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Substituent-Induced ^{1}H Chemical Shifts of 3-Substituted Camphors

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The high-field ^{1}H NMR analysis of 3-substituted camphors with OH, OMe, SMe, NHMe, NMe_2 and Me substituents at *endo* and *exo* positions, and also with an oxo substituent, is reported. The substituent-induced chemical shifts (SCS) obtained for these difunctional systems, including those from previous work on 3-halocamphors, were examined in view of multilinear correlations with steric and electronic parameters. The resultant data show a strong contribution from the electric field mechanism, principally for the protons closer to the substituent. Carbonyl group interference on the expected SCS for the α-proton is also observed, with less deshielding than those of substituted bornanes and norbornanes. **© 1997 by John Wiley & Sons, Ltd.**

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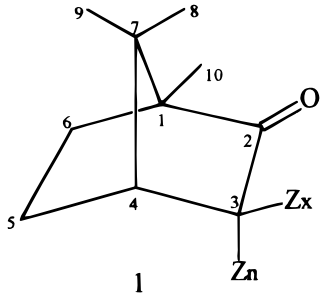
INTRODUCTION

The investigation of the influence of substituents on nuclear chemical shifts through the years has led to a large body of ^{13}C and ^{1}H data. Nevertheless, most of the proton chemical shift data have not been susceptible to interpretation. The major difficulty in the proton studies was that using low-field spectrometers the signals overlap in most of the spectra. Nowadays, high-field NMR allows the study of SCS data with a larger number of substituents and structures.[1–3] Comparative data for a wider range of substituent groups is worth obtaining in order to attempt to assess the possible mechanisms involved in the SCS variations, such as magnetic anisotropy, electric field, steric, inductive and solvent effects.[4–6] Also, the analysis of rigid and well defined structures is more valuable for SCS investigations than of those underlying conformational changes. Various interesting studies have been reported, e.g. for cyclohexane partial structures in steroids by Schneider *et al.*[7] and for bicyclic systems such as adamantanes, norbornanes and bornanes by Abraham and co-workers.[3,8] In most cases, the ^{1}H SCS studies involved halogen, hydroxy and oxo monosubstituents.

In the last few years, we have investigated ^{13}C NMR substituent effects in difunctional compounds. The two functional groups are at vicinal positions such as in 4-*tert*-butyl-2-substituted cyclohexanones,[9] where the carbonyl is a fixed group. The most interesting observation was that the ^{13}C SCS at the α_z and β_{CO} positions do not follow the general trend of the related substituted cyclohexanes, owing to interactions between the carbonyl group and the substituents. To extend these studies to ^{1}H NMR we have recently made a full high-field analysis of the 3-halocamphors,[10] where all protons were assigned and the possible mechanisms involved in the SCS data were considered in the context of multiple regression analyses with the steric (v),[11,12] electric field (σ_F)[13–15] and inductive (λ^e)[16] parameters. Although this treatment on a limited amount of data does not have statistical significance, it has led to good results showing that the operating mechanisms were the same as in the parent halogen-substituted bicycloalkanes,[8] with the exception of the α-proton.

To improve the statistical significance and also to diversify the nature of the substituents, this paper describes the 600 MHz analysis of 3-substituted camphors **1** (Z = OH, OMe, SMe, NHMe, NMe_2 and Me, at *endo* or *exo* positions, and oxo), including the above halogen series in the correlation treatment. The SCS values obtained are also compared with those from the



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cyclohexanone series[17] and with data for substituted cyclohexanes[7] and bicycloheptanes.[8]

RESULTS AND DISCUSSION

The 3-substituted camphor compounds **1** show $^1H,^1H$ coupling patterns very similar to those of the 3-halocamphors,[10] as expected from their structural similarities. Additional signals are present due to the methyl groups (NMe_2, NHMe, OMe, SMe and Me) and acidic protons (OH and NHMe) on the substituents, and splittings due to the vicinal coupling between the H-3 and the methyl substituent (Me) protons. The assignments, supported by NOE difference[18] and 2D (COSY-45 and HETCOR)[19,20] experiments, followed the same methodology which had been applied to the halogen derivatives. All the NMR measurements were made in CCl_4 to minimize possible solvent effects.

The SCS data are given in Table 1 and equations of the form

$$SCS(^1H) = a\sigma_F + bv(\lambda) + c \quad (1)$$

from multilinear treatment with steric and electronic parameters[11–16] are presented in Table 2. The latter include the data from the halogen compounds, but exclude the SCS data from compounds with acidic protons (OH and NHMe, owing to the possibility of forming intramolecular hydrogen bonding), and from the oxo-substituted compound (owing to changes in the C-3 hybridization) and from the protons that do not undergo significant changes (H-6n, H-6x, H-9 and H-10).

Comparison of the coefficients of the present equations with those of the equations for the previous halogen compounds shows an increase in the importance of either the inductive or the steric influence of the substituent. This is not surprising as a larger number of substituents with electronegative atoms (O and N) and bonded to a bulky group (Me) are involved.

The largest low-field shifts are observed at the α-position. The magnitudes of the SCS are very similar for both epimers. The correlation data show the greater importance of the electric field effect, with some contribution from the inductive mechanism. However, for the substituents of the same periodic family, the SCS data present considerable differences, in contrast to the corresponding σ_F values. This can be assigned both to the magnetic anisotropy of the C—Z bond for the substituents with heavier atoms and to the inductive effect for those of larger electronegativity. The exception is the unexpectedly low value for the 3-*endo*-dimethylaminocamphor compound. Another interesting point is that the camphor α-SCS are significantly smaller than those of the corresponding substituted bornanes and norbornanes,[8] reflecting the interference of the carbonyl group in the mechanisms that operate at this position. When comparisons for both substituted camphors and cyclohexanones in relation to the corresponding monosubstituted hydrocarbons are made,[5,8] the largest decrease is observed for larger dihedral angles (ϕ) between the C—Z and C=O bonds. Figure 1 illustrates the SCS changes ($SCS_{cycloketone} - SCS_{cycloalkane}$) for the *endo* and *exo* camphor system ($\phi_{CZ/CO} \approx 50–60°$) and for the equatorial ($\phi_{CZ/CO} \approx 0–10°$) and axial ($\phi_{CZ/CO} \approx 110–120°$) cyclohexanone system (data from AM1 calculations).

The deshielding increase for the heavier substituents due to the magnetic anisotropy is very evident in the 3-halocamphor series (as for the 2-haloheptanes)[8] for both the α- and β-protons. However, this is less evident

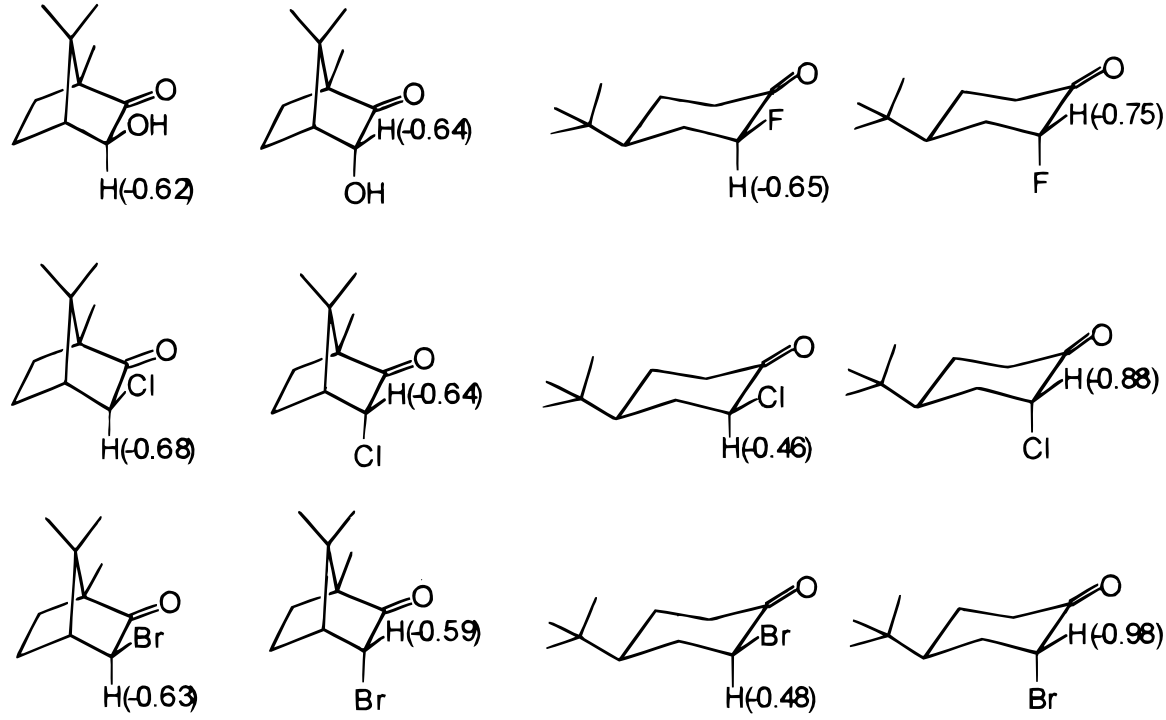

Figure 1. Comparisons between the SCS values for substituted cycloketones and cycloalkanes (values in parentheses are the results for $SCS_{ket} - SCS_{alk}$).

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Table 1. SCS values for 3-substituted camphors (ppm)[a]

		Substituent											
		endo							*exo*				
Proton	H[b]	OH	OMe	SMe	NHMe	NMe_2	Me	=O[c]	OH	OMe	SMe	NHMe	Me
H-3*n*	1.74 (d)	—	—	—	—	—	—	—	1.88 (s)	1.38 (s)	0.91 (s)	0.86 (s)	0.12 (q)
H-3*x*	2.25 (dt)	1.88 (d)	1.29 (d)	0.90 (d)	0.82 (d)	0.02 (d)	0.13 (m)	—	—	—	—	—	—
H-4	2.04 (t)	0.16 (t)	0.12 (t)	0.11 (t)	0.06 (t)	0.02 (t)	−0.11 (t)	0.47 (d)	0.00 (d)	−0.06 (d)	−0.02 (d)	−0.08 (d)	−0.24 (d)
H-5*n*	1.34 (m)	0.64 (m)	0.53 (m)	0.48 (m)	0.57 (m)	0.60 (m)	0.25 (m)	0.29 (m)	0.01 (m)	−0.03 (m)	0.12 (m)	−0.02 (m)	0.02 (m)
H-5*x*	1.93 (m)	−0.33 (m)	−0.35 (m)	−0.19 (m)	−0.40 (m)	−0.32 (m)	−0.21 (m)	0.20 (m)	0.04 (m)	0.02 (m)	0.11 (m)	0.03 (m)	0.04 (m)
H-6*n*	1.38 (m)	0.03 (m)	0.04 (m)	0.12 (m)	−0.09 (m)	0.05 (m)	−0.12 (m)	0.25 (m)	0.03 (m)	−0.03 (m)	0.08 (m)	0.07 (m)	0.09 (m)
H-6*x*	1.62 (m)	0.06 (m)	0.00 (m)	0.01 (m)	−0.01 (m)	−0.05 (m)	−0.03 (m)	0.26 (m)	−0.02 (m)	−0.05 (m)	−0.01 (m)	−0.01 (m)	−0.05 (m)
H-8	0.83 (s)	0.05 (s)	0.01 (s)	0.06 (s)	0.05 (s)	0.01 (s)	0.03 (s)	0.09 (s)	0.14 (s)	0.10 (s)	0.17 (s)	0.11 (s)	0.01 (s)
H-9	0.95 (s)	0.05 (s)	0.03 (s)	0.05 (s)	0.05 (s)	0.02 (s)	0.04 (s)	0.10 (s)	−0.02 (s)	−0.05 (s)	−0.04 (s)	−0.04 (s)	−0.03 (s)
H-10	0.86 (s)	0.02 (s)	−0.02 (s)	0.00 (s)	0.00 (s)	−0.03 (s)	−0.02 (s)	0.20 (s)	0.02 (s)	0.00 (s)	0.02 (s)	0.00 (s)	−0.01 (s)
H-11[d]	—	—	3.49 (s)	2.27 (s)	2.37 (s)	2.24 (s)	1.01 (d)	—	—	3.48 (s)	2.33 (s)	2.45 (s)	1.17 (d)

[a] In CCl_4 as solvent. Signal multiplicities are indicated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and double triplet (dt).
[b] δ for the camphor molecule.
[c] Bornane-2,3-dione.
[d] δ for the protons from the substituent methyl groups.

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Table 2. Parameters[a] and equations from multilinear correlations with the 3-substituted camphor SCS data[b]

Proton	Epimer				r^c
8	*exo*	$0.507\sigma_F$	$+0.444\nu$	−0.216	0.975
5*n*	*endo*	$0.727\sigma_F$	$+0.146\nu$	+0.283	0.812
5*x*	*exo*	$0.232\sigma_F$	$+0.162\nu$	−0.060	0.818
4	*endo*	$0.734\sigma_F$	-0.231ν	+0.033	0.986
4	*exo*	$1.133\sigma_F$	$+0.368\nu$	−0.466	0.977
3*n*	*exo*	$5.103\sigma_F$	$+0.219\lambda^e$	−0.190	0.957
3*x*	*endo*	$5.644\sigma_F$	$-0.033\lambda^e$	−0.175	0.958

[a] Parameters (values for OMe, SMe, NMe_2, Me): steric, ν (0.36, 0.64, 0.43, 0.52); electric field, σ_F (0.25, 0.25, 0.10, 0.00); inductive, λ^e (1.40, 0.75, 1.12, 0.80). See Ref. 10 for the halogen series.
[b] From Table 1, for Z = OMe, SMe, NMe_2, Me and from Ref. 10, for Z = F, Cl, Br, I.
[c] Correlation coefficient.

for the present compounds listed in Table 1 as only a comparison between SMe and OMe substituents can be made. The expected influence of the electric field effect with participation of the steric mechanism at the β-position is confirmed by the good correlations of the H-4 SCS, as shown in Table 2.

Although poor correlation coefficients were obtained for the H-5 protons (0.812 and 0.818; Table 2), the increasing participation of the steric effect against the electric field effect is remarkable, in comparison with the corresponding correlations for the halogen series.[10] This behaviour can be attributed to the preferred conformation of substituent methyl groups in compounds **1**, which is not predicted by the steric and/or electronic parameters. Thus, the expected C_3—Z_{3n} dipole-induced C_5—H_{5n} charge polarization effect[6] is shown to be very dependent on the nature of the substituent. On the other hand, the steric effect plays a very effective role at H-8 for the *exo* substituents, leading to an excellent multilinear correlation (0.975; Table 2), confirming the expected importance of this mechanism at this position.

CONCLUSION

The analysis of the coefficients from the correlations (Table 2) with the previous halogen series[10] show, in addition to the field effect, the importance of the influence of the electronegativity of the second-row elements (F, O, N) for the protons which are closest to the substituent. On the other hand, for the protons far away from the substituent, an increase in importance of the steric mechanism occurs due to the presence of the bulky methyl groups and heavier atoms.

The present data show that the chemical shifts of a proton bonded to a substituted carbon, vicinal to another substituted carbon, do not follow the trends of the corresponding proton in monosubstituted compounds. This can be attributed to either dipolar or orbital interactions between the two vicinal groups.[9] The substituent effects on protons far away from the substituted carbon are not affected by these vicinal group interactions. However, the present data for vicinal-difunctional compounds show that the electric field mechanism plays an important role in the proton substituent-induced shifts, mostly for the protons closer to the substituted carbon. The differences between substituents of the same periodic family are due to the influence of the magnetic anisotropy and of the inductive and steric effects, taking into account the distance and the nature of the substituent.

EXPERIMENTAL

Spectra

The ^1H NMR spectra were recorded in 5 mm tubes (with a coaxial capillary tube containing acetone-d_6, for the lock) in carbon tetrachloride at concentrations of 0.15 mol l^{-1}, with TMS as reference, using a Bruker AM 600 spectrometer, over eight scans with spectral width *ca.* 5400 Hz in 32K memory space, giving a digital resolution of *ca.* 0.33 Hz per point (LB ≈ -1.3, GB ≈ 0.3). The assignment of the chemical shifts from the complex multiplets was achieved by spectral simulation and aided by the inspection of 2D ^1H, ^{13}C correlation spectra.[10,20]

Compounds

Camphor and 2,3-bornanedione were obtained from Aldrich and used without further purification. Purifications by preparative HPLC were performed with *n*-heptane–methyl *tert*-butyl ether (99:1) as eluent.

The 3-methylthio derivatives were prepared by Sholz's method.[21] The epimeric mixture was separated by HPLC, yielding 50% of the *endo* and 40% of the *exo* epimer. Analysis: calculated, C 66.62, H 9.15, S 16.17%; found, C 66.34, H 8.96, S 16.30% (*endo*) and C 66.66, H 9.01, S 15.99% (*exo*). IR (ν_{CO}, cm^{-1}), 1738.2 (*endo*) and 1744.0 (*exo*). Mass spectra ($M^{+\cdot}$), *m/z* 198.

For the preparation of the 3-methyl derivatives, the procedure of Hutchinson and Money[22] was used, followed by HPLC separation of the epimers.

The preparations of 3-*endo*- and 3-*exo*-*N*-methylaminocamphor and the 3-*endo*-*N*,*N*-dimethylaminocamphor were described by Daniel and Pavia.[23] The epimers were separated by column chromatography (silica gel column and chloroform–1% methanol as eluent) and the dimethyl compound was purified by HPLC.

The 3-hydroxy compounds were prepared by the reaction of *m*-chloroperbenzoic acid with camphor trimethylsilyl enol ether in dry hexane.[24] Epimer separation was performed by column chromatography (silica gel column and hexane–5% diethyl ether as eluent).

A mixture of the above 3-hydroxy derivatives (without purification) was subjected to reaction with methyl iodide in dimethyl sulfoxide and solid sodium hydroxide at 25 °C for 1 h. Addition of water, extraction with dichloromethane and by purification by HPLC yielded 33% of 3-*endo*-methoxycamphor and 14% of the corresponding *exo* epimer. Analysis: calculated, C 72.49, H 9.95%; found, C 72.41, H 9.33% (*endo*) and C 72.36, H 9.84% (*exo*). IR (ν_{CO}, cm^{-1}), 1737.10 (*endo*) 1745.90 (*exo*). Mass spectra ($M^{+\cdot}$), *m/z* 182.

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