JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2002; **15:** 801–807
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.538

NMR chemical shifts as probes for steric effects in mono- and disubstituted adamantanes†

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Received 19 March 2002; revised 26 April 2002; accepted 2 May 2002

epoc ABSTRACT: Substituent effects are widely used to investigate the factors affecting carbon-13 chemical shifts. Adamantane and its derivatives are convenient probes for relative contributions to these factors owing to their symmetry and relative absence of ring strain. We have extended our studies on NMR chemical shifts of 1- and 2-methyladamantanes to hydroxy, bromo, methoxy and acetamide substituents and also certain disubstituted (one of the groups being methyl) analogs. DFT/GIAO calculations at the B3LYP/6–31G(d,p) level show that, except for α-effects, steric interactions are mainly responsible for substituent effects on chemical shifts. The CHARGE program is particularly well suited for localizing these effects and estimating their approximate shape and range.
Additional material for this paper is available from the epoc website at http://www.wiley.com/epoc

KEYWORDS: adamantanes; substituent effects; steric interactions; DFT/GIAO calculations; ^{1}H and ^{13}C chemical shifts

INTRODUCTION

Steric requirements for molecular recognition have led to renewed interest 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] NMR techniques have been widely employed in structural determination and should be very useful for this purpose. Chemical shifts of substituted adamantanes, in particular, appear to be convenient probes for steric effects owing to their rigid geometries and molecular symmetry.[2]

The extraordinary sensitivity of magnetic nuclei to their immediate surroundings was recognized since the early days of NMR spectroscopy and several different techniques are routinely used for structure determination. Steric effects on NMR chemical shifts have been extensively studied over the years and a large body of empirical data relating substituent effects to nuclear shielding exists in the current literature. There are, however, several important cases in which further theoretical work is desirable in order to sort out the relative importance of different contributions.[3,4]

The most common of these approaches is to evaluate the effects of substituents on model systems in which van der Waals interactions lead to shielding of particular nuclei.[5,6] For carbon-13 chemical shifts that are widely used in structural analysis of organic compounds, analysis of substituent effects on rigid bicyclo[*m.n.o.*]alkanes and 2-adamantanes offers an insight into specific contributions of intramolecular interactions to these effects.[7] We used carbon-13 NMR chemical shifts of 1- and 2-methyladamantanes to compare steric interactions in these systems and probe their effects on the respective geometries and charge distributions.[2] As it would be interesting to increase the number of examples and to verify to what extent their influence may be quantified, a similar approach was applied to a series of mono- and disubstituted analogs of 1- and 2-methyladamantanes, where the substituent is Me, Br, OH, OMe and NHAc (Fig. 1), thus covering groups of atoms of varying size and electronegativity that can be used for comparison purposes.

We calculated chemical shifts and geometries and charge distributions of several of these systems which could shed light on the origin of their respective substituent effects. These results are very useful in separating steric contributions from those that are mainly of an electronic nature and evaluating the respective shape and volume of groups that are responsible for steric effects.

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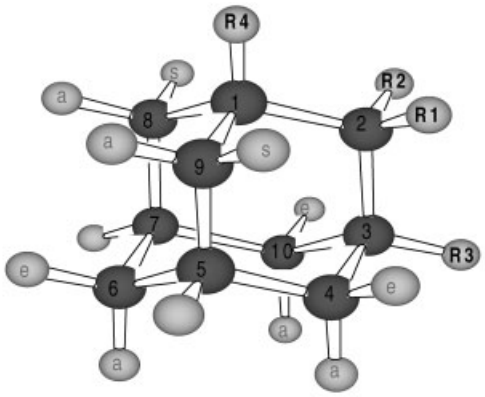
†Presented in part at the Sixth Latin American Conference on Physical Organic Chemistry (CLAFQO-6), held at Isla Margarita, Venezuela, during December 2001.
Contract/grant sponsor: Programa de Apoio a Núcleos de Excelência (PRONEX); *Contract/grant number:* 124/06.



	R_1	R_2	R_3	R_4
1	H	H	H	H
2	CH_3	H	H	H
3	OH	H	H	H
4	Br	H	H	H
5	OCH_3	H	H	H
6	NHAc	H	H	H
7	H	CH_3	H	H
8	CH_3	CH_3	H	H
9	OH	CH_3	H	H
10	Br	CH_3	H	H
11	OCH_3	CH_3	H	H
12	NHAc	CH_3	H	H
13	H	H	CH_3	H
14	H	H	CH_3	CH_3
15	H	H	CH_3	OH
16	H	H	CH_3	Br
17	H	H	CH_3	OCH_3
18	H	H	CH_3	NHAc
19	H	H	H	CH_3
20	H	H	H	OH
21	H	H	H	Br
22	H	H	H	OCH_3
23	H	H	H	NHAc

Figure 1. Adamantanes studied

EXPERIMENTAL

In order to avoid any type of problem with comparison of data from different sources,[5] all carbon-13 chemical shifts were obtained from Ref. 3. Hydrogen chemical shifts for adamantane and 2-methyladamantane are from Ref. 8.

Calculations were carried out with the Gaussian 98 package of molecular orbital programs.[9] All geometries were optimized fully using the B3LYP/6–31G(d,p) basis set and were also employed for chemical shift calculations. For the case of hydroxy, methoxy and acetamide substituents, only one of the low-energy conformers was calculated. Isotropic magnetic shielding values 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 calculated from structural data using version 6A of the CHARGE program.[10] As it still does not include nitrogen, data for acetamides are not included.

RESULTS AND DISCUSSION

Calculated versus experimental shifts

Calculated and experimental carbon-13 chemical shifts are given in Table 1. As expected, the largest deviations

Table 1. Calculated versus experimental ^{13}C chemical shifts (TMS: C = 191.8 ppm)

	1			**2**			**3**		
Carbon	Calc.	Obs.	Δ	Calc.	Obs.	Δ	Calc.	Obs.	Δ
C1	32.0	28.5	3.5	36.9	34.0	2.9	40.4	34.7	5.7
C2	39.2	37.8	1.4	42.4	39.1	3.3	75.5	74.7	0.8
C3	32.0	28.5	3.5	37.0	34.0	3.0	36.7	34.7	2.0
C4	39.2	37.8	1.4	33.6	31.4	2.2	33.3	31.2	2.1
C5	32.0	28.5	3.5	32.1	28.6	3.5	31.4	27.8	3.6
C6	39.2	37.8	1.4	39.7	38.7	1.0	39.0	37.8	1.2
C7	32.0	28.5	3.5	31.8	28.3	3.5	31.1	27.3	3.8
C8	39.2	37.8	1.4	40.8	39.6	1.2	37.7	36.7	1.0
C9	39.2	37.8	1.4	33.6	31.4	2.2	33.5	31.2	2.3
C10	39.2	37.8	1.4	40.7	39.6	1.1	38.0	36.7	1.3
	4			**5**			**6**		
	Calc.	Obs.	Δ	Calc.	Obs.	Δ	Calc.	Obs.	Δ
C1	40.3	36.5	3.8	37.6	31.5	6.1	36.8	32.1	4.7
C2	77.4	63.7	13.7	83.8	83.3	0.5	52.4	53.5	−1.1
C3	40.4	36.5	3.9	31.9	31.5	0.4	37.2	32.1	5.1
C4	33.8	31.7	2.1	33.6	31.5	2.1	34.7	32.0	2.7
C5	31.2	27.7	3.5	31.2	27.6	3.6	31.1	27.4	3.7
C6	39.4	38.0	1.4	39.1	37.7	1.4	39.1	37.7	1.4
C7	30.9	27.0	3.9	31.3	27.6	3.7	31.0	27.3	3.7
C8	40.5	38.8	1.7	38.4	36.6	1.8	39.3	37.3	2.0
C9	33.7	31.7	2.0	34.0	31.5	2.5	34.8	32.0	2.8
C10	40.6	38.8	1.8	37.6	36.6	1.0	39.1	37.3	1.8

	7	**8**			**9**		
	Calc.	Calc.	Obs.	Δ	Calc.	Obs.	Δ
C1	36.9	40.9	37.4	3.5	44.6	39.3	5.3
C2	42.4	43.0	—	—	75.0	73.8	1.2
C3	36.9	40.9	37.4	3.5	41.2	39.3	1.9
C4	40.7	35.5	33.3	2.0	34.7	33.1	1.6
C5	31.8	31.9	27.7	4.2	31.1	27.2	3.9
C6	39.7	40.6	39.3	1.3	39.4	38.5	0.9
C7	32.0	31.9	27.7	4.2	31.6	27.7	3.9
C8	33.7	35.5	33.3	2.0	37.0	35.2	1.8
C9	40.8	35.5	33.3	2.0	35.1	33.1	2.0
C10	33.7	35.5	33.3	2.2	36.8	35.2	1.6

	10			**11**	**12**	**13**	**14**
	Calc.	Obs.	Δ	Calc.	Calc.	Calc.	Calc.
C1	45.7	42.2	3.5	36.6	42.5	32.2	34.1
C2	97.7	82.3	15.4	78.9	59.7	45.0	51.1
C3	45.7	42.2	3.5	42.2	39.8	33.6	34.2
C4	37.6	34.6	3.0	34.5	34.7	45.1	44.7
C5	31.0	27.3	3.7	31.0	30.8	32.3	32.6
C6	40.4	39.4	1.0	39.6	39.6	38.8	38.2
C7	31.3	27.5	3.8	31.8	31.2	32.2	32.6
C8	37.6	36.0	1.6	36.3	35.6	38.8	44.8
C9	37.5	34.6	2.9	34.7	34.9	38.7	44.7
C10	37.5	36.0	1.5	36.9	35.7	45.2	44.8

are observed for bromo-substituted derivatives, where 'heavy atom effects' must be considered.[11] Other differences are observed where the substituent contains oxygen or nitrogen atoms and rotation around the C—O or C—N bonds leads to significant conformational effects on carbon or hydrogen chemical shifts.[12] In all cases, given the uncertainties in respective assignments, consistent orders of chemical shifts are predicted by calculations.

Although calculations for hydrogen chemical shifts at this level do not give satisfactory results, remarkable progress has been made with successive generations of

Table 1. Continued.

	15			**16**			**17**	**18**
	Calc.	Obs.	Δ	Calc.	Obs.	Δ	Calc.	Calc.
C1	68.8	68.9	−0.1	81.0	65.7	15.3	73.2	53.2
C2	53.9	52.2	1.7	56.2	55.9	0.3	46.0	50.3
C3	36.9	33.4	3.5	38.9	35.0	3.9	36.4	35.6
C4	44.4	43.3	1.1	43.7	42.5	1.2	44.5	44.3
C5	34.1	31.0	3.1	36.3	32.5	3.8	33.8	33.2
C6	37.8	35.4	2.4	37.3	34.7	2.4	38.2	37.8
C7	33.6	31.0	2.6	36.3	32.5	3.8	33.7	32.9
C8	43.3	44.6	−1.3	50.0	48.4	1.6	45.2	42.8
C9	47.5	44.6	2.9	49.9	48.4	1.5	39.5	46.0
C10	44.4	43.3	1.1	43.8	42.5	1.3	44.8	44.0

	19			**20**			**21**		
	Calc.	Obs.	Δ	Calc.	Obs.	Δ	Calc.	Obs.	Δ
C1	33.5	29.7	3.8	68.0	67.9	0.1	81.0	66.5	14.5
C2	45.1	44.6	0.5	48.0	45.3	2.8	50.4	49.4	1.0
C3	32.2	28.9	3.3	34.2	30.8	3.4	36.3	32.6	3.7
C4	38.7	38.9	−0.2	38.3	36.1	2.2	37.6	35.7	1.9
C5	32.3	28.9	3.4	34.3	30.8	3.5	36.4	32.6	0.2
C6	38.8	36.9	1.9	38.2	36.1	2.1	37.7	35.7	2.0
C7	32.3	28.9	3.4	33.5	30.8	2.7	36.4	32.6	4.2
C8	45.1	44.6	0.5	43.7	45.3	−1.6	50.5	49.4	1.1
C9	45.1	44.6	0.5	48.1	45.3	2.8	50.5	46.4	4.1
C10	38.8	36.9	1.9	38.2	36.1	2.1	37.7	35.7	2.0

	22			**23**		
	Calc.	Obs.	Δ	Calc.	Obs.	Δ
C1	72.4	71.9	0.5	52.5	51.6	0.9
C2	40.1	41.2	−1.0	43.3	41.5	1.8
C3	33.9	30.7	3.2	32.8	29.4	3.4
C4	38.3	36.7	1.6	38.2	36.4	1.8
C5	33.9	30.7	3.2	33.1	29.4	3.7
C6	38.7	36.7	2.0	38.1	36.4	1.7
C7	33.6	30.7	2.9	33.1	29.4	3.7
C8	45.7	41.2	4.5	44.4	41.5	2.9
C9	40.2	41.2	−1.0	46.3	41.5	4.8
C10	38.7	36.7	2.0	37.9	36.4	1.5

the CHARGE Program, as exemplified for hydrogen chemical shifts of adamantane (Table 2). As chemical shifts of hydrogen nuclei are very sensitive to other nuclei in the vicinity and may be instrumental distinguishing steric and electronic effects,[13] they are included in the present analysis (Table 3). The case of steric interactions is of particular interest. For 2-methyladamantane, for example, version 6A of the CHARGE program predicts that the hydrogen on the β-carbon that is *syn* to the methyl group will be deshielded by 0,38 ppm relative to its *anti* counterpart while the experimental value is 0,44 ppm.[8] Reliable assignments of hydrogen chemical shifts of these compounds are scarce, so in order to make meaningful comparisons, interpretation is based on calculated rather than observed chemical shifts.

Monosubstitued adamantanes

Substituent effects are commonly denoted by their position relative to the group that is introduced.[14] They are given in Tables 4 and 5. In general, electronegative

Table 2. Experimental versus calculated ^{1}H chemical shifts for adamantane by the CHARGE program

	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

Table 3. Calculated ^{1}H chemical shifts for substituted adamantanes using the CHARGE 6A program

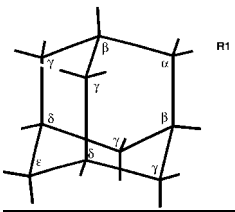
Hydrogen	1	2	3	4	5	7	8	9	10	11	13	14	15	16	17	19	20	21	22
H1	1.95	1.94	2.17	2.21	2.21	1.94	1.51	2.11	2.09	2.07	1.98	—	—	—	—	—	—	—	—
H2a	1.71	2.10	4.41	4.82	3.89	—	—	—	—	—	1.54	1.37	1.72	1.92	1.64	1.54	1.54	2.10	1.81
H2s	1.71	—	—	—	—	2.10	—	—	—	—	1.54	1.37	1.77	1.92	1.72	1.54	1.54	2.10	1.89
H3	1.95	1.94	2.14	2.21	2.20	1.94	1.51	2.07	2.08	2.07	—	—	—	—	—	1.98	2.00	2.10	2.03
H4a	1.71	1.49	1.51	1.53	1.31	1.64	1.40	1.46	1.44	1.09	1.54	1.55	1.56	1.62	1.58	1.72	1.73	1.79	1.75
H4e	1.71	1.86	2.15	2.42	2.27	1.65	1.87	2.31	2.62	2.50	1.54	1.57	1.58	1.66	1.56	1.73	1.75	1.83	1.73
H5	1.95	1.97	1.98	2.05	1.97	1.98	2.00	2.02	2.08	2.01	1.98	2.01	2.03	2.13	2.06	1.98	2.00	2.10	2.03
H6a	1.71	1.72	1.73	1.76	1.72	1.72	1.70	1.73	1.76	1.73	1.73	1.74	1.75	1.81	1.75	1.72	1.72	1.79	1.73
H6e	1.71	1.72	1.73	1.76	1.73	1.72	1.70	1.73	1.76	1.71	1.72	1.75	1.77	1.85	1.78	1.73	1.73	1.83	1.77
H7	1.95	1.98	1.98	2.05	1.98	1.97	2.00	1.99	2.06	2.00	1.98	2.01	2.03	2.13	2.04	1.98	2.00	2.10	2.01
H8a	1.71	1.65	1.67	1.76	1.65	1.86	1.86	1.90	1.95	1.94	1.73	1.56	1.93	2.12	1.95	1.54	1.91	2.10	1.93
H8s	1.71	1.64	1.68	1.76	1.68	1.49	1.41	1.50	1.55	1.51	1.72	1.56	1.93	2.11	1.94	1.54	1.91	2.10	1.93
H9a	1.71	1.48	1.53	1.53	1.25	1.64	1.41	1.48	1.44	1.16	1.72	1.55	1.90	2.11	1.82	1.54	1.54	2.10	1.81
H9s	1.71	1.86	2.12	2.43	2.29	1.65	1.86	2.26	2.62	2.45	1.73	1.56	1.97	2.12	1.91	1.54	1.54	2.10	1.88
H10a	1.71	1.64	1.68	1.76	1.70	1.48	1.41	1.49	1.55	1.49	1.54	1.55	1.56	1.62	1.56	1.72	1.73	1.79	1.73
H10e	1.71	1.65	1.67	1.76	1.67	1.86	1.86	1.90	1.95	1.80	1.54	1.56	1.58	1.66	1.60	1.73	1.75	1.83	1.77

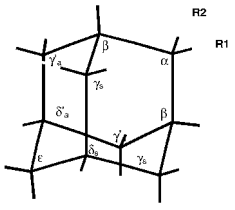
substituents lead to much larger α-effects than methyl groups while other effects vary with the substituent but do not deviate significantly in magnitude and sign.

It appears that, as was observed for the methyl group,[2] substituents on the 2-carbon result in considerable *γ-gauche* effects, shielding the respective carbon nuclei by approximately 6 ppm (Table 4). Hydrogen chemical shifts calculated by the CHARGE program also reflect these steric effects, as is readily apparent from comparison of chemical shifts for geminal hydrogens (Table 3). As observed for 2-methyladamantane,[2] hydrogen nuclei under compression are deshielded; thus the 'inside' hydrogens on the *β*-carbon that interact with the substituent are easily identified. In contrast to that observed for carbon, the magnitude of this effect varies considerably, following qualitatively the 'size' (i.e. approximate volume and shape) of the substituent as exemplified by comparison of methyl and bromo substituents to evaluate the respective volume and of hydroxy and methoxy for the respective shapes. These results can be rationalized by the different factors that are responsible for the respective chemical shift differences.[15] Shielding of carbon nuclei arises from changes in bond angles and dihedral angles[16] and also carbon–hydrogen bond polarization, whereas if significant reductions in C—H bond lengths are observed, as is the case here, deshielding of hydrogen nuclei is due principally to bond polarization.[15]

The effect of different substituents on the 1-carbon of adamantane may be compared with that of the methyl

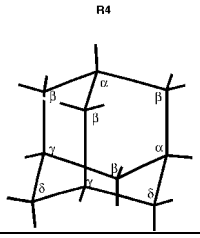
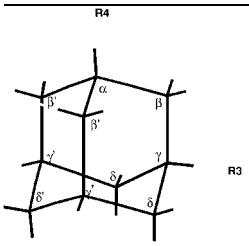
Table 4. Substituent effects on the 2-carbon

Structure		**2** R1 = CH_3	**3** OH	**4** Br	**5** OCH_3	**6** NHAc
	α	1.3	36.9	25.9	45.5	15.7
	β	5.5	6.2	8.0	3.0	3.6
	γ	−6.4	−6.6	−6.1	−6.3	−5.8
	γ′	1.8	−1.1	1.0	−1.2	−0.5
	δ	0.1	−0.7	−0.8	−0.9	−1.1
	δ′	−0.2	−1.2	−1.5	−0.9	−1.2

		8 R1 = CH_3	**9** OH	**10** Br
	α	—	34.6	43.1
	β	3.4	5.3	8.2
	γ_s	−6.3	−6.5	−5.0
	γ'_a	1.8	3.7	4.5
	δ_s	−0.6	−1.1	−1.0
	δ'_a	−1.0	−1.0	−1.2
	ε	0.5	−0.3	—

R_2 = CH_3.

Table 5. Substituent effects on a the 1-carbon

Structure		**19** R4 = CH_3	**20** OH	**21** Br	**22** OCH_3	**23** NHAc
	α	1.2	39.4	38.0	43.4	23.1
	β	6.8	7.5	11.6	3.4	3.7
	γ	0.4	2.3	4.1	2.2	0.9
	δ	−0.9	−1.7	−2.1	−1.1	−1.4
		15 R4 = OH	**16** Br			
	α	40.0	36.8			
	β	7.6	11.3			
	β'	7.7	11.5			
	γ	−1.3	5.3			
	γ'	2.1	3.6			
	δ	−1.3	−2.1			
	δ'	−1.5	−2.2			

R3 = CH_3.

group in Table 5. As expected, large α-effects are observed for electronegative substituents, although for bromo this effect is considerably higher than that for substituents on the 2-carbon. Other effects do not seem to follow any specific pattern.

Calculations of bond lengths and charge distributions are included in the supplementary material and may throw some light on the origin of these effects. As expected, α-effects are clearly related to electronegativity, although if this were the sole factor, α-effects for hydroxy and methoxy substituents should be comparable and considerably larger than for bromo, which, in turn, should be slightly smaller than for acetamide. There is much less charge on the α-carbon of 1-bromoadamantane than on the corresponding carbons of the hydroxy, methoxy or acetamide derivative. The large α-effect for the bromo substituent should therefore be almost entirely due to the large C—Br bond length (2.016 Å for 1-bromoadamantane and 2.009 Å for 2-bromoadamantane are by far the longest carbon–substituent bonds in the series). This rationalization is also in agreement with the larger 1-bromo over 2-bromo α-effects. Other effects are consistent with relative charge of the α-carbon on the other compounds, although their relative magnitudes should probably result in smaller chemical shift differences between hydroxy and methoxy derivatives.

The large β-effect of the 1-methyl substituent was ascribed to the significant increase in length of the Cα—Cβ bonds while other bond lengths only decrease very slightly.[2] This is clearly not the case with more electronegative substituents since they experience a reduction in their respective Cα—Cβ bond lengths. For substituents bound to oxygen or nitrogen, β-effects are subject to hyperconjugation with lone pairs and concomitant charges in bond lengths, angles and charge distributions which can be significant for certain conformations.[12,13] On the other hand, for the bromo substituent, reduction in Cα—Cβ bond lengths is compensated by a significant increase in the Cβ—Cγ bond lengths.

Large remote effects are also worthy of comment. Where substituent effects lead to changes in bond angles and dihedral angles, these factors must be taken into account,[16] and a distinction between different contributions is considerably more difficult. Variations in bond lengths are observed on introduction of substituents on the γ-positions and variations in carbon-13 chemical shifts almost certainly result from changes in geometry rather than other types of substituent effects more commonly invoked.[14] Nevertheless, some effects are perfectly clear, such as the considerably larger long-range steric effect of bromo substituents over methyl groups on hydrogens on the δ-carbon. Once located, these effects can be readily associated with the factors responsible for steric effects by comparison of corresponding bond lengths and charge distributions.[15]

Disubstitued adamantanes

The introduction of a second methyl group on the 1- or 2-carbon atom increases the number of steric repulsions. When the methyl group is on the same carbon atom as the substituent, as is the case with 2-substituted adamantanes, an additional interaction between these substituents is observed. For 1-substituted adamantanes, the second

substituent is introduced on one of the γ-carbon atoms, increasing interactions with the groups between substituents and also those in the neighborhood of the new substituent. For disubstituted adamantanes, substituent effects are therefore considered relative to respective methyl adamantanes.

Comparison of mono- and disubstituent effects reveals that, except for the case of bromo derivatives, similar increments are observed irrespective of the presence of a methyl substituent. When a bromo substituent is introduced on the same carbon atom as the methyl group, the α-effect increases by almost 50%. Recourse to bond lengths also provides a rationalization since here the C_2—Br bond of the disubstituted derivatives is 0.045 Å longer than that of monosubstituted derivative, whereas the C_1—Br bond in the disubstituted derivative is only 0.001 Å longer than that of the monosubstituted derivative. Here, too, hydrogen chemical shifts reflect the direction and extent of steric interactions.

NMR CHEMICAL SHIFTS AS PROBES FOR STERIC EFFECTS

As has been shown for these model compounds, steric effects can contribute to substituent chemical shifts for both neighboring and distant nuclei and may be transmitted through space or through bonds. Their relative importance is proportional to factors related to changes in shielding of particular nuclei. The effect of electronegative atoms predominates when they are bonded to carbon nuclei or close in space to hydrogen nuclei and may be reinforced or attenuated by steric effects. In all other situations NMR chemical shifts respond mainly to steric effects, carbon nuclei reflecting mainly changes in geometry (bond lengths and angles) and hydrogen nuclei reflecting mainly changes in charge distribution. Taken together, these chemical shifts clearly reflect the extent and direction of steric interactions associated with different types of substituents.

Acknowledgements

P.R.S. has a fellowship from the CNPq. J.D.Y. has a fellowship from PIBIC/CNPq. This work was supported by Grant 124/06 from the Programa de Apoio a Núcleos de Excelência (PRONEX). We are grateful to Professor R. Abraham for use of the CHARGE program and Professor R. Rittner for assistance with its use.

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