl substituent effects on chemical shifts. Both its hydrogen[18] and its carbon[10] spectrum have been fully interpreted. As the case with 2-haloadamantanes (**13**–**15**), the largest substituent effects are observed for H-4e and H-9s, and the hydrogens that are subject to steric interactions with the substituent lead to substantial γ-*gauche* effects on C-4 and C-9.

Calculations reveal that the corresponding C—H bonds are shortened and charge on the carbons increases whereas that on the hydrogen decreases, in line with bond polarization. Both DFT and DFT/CHARGE 6A calculations of substituents effects reflect the magnitude of the shielding experienced by carbon and the deshielding experienced by hydrogen fairly well and are used in the investigation of the remaining 1- and 2-alkyladamantanes (Tables 5–7).

For 2-ethyl- and 2-isopropyladamantanes, there are low-energy conformers with the same arrangement as the methyl group (one of the hydrogens of the substituent lies between H-4e and H-9s) and similar bond polarization will be observed in the respective C—H bonds. The other methyl group(s) will point in the direction of H-1 (H-3) and should lead to additional interactions with these groups. This arrangement is not possible for the *tert*-butyl group and steric interactions will be much more substantial.

Table 5. Substituent effects on ^{13}C chemical shifts of R_1[10]

R_1	α	β	γ	δ
Me	1.2	6.8	0.4	−0.9
Et	3.9	4.5	0.4	−0.2
i-Pr	4.1	5.6	0.5	−0.2
t-Bu	3.9	5.0	0.6	−0.2

Table 6. Substituent effects on ^{13}C chemical shifts of R_2[20]

R_2	α	β	γ_{syn}	γ_{anti}	δ_{syn}	δ_{anti}	ϵ
Me	1.3	5.5	−6.4	1.7	0.1	−0.2	0.9
Et	10.0	4.5	−4.8	2.9	1.5	1.2	2.0
i-Pr	6.6	3.5	−5.8	1.8	0	−0.2	−2.8

The respective steric interactions can be located by hydrogen chemical shifts (Table 7). For 2-ethyladamantane (**7**), the carbon–carbon bond of the substituent forms a dihedral angle of 170° with the C-1—C-2 bond. This geometry results in interactions of one of the methylene hydrogens and H-4e/H-9s, deshielding these hydrogens, as was the case for 2-methyladamantane (**6**). In this case, one of the hydrogens of the methyl group points in the direction of H-3 and it is deshielded relative to the other tertiary hydrogens. In 2-isopropyladamantane (**8**), the second methyl group of the substituent points in the direction of H-1 and it is also strongly deshielded. Finally, for 2-*tert*-butyladamantane (**9**), the molecule is considerably distorted; however there are strong

Table 7. Alkyl substituent effects on hydrogen chemical shifts of adamantane calculated by DFT-B3LYP/6–31G(d,p)

	Substituent in R_1				Substituent in R_2			
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**
H-1	—	—	—	—	−0.18	−0.23	0.20	0.37
H-2a	−0.23	0.14	−0.50	0.01	0.11	−0.16	−0.52	−0.24
H-2s	−0.24	−0.47	0.22	−0.06	—	—	—	—
H-3	0.08	0.11	0.11	0.11	−0.20	0.12	0.19	0.35
H-4a	−0.07	−0.05	−0.06	−0.08	−0.27	−0.28	−0.27	−0.20
H-4e	−0.11	−0.09	−0.12	−0.12	0.24	0.22	0.18	0.44
H-5	0.09	0.06	0.10	0.13	−0.09	−0.09	−0.07	−0.03
H-6a	−0.07	−0.06	−0.07	−0.07	−0.05	−0.06	−0.05	−0.05
H-6e	−0.09	−0.08	−0.11	−0.10	−0.04	−0.05	−0.04	−0.05
H-7	0.11	0.12	0.12	0.13	−0.04	0.00	−0.02	0.01
H-8a	−0.22	−0.46	0.23	0.02	0.10	0.07	0.11	0.07
H-8s	−0.23	0.13	−0.50	−0.07	−0.02	0.00	−0.07	−0.06
H-9a	−0.23	−0.32	−0.15	−0.07	−0.26	−0.27	−0.26	−0.17
H-9s	−0.24	−0.33	−0.17	0.00	0.26	0.16	0.20	0.37
H-10a	−0.07	−0.09	−0.06	−0.09	0.07	0.10	0.08	0.10
H-10e	−0.11	−0.13	−0.10	−0.12	−0.03	−0.08	−0.08	−0.04

interactions with H-1, H-3, H-4e and H-9s, as reflected by the deshielding they experience, the shorter C—H bonds and the charge distribution between respective carbons and hydrogens.

With respect to the tertiary alkyladamantanes, similar probes can be applied. For 1-ethyladamantane (**3**), the dihedral angle between C-9—C-1—C_R—CH_3 is 180°. It leads to two different effects: the hydrogens on the methylene group of the substituent interact with H-2s, H-8a, H-9a and H-9s, lengthening the respective C—H bonds while the hydrogens of the methyl group interact with H-2a and H-8s, deshielding these hydrogens since the respective C—H bond length is shorter. Hence, depending on the respective positions of the hydrogens involved, both C—H bond polarization and inverse bond polarization may be observed. In 1-isopropyladamantane (**4**), the methyl groups of the substituent point in the direction of H-8a/H-9a and H-2s/H-9s since these respective C—H bonds are polarized. H-2s and H-8a are strongly deshielded because they are closer in space to the hydrogens of methyl group. At the same time, H-2a and H-8s are shielded owing to the inverse bond polarization of the C—H bond. Finally, for 1-*tert*-butyladamantane (**5**), it appears that hydrogens subject to steric interactions are not deshielded, although the C—H bond is polarized. Here C—C bonds are considerably lengthened and it may be that shielding arising from shorter C—H bonds is compensated by deshielding from longer C—C bonds. This possibility will be further investigated.

The analysis above can be confirmed by inspection of the distances between the substituent and the affected hydrogen and by the geometries depicted in Fig. 2.

The lengths of the carbon–substituent bonds are given in Table 4 and substituent effects of the alkyl group on carbon-13 chemical shifts are given in Tables 5 and 6.[10] As is apparent from these data, distortion of the molecular framework will be much larger for the halogen substituents and increases with their respective van der Waals radii.

For alkyladamantanes substituted in a tertiary position, carbon–carbon bonds connected to C-1 increase in length whereas the remaining carbon–carbon bonds decrease very slightly relative to adamantane (see Supplementary material).[1] Comparing the methyl group with the other alkyl substituents, in general, the average carbon–carbon bonds connected to C-1 are the shortest and the C—C bonds connected to δ-carbons are the longest, C—C and C—H bond effects compensating one another (see above).

The substituent on R_2 must be responsible for secondary effects. Its interaction with H-9s and H-4e will result in torsion around C-2—C-3/C-5—C-9 and C-3—C-4/C-4—C-5 bonds. The alkyl group will, in turn, be responsible for torsion around the C-1—C-2/C-1—C-9 and C-1—C-8/C-3—C-10 bonds, resulting in distortions of the molecular framework. In addition to the torsion around certain bonds, there are noticeable (see Supplementary material) increases or decreases in bond angles. Angular effects on carbon-13 chemical shifts[14] must contribute to γ_{anti}, δ and effects.

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REFERENCES

1. Seidl PR, Leal KZ. *J. Mol. Struct. (THEOCHEM)* 2001; **539**: 159–162.
2. Seidl PR, Leal KZ, Yoneda JD. *J. Phys. Org. Chem.* 2002; **15**: 801–807.
3. Carey FA, Sundberg RJ. *Advanced Organic Chemistry, Part A: Structure and Mechanisms* (4th edn). Kluwer/Plenum: New York, 2000; Chapt. 3.
4. Topic DV, Pejov L. *J. Chem. Inf. Comput. Sci.* 2001; **41**: 1478–1487.
5. Frisch MJ, Trucks GW, Schlegel HB, Gill PMW, Johnson BG, Robb MA, Cheeseman JR, Keith TG, Peterson GA, Montgomery JA, Raghavachari K, Al-Laham MA, Zakrzewski VG, Ortiz JV, Foresman JB, Cioslowski J, Stefanov BB, Nanayakkara A, Challacombe M, Peng CY, Ayala PY, Chen W, Wong NW, Andress JL, Replogle ES, Gomperts R, Maritn RL, Fox DJ, Binkley JS, Defrees DJ, Baker J, Stewart JP, Head-Gordon M, Gonzalez C, Pople JA. *Gaussian 98*. Gaussian: Pittsburg, PA, 1998.
6. Abraham RJ, Alinger NJ. *J. Chem. Soc. Perkin Trans. 2* 1999; 441–448.
7. Burkert U, Alinger NL. *Molecular Mechanics*. ACS Monograph 177. American Chemical Society: Washington, DC, 1982.
8. Abraham RJ, Warne MA, Griffiths L. *J. Chem. Soc. Perkin Trans. 2* 1997; 2151–2160.
9. Gunther H. *NMR Spectroscopy* (2nd edn). Wiley: Chichester, 1994.
10. Whitesell JK, Minton MA. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*. Chapman and Hall: London, 1987.
11. Marchand AP. *Stereochemical Applications of NMR Studies in Rigid Bicyclic Systems*. Verlag Chemie: Deerfield Beach, FL, 1982.
12. Pihlaja K, Kleinpeter E. *Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis*. VCH: New York, 1994.
13. Seidl PR, Leal KZ, Costa VEU, Mollmann MES. *Magn. Reson. Chem.* 1998; **36**: 261–266.
14. Barfield M. *Magn. Reson. Chem.* 1998; **36**: 93–103.
15. Abraham RJ. *Prog. in Nucl. Magn. Reson. Spectrosc.* 1999; **35**: 85–152.
16. Abraham RJ, Warne MA, Griffiths L. *J. Chem. Soc., Perkin Trans. 2* 1997; 881–886.
17. Della EW, Lochert IJ, Peralta JE, Contreras RH. *Magn. Reson. Chem.* 2000; **38**: 395–402.
18. Fisher J, Gradwell M. *J. Magn. Reson.* 1992; **38**: 338–346.