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^{1}H chemical shifts in NMR. Part 24[†]—proton chemical shifts in some *gem*-difunctional compounds: 3-*endo*- and 3-*exo*-substituted norbornanones

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ABSTRACT: The complete assignment of the ^{1}H and ^{13}C NMR chemical shifts, from 2D techniques and spectra recorded at 500 MHz, for 3-substituted norbornanones with Cl, Br, I, SMe and SeMe substituents at *endo* and *exo* positions and 3-*exo*-hydroxynorbornanone is reported. The observed ^{1}H chemical shifts are compared with the corresponding calculated values using the semi-empirical CHARGE method and *ab initio* calculations at the B3LYP/6–311++G(d,p) theory level. The molecular geometries were obtained through Density Functional Theory (DFT) methods. Good agreement between the experimental and both sets of calculated values is observed with the CHARGE calculations being more accurate for this series. This illustrates the utility of the CHARGE program for chemical shift assignments and also as a tool for the elucidation of chemical structures. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: ^{1}H and ^{13}C NMR; norbornanones; NMR calculations; GIAO; CHARGE

INTRODUCTION

The influence of the carbonyl group on the chemical shifts of neighbouring protons has been of interest since the early days of NMR spectroscopy, the low-field chemical shift of the aldehyde proton being a conspicuous example. This was explained as due to the carbonyl anisotropy and the standard description of this anisotropy due to Jackman[2] is one of the most well known illustrations in NMR spectroscopy. The question of an appropriate description of the carbonyl anisotropy has been recently reviewed,[1b] but a brief account of the main related papers is also given here.

Jackman[2] had suggested that there is a large diamagnetism in the direction normal to the nodal plane of the π-orbitals, whereas Pople's[3] calculations indicated a paramagnetism centred on the carbon atom, large in the x direction and the largest diamagnetism on the O atom in the z direction (i.e. along the C=O bond). These and other early investigations are well reviewed by Bothner-By and Pople.[4]

The general carbonyl group (R_1COR_2) has no elements of symmetry and therefore has, in principle, three different magnetic susceptibilities (χ_x, χ_y and χ_z) along the three principal axes. A number of investigations, commencing with that of Zurcher,[5] have used this description of the C=O anisotropy with the McConnell[6] equation together with the electric field effect of the C=O to explain the observed substituent-induced chemical shifts (SCS) of the carbonyl group in ketones.[7–11] More recent analysis[1b] used the CHARGE program, which includes the carbonyl anisotropy and electric field plus an oxygen but not carbon steric term. Version CHARGE8c is used in this study.

A general calculation of the ^{1}H chemical shifts for carbonyl compounds using the *ab initio* gauge independent atomic orbital (GIAO) method has not been reported to date, the basis set dependence of such calculations being a severe problem. A recent investigation by Lampert *et al.*[12] for phenol and benzaldehyde derivatives (15 compounds) led to deviations of *ca.* 0.5–1.0 ppm depending on the procedure and basis set used and this may well represent the limit of accuracy of such calculations.

Most of the above investigations considered only aliphatic ketones and they therefore obtained the anisotropy for an isolated saturated carbonyl group. However, the simultaneous presence of a carbonyl group and a substituent attached to the same carbon results in changes in the carbonyl electronic density, which has been explained by the occurrence of orbital interactions.

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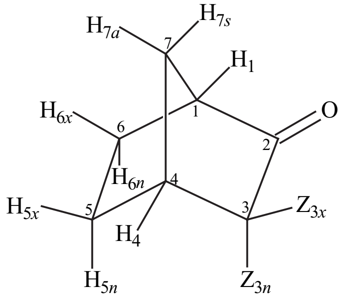
[†]For Part 23 see Ref. [1a]

This has been illustrated by the anomalous substituent chemical shifts observed for several series of α-substituted carbonyl compounds.[13]

Camphor derivatives are useful compounds for the study of ^{1}H chemical shifts, because they have a rigid geometry and all protons are non-equivalent and reasonably well resolved in high-field NMR spectra. The ^{1}H NMR chemical shifts for the α-halocamphors, from spectra at 600 MHz, have been published,[14] and also the corresponding ^{13}C chemical shifts for a series of α-substituted camphors bearing 10 different substituents including the halogens.[15] The calculated ^{1}H chemical shifts for the parent compounds norbornane and camphor have been obtained, through the CHARGE routine, and showed very good agreement with the experimental results.[11,16]

The norcamphors or norbornanones are better models for such calculations, since they do not have the three methyl groups attached to C-1 and C-7, and, thus, there is no additional steric interaction with a substituent on the C-3 carbon atom. Therefore, we present here a study of these compounds all of which have a rigid geometry, with no unusual steric effects, and bearing two *geminal* functional groups: the 3-*endo*- and 3-*exo*-substituted norbornanones (Z = Cl, Br, I, OH, SMe and SeMe) (Scheme 1). They were chosen as a probe to check whether the CHARGE program, properly parametrised for the carbonyl group,[16] can be used to estimate the proton chemical shifts for this series of disubstituted compounds. We also compare the chemical shifts predicted by CHARGE with those calculated by the GIAO method.

It must be emphasised that despite the compounds having been known for some decades (except the *endo* iodo derivative and both isomers of methylthio and methylseleno derivatives) the papers on these compounds[17–22] do not include the corresponding ^{1}H-NMR data. In several instances only the chemical shift for the H-3 proton is given,[20,21,23] or for groups of protons as unresolved multiplets.[22,24,25]



1: Z_{3x}=H; Z_{3n}=H
2: Z_{3x}=Cl; Z_{3n}=H
3: Z_{3x}=H; Z_{3n}=Cl
4: Z_{3x}=Br; Z_{3n}=H
5: Z_{3x}=H; Z_{3n}=Br
6: Z_{3x}=I; Z_{3n}=H
7: Z_{3x}=H; Z_{3n}=I
8: Z_{3x}=OH; Z_{3n}=H
9: Z_{3x}=SMe; Z_{3n}=H
10: Z_{3x}=H; Z_{3n}=SMe
11: Z_{3x}=SeMe; Z_{3n}=H
12: Z_{3x}=H; Z_{3n}=SeMe

Scheme 1. Molecules studied and their numbering

THEORY

As the theory has been given previously[1b,11,16] only a brief summary of the latest version (CHARGE8c) will be given here. The theory distinguishes between short-range substituent effects over one, two and three bonds, which are attributed to the electronic effects of the substituents, and long-range effects due to the electric fields, steric effects and anisotropy of the substituents.

Short-range effects

The CHARGE scheme calculates the effects of neighbouring atoms on the partial atomic charge of the atom under consideration based upon classical concepts of inductive and resonance contributions. If we consider an atom I in a four-atom fragment I-J-K-L the partial atomic charge on I (q_I) is due to three effects. There is an α effect from atom J given by the difference in the electronegativity of atoms I and J. A β effect from atom K proportional to both the electronegativity of atom K and the polarisability of atom I. There is also a γ effect from atom L given by the product of the atomic polarisabilities of atoms I and L for I = H and L = F, Cl, Br, I. However, for chain atoms (C, N, O, S etc.) the γ effect (i.e. C—C—C—H) is parameterised separately and is given by $A + B\cos\theta$ where θ is the C—C—C—H dihedral angle and A and B empirical parameters. Full details including the appropriate equations are given in Ref. [16].

The total charge is given by summing these effects and the partial atomic charges (q_I) converted to shift values using the equation

$$\delta = 160.84q_I - 6.68 \tag{1}$$

Long-range effects

The effects of distant atoms on the proton chemical shifts are due to steric, anisotropic and electric field contributions. H—H steric interactions are shielding in alkanes and deshielding in aromatics and X—H (X = C, O, Cl, Br, I) interactions deshielding, according to a simple r^{-6} dependence:

$$\delta_{\text{steric}} = a_S/r^6 \tag{2}$$

where a_S is the steric coefficient for any given atom.

The effects of the electric field of the C—X bonds (X = H, F, Cl, Br, I, O) on the C—H protons are obtained from the component of the electric field along the C—H bond. The electric field for a single bonded atom (e.g. =O) is calculated as due to the charge on the oxygen atom and an equal and opposite charge on the attached carbon atom. The vector sum gives the total electric field at the proton and the component of this field along the C—H bond is proportional to the proton chemical shift.

The magnetic anisotropy of a bond with cylindrical symmetry (e.g. C≡C) is obtained from the appropriate McConnell[6] equation:

$$\delta_{\text{anis}} = \frac{\Delta\chi(3\cos^2\varphi - 1)}{3R^3} \tag{3}$$

In Eqn (3) R is the distance from the perturbing group to the nucleus of interest in Å, φ is the angle between the vector R and the symmetry axis and $\Delta\chi$ the molar anisotropy of the C≡C bond. ($\Delta\chi = \chi_{\text{parl}} - \chi_{\text{perp}}$) where χ_{parl} and χ_{perp} are the susceptibilities parallel and perpendicular to the symmetry axis, respectively.

For a non-symmetric group such as the carbonyl group, Eqn (3) is replaced by the full McConnell equation:

$$\delta_{\text{anis}} = \frac{[\Delta\chi_{\text{parl}}(3\cos^2\theta_1 - 1) + \Delta\chi_{\text{perp}}(3\cos^2\theta_2 - 1)]}{3R^3} \tag{4}$$

where θ_1 and θ_2 are the angles between the radius vector R and the x and z axes, respectively and $\Delta\chi_{\text{parl}}$ ($\chi_z - \chi_x$) and $\Delta\chi_{\text{perp}}$ ($\chi_y - \chi_x$) are the parallel and perpendicular anisotropy for the C═O bond, respectively.

The effect of the excess π electron density at a given carbon atom on the proton chemical shifts of the neighbouring protons is given by Eqn (5) where Δq_α and Δq_β are the excess π electron density at the α and β carbon atoms, respectively. The π electron densities are calculated using Huckel theory parameterised to reproduce the values obtained from ab initio calculations.[1b]

$$\delta_\pi = 10.0\,\Delta q_\alpha + 2.0\,\Delta q_\beta \tag{5}$$

The above contributions are added to Eqn (1) to give the calculated shift of Eqn (6).

$$\delta_{\text{total}} = \delta_{\text{charge}} + \delta_{\text{steric}} + \delta_{\text{anis}} + \delta_{\text{el}} + \delta_\pi \tag{6}$$

APPLICATION TO ALICYCLIC DIFUNCTIONAL COMPOUNDS

For the norbornanones considered here all the short-range effects, C(X)—C═O, have already been parametrised in previous papers of this series.[16,26,27] The electric field effect is calculated directly from the partial atomic charges, thus the only long-range effects to consider are the parallel and perpendicular anisotropies of the carbonyl group and the CO steric effect. The steric effect of the aliphatic CO group was found to be due solely to the carbonyl oxygen. We assume the same for these alicyclic systems and also use the values obtained previously for the carbonyl group anisotropy and the steric coefficient for the carbonyl oxygen, i.e. the coefficient a_S in Eqn (2) for the carbonyl oxygen.[1b,11,16] The steric effect of selenium was fitted with a value of a_S of 100.0 Å.[6]

EXPERIMENTAL

Compounds

For the separation of the diastereoisomers a HPLC Waters PrepLC 4000, with a C-18 100 Å apolar column, and UV–Vis Waters 484 detector, was used. Separations of halonorbornanones isomers by preparative HPLC were performed with methanol–water (4:1) as eluent and to 3-methylthio and 3-methylselenonorbornanones isomers with methanol–water (1:1).

The 3-*exo*-chloronorbornanone (**2**) compound was obtained from the reaction of norbornanone and sulphuryl chloride,[28] being purified through column chromatography (70–230 silica gel, Aldrich, and $CHCl_3$ as eluent), yield 50%. The 3-*endo*-chloronorbornanone (**3**) was obtained by epimerisation of **2** using sodium methoxide in methanol. The isomers were obtained as a 2:1 (*exo*:*endo*) mixture, and compound **3** was isolated by HPLC which led to 7.5% of the pure *endo*-isomer. 3-*exo*-bromonorbornanone (**4**) was prepared by reacting norbornanone with bromine in diethyl ether and purified by column chromatography (70–230 silica gel, Aldrich, and $CHCl_3$ as eluent), yield 72%. The epimerisation of **4** led to a 1:1 mixture of two isomers, which were also separated by HPLC, yielding 23% of the pure *endo*-isomer. For the preparation of the *exo*-iodo derivative, an iodine solution in THF was added to the lithium enolate of norbornanone.[14] The mixture of diasteroisomers was obtained in 71% yield, which was analysed by GC-MS, showing a 3:1 proportion of the *exo*- (**6**) to the *endo*-isomer (**7**). The isomers were separated by HPLC. The compound **8** (3-*exo*-hydroxynorbornanone) was prepared according Jauch,[25] by the reaction of *m*-chloroperbenzoic acid with norbornanone trimethylsilyl enol ether in dry pentane. The 3-*exo*-methylthio derivative (**9**) was prepared by Scholz's[29] method, being purified by distillation (b.p. 86 °C/1.6 mmHg), yield 47%. The epimerisation of (**9**) led to a 1:1 mixture of two isomers *exo* and *endo*, which were also separated by HPLC. The preparation of 3-*exo*-methylselenonorbornanone was performed by Liotta[30] method and purified by column chromatography flash (230–400 silica gel, Aldrich, and hexane-ether 9:1 as eluent), yield 22%. 3-*endo*-methylselenonorbornanone (**12**) was obtained by epimerisation of **11** and isolated by HPLC.

Spectra

^{1}H- and ^{13}C-NMR spectra were obtained on a Varian INOVA 500 spectrometer and Bruker DRX 500 operating at 499.88 and 500.13 MHz for ^{1}H and 125.70 and 125.77 MHz for C^{13}, respectively. DEPT, gCOSY, gHSQC and gHMBC experiments were also performed. The spectra were recorded in 20 mg cm^{-3} $CDCl_3$ solutions with a probe temperature of *ca.* 300 K and referenced to TMS. Typical running conditions (^{1}H spectra) were 128 transients, spectral width 3250 Hz and 32 K data points zero-filled to 128 K. For the 2D experiments were conducted using the standard Varian sequences. ^{13}C spectra were recorded using 512 transients, spectral width 32,000 Hz and 128 K data points zero-filled to 512 K. For the gHMBC experiment a J value of 8 Hz was used.

Theoretical calculations

All the structures were minimised using the Gaussian 98W program.[31] For the SMe and SeMe derivatives were constructed the potential energy surfaces (dihedral CH_3—Z—C_3—C_2) and was obtained two possible conformers to *exo* isomers and three possible conformers to *endo* isomers. All the compounds, except iodine derivatives were optimised at B3LYP/6–311+G(d,p) level of theory. For the iodine derivatives the 6–311+G(d,p) basis set could not be used. In this case the 3–21G basis set was used.

The chemical shifts were referenced to methane (minimised and calculated in the same manner) and converted to TMS using the methane experimental chemical shift ($\delta = 0.23$ ppm). In both programs, the chemical shifts to SMe and SeMe derivatives, were calculated using the weight average of the chemical shifts to each conformer.

The ^{1}H chemical shifts were calculated with GIAO method and CHARGE8c program. The latter is available as part of NMRPredict,[32] a modelling, ^{1}H and ^{13}C software package.

SPECTRAL ASSIGNMENTS

The assignments of the spectra of the parent compound, norbornanone (**1**), had been already reported from the study of various deuterated norbornanone derivatives,[33] and recently confirmed.[11] The spectra of the remaining compounds (**2–12**) were assigned using the well known substituent effects and assisted by DEPT, gCOSY, gHSQC and gHMBC experiments, as needed. The experimental ^{1}H and ^{13}C chemical shifts are presented in Tables 1 and 2, respectively.

RESULTS AND DISCUSSION

We note that in Table 1 while some protons present almost the same chemical shifts as the parent compound (**1**), others are remarkably affected by the substituent. Thus, the average values for H-1 (2.7), H-4 (2.7), H-6_n (1.6) and H-6_x (1.8) are very close to the ones of compound **1** (2.6, 2.7, 1.5 and 1.8, respectively). However, the chemical shifts for the remaining protons are deshielded either in relation to **1** or from a set (*exo* or *endo*) in relation to the other set. Thus, H-5_n is deshielded in relation to H-5_x (for the *endo* derivatives), and H-5_x in relation to H-5_n (for the *exo* derivatives), by ~0.5 ppm. For H-7_s and H-7_a there is a deshielding effect of 0.2 ppm for the *endo* derivatives in relation to **1**, while for the *exo* derivatives this occurs just for H-7_s (~0.6 ppm). These effects are almost the same regardless of the substituent. However, for H-3_n and H-3_x chemical shifts, which are highly affected by the substituent, the deshielding effect increases with the size of the substituent atom (for O, Cl, Br and I). Indeed for the SMe and SeMe derivatives the deshielding increases with the atom polarisability. This effect is larger for the *endo* compounds.

The substituent effect on the two protons 5, for both series, is due to all the long-range effects and not just to the steric effect since they are very similar for all substituents. A smaller but similar effect is observed for the proton H-7_s of the *exo* compounds. For the proton H-7_a, which is far from the substituent in the *endo*-derivatives, the *W* arrangement between H-7_a and the

Table 1. ^{1}H Chemical Shifts (ppm)[a] for 3-*endo*- and 3-*exo*-substituted norbornanones

Substituent		Atom										
		1	3_x	3_n	4	5_x	5_n	6_x	6_n	7_s	7_a	CH_3
H		2.59 (d)	2.06 (dd)	1.84 (dd)	2.67 (s)	1.80 (m)	1.44 (m)	1.81 (m)	1.52 (dd)	1.73 (m)	1.56 (d)	—
Cl	*exo*	2.72 (s)	—	3.67 (d)	2.73 (s)	1.95 (m)	1.49 (m)	1.85 (m)	1.55 (m)	2.27 (m)	1.60 (m)	—
	endo	2.76 (d)	4.13 (d)	—	2.81 (s)	1.69 (m)	2.03 (m)	1.91 (m)	1.58 (m)	1.83 (m)	1.78 (m)	—
Br	*exo*	2.73 (d)	—	3.83 (d)	2.79 (d)	1.97 (m)	1.52 (m)	1.84 (m)	1.57 (m)	2.30 (m)	1.63 (m)	—
	endo	2.75 (d)	4.32 (d)	—	2.83 (s)	1.74 (m)	2.06 (m)	1.89 (m)	1.56 (m)	1.91 (m)	1.85 (m)	—
I	*exo*	2.69 (dd)	—	4.14 (d)	2.81 (s)	1.90 (m)	1.59 (m)	1.81 (m)	1.57 (m)	2.28 (m)	1.68 (m)	—
	endo	2.73 (d)	4.64 (s)	—	2.77 (s)	1.81 (m)	2.00 (m)	1.74 (m)	1.48 (m)	2.02 (m)	1.94 (m)	—
OH	*exo*	2.60 (dd)	—	3.52 (dd)	2.56 (d)	1.81 (m)	1.42 (m)	1.83 (m)	1.50 (m)	2.17 (m)	1.57 (m)	—
Sme	*exo*	2.67 (d)	—	2.72 (d)	2.53 (d)	1.88 (m)	1.50 (m)	1.86 (m)	1.55 (m)	2.20 (m)	1.48 (m)	2.25 (s)
	endo	2.68 (d)	3.20 (d)	—	2.76 (s)	1.63 (m)	1.95 (m)	1.86 (m)	1.52 (m)	1.77 (d)	1.71 (d)	2.22 (s)
SeMe	*exo*	2.68 (d)	—	3.02 (d)	2.57 (d)	1.88 (m)	1.48 (m)	1.82 (m)	1.56 (m)	2.18 (m)	1.50 (d)	2.17 (s)
	endo	2.69 (d)	3.47 (d)	—	2.74 (d)	1.53 (m)	1.90 (m)	1.85 (m)	1.68 (m)	1.82 (d)	1.76 (d)	2.13 (s)

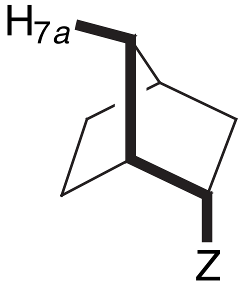
[a] In $CDCl_3$ as solvent. Signal multiplicities are indicated as singlet (s), doublet (d), double doublet (dd) and multiplet (m).

Table 2. ^{13}C Chemical Shifts (ppm)[a] for 3-*endo*- and 3-*exo*-substituted norbornanones

Substituent		Atom							
		1	2	3	4	5	6	7	CH_3
H		49.9	218.3	45.3	35.4	27.2	24.2	37.7	—
Cl	*exo*	48.6	210.5	59.3	44.2	25.6	23.7	34.3	—
	endo	48.8	210.2	63.5	42.2	20.8	25.6	34.4	—
Br	*exo*	49.1	210.8	49.6	44.5	26.3	23.5	35.0	—
	endo	48.3	210.2	55.2	44.2	22.7	25.1	35.7	—
I	*exo*	49.8	212.2	28.1	45.7	27.1	23.0	36.5	—
	endo	47.2	211.9	35.3	42.8	26.5	24.6	36.2	—
OH	*exo*	48.1	217.5	75.7	41.5	24.3	23.5	34.3	—
SCH_3	*exo*	49.0	213.8	53.6	41.5	27.1	24.8	35.5	15.2
	endo	50.1	214.9	57.3	40.1	21.9	25.2	36.5	15.4
$SeCH_3$	*exo*	49.6	214.8	46.2	42.1	27.7	24.7	36.4	5.2
	endo	49.8	215.6	50.3	40.6	23.8	24.9	37.4	4.5

[a] In $CDCl_3$ as solvent.

halogen atom seems to be responsible for the favourable interaction between the involved orbitals (Scheme 2).[34] The complete SCS data for all 3-substituted norbornanones studied are given in Table 3.



Scheme 2. *W* arrangement between H-7*a* and the substituent *Z*

Despite the apparent absence of a steric effect between H-5$_n$ and the substituent, there is a shielding effect for the C-5 chemical shift (Table 2) in compounds **3** (*endo*-Cl), **5** (*endo*-Br), **10** (*endo*-SMe), **12** (*endo*-SeMe), and not for compound **7** (*endo*-I). This could indicate a steric compression between the substituent and H-5$_n$, which does not occur for the iodo-derivative due to the long C—I bond length in comparison to C—Z (Z = Br, Cl, S, Se) bonds. No significant shielding or deshielding effect is observed for C-1, C-4, C-6 and C-7, within the two sets of the substituted norbornanones (**2**–**12**). Obviously, C-3 is deshielded due to the α-substituent effect, but to a smaller extent than for the corresponding norbornanes, which may due to the occurrence of an interaction between n_X and π^*_{CO} orbitals.[13]

The experimental chemical shifts are compared with the CHARGE and *ab initio* GIAO calculated values given

Table 3. SCS values for 3-substituted norbornanones (ppm)[a]

	Substituent											
	endo						*exo*					
Atom	H[b]	Cl	Br	I	SMe	SeMe	Cl	Br	I	OH	SMe	SeMe
1	2.59	0.17	0.16	0.14	0.09	0.10	0.13	0.14	0.10	0.01	0.08	0.09
3_x	2.06	2.07	2.26	2.58	1.14	1.14	—	—	—	—	—	—
3_n	1.84	—	—	—	—	—	1.83	1.99	2.30	1.68	0.88	1.18
4	2.67	0.14	0.16	0.10	0.09	0.07	0.06	0.12	0.14	−0.11	−0.14	−0.10
5_x	1.80	−0.11	−0.06	0.01	−0.17	−0.27	0.15	0.17	0.10	0.01	0.08	0.08
5_n	1.44	0.59	0.62	0.56	0.51	0.46	0.05	0.085	0.15	−0.02	0.06	0.04
6_x	1.81	0.10	0.08	−0.07	0.05	0.04	0.04	0.03	0.00	0.02	0.05	0.01
6_n	1.52	0.06	0.04	−0.04	0.00	0.16	0.03	0.05	0.05	−0.02	0.03	0.04
7_s	1.73	0.10	0.18	0.29	0.04	0.09	0.54	0.57	0.55	0.44	0.47	0.45
7_a	1.56	0.22	0.29	0.38	0.15	0.20	0.04	0.07	0.12	0.01	−0.08	−0.06
CH_3[c]	—	—	—	—	2.22	2.13	—	—	—	—	2.25	2.17

[a] In $CDCl_3$ as solvent.
[b] δ for the norbornanone molecule.
[c] δ for the substituent methyl protons.

Table 4. Experimental versus calculated ^{1}H chemical shifts (ppm) for 3-exo-substituted norbornanones and root-mean-square error (r.m.s)

Substituent		Atom										
		1	3_n	4	5_x	5_n	6_x	6_n	7_s	7_a	CH_3	r.m.s
Cl *exo*	$CDCl_3$	2.72	3.67	2.73	1.95	1.49	1.85	1.55	2.27	1.60	—	—
	CHARGE	2.78	3.68	2.74	1.92	1.51	1.79	1.66	2.45	1.51	—	**0.08**
	GIAO	2.36	3.37	2.41	1.83	1.29	1.72	1.39	2.19	1.36		**0.21**
Br *exo*	$CDCl_3$	2.73	3.83	2.79	1.97	1.52	1.84	1.57	2.30	1.63	—	—
	CHARGE	2.78	3.94	2.79	1.90	1.50	1.76	1.62	2.54	1.52	—	**0.10**
	GIAO	2.42	3.54	2.48	1.89	1.34	1.72	1.40	2.25	1.35		**0.20**
I *exo*	$CDCl_3$	2.69	4.14	2.81	1.90	1.59	1.81	1.57	2.28	1.68	—	—
	CHARGE	2.76	4.16	2.84	1.87	1.48	1.75	1.61	2.55	1.51		**0.12**
	GIAO	2.50	3.20	2.41	1.89	1.30	1.68	1.35	2.26	1.34		**0.29**
OH *exo*	$CDCl_3$	2.60	3.52	2.56	1.81	1.42	1.83	1.50	2.17	1.57	—	—
	CHARGE	2.70	3.55	2.50	1.92	1.48	1.88	1.79	2.08	1.62		**0.12**
	GIAO	2.29	3.40	2.42	1.77	1.30	1.74	1.41	2.14	1.41		**0.14**
SMe *exo*	$CDCl_3$	2.67	2.72	2.53	1.88	1.50	1.86	1.55	2.20	1.48	2.25	—
	CHARGE	2.74	2.95	2.92	1.89	1.40	1.82	1.62	2.29	1.59	2.12	**0.16**
	GIAO	2.41	2.26	2.28	1.82	1.37	1.73	1.42	2.24	1.42	2.22	**0.21**
SeMe *exo*	$CDCl_3$	2.68	3.02	2.57	1.88	1.48	1.82	1.56	2.18	1.50	2.17	—
	CHARGE	2.74	3.08	2.58	1.87	1.41	1.80	1.61	2.04	1.59	2.24	**0.07**
	GIAO	2.47	2.51	2.29	1.85	1.39	1.73	1.44	2.21	1.26	2.11	**0.22**

in Tables 4 and 5. There is a very good agreement between the experimental and CHARGE data. Only for a few cases, as for the 3-*endo* and 3-*exo* protons in SMe derivatives, were deviations larger than 0.2 ppm observed, but most data showed small deviations ranging from 0.01 to 0.13 ppm. For all 11 compounds with 163 different ^{1}H chemical shifts, the CHARGE gave an r.m.s error ranging from 0.07 to 0.16 ppm, which is satisfactory. There is a significant difference in the calculated shifts of H-5_n and H-6_n in the *exo*-derivatives (r.m.s average = 0.07 ppm) in relation to the *endo*-derivatives (r.m.s average = 0.17 ppm), indicating that the program is overestimating the substituent effects for the last set.

The calculated shifts from the quantum mechanical GIAO calculations are also given in Tables 4 and 5. They are in general less accurate than the CHARGE calculations as it was noted in a previous paper.[35] The 3-21G basis set used for iodo compounds is too inaccurate to be of use in ^{1}H NMR calculations. This suggests that in the halogen family post-third-row atoms (post-Br) cannot

Table 5. Experimental versus calculated ^{1}H chemical shifts (ppm) for 3-*endo*-substituted norbornanones and root-mean-square error (r.m.s)

Substituent		Atom										
		1	3_x	4	5_x	5_n	6_x	6_n	7_s	7_a	CH_3	r.m.s
Cl *endo*	$CDCl_3$	2.76	4.13	2.81	1.69	2.03	1.91	1.58	1.83	1.78		—
	CHARGE	2.77	4.11	2.73	1.66	2.14	1.77	1.74	1.96	1.73	—	**0.10**
	GIAO	2.37	3.90	2.50	1.54	2.08	1.79	1.52	1.53	1.55		**0.20**
Br *endo*	$CDCl_3$	2.75	4.32	2.83	1.74	2.06	1.89	1.56	1.91	1.85		—
	CHARGE	2.77	4.35	2.78	1.69	2.25	1.78	1.75	1.95	1.71	—	**0.09**
	GIAO	2.39	4.16	2.52	1.60	2.18	1.80	1.56	1.61	1.62		**0.19**
I *endo*	$CDCl_3$	2.73	4.64	2.77	1.81	2.00	1.74	1.48	2.02	1.94		—
	CHARGE	2.73	4.60	2.83	1.68	2.28	1.75	1.71	1.95	1.68	—	**0.16**
	GIAO	2.37	4.09	2.25	1.54	2.80	1.66	1.51	1.57	1.71		**0.43**
SMe *endo*	$CDCl_3$	2.68	3.20	2.76	1.63	1.95	1.86	1.52	1.77	1.71	2.22	—
	CHARGE	2.66	3.66	2.97	1.74	2.05	1.80	1.74	1.82	1.71	2.13	**0.12**
	GIAO	2.34	2.65	2.53	1.52	1.95	1.78	1.65	1.55	1.51	2.29	**0.23**
SeMe *endo*	$CDCl_3$	2.69	3.47	2.74	1.53	1.90	1.85	1.68	1.82	1.76	2.13	—
	CHARGE	2.73	3.41	2.94	1.75	1.95	1.78	1.74	1.85	1.74	2.05	**0.11**
	GIAO	2.37	2.94	2.53	1.55	1.80	1.77	1.67	1.60	1.55	2.15	**0.22**

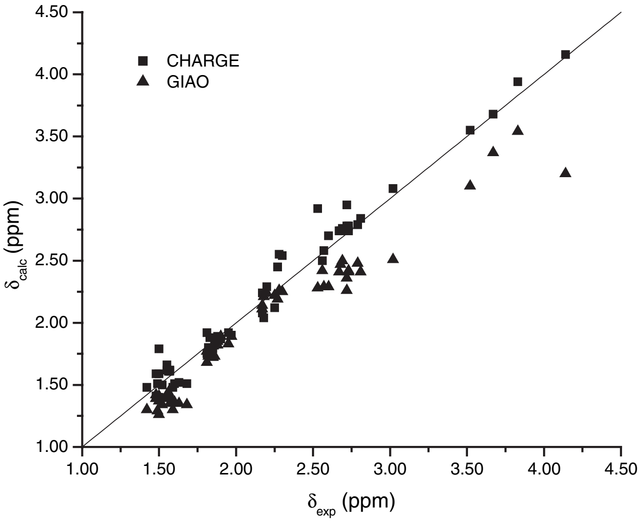


Figure 1. Scatter plot of experimental versus predicted chemical shifts for 3-*exo*-substituted norbornanones

be calculated to any meaningful precision using this method (r.m.s error 0.29 and 0.43 for *exo* and *endo* derivatives, respectively).

To eliminate the importance of a predictor and see how good the correlation between calculated versus experimental data is, we compiled the data set in scatter plots. The scatter plot (Figs. 1 and 2) shows that, in general, the results calculated through the CHARGE program slightly overestimate the observed chemical shifts. Moreover, ^{1}H chemical shifts calculated using the GIAO method are underestimated. The correlation coefficient, *r*, is 0.98 for CHARGE and 0.96 for GIAO. The r.m.s. error values are 0.11 for CHARGE and 0.23 for GIAO. We also analysed the data to see which model produces the greatest number of hits closest to the observed chemical shifts. CHARGE produces the largest number of best hits (75%), while GIAO is better only in 25% of the hits.

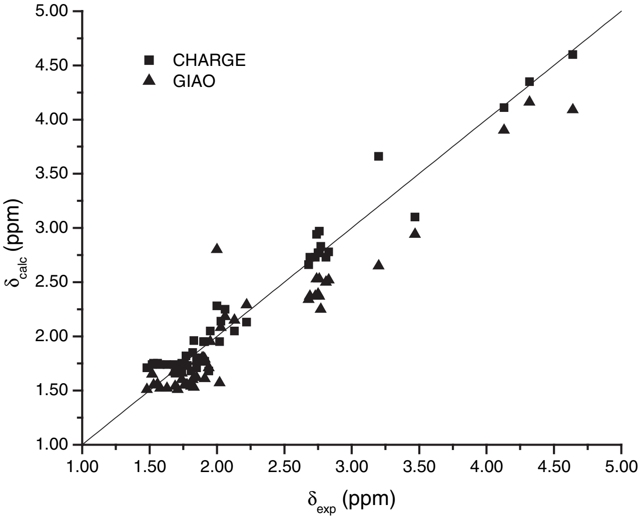


Figure 2. Scatter plot of experimental versus predicted chemical shifts for 3-*endo*-substituted norbornanones

The comparative study for these disubstituted compounds shows that the calculations by CHARGE better reproduce the experimental shifts than the GIAO calculations.

CONCLUSIONS

Unequivocal assignments for the ^{1}H and ^{13}C chemical shifts of the 3-*endo*- and 3-*exo*-substituted norbornanones with Cl, Br, I, SMe and SeMe substituents and 3-hydroxynorbornanone, were deduced from the 1D spectra at 500 MHz, using the DEPT sequence and the 2D gCOSY, gHSQC and gHMBC experiments. The calculated ^{1}H chemical shifts using the CHARGE8c routine were in good agreement with the experimental results. The r.m.s error for each compound was in the range 0.07–0.17. The GIAO are less accurate than the CHARGE calculations when assessed by scatter plots, r.m.s. errors and number of best hits. CHARGE provides a rapid and practical useful tool, which can be used to give reliable ^{1}H chemical shift predictions 3-substituted 2-norbornanones.

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