Proton chemical shifts in NMR. Part 13.[1] Proton chemical shifts in ketones and the magnetic anisotropy and electric field effect of the carbonyl group

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The proton resonance spectra of a variety of cyclic ketones including 2-*tert*-butylcyclohexanone, 4-*tert*-butylcyclohexanone, fenchone, *trans*-1-decalone, androstan-3-one, androstan-17-one, androstane-3,17-dione and androstane-3,11,17-trione were obtained and completely assigned. These data together with previous literature data allowed the determination of the carbonyl substituent chemical shifts (SCS) in a variety of cyclic molecules. These SCS were analysed in terms of the carbonyl electric field, magnetic anisotropy and steric effect for long-range protons together with a model (CHARGE6) for the calculation of the two-bond and three-bond effects.

The anisotropic effect of the carbonyl bond was found to be well reproduced with an asymmetric magnetic anisotropy acting at the carbon atom with values of $\Delta\chi_{parl}$ and $\Delta\chi_{perp}$ of 17.1 and 3.2 (10^{-30} cm^3 molecule^{-1}). This together with the electric field effect of the carbonyl group gave good agreement with the observed proton shifts without the need to invoke any steric effects. The short range effects of the carbonyl group (*i.e.* HCC=O) were modelled by a cos θ function which was found to be dependant on the ring size of the cyclic ketone *via* the CC(O)C bond angle.

This model gives the first comprehensive calculation of the SCS of the carbonyl group. For the data set of *ca.* 200 proton chemical shifts spanning *ca.* 2 ppm the rms error of the observed *vs.* calculated shifts was 0.11 ppm.

Introduction

The influence of the carbonyl group on the chemical shifts of neighbouring protons has been the subject of considerable debate and some controversy since the beginning of organic NMR and the standard descripton of the C=O anisotropy (Fig. 1) must be one of the most well known illustrations in NMR.[2] Despite this interest there is still no definitive investigation of the carbonyl substituent chemical shifts (SCS) in a sufficiently wide variety of compounds to rigorously test the known interactions determining the proton chemical shifts in simple ketones.

The early investigations concentrated on the carbonyl anisotropy and Narasimhan and Rogers[3] concluded that the proton chemical shifts in formamide and DMF were entirely due to the C=O anisotropy. However even the C=O anisotropy was uncertain as Jackman[4] suggested that there is a large diamagnetism in the direction normal to the nodal plane of the π-orbitals whereas Pople's calculations[5] suggested a paramagnetism centred on the carbon atom, large in the *y* direction and the largest diamagnetism on the O atom in the *x* direction (*i.e.* along the C=O bond). An authoritative review of these and other early investigations has been given by Pople and Bothner-By.[6]

In his pioneering treatment of proton chemical shifts, Zurcher[7] was limited to observing only the methyl groups in steroids but concluded that both the C=O bond anisotropy and the electric field effect were needed to explain the observed SCS. Zurcher used the McConnell equation[8] to calculate the C=O anisotropy and also used the carbonyl dipole to calculate the electric field effect. Due to lack of data Zurcher did not consider near (<4 bonds) protons nor did he need to invoke any steric effects of the carbonyl group.

ApSimon and co-workers,[9] again using only the methyl groups of steroids for their data, reformulated the McConnell equation in order to obtain the anisotropy effects on near nuclei (<3 Å away from the substituent). They also found that both anisotropy and electric field effects were necessary to predict the SCS of the carbonyl group. Subsequently Homer *et al.*[10] observed that the original McConnell equation was just as accurate in their investigations. Toyne[11] reviewed the literature calculations of the C=O anisotropy in which the position of the magnetic dipole varied from the carbon atom to the oxygen atom. He concluded that taking the dipole to be approximately mid-way along the C=O bond at 0.6 Å produced the best results. More recently Schneider *et al.*[12] obtained all the proton shifts in three keto steroids and analysed these SCS in terms of both anisotropy and electric field effects. They obtained rather large values for the carbonyl anisotropy (see later) and also they were not able to calculate the chemical shifts of the protons vicinal to the carbonyl group. Recently Williamson *et al.*[13] performed similar calculations for the α C–H protons in proteins. They used the known crystal structures of the proteins and included electric field and anisotropic effects, the latter from both the C=O bonds and also from the aromatic residues present. They obtained good agreement with the observed data when both the electric field and anisotropy terms were included. As these proton shifts were measured in aqueous solution the electric field effect is considerably diminished compared to non polar solvents. Again protons vicinal to the C=O bond were excluded from their treatment.

We give here the complete assignment of the proton spectra of 2-*tert*-butylcyclohexanone (**1**), 4-*tert*-butylcyclohexanone (**2**), fenchone (**3**), *trans*-1-decalone (**4**), androstan-3-one (**5**), androstan-17-one (**6**), androstane-3,17-dione (**7**) and androstane-3,11,17-trione (**8**). In addition the spectra of norbornanone (**9**) and camphor (**10**) are remeasured.

These plus previous literature results provide sufficient data for an analysis of carbonyl SCS based on a previous model of proton chemical shifts.[1] In previous parts of this series this model, which is based on simple charge calculations over one, two and three bonds and steric, electric field and anisotropic contributions over > three bonds, has been applied successfully to a variety of saturated hydrocarbons,[14,15] haloalkanes[16] and

ethers.[1] We shall show that this model provides a quantitative treatment for carbonyl SCS and that these are due to electric field and anisotropic effects of which the electric field effect is the major contributor.

Theory

As the theory has been detailed previously[1,17] only a brief summary of the latest version (CHARGE6) is given here. The theory distinguishes between substituent effects over one, two and three bonds, which are attributed to the electronic effects of the substituents, and longer range effects due to the electric fields, steric effects and anisotropy of the substituents. The CHARGE scheme calculates the effects of 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 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 and a γ effect from atom L given by the product of the atomic polarisabilities of atoms I and L. The important carbon γ effect (*i.e.* CCCH) is parametrised separately and is given by a simple cosθ dependance where θ is the CCCH dihedral angle. There are also routines for the methyl γ effect and for the decrease in the γ effect of the electronegative oxygen and fluorine atoms for CX_2 and CX_3 groups.

The total charge is given by summing these effects and the partial atomic charges (q) converted to shift values using eqn. (1).

$$\delta = 160.84q - 6.68 \quad (1)$$

The effects of more distant atoms on the proton chemical shifts are due to steric, anisotropic and electric field contributions. H · · · H steric interactions were found to be shielding and X · · · H (X = C, F, Cl, Br, I) interactions deshielding according to a simple r^{-6} dependance [eqn. (2)], where a_S is a coefficient for the steric effect of the atom.

$$\delta_{steric} = a_S/r^6 \quad (2)$$

Furthermore any X · · · H steric contributions on a methylene or methyl proton resulted in a push-pull effect (shielding) on the other proton(s) on the attached carbon.

The effects of the electric field of the C–X bonds (X = H, F, Cl, Br, I, O) were calculated from eqn. (3) where A_Z was determined as 3.67×10^{-12} esu (63 ppm au) and E_Z is the component of the electric field along the C–H bond. The electric field for a univalent atom (*e.g.* fluorine) is calculated as due to the charge on the fluorine atom and an equal and opposite charge on the attached carbon atom. The vector sum gives the total electric field at the proton concerned and the component of the electric field along the C–H bond considered is E_Z in eqn. (3). This

$$\delta_{el} = A_Z E_Z \quad (3)$$

procedure is both simpler and more accurate than the alternative calculation using bond dipoles.

The magnetic anisotropy of the C–C bond was originally included using the McConnell equation [eqn. (4)] for a bond with cylindrical symmetry as illustrated in Fig. 1 for the carbonyl group.

$$\delta_{an} = \Delta\chi^{C-C}(3\cos^2\varphi - 1)/3R^3 \quad (4)$$

In eqn. (4) R is the distance from the perturbing group to the nucleus of interest in Å and is taken from the mid-point of the perturbing group for a symmetric bond such as the C–C bond,

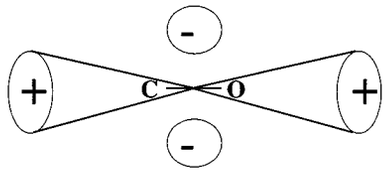


Fig. 1 Representation of the anisotropy in an axially symmetric molecule. Note, the signs refer to the change in the δ values, not to the shielding.

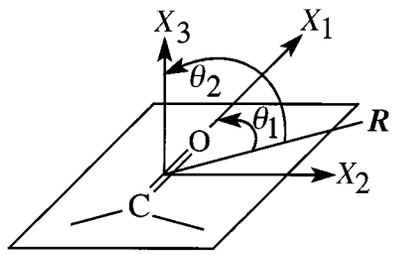


Fig. 2 The principal axes of the carbonyl bond.

φ is the angle between the vector R and the symmetry axis and $\Delta\chi^{C-C}$ the molar anisotropy of the C–C bond. ($\Delta\chi^{C-C} = \chi^{C}_{parl} - \chi^{C}_{perp}$) where χ^{C}_{parl} and χ^{C}_{perp} are the susceptibilities parallel and perpendicular to the symmetry axis respectively.

These contributions were then added to the shifts of eqn. (1) to give the calculated shift of eqn. (5).

$$\delta_{total} = \delta_{charge} + \delta_{steric} + \delta_{an} + \delta_{el} \quad (5)$$

Application to the carbonyl group

The vicinal (HCC=O) effects are treated separately in CHARGE and these will need to be evaluated from the observed data. The carbonyl group also has in principle steric, electric field and anisotropic effects on protons more than three bonds distant, thus all these have to be incorporated into the model. The steric effects of both the carbonyl carbon and oxygen atoms are not known and therefore a value of the coefficient a_S in eqn. (2) for these atoms must be determined. We assume that the ketone carbon atom has a similar steric effect to a saturated carbon, thus the same value of a_S is used. The value of a_S for the carbonyl oxygen atom is unknown and needs to be obtained. This and the associated push-pull coefficient are the only additional parameters required for the steric effect.

The electric field of the carbonyl group is calculated in an identical manner to that for any C–X bond. The electric field is calculated as due to the charge on the oxygen atom and an equal and opposite charge on the carbon atom. As the oxygen charge is already calculated in CHARGE and the coefficient in eqn. (3) is known the electric field effect is given immediately without any further parametrisation.

The anisotropic effect of the carbonyl group also needs to be calculated. The C=O group is not an axially symmetric group and has different magnetic susceptibilities (χ_1,χ_2 and χ_3) along the X_1, X_2 and X_3 axes respectively (Fig. 2). There are two anisotropy terms required for a non-axially symmetric group and thus the full McConnell equation [eqn. (6)] must be used.

$$\delta_{an} = [\Delta\chi_1(3\cos^2\theta_1 - 1) + \Delta\chi_2(3\cos^2\theta_2 - 1)]/3\boldsymbol{R}^3 \quad (6)$$

In eqn. (6) θ_1 and θ_2 are the angles between the radius vector $\boldsymbol{R}$ and χ_1 and χ_3 respectively and $\Delta\chi_1$ ($\chi_1 - \chi_2$) and $\Delta\chi_2$ ($\chi_3 - \chi_2$) are the two anisotropies for the C=O bond which may be termed the parallel and perpendicular anisotropy respectively. In order to apply this calculation to ketones the two anisotropies need to be determined and also it is necessary to determine the effect of the position of the magnetic dipole along the C=O bond.

Experimental

Materials

2-*tert*-Butylcyclohexanone (**1**) was synthesised by the oxidation of 2-*tert*-butylcyclohexanol (Aldrich Chem. Co.) using chromic acid. 4-*tert*-Butylcyclohexanone (**2**), fenchone (**3**), *trans*-1-decalone (**4**), norbornanone (**9**) and camphor (**10**) were also obtained from Aldrich. 5α-Androstan-3-one (**5**), 5α-androstan-17-one (**6**), 5α-androstane-3,17-dione (**7**) and 5α-androstane-3,11,17-trione (**8**) were kindly donated by GlaxoWellcome. The solvents were obtained commercially, stored over molecular sieves and used without further purification.

Spectrometers and spectral details

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX400 spectrometer operating at 400.14 MHz for proton and 100.63 MHz for carbon. Spectra for **2**, **4**, **5** and **7** were recorded on a Varian 600 (EPSRC service, Edinburgh University) and **7** and **8** on a Varian 750 MHz spectrometer (GlaxoWellcome). HMQC, HMBC and NOE experiments were carried out on the Varian 750 MHz spectrometer.

Spectra were recorded in 10 mg cm^{-3} solutions (^{1}H) and *ca.* 50 mg cm^{-3} (^{13}C) with a probe temperature of *ca.* 25 °C in $CDCl_3$ and referenced to TMS unless otherwise stated. Typical ^{1}H conditions were 128 transients, spectral width 3300 Hz, 32k data points, giving an acquisition time of 5 s and zero-filled to 128 k to give a digital resolution of 0.025 Hz.

2D Experiments were performed on the AMX400 and the Varian 750 MHz spectrometers using the standard Bruker COSY-DQF and HXCO-BI and the standard Varian HMQC and GHMQC-DA pulse sequences.[18,19] The geometries of the compounds investigated were obtained by geometry optimizations using the GAUSSIAN94 programme at the RHF/6-31G* level.[20] Full details of these optimizations and geometries are given in ref. 21. The GAUSSIAN94 calculations were performed on the University of Liverpool Central Computing facility, and the CHARGE computations were performed on a PC.

Compound assignments

The assignments of compounds **1**–**10** are given in Tables 2 to 5.

2-*tert*-Butylcyclohexanone (1). The ^{1}H spectra of **1** in $CDCl_3$ consists of a number of complex patterns which were assigned from a HET-CORR experiment with the aid of a literature ^{13}C assignment.[22] This gave the assignment of H2 (δ 2.15) uniquely and the assignments of the protons of the various CH_2 groups. The assignments of the 3, 4 and 5 axial and equatorial protons were made on the basis of their fine structure. The 3e, 5e and 4e protons have complex splitting patterns centered at δ 2.18, 2.06 and 1.90 respectively, the 4a, 5a and 3a protons have characteristically axial splitting patterns centered at δ 1.64, 1.66 and 1.47 respectively. The 6e and 6a protons give a strongly coupled multiplet centred at δ 2.28 and inspection of the splitting pattern suggests that H6e is to lower field. This provisional assignment contrasts with that predicted from the calculations (Table 3) in which the two protons are reversed.

4-*tert*-Butylcyclohexanone (2). The H2a and H2e protons are easily assigned as they are the most low field and further examination of the splitting pattern (again an AB type) shows that H2e is at δ 2.356 and the H2a at δ 2.272. The H3e proton is at δ 2.079 but even at 600 MHz the H3a and H4a protons are coincident at δ 1.450.

Fenchone (1,3,3-trimethylbicyclo[2.2.1]heptan-2-one) (3). The assignment of this compound was straightforward, the only difficulty encountered was the assignment of the 7*syn* and 7*anti* protons. This was performed by examining the NOE from the 3exo methyl group, assuming that there would be an NOE to the 7*syn* proton but not to the 7*anti* which formed the basis of the assignment. From this experiment we assign 7*syn* at δ 1.80 and 7*anti* at δ 1.54.

The H4 proton is a multiplet with integration 1 centered at δ 2.14, the 5x, 5n, 6x and 6n protons were all assigned by analysis of splitting patterns and examination of a HET-CORR spectrum using a literature ^{13}C assignment.[23]

***trans*-1-Decalone (4).** The assignment of this compound was performed by a variety of methods, the analysis of the AB pattern at δ 2.24–2.32 corresponding to the 2a and 2e protons was carried out using the LAOCOON programme.[24] The results of these analyses are reported separately.[25] The other protons were assigned by connectivity (HMBC), coupling (COSY-DFTP) and H–C correlation (HMQC) experiments.

5α-Androstan-3-one (5). The 600 MHz spectrum of this compound consists of 30 closely coupled protons over a range of 2.4 ppm. Analysis of the multiplets between δ 2.40 and 2.22 shows that unusually the axial 2β proton is downfield of the equatorial 2α proton, due to the combined deshielding effects of the axial C19 methyl group and the vicinal 3-keto group. Further analysis of COSY and HET-CORR experiments at 750 MHz confirms the previous assignment given by Schneider[12] of the 400 MHz spectrum though in ref. 12 only the SCS were given.

5α-Androstan-17-one (6). The assignment of this compound has also been reported previously[12] though again only the SCS were given. Again analysis of COSY and HET-CORR experiments at 750 MHz confirms the assignment.

5α-Androstane-3,17-dione (7). The lowfield part of the ^{1}H spectrum reveals two well separated AB patterns due to the C2 and C16 protons and a HET-CORR plot together with a previous ^{13}C assignment[23] showed that the 16β proton is the most downfield. A strong correlation with this proton in the COSY plot identified the 16α and C15 protons. Analysis of the splitting patterns assigned 15α at δ 1.946 and 15β at δ 1.520. The COSY correlations of the C15 protons assigned the H14 at δ 1.294 and this process was repeated for all the ring protons.

These assignments were confirmed from a calculated spectrum using the Bruker WIN-DAISY programme[18] of all the protons in this compound except the H6 and H7 protons which even at 600 MHz are a very strongly coupled multiplet. The results of this analysis are reported elsewhere.[25]

5α-Androstane-3,11,17-trione (8). Although this is the most substituted of the 5α-androstanes studied, the spectrum of this compound showed considerable overlap at 400 MHz and thus the spectrum was obtained at 750 MHz. This together with the ^{13}C spectrum, COSY, HMQC and HMBC experiments were sufficient to obtain a complete assignment of this compound. Again a detailed analysis including the coupling constants is given in ref. 25.

The spectra of **9** and **10** were also re-examined in detail because of the importance of these compounds in the parametrisation (see later).

Norbornanone (9). The proton spectrum of **9** was given previously[26] and the assignment was confirmed by a COSY plot.

Camphor (10). The assignment of the proton spectrum of **10** has been the subject of some controversy.[26–28] Both COSY and HET-CORR experiments were performed in order to check the assignment. Sanders and Hunter[27] assigned all the protons in this molecule including the three methyl groups on the basis of a series of elegant NOE experiments and this assignment was subsequently confirmed by Kaiser *et al.*[28] Our experiments also

Table 1 Proton SCS for the 3-keto, 11-keto and 17-keto group in 5α-androstane

	3-keto[a]		11-keto[a]		17-keto[a]	
Proton	This work	Ref. 12	This work[b]	Ref. 12	This work	Ref. 12
1α	0.48	0.45	−0.15	−0.13	0.04	*c*
1β	1.67	1.66	0.74	0.74	−0.02	0.01
2α	0.81	0.77	0.04	*c*	*c*	*c*
2β	0.99	0.96	0.06	*c*	*c*	*c*
3α	—	—	—	−0.04	−0.03	*c*
3β	—	—	—	−0.02	*c*	*c*
4α	0.86	0.84	*c*	*c*	0.07	0.07
4β	1.05	1.02	0.02	*c*	0.03	0.07
5 (CH)	0.49	0.45	−0.05	−0.07	0.05	*c*
6α	0.10	0.11	0.03	*c*	0.03	0.03
6β	0.10	0.11	*c*	*c*	0.03	0.03
7α	0.05	0.03	0.19	0.19	0.06	0.04
7β	0.07	0.04	0.15	0.10	0.09	0.09
8 (CH)	0.05	0.05	0.34	0.36	0.28	0.26
9 (CH)	0.07	0.07	0.94	1.00	0.04	0.03
11α	0.03	0.02	—	—	0.14	0.12
11β	0.12	0.13	—	—	*c*	*c*
12α	0.03	0.02	1.05	1.15	0.14	0.12
12β	0.02	0.02	0.61	0.54	0.09	0.08
14 (CH)	0.03	0.02	0.62	0.64	0.37	0.37
15α	0.02	*c*	0.14	0.12	0.30	0.27
15β	0.03	*c*	0.11	0.08	0.37	0.35
16α	0.02	0.03	0.18	0.16	0.48	0.49
16β	0.03	0.03	0.09	0.16	0.82	0.89
17α	0.03	*c*	—	0.22	—	—
17β	0.04	−0.02	—	0.03	—	—
18-Me	0.04	0.03	−0.07	−0.03	0.17	0.17
19-Me	0.24	0.23	0.18	0.22	0.02	0.02

[a] δ(ketone) − δ(androstane). [b] δ(**8**) − δ(**7**). [c] SCS < 0.01 ppm.

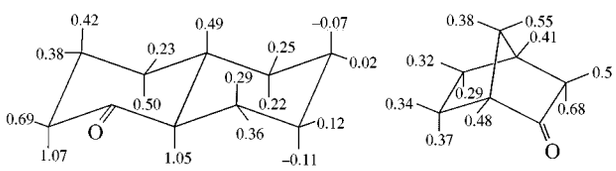


Fig. 3 Carbonyl SCS in *trans*-1-decalone and norbornanone.

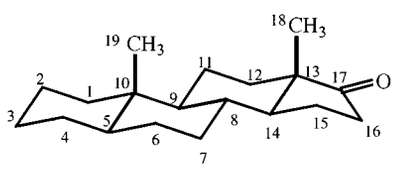


Fig. 4 Nomenclature used for 5α-androstan-17-one.

confirmed this assignment though the chemical shifts measured here differ slightly from those recorded previously.

Results

The above data combined with the proton chemical shifts of the parent compounds given previously[15] allow the carbonyl SCS to be obtained in these compounds. The carbonyl SCS for **4** *vs. trans*-decalin and **9** *vs.* norbornane are given in Fig. 3. Also the SCS for the carbonyl group at the 3, 11 and 17 positions in the steroid nucleus obtained here from the data for compounds **6**, **7** and **8** together with the proton chemical shifts of androstane are given and compared with the results obtained by Schneider *et al.*[12] in Table 1. In ref. 12 only the SCS were tabulated not the actual proton chemical shifts. Also the SCS for the 11-keto group has been obtained in this investigation as δ(**8**) − δ(**7**) whereas Schneider *et al.*[12] obtained this SCS directly from the analysis of 11-keto androstane. The excellent agreement of the two sets of results in Table 1 is impressive and the additivity of the SCS values in the steroid nucleus is very clearly shown by the agreement of the two sets of values for the SCS of the 11-keto group.

The carbonyl SCS in these well defined systems are of some interest. In general the γ effect of the carbonyl oxygen atom (*i.e.* HCC=O) is strongly deshielding with however an orientational dependance. For example, in *trans*-decalone the SCS of the carbonyl group on H2ax (1.07) and H9 (1.05) is significantly greater than on H2eq (0.69) and this pattern is reproduced in the cyclohexanes and steroids. In contrast in norbornanone the SCS of the carbonyl on H3*endo* (0.68) is similar to that on H3*exo* (0.59) and again this is observed in camphor. The long range (>3 bonds) effects of the carbonyl group are also large and extend over both the bicycloheptene and decalin system. The effects are usually deshielding with only the 5ax and 6ax protons in *trans*-decalone showing an upfield shift. This pattern is also observed in the steroid nucleus (Table 1) where very few of the protons show an upfield SCS and these shifts are usually very small with the proton far removed from the keto group. The only marked exception to this is the SCS of the 11-keto group at the 1α proton (−0.15 ppm) and this is accompanied by a large positive SCS (0.74 ppm) at the 1β proton. The combined effect of these shifts is so large that these two methylene protons occur at the two extremes of the proton spectrum in **8** (apart from the methyl groups). We shall show that these shifts may be completely explained by our present theories.

The data collected in Tables 2–5 provide a rigorous test of the application of both the CHARGE model and also present theories of carbonyl SCS to these compounds. The compounds listed in the tables are all of fixed conformation with the possible exception of the five membered rings of cyclopentanone and ring D of the steroid nucleus, which may exhibit some conformational flexibility. The GAUSSIAN94 (6-31G*) calculations gave the cyclopentanone geometry as the half-chair (Cs) conformation in agreement with both molecular mechanics (PCMODEL) calculations[31] and the experimental gas phase geometries.[32] Similar calculations for the saturated ring D of androstan-3-one gave the same geometry as obtained for androstane,[15] *i.e.* as a C13-envelope with C14, C15, C16 and

Table 2 Observed *vs.* calculated proton chemical shifts (δ) of acyclic and cyclic ketones

Compound		Obs.[a]	Calc.	Compound		Obs.[b]	Calc.
Acetaldehyde	Me	2.20	1.96	*trans*-1-Decalone	2a	2.33	2.27
	CHO	9.78	9.70		2e	2.36	2.34
					3a	1.67	1.69
Acetone	Me	2.17	1.83		3e	2.05	2.05
					4a	1.43	1.34
Cyclopentanone	Hα	2.17	2.22		4e	1.77	1.82
	Hβ	1.98	1.93		5a	1.15	0.98
					5e	1.79	1.63
Pinacolone	Me	2.14	1.88		6a	1.18	1.27
	^{t}Bu	1.13	1.26		6e	1.70	1.69
					7a	1.14	1.20
Cyclohexanone	H2,6	2.33	2.24		7e	1.79	1.67
	H3,5	1.88	1.82		8a	1.25	1.34
	H4	1.71	1.77		8e	1.91	1.77
					9	1.95	1.84
					10	1.37	1.31

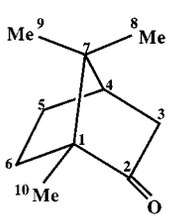
[a] Ref. 29. [b] This work.

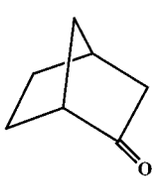
Table 3 Observed *vs.* calculated chemical shifts in substituted cyclohexanones

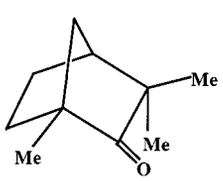
	2-Methyl-cyclohexanone		3-Methyl-cyclohexanone		4-Methyl-cyclohexanone		2-*tert*-Butyl-cyclohexanone		4-*tert*-Butyl-cyclohexanone	
Proton	Obs.[a]	Calc.	Obs.[a]	Calc.	Obs.[a]	Calc.	Obs.[b]	Calc.	Obs.[b]	Calc.
2a	2.43	2.30	2.01	1.84	2.32	2.22	2.15	1.95	2.27	2.23
2e	—	—	2.35	2.27	2.36	2.31	—	—	2.36	2.33
3a	1.38	1.44	1.89	1.77	1.41	1.31	1.47	1.47	1.45	1.32
3e	2.10	1.82	—	—	2.00	2.00	2.18	2.00	2.08	2.07
4a	1.67	1.65	1.34	1.31	1.89	1.77	1.64	1.64	1.45	1.45
4e	1.84	1.93	1.89	1.90	—	—	1.90	1.94	—	—
5a	1.67	1.64	1.66	1.66	1.41	1.31	1.66	1.59	1.45	1.32
5e	2.07	2.01	2.01	2.02	2.00	2.00	2.06	2.00	2.08	2.07
6a	2.30	2.21	2.25	2.21	2.32	2.22	2.32	2.23	2.27	2.23
6e	2.37	2.31	2.35	2.31	2.36	2.31	2.26	2.33	2.36	2.33
^{t}Bu	—	—	—	—	—	—	0.99	0.95	0.90	0.91

[a] Ref. 30. [b] This work.

Table 4 Calculated *vs.* observed chemical shifts in bicycloheptane systems







	Camphor **10**		Norbornanone **9**		Fenchone **3**	
Proton	Obs.[a]	Calc.	Obs.[b]	Calc.	Obs.[c]	Calc.
1	—	—	2.60	2.62	1.15(Me)	1.00(Me)
3x	2.35	2.51	2.06	2.28	—	—
3n	1.84	1.78	1.84	1.89	—	—
4	2.09	2.18	2.67	2.61	2.14	2.16
5x	1.95	2.05	1.79	1.85	1.80	1.90
5n	1.34	1.37	1.45	1.46	1.70	1.52
6x	1.68	1.93	1.81	1.78	1.54	1.75
6n	1.40	1.64	1.53	1.58	1.37	1.66
7*s*	—	—	1.73	1.76	1.80	1.96
7*a*	—	—	1.56	1.63	1.54	1.36
8(Me)	0.84	0.98	—	—		
9(Me)	0.96	0.95	—	—		
10(Me)	0.92	1.05	—	—		
3x(Me)	—	—	—	—	1.04	1.07
3n(Me)	—	—	—	—	1.04	0.99

[a] Data from ref. 25, assignments from refs. 26 and 27. [b] Ref. 25. [c] This work.

C17 more or less in a plane with only a 9.5° twist. In the 17-keto compounds (**6**, **7** and **8**) the GAUSSIAN (and PCMODEL) calculations gave the conformation of ring D as a C14 envelope with C13, C15, C16 and C17 almost coplanar and this is in agreement with the observed coupling constants for ring D.[21]

In the CHARGE model the γ effects of the substituents are considered to be due to electronic effects and therefore they are modelled on a simple empirical basis. For the ketones studied here we initially made the assumption that the electronic γ effects of the carbonyl carbon (HCCC=O) are the same as for a saturated carbon atom which is already incorporated into the CHARGE scheme. Subsequently a small correction (0.1 ppm) was added. However the γ effects of the carbonyl oxygen (HCC=O) need to be determined. As mentioned earlier inspection of the data of Fig. 3 and Tables 1–5 shows that there is clearly an orientation dependance of the carbonyl γ SCS. In the similar analysis of saturated carbon (HCCC) and oxygen (HCCO) γ effects a simple angular function ($A + B\cos\theta$) was found to be appropriate with values of the coefficients A and B determined by the observed data. Thus this approach was initially used here. However more detailed inspection of the observed data showed that the carbonyl γ SCS were also dependant on the bond angle (α) of the carbonyl group (CC(O)C). In particular the five-membered ring ketones with carbonyl bond angles *ca.* 106–109° have quite different SCS to the six-membered ketones with bond angles *ca.* 115–116°. This additional functionality was therefore incorporated into the carbonyl oxygen γ effect again as a simple cos α dependance. The coefficients in this equation were then determined from the observed SCS by an iterative least mean squares calculation to give finally eqn. (7) for the carbonyl gamma effect (GSEF).

Table 5 Observed[a] *vs.* calculated chemical shifts in 5α-androstanones

	3-one (**5**)		11-one		17-one (**6**)		3,17-dione (**7**)		3,11,17-trione (**8**)	
Proton	Obs.	Calc.	Obs.[b]	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
1α	1.35	1.44	0.76	0.80	0.91	0.97	1.35	1.44	1.22	1.26
1β	2.03	2.00	2.40	2.43	1.65	1.60	2.03	2.00	2.77	2.86
2α	2.29	2.21	1.50	1.51	1.49	1.53	2.31	2.21	2.27	2.19
2β	2.39	2.44	1.41	1.44	1.42	1.44	2.39	2.44	2.45	2.44
3α	—	—	1.19	1.19	1.18	1.25	—	—	—	—
3β	—	—	1.65	1.67	1.67	1.69	—	—	—	—
4α	2.08	2.03	1.23	1.08	1.29	1.38	2.11	2.05	2.12	2.02
4β	2.27	2.06	1.23	1.33	1.25	1.09	2.26	2.07	2.28	2.08
5	1.51	1.61	0.99	1.03	1.07	1.10	1.56	1.62	1.51	1.56
6α	1.32	1.48	1.23	1.42	1.25	1.43	1.38	1.53	1.41	1.56
6β	1.32	1.36	1.23	1.28	1.25	1.32	1.38	1.40	1.37	1.40
7α	0.96	1.19	1.12	1.25	0.97	1.26	1.01	1.31	1.20	2.16
7β	1.75	1.93	1.79	1.99	1.77	2.00	1.84	2.05	1.99	1.40
8	1.33	1.19	1.65	1.57	1.56	1.36	1.59	1.43	1.93	1.87
9	0.75	0.86	1.69	1.76	0.72	0.81	0.80	0.91	1.74	1.91
11α	1.56	1.56	—	—	1.67	1.56	1.70	1.60	—	—
11β	1.38	1.48	—	—	1.27	1.41	1.40	1.47	—	—
12α	1.12	1.01	2.25	2.01	1.23	1.18	1.27	1.20	2.32	2.21
12β	1.72	1.65	2.25	2.28	1.80	1.79	1.83	1.82	2.44	2.47
14	0.92	0.82	1.54	1.27	1.26	1.14	1.29	1.17	1.91	1.66
15α	1.65	1.65	1.77	1.75	1.93	2.18	1.95	2.20	2.09	2.31
15β	1.17	1.53	1.23	1.61	1.51	2.13	1.52	2.15	1.63	2.24
16α	1.60	1.56	1.72	1.62	2.06	2.26	2.08	2.27	2.26	2.35
16β	1.64	1.63	1.72	1.69	2.43	2.27	2.45	2.28	2.54	2.36
17α	1.15	1.05	1.35	1.14	—	—	—	—	—	—
17β	1.43	1.60	1.45	1.68	—	—	—	—	—	—
18(Me)	0.72	0.76	0.66	0.87	0.86	1.03	0.89	1.05	0.82	1.19
19(Me)	1.02	1.00	1.01	0.93	0.81	0.77	1.04	1.01	1.22	1.18

[a] This work. [b] δ values from SCS (Table 1) and δ(5α-androstane), ref. 15.

$$GSEF = 0.09\,(2.0 - 3.0\cos a)(2.0 - \cos\theta) \qquad (7)$$

This equation gave generally good agreement for all the vicinal protons in the data set (a total of 50 protons). These results will be discussed later.

Long-range effects

The interactions considered to be responsible for the long range effects of the carbonyl group have been documented earlier as steric, electric field and magnetic anisotropy effects. We are now in a position to test these theories against the observed data presented in the tables. It is convenient to consider first the electric field effect as there are no additional parameters required to calculate the electric field effects of the carbonyl group from eqn. (3). There is the implicit assumption that the charges used in eqn. (3) provide a reasonable measure of the electric field of the carbonyl group. The partial atomic charges calculated in the CHARGE routine have been derived from the observed molecular dipole moments and the extent of the agreement provides one check of the electric field calculation. The calculated and observed (in parenthesis) dipole moments (in debye) of formaldehyde, acetaldehyde, acetone and cyclohexanone are 2.28 (2.34), 2.68 (2.68), 3.03 (2.86) and 3.03 (3.08) and the excellent agreement provides strong support for the use of these charges in the calculations. As the coefficient in eqn. (3) is known together with the molecular geometries the electric field effect of the carbonyl group at any proton more than three bonds removed from the carbonyl oxygen atom is given immediately. These values will be discussed later.

In contrast to the above, the steric and anisotropic terms are not known and both the steric coefficient a_s [eqn. (2)] for the oxygen atom and the magnetic anisotropies $\Delta\chi_1$ and $\Delta\chi_2$ [eqn. (6)] need to be evaluated. In addition there is a push-pull coefficient for the steric effect and also the position of the magnetic anisotropy along the carbonyl bond needs to be determined. It is because of this multifunctional parametrisation that it is essential to have a large and diverse data set. The data set of the non-vicinal protons used here comprises 112 proton shifts and the iterations were achieved using a non-linear least mean squares programme (CHAP8).[33] The iterations were initially carried out on the observed SCS in order to eliminate any errors in the calculated shifts of the parent hydrocarbons, but subsequently the observed chemical shifts were used. The results are of some interest. All the iterations including the steric term plus the anisotropy terms gave no better results than the corresponding iterations without the steric term. Thus the steric term for the carbonyl oxygen atom was removed. Also the values of the parallel anisotropy ($\Delta\chi_1$) obtained from the iterations were always much larger than those for the perpendicular anisotropy $\Delta\chi_2$.

These calculations were all performed with the carbonyl anisotropies placed at the midpoint of the C=O bond. It was found that the best iteration still gave significant errors for some protons in the bicycloheptanones (Table 4). In particular the observed 6*exo* and 6*endo* SCS were much smaller than calculated. However placing the anisotropy at the carbonyl carbon atom gave much better agreement for these protons without any significant effect for the remaining protons in the data set. The final values of the anisotropies obtained were $\Delta\chi_1$ 17.1 and $\Delta\chi_2$ 3.2 (10^{-30} cm^3 molecule^{-1}) and these together with the results obtained can now be considered.

The observed *vs.* calculated proton shifts for the ketones considered are given in Tables 2–5 and it is of some interest to consider these results. The general agreement of the observed *vs.* calculated shifts is very good and the great majority of the observed shifts are reproduced to better than 0.1 ppm. This is as good as could be expected as the observed *vs.* calculated proton shifts for the corresponding hydrocarbons are only to *ca.* 0.1 ppm. The agreement is particularly striking for the chair conformations of decalone (Table 2) and the methylcyclohexanones (Table 3) with no error larger than 0.2 ppm. Also the general agreement for the steroid ketones is encouraging though in this quite sterically compressed system there are

larger errors in the calculated shifts for some of the protons in the base hydrocarbon androstane. In particular the 7β and 15β protons are the only resolved protons in androstane with errors >0.2 ppm probably due to large steric interactions and this transfers to the steroid ketones. The good agreement for the C1 protons in the 3,11,17-trione (Table 5) is particularly noteworthy as the 1β proton in the 11-ketosteroids is very close to the 11-keto oxygen and the SCS for this proton provides a critical test of the model. Indeed Schneider *et al.*[12] noted that the 1β proton deviated appreciably (by 0.6 ppm) from their calculated value, based on a dipole model of the electric field and ApSimon's anisotropy equation.

The calculated shifts in the bicycloheptanone systems are also in generally good agreement with the observed shifts (Table 4) though there are some significant errors. It may be significant that in the bicycloheptane system it was necessary to consider possible orbital interactions between the bridging C7 carbon and the ring carbons in order to reproduce the observed shifts in these molecules using the CHARGE model.[17] However the largest errors in Table 4 are for the 6*exo* and 6*endo* protons in camphor and fenchone in which both the calculated proton shifts and the SCS are much less than the observed values (by *ca.* 0.2–0.3 ppm). This deviation does not appear to be a function of the bicyclic ring system as in norbornanone both the calculated shifts and the SCS at the C6 protons are in good agreement with the observed values. Why the introduction of methyl groups should affect the SCS of the carbonyl group is not clear. The proton shifts of camphor were obtained in solvents of varying polarity (CCl_4, $CDCl_3$, acetone and methanol) in order to determine if any intramolecular hydrogen bonding between the carbonyl oxygen and the methyl protons was occurring but the shifts were as expected with no evidence of any such interaction.

The only acyclic compounds investigated are the simple compounds in Table 2 as all other acyclic ketones exist in two or more conformations. The observed shifts for acetone and acetaldehyde are both slightly greater than calculated and this may be due to solvation effects. On the reaction field model for any given solvent the solvation shifts are proportional to both the dipole moment and to the reciprocal of the volume of the solute.[34] Thus in these small polar molecules solvent effects will be most pronounced.

The values of the carbonyl anisotropy determined here are also of interest. In all the iterations performed the value of the parallel anisotropy $\Delta\chi_1$ remained reasonably constant at *ca.* 20 (10^{-30} cm^3 $molecule^{-1}$). In the final iteration the value obtained was 17.1. However the value of the perpendicular anisotropy $\Delta\chi_2$ varied considerably with both positive and negative values obtained during the iterations. The last iteration gave a value of 3.2. The variability is a consequence of the small effect this parameter has on the proton chemical shifts. The only definitive method of determining this parameter would be to obtain SCS from protons situated both at the sides and immediately above the carbonyl group. Although examples of the first type are present in the collected data (*e.g.* the C8 protons in 1-decalone) we were unable to obtain suitable compounds in which protons were situated immediately above the carbonyl group.

The value of the carbonyl anisotropy obtained here (*cf.* Fig. 2) is $\chi_1 - \chi_2$ 17.1 and $\chi_3 - \chi_2$ 3.2, hence $\chi_1 - \chi_3$ equals 13.9. Comparison with the results of previous investigations is not facilitated by the different nomenclatures used. Zurcher[7] defined $\Delta\chi_1 = \chi_1 - \chi_3$ and $\Delta\chi_2 = \chi_2 - \chi_3$. ApSimon[9] and also Schneider[12] and Williamson[13] write the anisotropy equation [*cf.* eqn. (6)] as $(1 - 3\cos^2\theta)$ which merely reverses the sign of $\Delta\chi$. Also the definition of the *x*, *y*, and *z* axes differs in these investigations. Converting to the nomenclature of Fig. 2 and eqn. (6) gives values of $\chi_1 - \chi_2$, $\chi_3 - \chi_2$ and $\chi_1 - \chi_3$ of 17.1, 3.2, 13.9 (this work), 13.5, −12.2, 25.7 (ref. 7), 21, −6, 27 (ref. 9), 24, −12, 36 (ref. 12) and 4, −9, 13 (ref. 13). There is generally reasonable agreement for the value of the parallel anisotropy ($\chi_1 - \chi_2$ or $\chi_1 - \chi_3$) apart from Williamson's value but the value of $\chi_3 - \chi_2$ is not well defined. This reinforces the caveat above concerning the uncertainty in the value of $\Delta\chi_2$. It is probable that Schneider[12] used the correction to the McConnell eqn. (6) given by ApSimon though this is not explicitly stated in ref. 12 and this may affect the values of the anisotropies they obtained.

Table 6 Calculated *vs.* observed SCS for *trans*-1-decalone (**4**) with the electric field and anisotropy contributions

Proton	Obs.	Calc.	Electric field	Anisotropy
2a	1.07	1.08	—	—
2e	0.69	0.73	—	—
3a	0.42	0.34	0.23	−0.07
3e	0.38	0.30	0.18	0.07
4a	0.51	0.47	0.12	0.30
4e	0.23	0.31	0.15	0.12
5a	0.22	0.11	0.04	0.07
5e	0.26	0.12	0.06	0.03
6a	−0.07	0.02	0.05	−0.04
6e	0.02	0.03	0.03	−0.01
7a	−0.11	−0.05	0.01	−0.05
7e	0.11	0.01	0.06	−0.05
8a	0.32	0.40	0.18	−0.22
8e	0.37	0.30	0.20	−0.21
9H	1.07	1.06	—	—
10H	0.49	0.35	0.24	−0.09

It is of some interest to consider the actual magnitudes of the various contributions to the carbonyl SCS and Table 6 gives the observed *vs.* calculated SCS for *trans*-1-decalone with the calculated electric field and anisotropy contributions. The table clearly shows that both effects are important in determining carbonyl SCS. The table also shows that other contributions are present in determining the SCS. For example, the sum of the electric field plus anisotropy contributions for the 8a and 8e protons are −0.04 and −0.01 ppm whereas the calculated SCS are +0.40 and +0.30 ppm. The additional contribution in this case stems from the H···H steric interaction. The 8a and 8e protons in *trans*-decalin experience a large high-field shift due to the proximity of the 1a and 1e protons and these protons are *upfield* from axial cyclohexane (δ 0.93 *vs.* 1.18 for the axial protons and δ 1.54 *vs.* 1.68 for the equatorial protons) as a result. This steric interaction is removed when these protons are replaced by the carbonyl group giving an additional low-field shift. This effect is also observed in the SCS of H10 in which there is a 1,3-diaxial H–H interaction with H1ax in *trans*-decalin which is absent in 1-decalone. Apart from these special cases the anisotropic and electric field contributions determine the carbonyl SCS though the relative size of these contributions varies considerably with the orientation of the proton from the carbonyl group.

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