^{1}H Chemical Shifts in NMR. Part 19[1]. Carbonyl Anisotropies and Steric Effects in aromatic aldehydes and ketones.

Raymond J. Abraham* and Mehdi Mobli
Chemistry Department, The University of Liverpool, P.O.Box 147, Liverpool L69 3BX
and
Richard J.Smith, GlaxoSmithKline, New Frontiers Science Park, Harlow, Essex CM19 5AW

The ^{1}H Chemical Shifts of benzaldehyde, 2-chloro, 2-hydroxy and 2-methoxy benzaldehyde, acetophenone, 2-methoxy and 2-hydroxy acetophenone, indanone, anthraquinone, fluorenone, anthrone, α-tetralone, 2,4,6-trimethyl acetophenone, 9-acetylanthracene, 9-anthranaldehyde and benzosuberone were obtained and completely assigned in $CDCl_3$ and DMSO solution. In anthrone a keto-enol tautomerism (anthrone/9-hydroxyanthracene) was observed by NMR in hydrogen bonding solvents but not chloroform. The % of enol is linearly dependant on the Kamlett β hydrogen bonding parameter of the solvent, not the solvent relative permitivity.

The chemical shift data allowed the determination of the carbonyl substituent chemical shifts (SCS) in these molecules. These were analysed in terms of the carbonyl electric field, magnetic anisotropy and steric effects for long-range protons together with a model (CHARGE7) for the calculation of the two-bond and three bond effects. The SCS of the carbonyl bond was reproduced with an asymmetric magnetic anisotropy acting at the midpoint of the carbonyl bond with values of $\Delta\chi$ parll and $\Delta\chi$ perp of 6.36 and –11.88 (10^{-30} cm^3/molecule) plus a steric term from the oxygen atom and the C=O electric field effect. The short range effects of the carbonyl group on the aldehyde proton were modelled using the appropriate β functions in the CHARGE routine. For the 9-substituted anthracenes the Hückel π calculation was modified to account for the ^{1}H chemical shifts of the H-10 protons. This model gave a comprehensive calculation of the ^{1}H chemical shifts of these aromatic aldehydes and ketones. For the data set of 129 chemical shifts ranging from 2.5 to 11.5 δ the rms error of the observed vs calculated shifts was 0.094 ppm.

The CO anisotropy and oxygen shielding differ appreciably from the corresponding values for the aliphatic aldehydes and ketones but are similar to the values for the CO group of amides, illustrating the effect of conjugation on these parameters. The model was used in the

conformational analysis of some related compounds. In 2-chlorobenzaldehyde the chemical shift calculations support a non-planar molecule with the aldehyde/ ring dihedral angle in the trans conformer of ca 25^0. In the strained 7-membered ring of benzosuberone, the model was used to test calculated geometries. The ab initio geometry at the B3LYP(6-31++G(d,p)) level gave the best agreement with the observed shifts.

Introduction

The influence of the carbonyl group on the chemical shifts of neighbouring protons has been of interest since the early days of NMR, the low field chemical shift of the aldehyde proton being a conspicuous example. This was explained by Jackman[2] as due to the carbonyl anisotropy and the standard description of this anisotropy (figure 1) is one of the standard illustrations in NMR. However even this explanation was contentious as Jackman suggested that there is a large diamagnetism in the direction normal to the nodal plane of the π-orbitals (y-axis, fig. 1) whereas Pople's calculations[3] suggested 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 Pople and Bothner-By[4].

The general carbonyl group ($R_1.CO.R_2$) 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 (figure 1). This gives two anisotropic susceptibilities which are usually termed the parallel $\Delta\chi_{parl}$ (χ_z - χ_x) and perpendicular $\Delta\chi_{perp}$ (χ_y - χ_x) anisotropies.

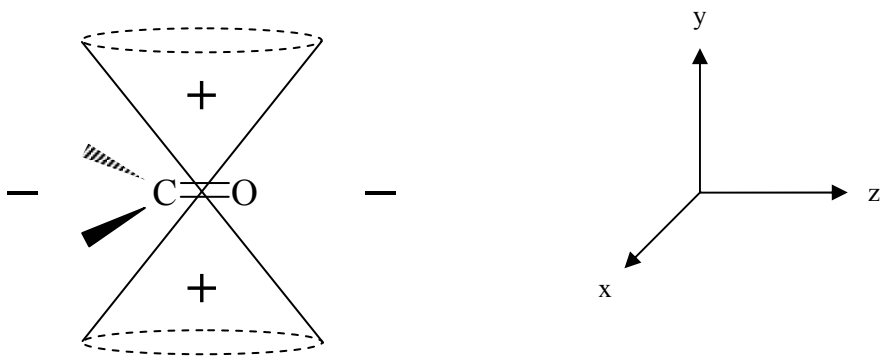


Figure 1. Classical depiction of the shielding of the carbonyl anisotropy.

A number of investigations commencing with that of Zürcher[5] have used the above description of the C=O bond anisotropy with the McConnell equation[6] together with the electric field effect of the C=O to explain the observed SCS of the carbonyl group in ketones[7,8,9,10] and

peptides[11]. None of these calculated the chemical shifts of the protons vicinal to the carbonyl group. An investigation which did include all the protons in the ketones studied was given in a previous part of this series[12]. This data was subsequently refined[12a] using the CHARGE7 routine, including the carbonyl anisotropy and electric field plus an oxygen but not a carbon steric term.

Apart from the investigations mentioned above no calculation of the ^{1}H shifts in these compounds has been given. In particular a general calculation of the ^{1}H chemical shifts for carbonyl compounds using the *ab initio* GIAO method has not been reported to date, the basis set dependance of such calculations being a severe problem. A recent investigation by Lampert et al[13] compared the observed vs calculated NMR chemical shifts for phenol and benzaldehyde and for 13 substituted derivatives, using a variety of basis sets and computational procedures within the Gaussian94 program. The calculated shielding of the aromatic protons with respect to methane varied by 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.

The classical investigations above considered only aliphatic ketones apart from that of Williamson on peptides[11] and therefore the anisotropy for a saturated carbonyl group was obtained. However when the carbonyl is attached to an aromatic group it will be conjugated and this is likely to affect the carbonyl anisotropy. This was noted by Jackman[2] who suggested that the inconsistency of Pople's model when applied to amides may be due to the assumption that the anisotropy of the carbonyl group in amides is similar to that in aldehydes and ketones.

The effect of conjugation on the carbonyl group anisotropy may also be determined from the chemical shielding tensor. Wasylishen et al.[14] used MASNMR to determine the chemical shift tensors for the carbonyl carbon of acetaldehyde, 3,4-dibenzyloxy-benzaldehyde and 3,4-dimethoxy benzaldehyde. There was a significant difference (>25%) between the shift tensors for the carbonyl carbon of acetaldehyde and those for the carbonyl carbons of the benzaldehydes, which were identical (within the error margin of the observations). These results suggest strongly that the anisotropy of the carbonyl group should be treated separately for aromatic and aliphatic systems and this is the basis for the present investigation.

We present here the complete assignment of a the ^{1}H NMR spectra of benzaldehyde (**1**), 2-chloro, 2-hydroxy and 2-methoxy benzaldehyde (**2, 3, 4**), acetophenone (**5**), 2-methoxy and 2-hydroxy acetophenone (**6, 8**), indanone (**7**), anthraquinone (**9**), fluorenone (**10**), anthrone (**11**), α-tetralone (**12**), 2,4,6-trimethyl acetophenone (**13**), 9-acetylanthracene (**14**), 9-anthranaldehyde (**15**) and benzosuberone (**16**) (scheme 1) in $CDCl_3$ and DMSO. The solvent of choice in

pharmaceutical investigations is often DMSO rather than $CDCl_3$ thus we present here the data for both solvents as part of a comprehensive comparison of ^1H chemical shifts in the two solvents. The compounds were selected on the basis that they had the carbonyl group in as many different orientations w.r.t the ring system as possible. These provide sufficient data for a complete analysis of the aromatic carbonyl substituent effects and we shall show that the C=O anisotropy for these molecules is very different from that for aliphatics and indeed more similar to that for amides.

Theory

As the theory has been given previously[1,12,15] only a brief summary of the latest version (CHARGE7) 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 is due to three effects. There is a 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.

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

$$\delta = 160.84q - 6.68 \qquad \textbf{(1)}$$

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 (eqn. 2) where a_S is the steric coefficient for any given atom.

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

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 CH 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 eqn (eqn 3) .

$$\delta_{anis} = \Delta\chi\,(3\cos^2\varphi - 1)/\ 3R^3 \qquad \textbf{(3)}$$

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 anisotropy of the C≡C bond. ($\Delta\chi = \chi_{parl} - \chi_{perp}$) 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 eqn (eqn 4) where θ_1 and θ_2 are the angles between the radius vector R and the x and z axes respectively (fig. 1) and $\Delta\chi_{parl}$ ($\chi_z - \chi_x$) and $\Delta\chi_{perp}$ ($\chi_y - \chi_x$) are the parallel and perpendicular anisotropy for the C=O bond respectively.

$$\delta_{anis} = [\Delta\chi_{parl}\,(3\cos^2\theta_1 - 1) + \Delta\chi_{perp}\,(3\cos^2\theta_2 - 1)] / 3R^3 \qquad \textbf{(4)}$$

For aromatic compounds it is necessary to include the shifts due to the aromatic ring current and the π electron densities in the aromatic ring[1]. The equivalent dipole approximation was used to calculate the ring current shifts to give eqn. 5. In eqn. 5, *R* is the distance of the proton from the benzene ring centre, θ the angle of the *R* vector with the ring symmetry axis, μ the equivalent dipole of the aromatic ring and fc the π-electron current density for the ring, being 1.0 for substituted benzenes.

$$\delta_{rc} = fc\,\mu\,(3\cos^2\theta - 1) / R^3 \qquad \textbf{(5)}$$

The π electron densities are calculated from Huckel theory[16]. The standard coulomb and resonance integrals for the Huckel routine are given by eqn.6, where α_0

$$\alpha_r = \alpha_0 + h_r\beta_0 \qquad \textbf{(6)}$$

$$\beta_{rs} = k_{rs}\beta_0$$

and β_0 are the coulomb and resonance integrals for a carbon $2p_Z$ atomic orbital and h_r and k_{rs} the factors modifying these integrals for orbitals other than sp^2 carbon. For substituted aromatics the values of the coefficients h_r and k_{rs} in eqn.6 for the orbitals involving hetero atoms have to be

found. These were obtained so that the π densities calculated from the Huckel routine reproduce the π densities from *ab initio* calculations.

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.7 where Δq_α and Δq_β are the excess π electron density at the α and β carbon atoms.

$$\delta_\pi = 10.0\ \Delta q_\alpha + 2.0\ \Delta q_\beta \qquad \textbf{(7)}$$

The above contributions are added to eqn.1 to give the calculated shift of eqn.8.

$$\delta_{total} = \delta_{charge} + \delta_{steric} + \delta_{anis} + \delta_{el} + \delta_\pi + \delta_{rc} \qquad \textbf{(8)}$$

Application to aromatic carbonyl compounds.

For the aromatic carbonyl compounds considered here the only non-parametrised short-range effect is the C(Ar).CHO beta effect. 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[12a]. Assuming the same for the aromatic carbonyl group, the steric coefficient for the carbonyl oxygen needs to be determined, i.e. the coefficient a_S in eqn 2 for the carbonyl oxygen. Thus only the above four parameters are required in the CHARGE routine to specify the proton shifts in the compounds considered.

Experimental

The carbonyl compounds studied are identified and shown with the atom numbering in scheme 1. These compounds were obtained commercially[17], the solvents, also commercial were stored over molecular sieves and used without further purification. ^{1}H and ^{13}C NMR were obtained on a Bruker Avance spectrometer operating at 400.13MHz for proton and 100.63MHz for carbon. HSQC, HMBC and NOE experiments were also performed. The spectra were recorded in 10mg cm^{-3} solutions (^{1}H) and ca.30mg cm^{-3} (^{13}C) in $CDCl_3$ with a probe temperature of ca 300K and referenced to TMS unless indicated otherwise. Typical running conditions (^{1}H spectra) were 128 transients, spectral width 3300Hz and 32k data points zero-filled to 128k. This gave an acquisition time of 5s and a digital resolution of 0.025Hz. The observed ^{1}H chemical shifts are therefore accurate to 0.001ppm. The 2D experiments were conducted using the standard Bruker COSY-DQF pulse sequences[18]. The NMR spectra of indanone (**7),** 9-acetylanthracene (**14**) and benzosuberone, were obtained at GSK, using a Bruker Avance spectrometer operating at

700.13 MHz for the proton experiments, a Bruker Avance operating at 500.13 MHz for the carbon, HSQC and HMBC experiments and a Bruker Avance operating at 399.87 MHz for the NOE experiments. 9-methoxyanthracene was synthesised by methylating the enol tautomer of anthrone according to Meek et al[19].

Conformational

The geometries of the polycyclic molecules were obtained using the molecular mechanics program PCMODEL Version 7.0[20] with the MMFF94 forcefield. For the smaller molecules the geometries were further optimised using the Gaussian98 programme at the B3LYP/6-31G** level[21]. It has been shown[22] that the DFT level of theory generally obtained better geometries compared to other theoretical levels, especially for compounds with intra molecular hydrogen bonding. Anthraldehyde was also optimised at the B3LYP/6-31G** level as this was the geometry used previously for anthracene parameterisation[23]. 9-acetylanthracene was too large to run at these higher levels of theory but the 9-methoxy - and 9-hydroxy-anthracene were run at B3LYP/3-21G* level. All the calculations were carried out on a PC.

cis trans

Figure 2. cis and trans conformers in 2-substituted benzaldehydes.

The 2-substituted benzaldehydes (**2**, **3** and **4**) and acetophenones (**6, 8**) can exist as cis or trans conformers (figure 2). The trans conformer is usually the more stable form, due to steric effects, but where intramolecular hydrogen bonding occurs as in **3** and **8** the cis form would be expected to be more stable. To check that these compounds were in one conformation their geometries, energies and dipole moments were calculated using PCMODEL and the results are given in table 1. The conformer energy difference is so large for these compounds that they will only exist in one conformation, **2, 4** and **6** in the trans form and **3** and **8** in the cis form. A LIS investigation[24] found that compound **2** exists solely in the trans conformer in $CDCl_3$ solution. In

all these compounds except **2** (see below) the carbonyl is coplanar with the aromatic ring. The remaining polycyclic compounds can only exist in one conformation. Compounds **7, 9, 10, 11** and **15** are planar, **12** has an envelope cyclohexenone ring and **13** and **14** have the acetyl group orthogonal to the aromatic ring. LIS studies of the conformations of **7**[25], **12**[26], **13**[27], and **14** and **15**[28] in chloroform solution agreed with these results.

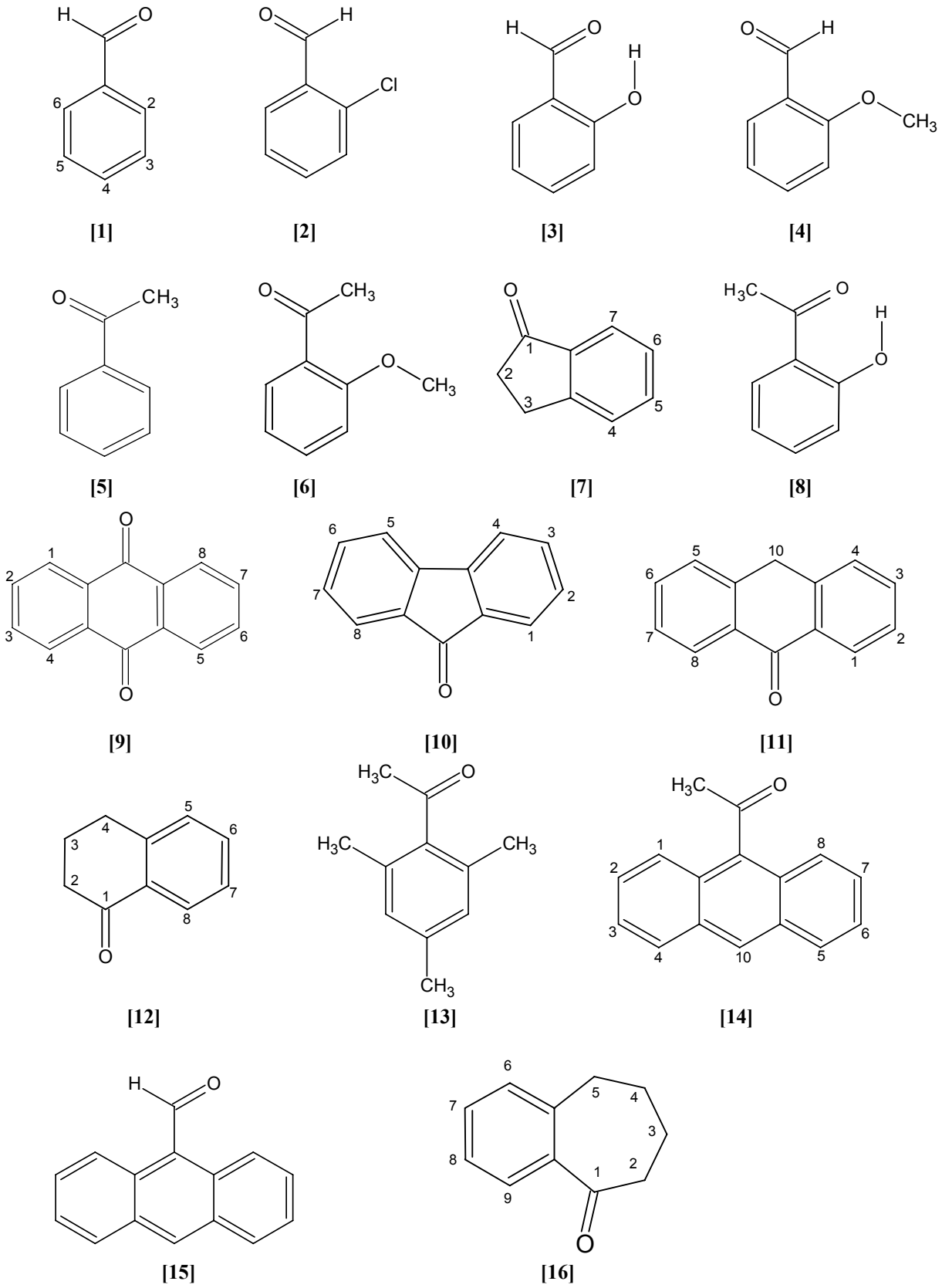
All these compounds were used for the parametrisation except for **2** and **16**. In **2** the PCMODEL geometry has a CO/ring dihedral angle of ca 40^0 but the *ab initio* geometry is planar. In **16** again the ring geometries for the molecular mechanics and various ab initio basis sets differ considerably. These molecules were therefore omitted from the calculations and will be considered subsequently.

Spectral Assignments

The spectra were obtained in $CDCl_3$ and DMSO. The assignments of the spectra of benzaldehyde **1** and acetophenone **5** are straightforward. Those of 2-chlorobenzaldehyde **2**[23], 2-hydroxybenzaldehyde **3**[29], indan-1-one **7**[25], 2-hydroxyacetophenone **8**[29], fluoren-9-one **10**[30], 2,4,6-trimethylacetophenone **13**[27], 9-anthraldehyde and 9-acetylanthracene, **14, 15**[28] have been given previously. The chemical shifts given here of dilute samples (approx. 5-10mg/cm^3) in $CDCl_3$ agree with this data, although in some cases the chemical shifts varied slightly due to concentration effects.

Table 1. Energies (kcal/mol), Dipole moments (D) and CO/Ring Dihedral Angles of the trans and cis conformers of 2-substituted benzaldehydes and acetophenones.

	Energy trans	Energy cis	ΔE $E_{cis}-E_{trans}$	Dipole (t)	Dipole (c)	CO/Ring Dihedral Angle (t)	CO/Ring Dihedral Angle (c)
[1] Benzaldehyde	31.26			4.37		0	
[2] 2-Chloro-benzaldehyde	27.18	33.06	5.88	4.14	6.59	0	0
[3] 2-Hydroxy benzaldehyde	33.67	25.78	-7.89	2.90	4.87	11.2	0
[4] 2-Methoxybenzaldehyde	39.63	47.61	7.98	5.09	5.56	0	0
[5] Acetophenone	36.10			4.37		0	
[6] 2-Methoxy-acetophenone	47.19			5.75	4.17	29.1	
[8] 2 Hydroxy acetophenone	36.36	30.57	-5.79	6.02	5.01	17.6	0



Scheme 1. Molecules studied and their numbering.

The spectrum of indanone **7** gave an AA'BB' pattern for the H2,3 protons. Expansion of the H2 region allowed the detection of the weak outer lines of the K,L quartet[31] which were of comparable intensity to the ^{13}C satellites. This allowed the full analysis of the spectrum using the Mestre-C programme[32] to give the chemical shifts of table 3 and couplings J_A = -19.38Hz, J_B = -17.53 Hz, Jcis = 8.56Hz and Jtrans = 3.44Hz. The geminal couplings J_A and J_B cannot be assigned from the spectrum but may be assigned to the 2-methylene and 3-methylene protons res. from literature data[33].

The spectrum of 2-methoxybenzaldehye (**4)** was assigned from the COSY plot. The couplings between the aldehyde hydrogen and H5 and between the methoxy group and H3 were observed in this plot and assigned H5 and H3. These couplings had been reported by Schaefer et al.[34] and are further evidence that the compound exists as the trans conformer in $CDCl_3$. Schaefer also noted that CHO..H3 couplings occurred in the cis conformer when it is stabilised due to intramolecular hydrogen bonding. The aldehyde coupling to H5 was observed for 2-chlorobenzaldehyde and 2-methoxybenzaldehyde and to H3 in 2-hydroxybenzaldehyde. The spectrum of compound **6** was assigned similarly to **4** from the COSY plot and again the coupling of the methoxy group to H3 was observed[34].

The spectrum of anthraquinone (**9**) consists of a doublet (Hα) and triplet (Hβ). The spectrum of anthrone (**11**) was assigned from the COSY plot as the CH_2 protons couple to H4 from which the remaining protons can be assigned. In DMSO the most abundant form of the substance was the enol tautamer. The enol spectrum was assigned by an NOE of the low field doublet with the OH proton, identifying the doublet as the H2 proton. The other ring protons were assigned from a COSY plot. The assignment was further confirmed by HMQC and HMBC experiments. The spectrum of α-tetralone (**12**) was assigned from the COSY plot. This agreed with a previous assignment[26].

9-Acetylanthracene (**14)** had been assigned previously[28] but H2 and H3 were not distinguished. An NOE experiment irradiating the methyl assigned H1. Irradiating the doublet of H4 allowed H3 to be identified but H2 and H3 were unresolved at 400 MHz. However the 700 MHz spectrum clearly separated the two peaks. In the COSY plot the long range coupling between H1 and H10 could be observed, as had been reported previously[35].

Table 2 Observed ^1H chemical shifts of substituted benzaldehydes and acetophenones in $CDCl_3$ and DMSO vs calculated shifts.

	Solvent	H2	H3	H4	H5	H6	CHO/ $COCH_3$	2-Subs.
[1] Benzaldehyde	CDCl3	7.880	7.532	7.632	-	-	10.025	-
	Calc.	*7.876*	*7.555*	*7.640*	-	-	*10.026*	-
	DMSO	7.920	7.619	7.728	-	-	10.027	-
[2] 2-Chlorobenzaldehyde	CDCl3	-	7.457	7.530	7.389	7.928	10.492	-
	Calc.	-	*7.566*	*7.669*	*7.463*	*7.924*	*10.421*	-
	DMSO	-	7.632	7.709	7.543	7.879	10.349	-
[3] 2-Hydroxybenzaldehyde	CDCl3	-	6.997	7.535	7.027	7.567	9.903	11.024
	Calc.	-	*7.071*	*7.533*	*7.167*	*7.662*	*9.893*	*10.298*
	DMSO	-	6.999	7.522	6.964	7.666	10.258	10.685
[4] 2-Methoxybenzaldehyde	CDCl3	-	6.990	7.548	7.027	7.830	10.478	3.933
	Calc.	-	*7.115*	*7.520*	*7.140*	*7.900*	*10.574*	*3.870*
	DMSO	-	7.234	7.689	7.081	7.699	10.371	3.923
[5] Acetophenone	CDCl3	7.960	7.459	7.562	-	-	2.604	-
	Calc.	*7.884*	*7.554*	*7.623*	-	-	*2.609*	-
	DMSO	7.958	7.528	7.639	-	-	2.582	-
[6] 2-Methoxyacetophenone	CDCl3	-	6.967	7.459	6.995	7.728	2.611	3.913
	Calc.	-	*7.098*	*7.480*	*7.127*	*7.723*	*2.619*	*3.827*
	DMSO	-	7.167	7.535	7.017	7.569	2.523	3.888
[8] 2-Hydroxyacetophenone	CDCl3	-	6.972	7.466	6.896	7.730	2.627	12.242
	Calc.	-	*7.088*	*7.524*	*7.171*	*7.608*	*2.627*	*12.833*
	DMSO	-	6.958	7.532	6.963	7.890	2.641	11.954
[13] 2,4,6-Trimethylacetophenone*	CDCl3	-	6.832	2.273*	-	-	2.449	2.215
	Calc.	-	*6.862*	*2.394**	-	-	*2.509*	*2.336*
	DMSO	-	6.895	2.264*	-	-	2.449	2.217

*methyl

The ^{1}H spectrum of benzosuberone (**16**) was assigned using ^{13}C, DEPT, HSQC and HMBC experiments at 500MHz. A separate proton experiment was run at 700MHz to resolve the overlapping multiplets of H2, H5 and H3, H4 in the aliphatic region.

The proton spectra of 9-methoxyanthracene was assigned from the ^{1}H and COSY spectrum at 400MHz, the assignment was confirmed by correlating the previously assigned ^{13}C spectrum[37] with the ^{1}H spectrum using the HMQC experiment. The H2 and H3 protons were overlapped and the centre of the second order pattern was taken as the chemical shift value.

The results from these assignments are given in tables 2, 3 and 7 and full details of all the

assignment experiments and spectra in ref 36.

Table 3. Observed vs Calculated ^{1}H chemical shifts (δ) of polycyclic aromatic carbonyl

compounds and derivatives in $CDCl_3$ and DMSO.

	Solvent	H1	H2	H3	H4	H5	H6	H7	H8	CHO/ $COCH_3$
[7] Indanone	CDCl3	-	2.695	3.152	7.480	7.586	7.371	7.766	-	-
	Calc.	-	*2.811*	*3.190*	*7.370*	*7.635*	*7.424*	*7.717*	-	-
	DMSO	-	2.629	3.110	7.587	7.665	7.418	7.639	-	-
[9] Anthraquinone	CDCl3	8.325	7.805	-	-	-	-	-	-	-
	Calc.	*8.413*	*7.721*	-	-	-	-	-	-	-
	DMSO	8.231	7.948	-	-	-	-	-	-	-
[10] Flourene-9-one	CDCl3	7.659	7.290	7.480	7.522	-	-	-	-	-
	Calc.	*7.745*	*7.307*	*7.410*	*7.603*	-	-	-	-	-
	DMSO	7.611	7.386	7.621	7.803	-	-	-	-	-
[11] Anthrone	CDCl3	8.361	7.456	7.589	7.465	-	-	-	4.351*	-
	Calc.	*8.130*	*7.468*	*7.639*	*7.544*	-	-	-	*4.159**	-
	DMSO	8.206	7.523	7.702	7.603	-	-	-	4.462*	-
[12] α-Tetralone	CDCl3	-	2.656	2.141	2.967	7.248	7.461	7.300	8.034	-
	Calc.	-	*2.554*	*2.228*	*2.916*	*7.369*	*7.591*	*7.392*	*7.962*	-
	DMSO	-	2.598	2.042	2.945	7.350	7.540	7.341	7.863	-
[14] 9-Acetylanthracene	CDCl3	7.847	7.523	7.495	8.038	-	-	-	8.489*	2.820
	Calc.	*7.784*	*7.566*	*7.595*	*8.119*	-	-	-	*8.674**	*2.793*
	DMSO	7.846	7.575	7.609	8.173	-	-	-	8.713*	2.804
[15] 9-Anthraldehyde	CDCl3	8.992	7.687	7.555	8.073	-	-	-	8.707*	11.541
	Calc.	*9.055*	*7.772*	*7.624*	*8.176*	-	-	-	*8.919**	*11.077*
	DMSO	9.038	7.759	7.644	8.238	-	-	-	9.020*	11.493
9-Hydroxyanthracene	DMSO	8.430	7.429	7.469	7.978	-	-	-	8.033*	10.220**
	THF	8.423	7.267	7.329	7.840	-	-	-	7.799*	-
	Calc.	*8.581*	*7.427*	*7.559*	*7.893*				*7.933**	*5.288***
9-Methoxyanthracene	CDCl3	8.300	7.470	7.470	7.996				8.224*	4.157
	Calc.	*8.535*	*7.611*	*7.607*	*8.042*				*8.545**	*3.944*

*H10, **OH

Results

Keto-enol tautomerism of anthrone. Although the formation of 9-hydroxy anthracene from anthrone by the addition of NaOH has been known many years[38] we were unable to find any mention in the literature of this tautomerism being observed by ^{1}H NMR and the proton NMR spectrum of the enol has not been described previously. The great majority of keto-enol equilibria involve the α proton of the ketone.(CH.C=O ↔ C=C.OH). The anthrone: 9-hydroxyanthracene equilibrium is exceptional as anthrone does not possess a proton α to the carbonyl group and it was therefore of some interest to describe it in detail. In chloroform there was no evidence of any enol form from the ^{1}H NMR spectrum. However in DMSO both conformers are observed as the slow exchange condition applies with the enol form the major form. Integration of the proton spectrum gave the distribution as 3:1 in favour of the enol form. The obvious interpretation of

the difference between $CHCl_3$ and DMSO in this equilibrium is that DMSO is stabilising the enol form through hydrogen bonding. The hydroxyl proton occurs at 10.22δ in DMSO and this is evidence of strong hydrogen bonding with the solvent. However Novak et al [39] observed that in pentane 1,3,5 triones the more polar keto form was stabilised by DMSO compared to chloroform and they proposed that this was due to solvation of the more polar keto form.

In order to distinguish these explanations the proton spectrum was obtained in a number of solvents of varying relative permittivity and hydrogen bonding ability and these results are given in table 4. In pyridine, methanol and acetone the two forms could be observed and their proportions determined. In THF it was necessary to add a catalytic amount of base (NaOH) in order for the equilibrium to proceed. Even in this case there was still slow exchange between the keto and enol forms and thus the proportions could be readily determined. It can be seen that the proportion of enol varies from 77% in DMSO to only 16% in acetone. Table 4 gives the free energy difference ΔE= E(keto)-E(enol) and also the relative permittivity and the Kamlett β parameter[40] of the solvents used. The latter is a measure of the hydrogen bonding ability of the solvent. It is clear from the results in table 4 that the relative proportions of the keto and enol forms bear little relationship to the relative permittivity of the solvent, but there is an excellent correlation between the proportion of enol and the Kamlett β parameter. Analysis gives a linear equation with a correlation coefficient (r) of 0.92. If the uncertain data for MeOD is removed the r value is increased to 0.97. This is strong support for the proposal that the formation of the enol in this case is due mainly to hydrogen bonding with the solvent and not to polarity effects. This contrasts with a previous study on intra vs inter-molecular hydrogen bonding in cis-cyclohexane-1,3-diol[41] in which the energy difference of the conformers involved (ax-ax vs eq-eq) was shown to correlate with the polarity of the solvent but with different coefficients for hydrogen bonding and non-hydrogen bonding solvents.

Table 4 The % enol form in the keto-enol tautomerization of anthrone in various solvents.

Solvent	$\mathbf{n_{enol}}$	**ΔE (kcal/mole)**	**ε**	**β**
DMSO	0.77	-0.720	46.7	0.76
Pyridine	0.66	-0.395	12.4	0.64
THF	0.37	0.317	7.6	0.55
MeOD	0.35	0.369	32.7	0.62*
Acetone	0.16	0.988	20.7	0.48

** data is not certain*

The Carbonyl Anisotropy.

The ^1H chemical shifts in $CDCl_3$ in tables 2 and 3 are sufficient to allow the full parameterisation in the CHARGE routine for aromatic carbonyl groups. All the data in the tables were used except the chemical shifts for 2-chlorobenzaldehyde (**2**) and benzosuberone (**16**) (see later) and also the hydroxyl hydrogens of compounds **3** and **8**. This gave a total of 129 shifts ranging from 2.8 to 11.5δ. As stated previously there are only four variables to be determined. These are the C(Ar).CHO beta effect, the carbonyl anisotropy $\Delta\chi_{parl}$ and $\Delta\chi_{perp}$ and the oxygen steric effect. The values of the parameters were obtained by use of a non-linear least mean square program CHAP8[42] which compares the observed *vs*. calculated chemical shifts. This gave $\Delta\chi_{parl}$ = 6.36, $\Delta\chi_{perp}$ = –11.88 (10^{-30} cm^3/molecule) and the oxygen steric coefficient a_s =38.4ppm $Å^6$. The rms error was 0.094 ppm for the whole dataset. The calculated and observed shifts are given in tables 2 and 3 and it can be seen that the agreement is excellent with the largest error for the ring protons ca 0.15ppm. This demonstrates the applicability of the CHARGE scheme to this important class of compounds. The values of the CO anisotropy and oxygen steric coefficient found here will be considered later.

A small change was made to the π calculation in CHARGE (eqn. 6) for the 9-substituted anthracenes. In the unmodified routine the H10 proton of anthraldehyde was calculated at much too large δ value (calc. 9.10 vs obs. 8.71). Conversely the H10 proton of 9-hydroxy anthracene was calculated at too low δ value (calc. 7.57 vs obs. 7.80). The calculated SCS have the correct signs (note H10 in anthracene is 8.43δ)[23] but are much too large. This difference is not due to the carbonyl anisotropy or to steric or electric field effects as these effects decrease very rapidly with distance (see table 5). Hückel theory tends to exagerate the π charges in compounds with very polarisable π systems such as the middle ring of anthracene and this was the reason for these anomalies. This effect did not happen with the 9-acetyl anthracene as the acetyl group is orthogonal to the ring, thus there is no conjugation with the π system.

In CHARGE the resonance integral coefficient (k_{rs} eqn 6) is –1.0 for benzenoid aromatics. To account for the polarisability of the middle ring of anthracene this coefficient for the C9,10 bonds with the α-carbons was modified. The two results above were used to optimise this value. Decreasing the value of this resonance integral to –1.25 gave reasonable agreement for both molecules and these calculated values are given in table 3. Most interestingly the chemical shift of H10 in 9-methoxyanthracene is also upfield of anthracene. The SCS of the methoxy group at H10 is –0.21ppm which is comparable to that of the hydroxy group (-0.36) even though both the MM and ab initio calculations gave the methoxy group orthogonal to the anthracene ring

and in consequence show no π effect. The observed SCs could be due to hyperconjugation or possibly to large vibrational motion of the methoxy group.

The use of CHARGE for Conformational Analysis

The CHARGE routine gives proton chemical shifts for the conformationally rigid molecules considered in good agreement with the observed shifts. A related question is whether the CHARGE routine can be used in conformationally mobile compounds to obtain conformational information. The compounds we wish to consider here are 2-chlorobenzaldehyde and benzosuberone. However before these are attempted it is necessary to consider a well-defined case such as benzaldehyde. The energy profile obtained from PCMODEL is shown in figure 3. The CHARGE routine gives an accurate calculation of the proton chemical shifts for the planar molecule but would it also reproduce the effects in the non-planar conformations? To test this the shifts were calculated for the various orientations of the aldehyde group and the rms deviation of the observed vs calculated shifts obtained. This curve is also shown in figure 3 with the energy profile. The ordinates differ in the two plots but the overall good agreement of the two curves is strong support for the use of CHARGE in the conformational analysis of these compounds.

2-chlorobenzaldehyde (**2**). The theoretical calculations gave conflicting geometries for the stable trans conformer. Gaussian98 using the B3LYP density function theory with the 6-31G** basis set gave a planar molecule which was also the case with the MMF94 forcefield of PCMODEL. In contrast the MMX force field in PCMODEL gave a minimum energy for a 40^0 ring/aldehyde torsional angle. Thus the proton chemical shifts were obtained from CHARGE for 10^0 rotations of the aldehyde from the plane and compared with the observed data. The best agreement was for a torsional angle of 25^0 with an rms error of 0.085ppm. There is no experimental data to support this result but it would appear a reasonable value.

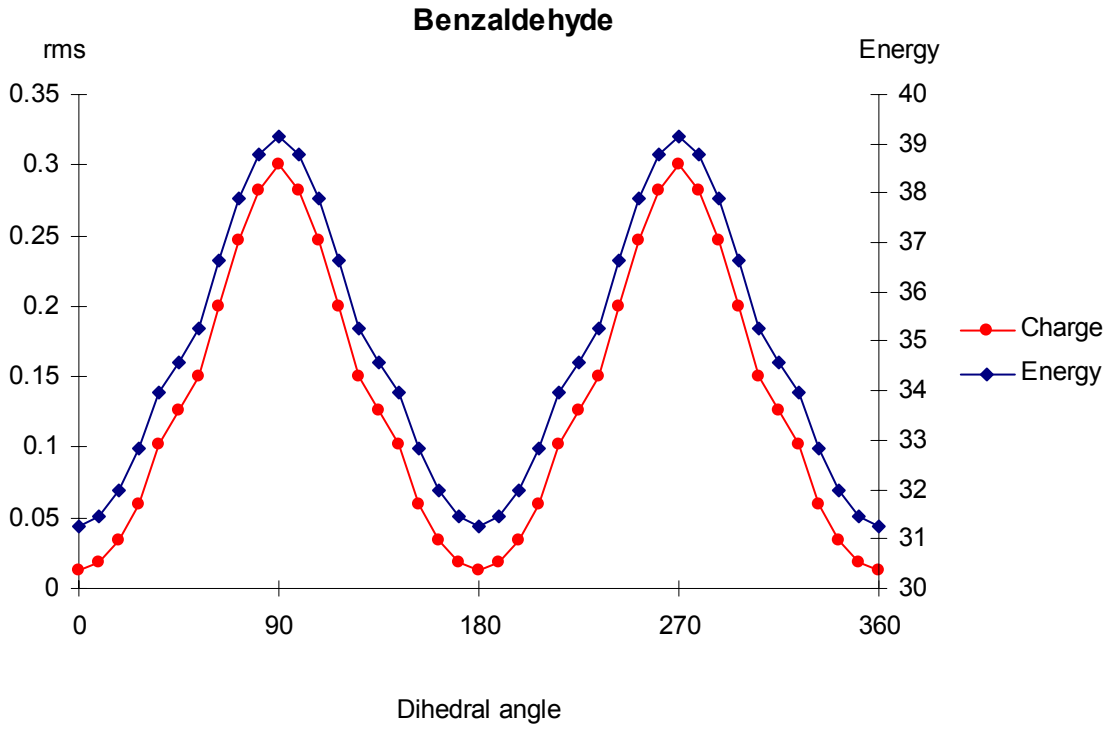


Figure 3. The energy (PCMODEL) and rms (CHARGE) calculations vs dihedral angle of benzaldehyde.

Benzosuberone (16). This molecule contains a seven-membered ring joined to a benzene ring (scheme 1). The seven-membered ring is in a chair conformation and is interconverting rapidly with its mirror image at room temperature, thus the two protons in each ring CH_2 groups are equivalent. The molecule was first minimized using the MMFF94 forcefield but the calculated ^1H chemical shift for H9 peri to the carbonyl was in error by ca 0.55ppm (table 5). This could be due to an incorrect geometry as the torsional strain in such a molecule is not easy to reproduce by molecular mechanics calculations. Thus the calculations were repeated with different optimised geometries including the MMX force field and *ab initio* calculations with both 3-21G* and 6-31++G(d,p) basis sets. The calculated shifts from CHARGE using these geometries are shown in table 5 together with the observed chemical shifts. The calculated shifts for protons other than H9 do not change appreciably but the values for H9 range from 7.175 to 7.836δ (exp. 7.717). Interestingly the best value for H9 is with the 3-21G basis set. However the rms error decreases as the level of theory increases with the best result for the larger basis set. The dihedral angle of the carbonyl with respect to the benzene ring changes significantly for the different geometries, from 67^0 (MMX), 53^0 (MMF94) to 32^0 (3-21G) and 42^0 (6-31G). Thus the results in table 5 suggest that an appropriate value for this dihedral angle is $37^0 \pm 5^0$. A LIS experiment[43] suggested that the dihedral angle of the carbonyl with respect to the benzene ring is 56 degrees, which

agrees with the value obtained with the MMX forcefield, but differs considerably from the value found here.

Table 5. Observed vs calculated ^{1}H chemical shifts of benzosuberone using different geometries.

Proton	Exp.	MMX	MMFF94	B3LYP (3-21G*)	B3LYP (6-31++G(d,p))
2	*2.733*	2.850	2.796	2.677	2.755
3	*1.813*	1.808	1.832	1.862	1.859
4	*1.882*	1.835	1.875	1.903	1.906
5	*2.931*	2.684	2.715	2.740	2.741
6	*7.196*	7.249	7.317	7.377	7.354
7	*7.415*	7.389	7.473	7.533	7.495
8	*7.297*	7.262	7.317	7.348	7.323
9	***7.717***	**7.175**	**7.349**	**7.836**	**7.557**
rms.		0.134	0.109	0.098	0.088

This result emphasises the necessity of using the correct geometry as input to CHARGE to obtain accurate proton chemical shifts. However we note that in this case the values from CHARGE for all the geometries used are very reasonable with the rms error ≈ 0.1ppm.

Solvent Effects.

When considering the effects of different solvents on ^{1}H chemical shifts it is important to distinguish between intrinsic solvent effects and those which occur as a result of a change in the solute conformation or structure due to the change in solvent. For convenience we will term the latter specific solvent effects. The intrinsic solvent effect of DMSO vs $CDCl_3$ may be due to the different anisotropy, polarity or polarisability of the two solvents[44]. The specific solvent effects may be due to polarity changes[45] and chemical effects in particular hydrogen bonding.

It is not proposed here to attempt any calculation of solvent effects but it is of interest to see whether it is possible to distinguish in the present data set intrinsic vs specific solvent effects. To evaluate the intrinsic solvent effects we considered all molecules in which only one conformation is possible. This covers all the data set except compounds **2**, **3**, **4**, **6** and **8**. Inspection of the data showed some simple regularities. For all the aliphatic and aldehyde protons in the data set the solvent shift is very small. $\Delta\delta$ (DMSO-$CDCl_3$) = -0.04 (± 0.02) ppm. For the aromatic protons in contrast the solvent shift is larger and of opposite sign, $\Delta\delta$ = +0.12 (± 0.05) ppm. for all the aromatic protons except those peri (or ortho) to the carbonyl group. In this case the solvent shift is reversed, $\Delta\delta$ = -0.11 (± 0.04) ppm. The only exception to these rules are the H10 protons in **14** and **15** which show large positive shifts with $\Delta\delta$ = +0.27 (± 0.04) ppm.

A possible interpretation of these effects is as follows. The anisotropic and polar contributions to Δδ are very small except for protons very close to the carbonyl group. The major effect for aromatic protons is due to the different polarisabilities of the two solvents and this effect is enhanced for very polarisable entities such as the middle ring of the anthracenes **14** and **15**.

The largest specific solvent shifts are as expected with the hydroxy compounds **3** and **8**. However most intriguingly the hydroxy protons in these compounds are shielded in DMSO compared to $CDCl_3$, by 0.34 and 0.29 ppm. res. even though the DMSO solvent is undoubtedly hydrogen bonding to these protons. A possible interpretation is that when the intra-molecular hydrogen bond in $CDCl_3$ is replaced by the inter-molecular H-bond in DMSO, the electric field and steric contributions to the OH chemical shift are ca the same, but the large anisotropic effect of the carbonyl on the intramolecular OH proton has now been replaced by the much less anisotropic SO group, giving rise to the observed shielding effect. In addition in **3** there is a large deshielding of the aldehyde proton in DMSO and this could be due to an increased % of the trans conformer in this solvent.

In the other confomationally mobile compounds **2**, **4**, and **6** the solvent effects generally follow the non-specific trends outlined above, thus there is no evidence from these shifts that there is a substantial % of the more polar cis conformer in DMSO.

Discussion

In CHARGE the components of the carbonyl substituent effect are given explicitly thus it is of interest to determine the proportions of the carbonyl anisotropy, electric field and steric effect at the various protons in the molecules. As the anisotropy and electric field are propoprtional to r^{-3} and the steric effect to r^{-6} obviously the steric effect will be significant only for near protons. Some illustrative examples are given in table 6 together with the C=O···H distance.

Comparison of the results for the near H1/H8 protons in 9-anthraldehyde (**15**) and 9-acetylanthracene (**14**) is of interest as in **15** the molecule is planar but in **14** the acetyl group is perpendicular to the anthracene ring plane. The effect of the carbonyl anisotropy is strongly deshielding in **15** but strongly shielding in **14**. In contrast the electric field and steric effects are the same sign in both molecules but much larger in **15** due to the closer proximity of the carbonyl group and H1/8. Comparison of the anisotropy and electric field contributions is well illustrated by the results for anthrone (**11**). They are both long range and all the protons of the compound

except H2 and H3 have significant shifts but the electric field contribution is always larger and in the peri protons (H1/8) predominant.

The steric term only becomes significant in compounds where the oxygen-hydrogen distance is relatively short (2.5-3Å). In some cases, e.g. H8 in α-tetralone it is larger than the anisotropy contribution but for the molecules studied here it is always less than the electric field term. At distances > 4 Å the steric term is negligible.

Table 6. Anisotropic, electric field and steric contributions of the carbonyl group SCS.

Compound	Proton	CO···H [Å]	$\delta_{C=O-AN}$	$\delta_{CO-EFLD}$	$\delta_{O-STERIC}$
[15] Anthraldehyde	H1/H8	2.32	0.246	0.337	0.241
[14] Acetylanthracene	H1/H8	2.93	-0.424	0.132	0.061
[12] α-Tetralone	H8	2.49	0.126	0.398	0.161
[7] Indanone	H7	2.83	0.086	0.311	0.074
[11] Anthrone	H1/H8	2.48	0.128	0.411	0.163
"	H2/H7	4.84	0.019	0.064	0.003
"	H3/H6	6.06	0.021	0.051	0.001
"	H4/H5	5.73	0.048	0.073	0.001
"	H10	4.90	0.094	0.161	0.003

It is of some interest to compare the values of the carbonyl anisotropy obtained here with those found in previous studies.The early investigations used different axes and nomenclature and these were converted by Abraham and Ainger[12] to the present nomenclature of figure 1 and eqn 4. The values of $\Delta\chi_{parl}$ and $\Delta\chi_{perp}$ obtained here are 6.4, -11.9, cf Zurcher[5], 13.5, -12.2; ApSimon[7] 21, -6; Schneider[10] 24, -12 ; Williamson[11] 4, -9 and Abraham[12a] 22.7, -14.8. There is a considerable difference between the present values and all the other investigations except those of Williamson. As noted earlier all the investigations except that of Williamson considered only aliphatic carbonyls. The values obtained by Williamson were based on the carbonyl anisotropy in peptides and proteins and it is interesting to see the close comparison between this value and our values for the aromatic carbonyl. This is precisely what would be expected on chemical grounds. The π electrons of the carbonyl group in amides are delocalised in a similar manner to those in aromatic ketones and this delocalisation cannot occur in saturated ketones. Clearly this delocalisation has a significant effect on the carbonyl anisotropy. This is of crucial importance when predicting proton chemical shifts.

Conclusion

The ^{1}H chemical shifts in a variety of aromatic aldehydes and ketones are predicted by the

CHARGE routine to within 0.1ppm. This together with previous results for aliphatic carbonyl compounds allows the CHARGE programme to predict the ^{1}H chemical shift of any aldehyde and ketone to essentially experimental accuracy. The carbonyl anisotropy in the aromatic ketones was shown to be similar to that in amides but much less than the value in aliphatic ketones..

The keto/enol tautomerism in anthrone/9-hydroxy anthracene was observed by NMR and the percentage of enol was shown to be proportional to the Kamlett β hydrogen bonding effect of the solvent and not to the solvent polarity.

Acknowledgements

We thank the EPSRC and GSK for a CASE research studentship (M.M.) and GSK for the 750 MHz spectrum of **7** and **14.** We thank Dr. M.H. Abraham for helpful discussions on the solvent parameter scales.

References

1.Part 18, R.J.Abraham and M.Reid, *J. Chem. Soc. Perkin Trans.2,* 2002, 1081.

2. L.M.Jackman, *Nucl.Mag.Res.Spec,* p 112-30, Pergamon Press,1959

3. J.A.Pople, *J..Chem.Phys*, 1962, **37**, 53,60.

4. A.A.Bothner-By and J.A.Pople, *Ann.Rev.Phys.Chem.*, 1965, **16**, 43.

5. R.F. Zurcher, *Prog.Nuclear.Mag.Res.Spec*, 1967, **2**, 205.

6. H.M.McConnell, *J..Chem.Phys*, 1957, **27**, 226.

7.a) J.W.ApSimon, P.V.DeMarco and D.W. Mathieson , *Tetrahedron*,1970, **26**, 119.

b) J.W.ApSimon and H.Beierbeck, Canad J.Chem.,1971, 49, 1328.

8. J. Homer and D.Callagham, *J.Chem.Soc.A*, 1968, 439.

9. K.J.Toyne, *Tetrahedron*,1973, **29**, 3889.

10. H.J.Schneider,U.Buchheit,N.Becker,G.Shmidt and U.Siehl, *J.Am.Chem.Soc*.,1985,**107**,7027.

11. a) M.P.Williamson and T.Asakura, *J.Mag.Res*., 1991,**94**,557.

b) ibid,1993, B101,63.

c) M.P.Williamson, T.Asakura, E.Nakamura and M.Demura, *J.Biomol.NMR*,1992,**2**,83.

12. R.J.Abraham and N.J.Ainger, *J.Chem.Soc.Perk.Trans.2,*1999, 441.

12a. R.J.Abraham, unpublished results.

13. H.Lampert, W.Mikenda, A.Karpfen and H.Kahlig,*J.Phys.Chem*.,1997,**101**,9610.

14. G. Wu, M.D. Lumsden, G.C. Ossenkamp, K. Eichele and R.E. Wasylishen, J. Phys. Chem., 1995. **99** ,15806.

15. R.J.Abraham, *Progress in NMR Spectroscopy*, 1999,**35**,85.

16. a) R.J.Abraham and P.E.Smith, *J.Comp. Chem*.,1987, **9**, 288.

b) R.J.Abraham and P.E.Smith*, J.Comp. Aid. Molec. Design*,1989, **3**, 175.

17. Aldrich Chem. Co. Eastmank Kodak Co., Rochester, USA.

18. Bruker XWINNMR version 3.0, Bruker AM, Silbersteifen, D-7512 Germany.

19. J.S.Meek, P.A.Monroe, C.J.Bouboulis, *J.Org.Chem.*,1963, **28**,2572.

20. *PC Model 7.0*. 1998, Serena Software: Box 3076, Bloomington, USA.

21. M.J.Frisch, G.W.Trucks, H.B.Schlegel, G.E.Scuseria, M.A.Robb, J.R.Cheeseman, V.G.Zakrzewski, J.A.Montgomery, Jr., R.E.Stratmann, J.C.Burant, S.Dapprich, J.M.Millam, A.D.Daniels, K.N.Kudin, M.C.Strain, O.Farkas, J.Tomasi, V.Barone, M.Cossi, R.Cammi, B.Mennucci, C.Pomelli, C.Adamo, S.Clifford, J.Ochterski, G.A.Petersson, P.Y.Ayala, Q.Cui, K.Morokuma, D.K.Malick, A.D.Rabuck, K.Raghavachari, J.B.Foresman, J.Cioslowski, J.V.Ortiz, A.G.Baboul, B.B.Stefanov, G.Liu, A.Liashenko, P.Piskorz, I.Komaromi, R.Gomperts, R.L.Martin, D.J.Fox, T.Keith, M.A.Al-Laham, C.Y.Peng, A.Nanayakkara, M.Challacombe, P.M.W.Gill, B.Johnson, W.Chen, M.W.Wong, J.L.Andres, C.Gonzalez, M.Head-Gordon, E.S.Replogle and J. A. Pople., *GAUSSIAN 98, Revision A9*. 1998, Gaussian inc.: Pittsburg PA.

22. J.B.Foresman and A.Frisch, Exploring Chemistry with Electronic Structure Methods, Gaussian

inc.,1993,Pittsburgh,USA.

23. R.J.Abraham,M.Canton,M.Reid and L.Griffiths, *J.Chem.Soc.Perk.Trans.2,*2000, 803.

24. R.J.Abraham,D.J.Chadwick and F.Sancassan, *J.Chem.Soc.Perk.Trans.2,*1984,1037.

25. R.J.Abraham,D.J.Chadwick and F.Sancassan, *J.Chem.Soc.Perk.Trans.2,*1989,1377.

26. R.J.Abraham and M.S.Lucas, *J.Chem.Soc.Perk.Trans.2,*1988,1269.

27. R.J.Abraham,H.A.Bergen and D.J.Chadwick, *J.Chem.Soc.Perk.Trans.2,*1983,1161.

28. R.J.Abraham,D.J.Chadwick and F.Sancassan, *J.Chem.Soc.Perk.Trans.2,*1988,169.

29. H. Lampert, W. Mikenda, A. Karpfen and H. Kählig, J. Phys. Chem. A, 1997. **101**, 9610.

30. F. Sancassan, G. Petrillo and R.J. Abraham, J. Chem. Soc., Perkin Trans 2, 1995, 1965.

31. R.J.Abraham, Analysis of High Resolution NMR Spectra, ch 4, Elsevier, London, 1971.

32. C. Cobas, J. Cruces and F. J. Sardina, *MestRe-C*. 2000, Universidad de Santiago de Compostela,

33. R.J.Abraham, J.Fisher and P.Loftus, *Introduction to NMR Spectroscopy*, p.23, J. Wiley 1988

34.a) T. Schaefer, R. Sebastian, D.M. McKinnon, P.W. Spevack, K.J. Cox and C.S. Takeuchi, Can. J. Chem, 1993. **71**, 960.

b) T. Schaefer, J. Peeling and A. Wildman, Org. Mag. Res, 1984. **22,** 477.

35. H.Günther, *NMR Spectroscopy*. 2nd ed. 1995: John Wiley &Sons.

36. M.Mobli, Annual report, Liverpool University, 2002.

37. J.L.Marshall, A.M.Ihrig and D.E.Miller *J.Mag.Res.*,1974,**16**, 439,

38. K.H.Meyer, Justus Liebigs Ann. Chem, 1911. **379**, 70.

39. P.Novak, D. Skare, S. Sekusak and D. Vikic-Topic, Croatia Chemica Acta, 2000. **73**,1153.

40. M.J. Kamlet, J.M. Abboud, M.H. Abraham, R.W. Taft, J. Org. Chem., 1983. **48**, 2877

41. R.J. Abraham, E.J. Chambers and W.A. Thomas, J. Chem. Soc. Perkin Trans. 2, 1993,1061.

42. Kuo SS, *Computer Applications of Numerical Methods,* ch 8,Addison-Wesley, London, 1972.

43. J.Epsztajn, A. Bieniek, J.Z. Brzezinski and H. Kalinowski, Tetrahedron, 1986. **42,** 3559.

44. P.Laszlo, Progress in NMR Spectroscopy, 1968, **3**, 203.

45. R.J.Abraham and E.Bretschneider, ch 13, Internal Rotation in Molecules, Ed. W.J.Orville-Thomas,Academic Press, NY, 1974.