Estimating the Magnitude of Steric Effects in Rigid Systems by NMR

Julliane Diniz Yoneda
Programa Pós-Graduação em Química Orgânica, Universidade Federal Fluminense, Niterói, RJ, Brazil

Peter Rudolf Seidl*
Escola de Química, Universidade Federal do Rio de Janeiro, CEP 21.949-900, Ilha do Fundão, RJ, Brazil.
pseidl@eq.ufrj.br

Kátia Zaccur Leal
Departamento de Físico-Química & Programa de Pós-Graduação em Química Orgânica, Universidade Federal Fluminense, CEP 24.020-150, Niterói, RJ, Brazil

Keywords: NMR chemical shifts, substituent effects, steric effects, bond lengths and angles, rigid systems.

Abstract: *The rapid advance of supramolecular chemistry has led to a better understanding of the forces and interactions that are responsible for many different phenomena. Among these, steric effects play an important role in determining the constraints to association between the species involved. Although the role of steric effects has been recognized for a long time, quantitative information has been mainly related to the comparison of these effects on a chemical reaction or conformational equilibrium rather than the properties of the group of atoms that is responsible for their manifestation. This situation has been changing with the increase in power of computational methods and the accumulation of data on model compounds that can be used for the purpose of comparison. Here we present a short review of our recent work on NMR of rigid carbocyclic systems and apply this type of approach to di- and triamantane systems. Our results show how NMR can be used to locate the segment of a molecule that is subjected to steric effects and evaluate the degree to which these effects will distort its geometry.*

Introduction

Steric requirements for molecular recognition have led to renewed interested in phenomena that may be associated with the volume and shape of certain groups. Information of this type may be estimated from several sources such as reaction rates, barriers to rotation, crystal packing, and calculations.[1] Although the role of steric effects has been recognized for a long time, quantitative information has been mainly related to the magnitude of these effects rather than the properties of the group of atoms that is responsible for their manifestation. This situation has been changing with the increase in the power of computational methods and the accumulation of data on model compounds that can be used for the purpose of comparison. Our recent work has shown that NMR can be used to locate steric effects and to evaluate their magnitude.[2-5]

Investigation of mono- and di-substituted adamantanes revealed that substituent effects on chemical shifts could be traced to changes in molecular geometry and charge distribution.[2-5] These data could also be used to separate steric contributions from those that are mainly of an electronic nature and to evaluate the shape and volume of groups that are involved in the corresponding interactions. Changes in geometry are reflected mainly by carbon chemical shifts whereas hydrogen chemical shifts can be used to verify the direction in which the substituent is pointing and how far it extends.[4]

Here we present a short review of our studies on adamantane and their extension to several substituted model systems such as norbornane, di- and triamantane, camphor and norcamphor (Figure 1). The results of our studies reveal that, in rigid systems, NMR is a reliable probe for locating steric effects. It can also be used to estimate their magnitude and, frequently, to trace their origin to changes in charge distribution, bond lengths and angles, as well as rotation around certain bonds.

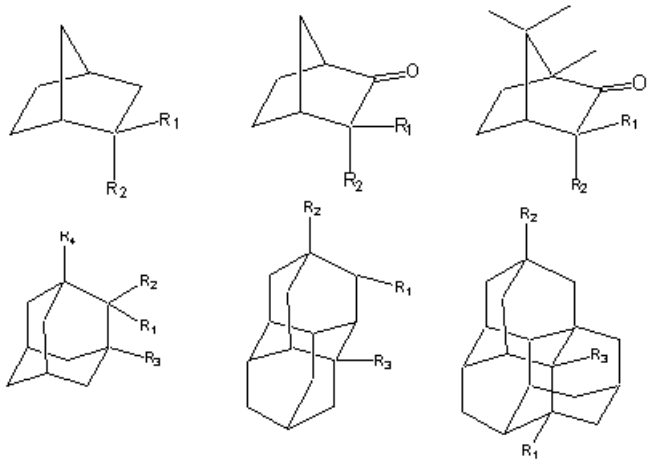


Figure 1. Model systems studied

Calculations and experimental data

Experimental ^{1}H and ^{13}C chemical shifts data were obtained from references 6 and 7. Where this data is not available they were calculated as below.

Calculations were run on the Gaussian 98 package of molecular orbital programs.[8] Geometries were optimized at the B3LYP/6-31G(d,p) level of theory and were also used for chemical shift calculations. Isotropic magnetic shielding tensors were calculated from optimized geometries using the GIAO method.[9] 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 the CHARGE 6A program.[10] In general the same tendencies were observed for experimental and calculated chemical shifts in both cases. Since the basis set used for geometry optimization does not have parameters for iodine, geometries of compounds with halogen substituents were also optimized by Molecular Mechanics (CHEM3D program, MM2 methods).[11]

Results and Discussion

- Observed vs. calculated shifts

As in the case of ^{1}H chemical shifts there is not much data in the literature on the compounds that were investigated, much of this data had to be calculated. Although these calculations do not always give satisfactory results, remarkable progress has been made with successive generations of the CHARGE

program as exemplified for hydrogen chemical shifts of adamantane (Table 1). Although a newer version of this program has been proposed[12] we have used version 6 in order to provide comparisons with our previous studies[2-5].

Table 1. Experimental ^{1}H chemical shifts (ppm) [6] versus calculated by CHARGE and Gaussian 98 programs.

Type of carbon	ADAMANTANE				
	Experimental	**CHARGE 3A**	**CHARGE 4A**	**CHARGE 6A**	**DFT**
CH	1.87	2.07	1.98	1.95	1.79
CH_2	1.75	1.2	1.35	1.70	1.79

- Substituent effects

Bond polarization is usually a consequence of a steric effect, and results in charge transfer from hydrogen to carbon, increasing the *s* character of the C-H bond, which is shortened on compression.[13] Both the negative charge on the carbon nucleus and the positive charge on the hydrogen nucleus increase, resulting in shielding of the carbon-13 nucleus and deshielding of the hydrogen nucleus. This effect is very well illustrated when comparing tetracyclic systems with their bicyclic counterparts (Figure 2), showing that the polarization occurs where van der Waals interactions are expected.[13]

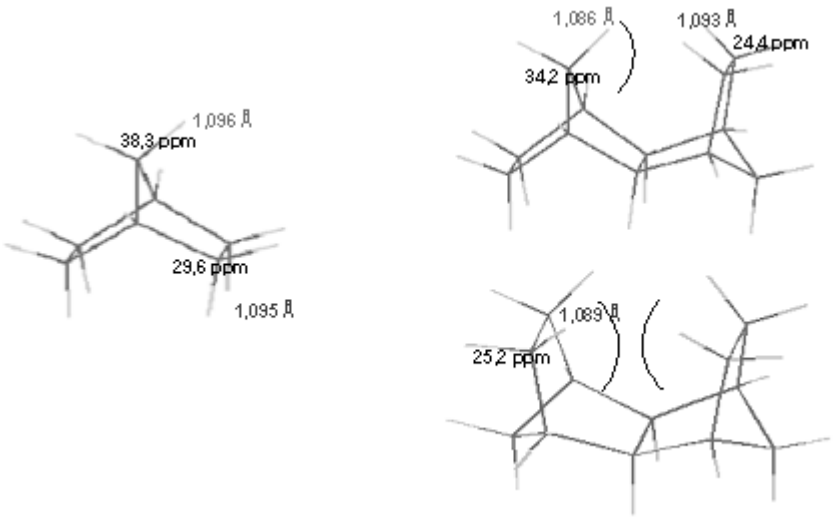


Figure 2. Bond polarization effect in tetracyclic dodecane compounds.[7,13]

Inverse bond polarization has also been observed on introducing methyl substituents in adamantane.[2] Substituent effects have been used extensively to probe the factors that are responsible for a certain type of behavior. However they are not easy to predict. As an example, take the effect of substituents on the rotational barrier of ethane (Figure 3). Although

the differences in energy are very small, and its “size“ or “bulk” is assumed to be smaller, chlorine leads to a higher barrier than that of bromine or a methyl group. Here hyperconjugation or other forms of resonance[14] may also play a role in stabilizing certain conformations but their discussion is beyond the scope of present article.

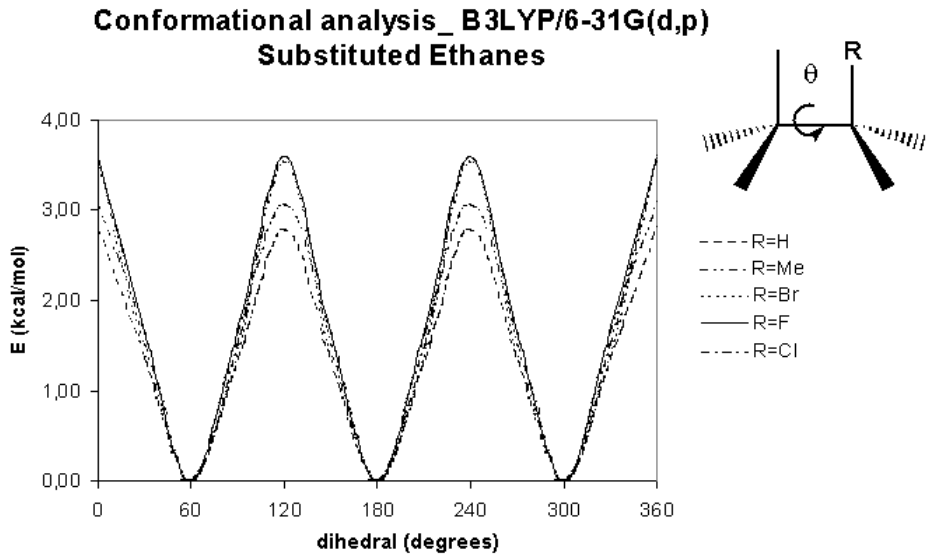


Figure 3. Substituent effects in ethanes

Figure 4 illustrates how, along with bond polarization, steric effects may also lead to bond compression or stretching, distortions in bond angles and rotation around bonds. The steric repulsion between the two methyl groups on 2,3-*endo*-methylnorbornane leads to a strong C-C bond stretching and to an increase in C-C-C bond angle as indicated in Figure 4. On the other hand in 3-*endo*-bromonorbornane the steric effect is reflected not only by the increase of the C-C-C bond angle but also by distortion of the dihedral angle □ (Figure 4) relative to unsubstituted norbornane.

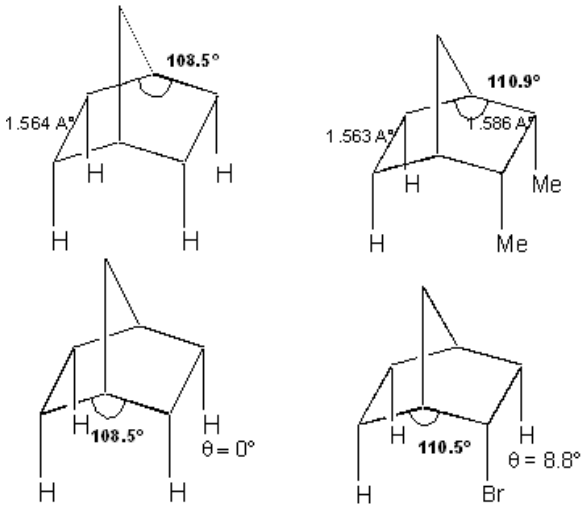


Figure 4. Steric effects in substituted norbornanes.

- Van der Waals radii

Studies on halogen substituents show the extent that steric effects can be related to the van der Waals radii of the substituent. The introduction of chlorine, bromine and iodine substituents in norbornane and adamantane systems (Figure 5) reveals that, as the van der Waals radii of the substituent becomes larger, the larger the polarization of the C-H bonds under steric compression and as consequence, the larger the degree of deshielding of the corresponding hydrogen.[6]

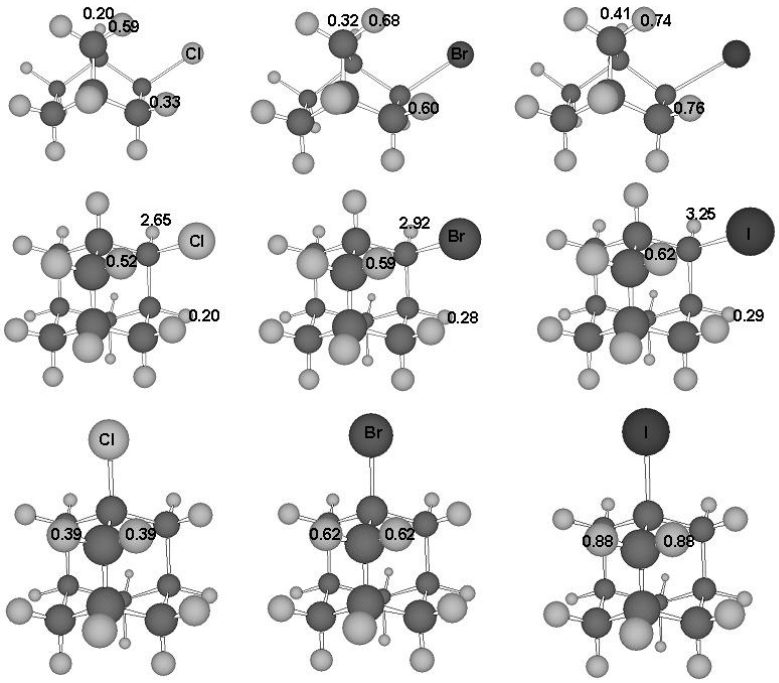
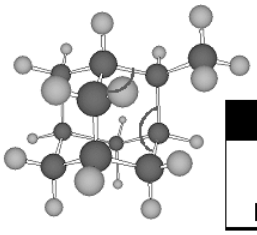


Figure 5. SCS in halonorbornanes and haloadamantanes [6]

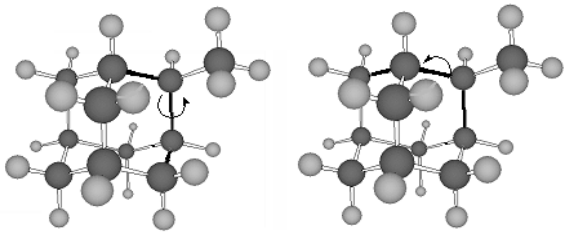
Steric effects on norbornyl and adamantyl systems can be observed for hydrogens that lie around 3.0 Å from Cl, 3.1 Å from Br and 3.3 Å from I. However, in less rigid systems, such as camphor and norcamphor, steric interactions seem to be relieved by angular distortions, which apparently do not seem to follow any predictable trend. [5]

- *Skeletal distortions*

Alkyl adamantanes substituted in a secondary position provide a good example of how the distortions increase with the size of the substituent but depend on conformational effects. Substituents such as ethyl and i-propyl groups can be accommodated among neighboring hydrogens in the same way as methyl group in the secondary position of adamantane (with a hydrogen pointing to the direction of the □ hydrogens of adamantane). However in the case of the t-butyl substituent this is not possible and the skeletal distortions are considerably more pronounced (Figure 6).



	H	2-Me	2-Et	2-iPr	2-tBu
C_2-C_1-C_9	109.3	110.8	110.9	110.8	113.1
C_2-C_3-C_4	109.3	111.0	111.0	111.0	113.2
H_{9a}-C_9-H_{9s}	106.9	106.4	106.5	106.4	106.3



	H	2-Me	2-Et	2-iPr	2-tBu
C_4-C_3-C_2-C_1	-59.9	-58.2	-58.3	-59.0	-54.4
C_3-C_2-C_1-C_8	-59.9	-61.6	-61.6	-61.1	-64.5

Figure 6. Distortions in bond angles and rotation around dihedral angles of 2-alkyladamantanes

- *Spatial orientation*

This approach can also be employed[3-5] to find the spatial orientation of a substituent. As an example, take the case of 1-ethyladamantane. The data on Table 1 indicate the direction a certain group is pointing and thus which conformer it corresponds to (Figure 7).

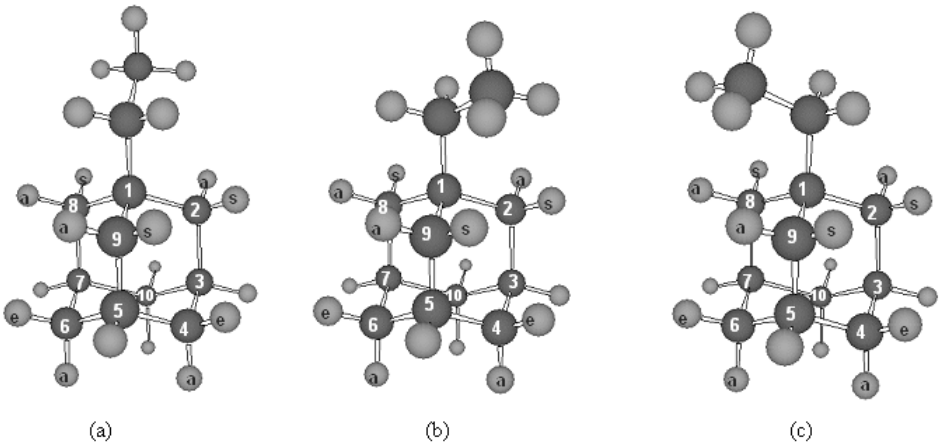


Figure 7. The three most stable conformers of 1-ethyladamantane.

From the ^{13}C chemical shifts (Table 2) of the □-carbons of 1-ethyladamantane, it appears that C_2 and C_8 are the more shielded carbons. The C_2-H_{2a} and C_8-H_{8s} bonds are polarized while all the other $C_□$-$H_□$ bonds reflect inverse bond polarization, reflected by deshielding of their respective hydrogens. Thus, it is possible to conclude that the ethyl group is pointing in the direction of H_{2a} and H_{8s} (Figure 7, conformer (a)). This approach can be used to find the spatial orientation of other alkyl groups.

Table 2. ^{13}C and ^{1}H chemical shifts (ppm) and bond lengths (Å) of 1-ethyladamantane calculated by the Gaussian 98 program

	^{13}C		^{1}H		Bond length
C_2	41.0	**H_{2a}**	1.93	**C_2-H_{2a}**	1.097
C_8	41.0	**H_{2s}**	1.32	**C_2-H_{2s}**	1.099
C_9	47.1	**H_{8a}**	1.32	**C_8-H_{8a}**	1.099
		H_{8s}	1.92	**C_8-H_{8s}**	1.097
		H_{9a}	1.47	**C_9-H_{9a}**	1.099
		H_{9s}	1.47	**C_9-H_{9s}**	1.099

- Applications

The relationship between these effects and the respective bond distances involved can be exemplified by disubstituted adamantanes (Figure 8). In 2-bromoadamantane steric interactions are minimized by diminishing the H-C-Br bond angle relative to unsubstituted adamantane (Figure 8a) and the C-Br bond length is not very different from that of a C-Br bond in a bromonorbornane substituted in a

secondary position. This decrease in angle is not observed in the case of a methyl substituent (Figure 8a). However, when introducing a methyl group in position 2 of 2-bromoadamantane (Figure 8b), a decrease in the H-C-Br angle is also observed, but it is smaller than in the case of the mono-substituted compound (Figure 8a). Thus, as this decrease in angle does not suffice to minimize the steric interactions, the C-Me bond is shortened while the C-Br bond is considerably stretched (Figure 8b).

As the C-Br bond is stretched, bromine approaches H_{4e} and H_{9s} leading to a stronger bond polarization of the C-H bonds involved. As a consequence the respective hydrogens are more deshielded, in line with the relationship between steric effects and interatomic distances (Figure 9).

Comparing mono- and di-substituted 2-bromo- and 2-methyladamantane (Figure 8c) it is readily apparent that the steric effect caused by bromine is larger than the one caused by the methyl group since that the halogen leads to a stronger bond polarization effect of the C□-H□gauche and, as consequence, to a more pronounced deshielding of the respective hydrogens. It indicates that bromine corresponds to a larger “size” or “bulk” than a methyl group, although the literature[15] indicates the opposite.

The case of fluorine is also worth comment. Analysis of fluorine substituent effects is more difficult owing to the strong electronegativity of this element. It leads to shortening of bond lengths to neighboring atoms (the exact opposite of what is observed for steric effects) and one effect may be compensating the other.

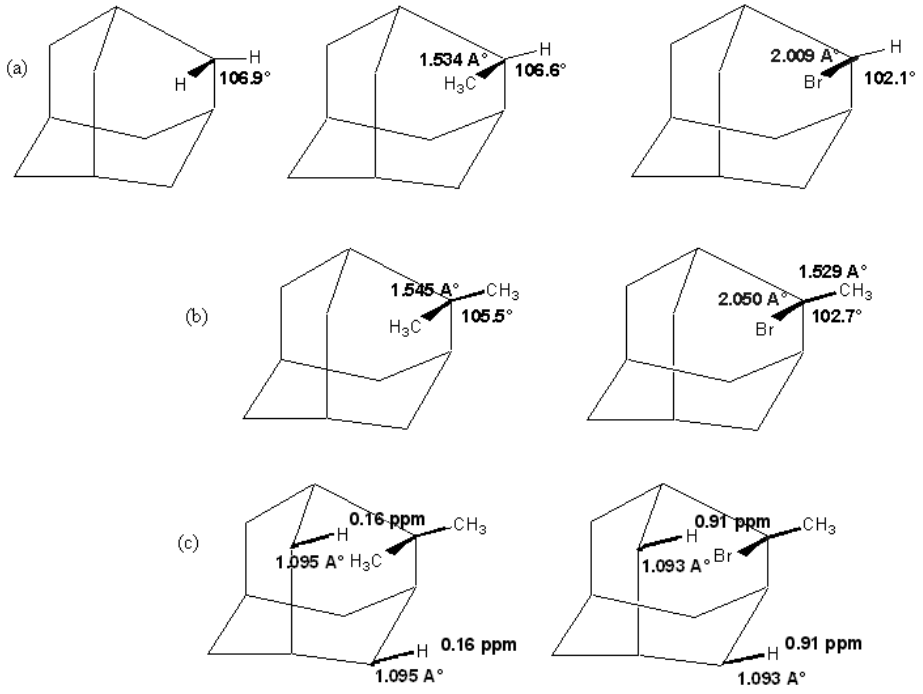


Figure 8. Adamantanes with bromine and methyl substituents in secondary positions (SCS calculated by the CHARGE 6A program are given in ppm, bond lengths in Å and bond angles in degrees).

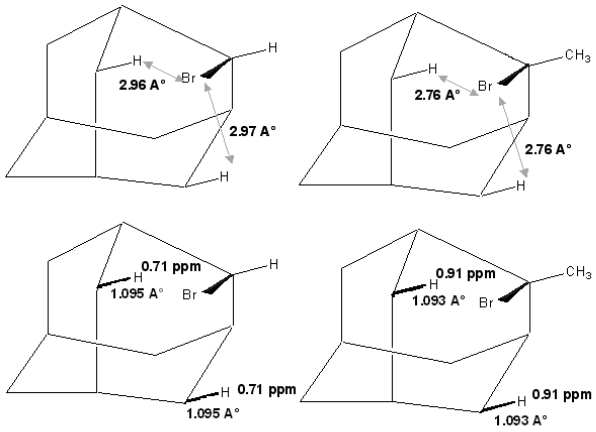


Figure 9. The steric effect of bromine in mono- and disubstituted adamantanes (SCS calculated by the CHARGE 6A program are given in ppm, bond lengths and internuclear distances in Å)

Although in the literature fluorine is not related to any kind of steric effect and in fluoronorcamphors and in 3-*endo*-flourocamphor it does not seem to cause any kind of angular distortion due to steric effects, in 3-*exo*-flourocamphor some bond angles change compared to camphor (Figure 10), thus fluorine may be causing a steric effect due to the interaction with the methyl group on the same side of the molecule.[5]

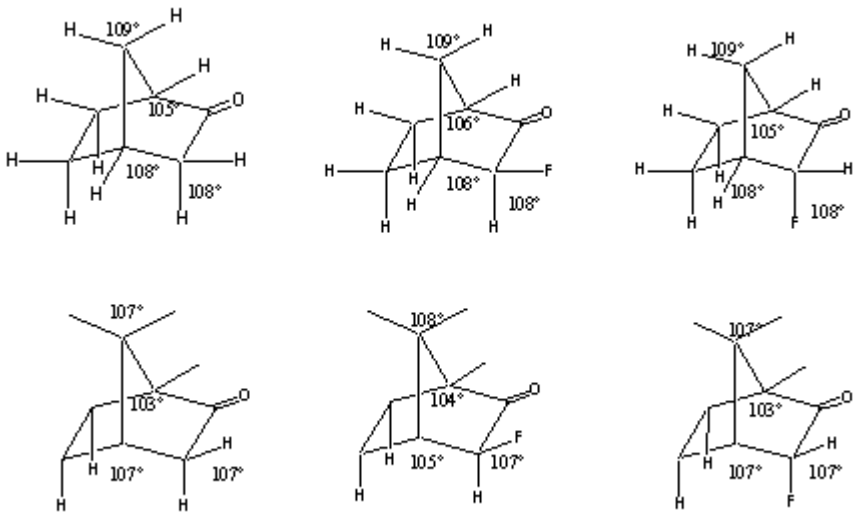


Figure 10. Bond angles of norcamphors and camphors with and without fluorine substituents in position 3.

Another interesting example of the use of NMR to locate and evaluate steric effects is the rationalization for the apparently “abnormal” chemical shifts of di- and triamantanes relative to adamantane (Figure 11). They can be compared to the effects caused by the introduction of a methyl group in the secondary position of adamantane (2-

methyladamantane), such as the stretching of the $C_{\square}$-$C_{\square}$ bonds and inverse bond polarization observed for the C-H bond geminal to the substituent, leading to deshielding of the chemical shifts of the ^{13}C nuclei involved, as reported in reference 16. These effects can also be observed for di- and triamantanes, when they are treated as adamantanes with "methyl" substituents (Figure 12).[16]

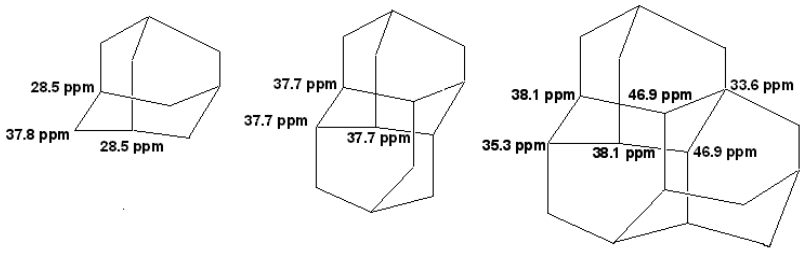


Figure 11. ^{13}C chemical shifts at the ring junctions of di- and triamantanes.[17]

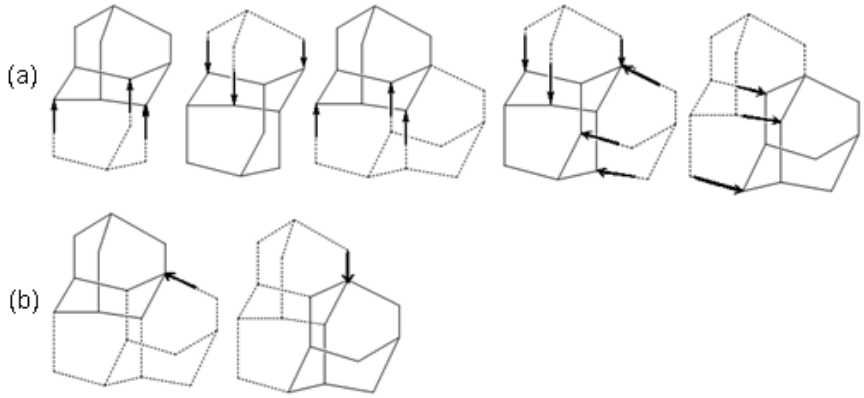


Figure 12. Introduction of "methyl groups" (arrows) in secondary (a) and tertiary (b) positions of adamantane (full lines) in di- and triamantanes.[16]

A similar effect of methyl group introduction in secondary position of adamantane occurs on di- and triamantane (Figure 12a): all the $C_{\square}$-$C_{\square}$ and C-H bonds at the ring junctions (where the "substituents" are introduced) are stretched about 0.003-0.007Å and 0.001-0.002Å respectively in di- and triamantanes compared to the adamantyl system.[16] Thus, there is a change in charge distribution and these effects are related to the deshielding observed for carbons at the ring junctions (Figure 11) related to the tertiary carbons of unsubstituted adamantanes, reflecting not only the inverse bond polarization effect but also C-C bond stretching.[16]

For triamantane the effect of methyl substituent introduction in a tertiary position of adamantane is also observed (Figure 12b). When a methyl group is introduced in this position, the $C_{\square}$-$C_{\square}$ bonds are stretched and an

inverse bond polarization effect is also observed for C□-H□ bonds. As consequence, the □ carbons are deshielded. This analysis can be applied to triamantanes, which would result in deshielding of the carbons in the ring junctions.[16]

Carbon nuclei at ring junctions discussed in the previous paragraphs can be compared to cyclohexanes with methyl substituents in an *axial* position. Thus, in 1-*cis*-3-*cis*-5-trimethylcyclohexane the same effect of C□-C□ and C□-H□ bond stretching is observed relative to cyclohexane. In this case the C-C bond stretching (Table 3) is more pronounced due to the conformational freedom, which is lost in rigid adamantane, di- and triamantane systems. This conformational freedom is reflected by comparison of angles and dihedral angles (degrees) in cyclohexane, adamantane and 1-*cis*-3-*cis*-5- trimethylcyclohexane (Table 3).

Table 3. Bond lengths (Å), angles and dihedral angles (degrees) in cyclohexane, adamantane and 1-*cis*-3-*cis*-5-trimethylcyclohexane

	Cyclohexane	Adamantane	1-*cis*-3-*cis*-5- trimethylcyclohexane
C-C	1.537	1.544	1.547
C□-H□	1.097	1.098	1.100
C_1-C_2-C_3	111.5	109.7	116.5
C_2-C_3-H_{3a} (Me)	109.1	109.3	114.4
C_1-C_2-C_3-C_{Me} (H_{3a})	65.9	59.9	81.5
H_{1a}-C_1-C_2-H_{2a} (Me)	173.5	178.9	158.5

Conclusion

NMR can be used not only to locate steric effects but also to estimate their magnitude. As originally suggested by Abraham,[6] halogen substituents lead to steric effects that can be associated with the respective van der Waals radii. They will result in interactions with hydrogens that are about 3.0 Å distant from Cl, 3.1 Å from Br and 3.3 Å from I (except in systems which can relieve steric interactions by angular distortions). Other probes, such as alkyl groups, reveal that skeletal distortions can also be associated with steric effects, and may be used to verify the spatial orientation of the substituent. Combinations of these probes can reinforce or mitigate effects.

There are several applications of this approach. This work illustrates the estimate of a "size" or "volume" of a certain group (Me vs. Br, halogens or alkyl groups) and the detection of smaller or "hidden" steric effects such as those attributed to F in substituted camphors and norcamphors. Thus, chemical shifts may reflect bond compression or stretching, bond polarization, distortions in bond angles and rotation around bonds.

Acknowledgements

J.D.Y. has a fellowship from CAPES. PRS has a fellowship from the ANP/FINEP PRH Program. We are grateful to Professor R. Abraham for use of the CHARGE program and to CENAPAD-SP for computational work.

References

1. Gallo, R.; *In Progress in Physical Organic Chemistry*; Taft, R.W., Ed.; Wiley, New York (1983).

2. Seidl, P.R.; Leal, K.Z.; *J Mol. Struct (THEOCHEM).* **539** (2001) 159.

3. Seidl, P.R.; Leal, K.Z.; Yoneda, J.D.; *J. Phys.Org.Chem*. **15** (2002) 801.

4. Seidl, P.R.; Yoneda, J.D.; Leal, K.Z.; *J.Phys.Org.Chem.* **18** (2005) 162.

5. Yoneda, J.D.; Seidl, P.R.; Leal, K.Z.; Campos, M.G.; Rittner, R.; *J.Mol.Struct. (THEOCHEM).* **767** (2006) 29.

6. Abraham, R.J.; *Progr. Nucl. Magn. Reson. Spectrosc.* **35** (1999) 85.

7. Whitesell, J.K.; Minton, M.A.; *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy;* Chapman and Hall, London (1987).

8. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Gill, P.M.W.; Johnson, B.G.; Robb, M.A.; Cheeseman, J.R.; Keith, T.G.; Peterson, G.A.; Montgomery, J.A.; Raghavachari, K.; Al-Laham, M.A.; Zakrzewski, V.G.; Ortiz, J.V.; Foresman, J.B.; Cioslowski, J.; Stefanov, B.B.; Nanayakkara, A.; Challacombe, M.; Peng, C.Y.; Ayala, P.Y.; Chen, W.; Wong, N.W.; Andress, J.L.; Replogle, E.S.; Gomperts, R.; Martin, R.L.; Fox, D.J.; Binkley, J.S.; Defrees, D.J.; Baker, J.; Stewart, J.P.; Head-Gordon, M.; Gonzalez, C.; Pople, J.A.; *Gaussian 98*, Gaussian Inc. Pittsburg, PA (1998).

9. Ditchfield, R.; *Mol. Phys.* **27** (1974) 789.

10. Abraham, R.J.; Ainger, N.J.; *J. Chem. Soc. Perkin Trans. 2*. (1999) 441.

11. Burkert, U.; Alinger, N.L.; *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington, DC (1982).

12. Abraham, R.J.; Reid, M.; *J. Chem. Soc. Perkin Trans. 2* (2002) 1081.

13. Seidl, P.R.; Leal, K.Z.; Costa, V.E.U.; Mollmann, M.E.S.; *Mag. Reson. Chem.* **1998**, *36*, 261-266.

14. Ritter, S. K.; *Chem. Eng. News*, **29** (2007) 37.

15. Carey, F.A.; Sundberg, R.J.; *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, 4th ed., Kluwer/ Plenum, New York (2000).

16. Yoneda, J.D.; Leal, K.Z.; Seidl, P.R.; *Ann. Magn. Reson.* **4** (2005) 9.

17. Duddeck, H.; Hollowood, F.; Karim, A.; McKerney, A.A.; *J. Chem. Soc. Perkin Trans. 2*. **60** (1979) 360.