^{1}H chemical shifts in NMR. Part 21[†] — Prediction of the ^{1}H chemical shifts of molecules containing the ester group: a modelling and *ab initio* investigation

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The ^{1}H NMR spectra of 24 compounds containing the ester group are given and assigned. These data were used to investigate the effect of the ester group on the ^{1}H chemical shifts in these molecules. These effects were analysed using the CHARGE model, which incorporates the electric field, magnetic anisotropy and steric effects of the functional group for long-range protons together with functions for the calculation of the two- and three-bond effects. The effect of the ester electric field was given by considering the partial atomic charges on the three atoms of the ester group. The anisotropy of the carbonyl group was reproduced with an asymmetric magnetic anisotropy acting at the midpoint of the carbonyl bond with values of $\Delta\chi_{parl}$ and $\Delta\chi_{perp}$ of 10.1×10^{-30} and -17.1×10^{-30} cm^3 molecule^{-1}. An aromatic ring current (=0.3 times the benzene ring current) was found to be necessary for pyrone but none for maleic anhydride. This result was confirmed by GIAO calculations. The observed ^{1}H chemical shifts in the above compounds were compared with those calculated by CHARGE and the *ab initio* GIAO method (B3LYP/6−31G**). For the 24 compounds investigated with 150 ^{1}H chemical shifts spanning a range of ca 10 ppm, the CHARGE model gave an excellent r.m.s. error (obs − calc) of <0.1 ppm. The GIAO calculations gave a very reasonable r.m.s. error of ca 0.2 ppm although larger deviations of ca 0.5 ppm were observed for protons near to the electronegative atoms. The accurate predictions of the ^{1}H chemical shifts given by the CHARGE model were used in the conformational analysis of the vinyl esters methyl acrylate and methyl crotonate. An illustration of the use of the CHARGE model in the prediction of the ^{1}H spectrum of a complex organic molecule (benzochromen-6-one) is also given. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{1}H chemical shifts; esters; conformational analysis; NMR prediction; *ab initio*

INTRODUCTION

The ester group is one of the most commonly encountered groups in chemistry and biology, being a constituent of all animal fats (glyceryl triesters) and the odour-producing constituent in many fruits and berries, such as octyl acetate in oranges and pentyl butyrate in strawberries. Many white wines gain their flavour and smell from the lactone shown in Fig. 1(A). Other important naturally occurring esters are the bee pheromone isopentyl acetate and the hallucinogenic ester nepetalactone [Fig. 1(B)] from the catnip plant. Ethyl oleate is produced naturally from oleic acid and ethanol (in drinks) and facilitates the release of potassium ions from brain cells, which in turn slows the release of neurotransmitters. This results in slurred speech and slow reflexes. Esters are also widely used as synthetic fibres for use in clothing (e.g. acrylics). γ-Butyrolactone is an industrial solvent and is the precursor of pyrrolidones, which are health additives, and of GHB, which has become notorious as a 'date rape' drug.[2]

Because of this common occurrence, it is surprising that the effect of the ester group on the ^{1}H NMR chemical shifts of organic compounds has not been properly investigated, apart from additive tables of chemical shifts.[3] Esterification was initially used for assignment purposes[4,5] as esterifying an OH group resulted in a large change in the neighbouring proton chemical shift.

Early investigations of the magnetic anisotropy of the carbonyl group sometimes included esters together with aldehydes and ketones.[6,7] Subsequently aldehydes, ketones and amides have been used to determine the carbonyl anisotropy,[8–20] which can vary significantly in the different compounds. More recent studies[15,16,19] have used the semiempirically determined parameters for the analysis of large systems such as proteins. Even here it has in some cases been necessary to determine certain parameters by use of *ab initio* calculations on small molecules.[19] By fully understanding the nature of the chemical shift in small molecules, the application to complex biological systems will mainly be limited by the accuracy of the modelling.

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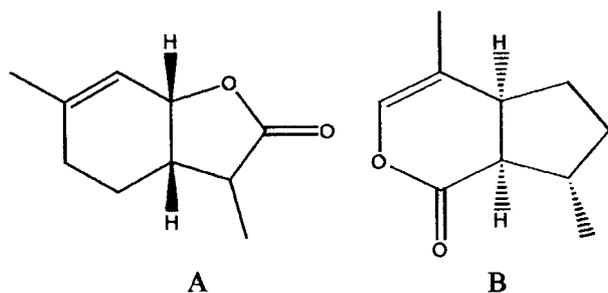
Figure 1. Important naturally occurring esters.

Conjugation with the aromatic system changes the anisotropy of the carbonyl group in aldehydes and ketones[18] to give values similar to those found for amides. It is possible that similar effects occur for esters and here a wide range of esters were selected to investigate fully the effect of the ester group. The compounds used have been divided into two categories. Those with rigid known structures are used to determine the parameters needed to describe accurately the effects of the ester group on the ^{1}H NMR chemical shifts (see Fig. 3), and those with less certain geometries are used for monitoring and modifying specific effects (see Fig. 4). The semiempirical CHARGE[21] model was used as the basis for this investigation. The CHARGE model has been shown to give a quantitative account of the ^{1}H chemical shifts of a wide variety of organic compounds and functional groups. We will show that once the appropriate parameterization has been performed, the CHARGE model is able to predict the ^{1}H NMR chemical shifts of esters to a high degree of accuracy. Also, by including the known coupling constants, we show how the CHARGE model can be used to predict the ^{1}H NMR spectra of esters.

An alternative method of calculating NMR chemical shifts is by the *ab initio* gauge-invariant atomic orbital (GIAO) method, in which the nuclear shielding tensor is calculated. Pulay *et al.*[22] in a discussion of the GIAO method noted that since the chemical shift range of ^{1}H is the smallest of all atoms it will be very sensitive to variation in the methodology such as the geometry and basis set. Also, since the protons are located on the periphery of the molecule, their chemical shifts will be more sensitive to intermolecular interactions (solvent effects, etc.), which have so far not been included in these calculations. However, recently this method was used to calculate ^{1}H chemical shifts in organic compounds. Lampert *et al.*[23] calculated the ^{1}H shifts of a range of aromatic aldehydes and phenols and Colombo *et al.*[24] used these calculations to determine the configuration of the 3-hydroxy metabolites of a synthetic steroid, tibolone. The major problem with these calculations is the basis set dependence. Colombo *et al.*[24] used a variety of basis sets and methodology (6−31G* and 6−31G** with HF, B3LYP, B3PW91) in their calculations. These six different calculations give variations in the calculated ^{1}H shifts of 0.5–1.5 ppm, depending on the particular proton considered. Bednarek *et al.* calculated the ^{1}H, ^{13}C and ^{15}N chemical shifts of a series of methyl benzoates and found good correlation for the heavy atoms but very inconsistent results for the ^{1}H chemical shifts.[25] Hence this method cannot be used to predict the ^{1}H shifts of an unknown compound as an uncertainty of 1.5 ppm

is too large to be of much use. We use a different approach in that only one theory and basis set will be used for the GIAO calculations. This is the recommended[26] B3LYP/6−31G** method in the Gaussian 03[27] program.

Comparison of chemical shift calculations by the GIAO method and CHARGE have been performed[1] on a series of halo compounds and good general agreement with the observed data was found for both methods. However, the GIAO calculations produced large errors for protons close to the halogens. No comparison of experimental data with GIAO calculations of ^{1}H chemical shifts of esters have been reported and we give here the first such study.

THE CONFORMATION OF ESTERS

In order to describe accurately the effect of the ester group on ^{1}H NMR chemical shifts, it is essential to obtain accurate molecular structures. The ester group is planar[28] with a barrier to rotation about the C—O single bond of 10–15 kcal mol^{-1} (1 kcal = 4.184 kJ).[29] Hence there are two different conformations, *cis* and *trans* (Fig. 2). It is clear from Fig. 2 that for R, R' = alkyl the dipole moment of the *trans* conformer will be much larger than that of the *cis* conformer and this observation led early investigators to conclude that the *cis* conformer is the more stable form.[28] A low-temperature matrix infrared study found that $E_{trans} - E_{cis}$ is ca 5 kcal mol^{-1} in methyl formate (R = H, R' = CH$_3$) and 8.5 kcal mol^{-1} for methyl acetate (R = R' = CH$_3$).[29] The higher energy difference in methyl acetate was explained as due to C=O· · ·Me steric hindrance in the *trans* conformer. In *tert*-butyl formate [R = H, R' = C(CH$_3$)$_3$] a ^{1}H NMR investigation at −90 °C found 15% of the *trans* form,[30] presumably due to the C=O· · ·*t*-Bu repulsion. Polar solvents have been used in an attempt to increase the proportion of the *trans* conformer. A study[31] using ^3J(H,C,O,C) coupling constants showed an increase in the *trans* conformer from 12% in toluene-d_8 to 30% in DMSO-d_6 at room temperature.

The stability of the *cis* conformer has been explained as due to dipole–dipole interactions,[32] lone pair σ^* interactions[33] and aromatic stabilization.[34] A recent study[35] of the conformation of esters, thiol esters and amides suggested that the electronegativity of the R' group was important, along with the steric interactions. The *trans* conformer was found to be favoured where R' was an electron-withdrawing group. We note that even in the case of methyl formate where the steric interactions are minimal the energy difference is such that we can expect to see only the planar *cis* conformer. The only cases where we can study the effects of the *trans* conformation on ^{1}H chemical shifts are in cyclic compounds, which are included in this study.
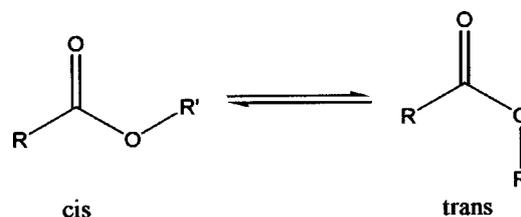
Figure 2. The *cis*–*trans* isomerism of esters.

THEORY

As the theory has been given previously,[18,36] only a brief summary of the latest version (CHARGE7[21]) 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 on 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 polarizability of atom I and also a γ effect from atom L given by the product of the atomic polarizabilities 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 parameterized separately and is given by $A + B \cos\theta$, where θ is the C—C—C—H dihedral angle and A and B are empirical parameters.

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

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

Long-range effects

The effects of distant atoms on the proton chemical shifts are due to steric, anisotropic and electric field contributions. H$\cdots$H steric interactions are shielding in alkanes and deshielding in aromatics and X$\cdots$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.

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

The effects of the electric field of the C—X bonds (X = H, F, Cl, Br, I, O) on the CH 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 being 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[37] equation:

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

where 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 $\Delta\chi$ is the anisotropy of the C≡C bond ($\Delta\chi = \chi_{\text{parl}} - \chi_{\text{perp}}$, where χ_{parl} and χ_{perp} are the susceptibilities parallel and perpendicular to the symmetry axis, respectively.

For a non-symmetric group such as the carbonyl group, Eqn (3) is replaced by the full McConnell equation [Eqn (4)], where θ_1 and θ_2 are the angles between the radius vector R and the x and z axes, respectively, and $\Delta\chi_{\text{parl}}$ ($\chi_z - \chi_x$) and $\Delta\chi_{\text{perp}}$ ($\chi_y - \chi_x$) are the parallel and perpendicular anisotropy for the C=O bond, respectively (cf. Fig. 7).

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

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.[38-40] The equivalent dipole approximation was used to calculate the ring current shifts to give Eqn (5),[41] where 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.

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

The π electron densities are calculated from Hückel theory. The standard Coulomb and resonance integrals for the Hückel routine[39,40] are given by

$$\alpha_r = \alpha_0 + h_r\beta_0 \tag{6}$$
$$\beta_{rs} = k_{rs}\beta_0$$

where α_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 heteroatoms have to be found. These were obtained so that the π densities calculated from the Hückel 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, respectively.

$$\delta_\pi = 10.0\Delta q_\alpha + 2.0\Delta q_\beta \tag{7}$$

The above contributions are added to Eqn (1) to give the calculated shift:

$$\delta_{\text{total}} = \delta_{\text{charge}} + \delta_{\text{steric}} + \delta_{\text{anis}} + \delta_{\text{el}} + \delta_\pi + \delta_{\text{rc}} \tag{8}$$

APPLICATION TO ESTERS

For the ester group, all the different contributions above must be determined. This includes the short-range γ effects from the carbonyl group and the oxygen, the steric effects of both oxygens in the ester group, the two magnetic anisotropies for the carbonyl group and the effect of the ester electric field. Also, any aromatic ring currents in the heteroaromatic rings (e.g. pyrone) need to be determined.

π Electron densities

The π electron densities were reproduced from those calculated from *ab initio* calculations. The results from *ab initio* calculations are very dependent on the basis set used and it was found previously[41,42] that the 3–21G basis set at the B3LYP level gave the best values of the dipole moments for the compounds investigated. Thus we use the π electron densities from this basis set to parameterize the Hückel calculations.

The π systems in the range of esters investigated are diverse, ranging from the simple π systems of methyl acrylate to the aromatic π systems of pyrone and coumarin and to the complex systems of maleic and phthalic anhydride. Because of this diversity, it was necessary for the CHARGE model to differentiate the various π systems encountered. For example, the non-aromatic π system of methyl acrylate differs from that of pyrone and coumarin. It was therefore necessary to treat these π systems separately. This was achieved by determining the appropriate values of the atomic orbital coefficients h_r and k_{rs} [Eqn (6)] and the Hückel integrals for the various π systems considered.

The pyrone and coumarin systems had to be defined separately, probably owing to the inadequate representation of the larger aromatic system by Hückel calculations. However, coumarin and isocoumarin have the same resonance integrals and the isocoumarin π electron densities are in good agreement with the 3–21G values.

The anhydrides were also defined separately as would be expected and, in a similar manner to the pyrone/coumarin case, maleic anhydride required different integrals from phthalic anhydride.

The accuracy of the π-electron densities calculated in the CHARGE scheme may be examined by comparing the calculated π-electron densities and dipole moments of these esters with those obtained by *ab initio* theory using the 3–21G basis set (Table 1). The good general agreement of the calculated vs observed dipoles in Table 1 is strong support for the calculations.

Table 1. π charges (milli-electrons) and dipole moments μ (D) for methyl acrylate (**15**), pyrone (**3**), coumarin (**12**), isocoumarin (**13**), phthalic anhydride (**11**) and maleic anhydride (**17**)

Compound	Atom	3–21G	CHARGE	Exp.
Methyl acrylate (*cis*)	C=O	95	81	
	CH	−19	−15	
	CH$_2$	77	77	
	μ	1.3	2.1	1.7[43]
Methyl acrylate (*trans*)	C=O	92	81	
	CH	−19	−15	
	CH$_2$	72	77	
	μ	1.9	2.8	1.7
Pyrone	C$_2$	24	31	
	C$_3$	−91	−64	
	C$_4$	76	71	
	C$_5$	−55	−42	
	C$_6$	58	60	
	μ	4.42	4.58	5.18[44]
Coumarin	C$_2$	−4	−26	
	C$_3$	−53	−20	
	C$_4$	69	72	
	C$_9$	−42	−50	
	C$_{10}$	68	21	
	μ	4.63	4.47	4.49[44]
Isocoumarin	C$_3$	−11	−14	
	C$_4$	−86	−82	
	C$_9$	41	29	
	C$_{10}$	−57	−44	
	C$_1$	75	29	
	μ	4.22	3.52	4.24[44]
Phthalic anhydride	C$_1$	99	98	
	C$_8$	−23	−24	
	μ	5.73	6.05	5.34[45,46]
Maleic anhydride	C$_1$	94	97	
	C$_2$	43	48	
	μ	4.0	3.5	4.14[45,46]

EXPERIMENTAL

All the compounds and solvents used were obtained commercially (Aldrich). The CDCl$_3$ solvent was stored over molecular sieves and used without further purification. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance spectrometer operating at 400.13 MHz for proton and 100.63 MHz for carbon. COSY, HMQC, HMBC and NOE experiments were also performed. The ^{1}H and COSY spectra of **4**, **9**, **10** and **14** were also obtained at 750 MHz at GSK Stevenage. The spectra were recorded in 10 mg cm^{-3} solutions (^{1}H) and ca 30 mg cm^{-3} (^{13}C) in CDCl$_3$ with a probe temperature of ca 300 K and referenced to TMS (as an internal standard) unless indicated otherwise.

COMPUTATIONAL

The geometries of all compounds (see Figs 3 and 4) used for parameterization were obtained using the G98/03W[27] software using the B3LYP theory with the 6–31G(d,p) basis set, except for **6** [where the 6–311++G(d,p) basis set was used because of hydrogen bonding; see Ref. 23] and **14** (see conformational analysis). The iterative parameterizations were performed using CHAP8.[47] The GIAO calculations were performed with both the geometry optimization and chemical shift calculations at the B3LYP/6–31G(d,p) level. The chemical shifts were referenced to methane and then converted to the ppm scale using an experimental value of 0.23 ppm for methane.[23] The population analysis required for the Hückel analysis was performed, on the geometries obtained, using the smaller 3–21G basis set. Monte Carlo simulations were performed using the GMMX routine in PCM[48] using both the MMX and MMFF94 force fields therein. LIS conformational analysis was performed according to the LIRAS3B analysis.[49] The predicted spectrum of **23** was obtained using the NMRPredict[50] software, which includes CHARGE after full parameterization of the ester group. The molecular geometries in this program are obtained using molecular mechanics.
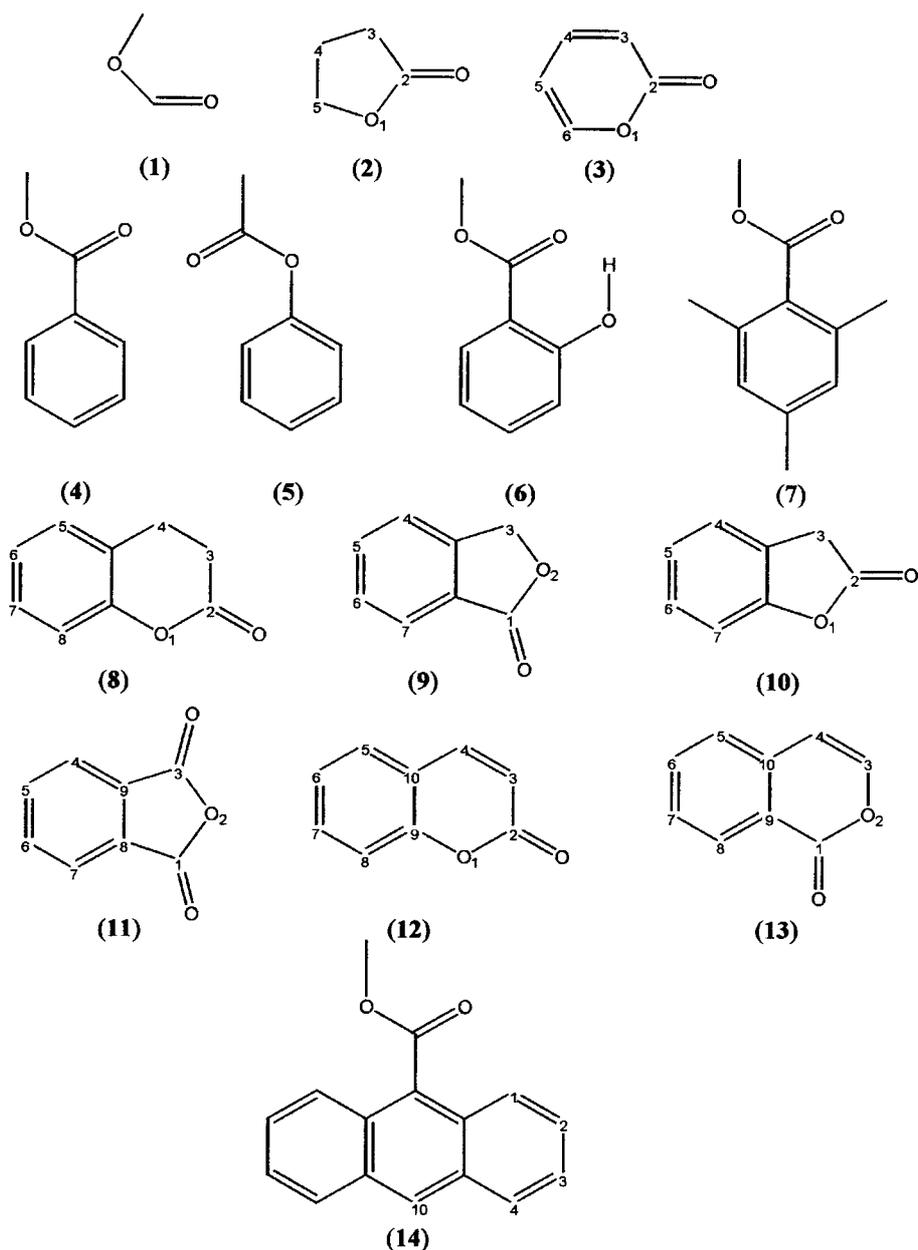
Figure 3. Ester compounds used for parameterization of CHARGE.

SPECTRAL ASSIGNMENT

Compounds **7**,[51] **8**,[52] **12**[52] and **13**[52] were previously assigned using LIS methods, although assignment of **12** was found to be reversed, for protons 3 and 4, and corrected. Full assignments of **1**,[53] **2**[54] and **3**[55] were also taken from the literature. Partial assignments of the protons of interest in compounds **15–22**[53,56–60] (F. Sancassan, personal communication, 2004) and **24**[61] were found in the literature.

Phthalic anhydride (**11**) was assigned using the HMBC experiment to find the three-bond coupling from the easily assigned carbonyl carbon to H 4/7. Phthalide (**10**) was assigned using a combination of 1D (^{1}H, ^{13}C and NOE) and 2D experiments (COSY, HSQC and HMBC). Methyl benzoate (**4**) and phenyl acetate (**5**) produced well-separated signals, and could be easily assigned using the proton spectra (H2/6 doublet, 3/5 and 4 multiplet distinguished by their

integrals). Methyl salicylate (**6**) produced a well-resolved spectrum consisting of two doublets and two triplets. The doublets could be easily assigned owing to large difference in chemical shift that they produced, H3 was shielded by the OH group and H6 deshielded by the ester group. From the COSY the triplets could then be easily assigned. 2-Coumaranone (**9**) was assigned by first assigning the H3, which is a singlet on its own; from H3 there is a coupling (both on the COSY and HMBC, from C3) to H4. This leaves the other doublet as H7. Further, there is a strong coupling from H4 to H5 in the COSY spectrum, leaving the other triplet as H6. Methyl anthracene-9-carboxylate (**14**) was assigned by an nOe experiment, H10 was irradiated to give H4/5 the other doublet could be assigned as the H1/8. Using this assignment, the ^{13}C experiment could be assigned using the HMQC and HMBC experiments. The assignment followed previous assignment of 9-acetylanthracene.[18] From
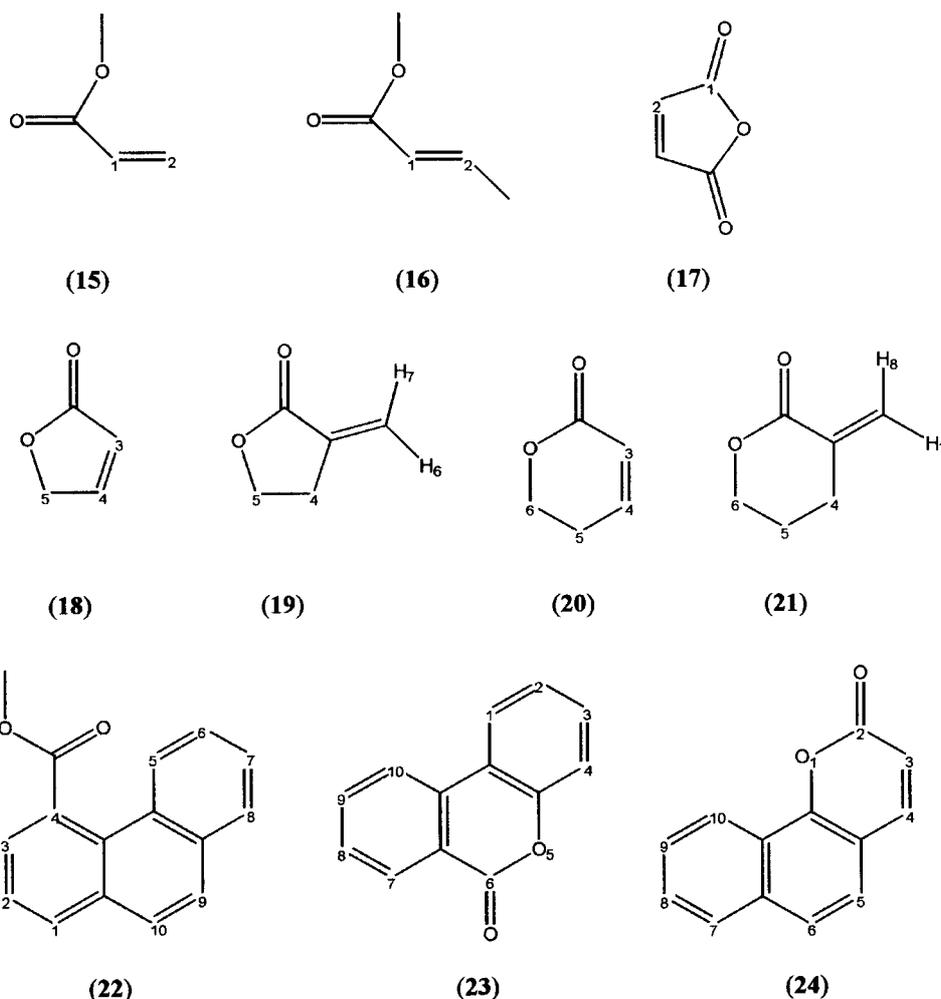
Figure 4. Compounds used for refinement and monitoring of determined parameters.

the carbon assignment, the remaining protons, which overlapped, could then be assigned using the HMQC spectra. Chromen-6-one (**23**) produced a well-resolved spectrum, consisting of four doublets and four triplets. The doublet at lowest chemical shift could be assigned as H4 due to the shielding from the oxygen attached to that ring. From that assignment, the rest of the protons on that ring could be assigned using the COSY spectrum. An NOE experiment irradiating H1 identified the doublet at 8.12 as H10, and using the COSY spectrum the rest of the protons could now be assigned. H7, which appears at 8.40, being deshielded by the carbonyl group, further supports the assignment.

Table 2 gives the experimental chemical shifts obtained here together with the chemical shifts calculated from CHARGE and from the GIAO calculations.

RESULTS

Conformational analysis

It is necessary to ensure before the ^{1}H chemical shifts of the esters can be considered that the conformations of the molecules investigated are known. Two molecules in particular, phenyl acetate and methyl anthracene-9-carboxylate, required detailed conformational examination, as follows.

Phenyl acetate (5)

The conformation of this compound is uncertain, since steric hindrance due to the phenyl group will prohibit the more conjugated planar conformation. The dihedral angle between the ester group and the benzene ring was determined from a lanthanide-induced shift (LIS) investigation using the LIRAS program;[51,52] full details will be given elsewhere (R. J. Abraham, F. Sancassan and M. Mobli, to be published). It is convenient to summarize here the results from this analysis.

An experimental geometry was obtained from the crystal structure and minimum energy geometries calculated by molecular mechanics (MMFF94) and *ab initio* [B3LYP and MP2 using the 6–31G(d,p) basis set]. The energy minimization using the B3LYP calculation produced two geometries, one with a planar geometry and the other with the ester group rotated out of the phenyl plane by 45°. There was a surprisingly small energy difference between the two conformers (0.16 kcal mol^{-1} in favour of the non-planar geometry). Both geometries were tested against the LIS varying the OC—O—C=C dihedral angle and the C—O—C bond angle. There was no agreement with the planar geometry, but good agreement with the twisted geometry. This was the geometry found in the crystal and also that obtained by MM calculations, hence we can use with

Table 2. Experimental and calculated ¹H chemical shifts of esters

Compound	Method	H	Me				
Methyl formate (**1**)	CDCl₃[53]	8.100	3.800				
	CHARGE	8.066	3.816				
	GIAO	8.024	3.628				
		H2	**H3**	**H4**			
γ-Butyrolactone (**2**)	CDCl₃[54]	2.490	2.260	4.320			
	CHARGE	2.503	2.028	4.296			
	GIAO	2.060	1.891	4.142			
		H3	**H4**	**H5**	**H6**		
Pyrone (**3**)	CDCl₃[55]	6.31	7.33	6.25	7.48		
	CHARGE	6.314	7.056	6.259	7.429		
	GIAO	6.045	7.000	5.835	7.650		
		H2	**H3**	**H4**	**Me**		
Methyl benzoate (**4**)	CDCl₃	8.042	7.434	7.552	3.918		
	CHARGE	8.076	7.556	7.568	3.903		
	GIAO	8.239	7.424	7.511	3.764		
		H2	**H3**	**H4**	**Me**		
Phenyl acetate (**5**)	CDCl₃	7.084	7.372	7.221	2.294		
	CHARGE	7.199	7.292	7.140	2.226		
	GIAO	7.276	7.365	7.169	2.020		
		H3	**H4**	**H5**	**H6**	**Me**	**OH**
Methyl salicylate (**6**)	CDCl₃	6.978	7.449	6.873	7.833	3.949	10.727
	CHARGE	7.080	7.457	7.160	7.973	3.904	11.212
	GIAO	7.150	7.547	6.877	8.085	3.914	11.078
		H3,5	**OMe**	**4Me**	**2,6Me**		
Methyl mesitoate (**7**)	CDCl₃[51]	6.840	3.880	2.280	2.270		
	CHARGE	6.911	3.834	2.397	2.335		
	GIAO	6.869	3.708	2.128	1.779		
		H3	**H4**	**H5**	**H6**	**H7**	**H8**
3,4-Dihydrocoumarin (**8**)	CDCl₃[52]	2.785	2.993	7.198	7.127	7.250	7.036
	CHARGE	2.863	3.081	7.115	6.976	7.114	6.939
	GIAO	2.367	2.722	7.103	7.071	7.306	7.040
		H3	**H4**	**H5**	**H6**	**H7**	
Phthalide (**9**)	CDCl₃	5.332	7.512	7.694	7.552	7.935	
	CHARGE	5.376	7.388	7.576	7.433	7.627	
	GIAO	5.084	7.382	7.608	7.533	8.028	
		H3	**H4**	**H5**	**H6**	**H7**	
2-Coumaranone (**10**)	CDCl₃	3.731	7.284	7.130	7.304	7.097	
	CHARGE	3.706	7.144	6.997	7.179	6.906	
	GIAO	3.287	7.262	7.107	7.318	7.029	
		H4	**H5**				
Phthalic anhydride (**11**)	CDCl₃	8.032	7.914				
	CHARGE	7.952	7.861				
	GIAO	8.013	7.785				
		H3	**H4**	**H5**	**H6**	**H7**	**H8**
Coumarin (**12**)	CDCl₃[52]	6.406	7.705	7.502	7.290	7.502	7.290
	CHARGE	6.446	7.695	7.624	7.233	7.513	7.270
	GIAO	6.142	7.310	7.296	7.203	7.515	7.274
		H3	**H4**	**H5**	**H6**	**H7**	**H8**
Isocoumarin (**13**)	CDCl₃[52]	7.276	6.505	7.432	7.717	7.520	8.286
	CHARGE	7.187	6.478	7.456	7.563	7.329	8.280
	GIAO	7.375	6.105	7.202	7.596	7.477	8.504

(*continued overleaf*)

Table 2. (*Continued*)

Compound	Method	H1	H2	H3	H4	H10	OMe
Methyl anthracene-9-carboxylate (**14**)	CDCl$_3$	8.006	7.533	7.477	8.028	8.516	4.172
	CHARGE	8.078	7.651	7.626	8.145	8.806	4.076
	GIAO	8.199	7.493	7.446	7.885	8.249	3.879

		H1	H2(*c*)	H2(*t*)	OME		
Methyl acrylate (**15**)	CDCl$_3$[53]	6.12	6.41	5.83	3.77		
	CHARGE	6.20	6.45	6.12	3.84		
	GIAO	6.13	6.70	5.89	3.59		

		Me	H1	H2	OMe		
Methyl crotonate (**16**)	CDCl$_3$[a]	1.88	5.85	6.98	3.72		
	CHARGE	1.81	5.80	7.05	3.85		
	GIAO	2.06	5.85	6.62	3.59		

		H					
Maleic anhydride (**17**)	CDCl$_3$[53]	7.09					
	CHARGE	6.96					
	GIAO	6.65					

		H3	H4	H5			
γ-Crotonolactone (**18**)	CDCl$_3$[56]	6.18	7.59	4.91			
	CHARGE	6.08	7.23	4.76			
	GIAO	6.05	7.36	4.69			

		H4	H5	H6	H7		
α-Methylene-γ-butyrolactone (**19**)	CDCl$_3$[57]	3.00	4.37	5.67	6.26		
	CHARGE	2.75	4.48	5.70	5.95		
	GIAO	2.65	4.09	5.62	6.48		

		H3	H4	H5	H6		
5,6-Dihydropyran-2-one (**20**)	CDCl$_3$[58]	6.05	7.10	2.50	4.44		
	CHARGE	6.05	7.09	2.39	4.30		
	GIAO	5.91	6.75	2.11	4.25		

		H4	H5	H6	H7	H8	
3-Methylene tetrahydropyran-2-one (**21**)	CCl$_4$[59]	2.60	2.00	4.31	5.46	6.29	
	CHARGE	2.43	1.86	4.30	5.67	6.21	
	GIAO	2.47	1.60	4.28	5.47	6.74	

		H4					
Methyl phenanthrene-4-carboxyate (**22**)	CCl$_4$[60]	8.05					
	CHARGE	7.80					
	GIAO	7.87					

		H1	H2	H3	H4		
Benzochromen-6-one (**23**)	CDCl$_3$	8.064	7.359	7.499	7.329		
	CHARGE	8.120	7.286	7.474	7.362		
	GIAO	8.032	7.311	7.467	7.319		
		H7	H8	H9	H10		
	CDCl$_3$	8.408	7.584	7.825	8.125		
	CHARGE	8.610	7.564	7.794	8.222		
	GIAO	8.624	7.533	7.729	8.032		

		H10					
Benzochromen-2-one (**24**)	CDCl$_3$[61]	8.53					
	CHARGE	8.37					
	GIAO	9.08					

[a] F. Sancassan, personal communication, 2004.

confidence the twisted structure for the parameterization and discard the flat geometry produced.

Methyl anthracene-9-carboxylate (14)

Again the dihedral angle from the ester group to the anthracene ring system is unknown. The angle in the crystal structure is 70°,[62] but this may not be the conformation in solution. The optimized geometry from the B3LYP/6−31G(d,p) calculation gave a dihedral angle of 48°. In this case, owing to the molecular symmetry, the LIS method is less well determined than for phenyl acetate, so an alternative approach was used.

The *ab initio* (B3LYP) method was used with different basis sets to run a series of potential energy scans varying the ester dihedral angle. The results are given in Fig. 5, where the minimum energy is set to 0 kcal mol^{-1} for all calculations to simplify the comparison.

We note that the minimum energy dihedral angle varies considerably depending on the basis set used. Larger basis sets more accurately approximate the orbitals by imposing fewer restrictions on the locations of the electrons in space.[26] Thus larger basis sets will increase the steric repulsion of the ester group and increase the minimum energy dihedral as observed. However, there is another intriguing observation from Fig. 5. The global energy maximum when using the more restricted 3−21G basis set is at 90° but with the larger basis sets the trend is reversed and the energy maximum is for the planar conformation. This is very significant as in the former case the molecule interconverts via the planar form and in the other case it is via the 90° conformation.

It is of interest that even at the 6−311++G(d,p) level where the optimized dihedral angle is at its largest (58°), it is still smaller than that found in the crystal structure (70°) in which crystal packing forces may have been expected to flatten the structure. We note also that a molecular mechanics calculation using the MMFF94 force field gave the dihedral
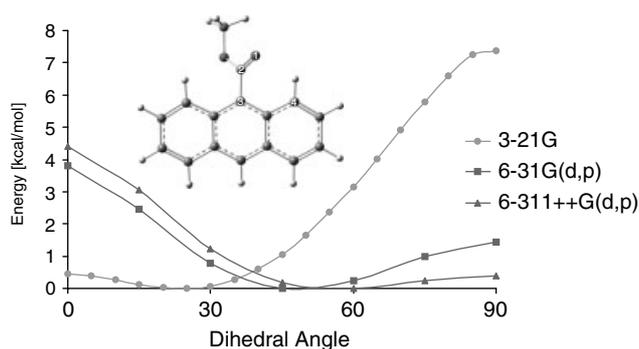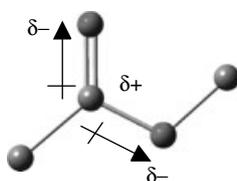
angle to be 75°, a very reasonable result in view of this analysis. We use henceforth the *ab initio*-calculated value of 58°, being close to the experimentally derived value from the crystal structure.

The results also illustrate the dangers of a very common procedure for calculating conformational energies. Often the energy profile is obtained at a minimum basis set (e.g. 3−21G) and then the minimum energy conformations are refined using higher basis sets. Because of the large variation in energy profile using different basis sets, one could fail to find global energy minima.

Effect of the ester group on the ^{1}H NMR chemical shifts

Short-range effects

The short-range effects of functional groups are obtained empirically in the CHARGE routine and this was simply achieved for the ester group from the data in Table 2. In particular, the gamma effects from both oxygens to aromatic, olefinic or aliphatic protons and the beta effect from the carbonyl oxygen atom were obtained using the rigid structures of compounds **1–16** and **18** and **20** plus **15** and **16** for the O=C—CH effect.

Electric field

The electric field in the CHARGE program is given directly from the partial atomic charges. For esters this resulted in a dipole acting along the C=O bond and two equal dipoles along each of the C—O—C bonds. As the charges must balance, the charge on the carbonyl oxygen produces an equal and opposite charge on the carbon atom. Similarly, the charge on each of the carbons in the C—O—C fragment is half that of the divalent oxygen.

The electric field produced was unreasonably large owing to treating each dipole separately, as this produces a larger charge on the carbonyl carbon than is given by the CHARGE routine (in the CHARGE routine the sum of all the charges in a molecule equals zero, but the charge on the central carbon atom is less than the sum of the charges on the two oxygen atoms). To resolve this problem, we considered the ester group as one system and not as the sum of a separate carbonyl and ether charge dipole (see Fig. 6). In this system, the partial atomic charges on the O=C—O atoms are responsible for the electric field effect. With this achieved, the charges on these atoms were varied to give good agreement with the observed chemical shifts. A reduction of 25% gave good agreement with the observed shifts.

Carbonyl anisotropy

The parallel ($\parallel$) and perpendicular ($\perp$) anisotropies of the carbonyl group ($\chi_z - \chi_x$ and $\chi_y - \chi_x$, respectively) in the McConnell equation [Eqn (4) and Fig. 7] need to be obtained. The anisotropies can be distinguished provided that the data set has protons in different orientations with respect to the plane of the C—C=O group (cf compounds **4**, **6**, **7**, **13** and **14**).

The anisotropic effects cannot be isolated from the steric and electric field terms, but as these effects are given by different equations, they can be differentiated. Utilizing

Figure 5. Potential energy scans of **14** about the O=C − C=C dihedral angle, using various basis sets.

Figure 6. The electric field model for esters in CHARGE.
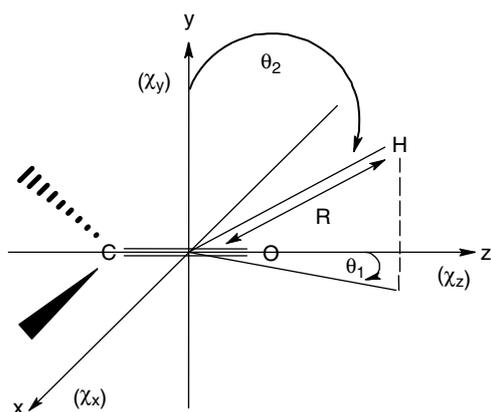
Figure 7. Anisotropy model in CHARGE.

the data from over 100 protons (compounds **1**–**14**) gives a well-determined data set from which the anisotropies were obtained.

The values for the parallel and perpendicular anisotropies were 10.1×10^{-30} and -17.1×10^{-30} cm^3 molecule^{-1}, respectively. The anisotropy contribution to the ^{1}H chemical shift for **7**, **13** and **14** is given in Table 3. For the protons perpendicular to the carbonyl group in **7** and **14,** a large negative effect is observed, whereas in **13** for the proton parallel to the carbonyl group an equally large positive effect is present.

Steric terms

The steric terms for both the oxygen atoms were determined. The steric term for the ether oxygen when included in the iteration (including compounds **1**–**14**) produced a very small contribution. To define this better, the chemical shift of H10 in **24** was used. The major difference between the SCS from the divalent oxygen to H6 of **6** and H10 of **24** is the orientation of the carbonyl group. In **24** the dominating long-range contribution to the chemical shift of H10 is from the oxygen steric term (0.19; cf. C=O anisotropy 0.06 and O—C=O electric field = 0.06). This allowed the steric term coefficient for the ether oxygen to be obtained as $40 \times$ Å^6.

The carbonyl oxygen steric term coefficient is important[17,18] and was determined iteratively from the data set as 85×10^{-30} cm^3 molecule^{-1}.

Table 3. Effect of the carbonyl anisotropy on the proton chemical shift

Compound	$\delta_{(anis)}$ (∥)	$\delta_{(anis)}$ (⊥)	$\delta_{(anis)}$
Methyl anthracene-9-carboxylate (**14**)			
H 1/8	−0.10	−0.34	−0.44
H 4/5	0.00	0.02	0.02
COOCH$_3$	−0.15	0.19	0.04
Methyl mesitoate (**7**)			
CH$_3$ (2,6)	−0.06	−0.21	−0.27
Isocoumarin (**13**)			
H 8	−0.20	0.35	0.15

Ring current effects

Analysis of the ^{1}H chemical shifts in Table 2 suggested that pyrone had an aromatic ring current, and when this was included in the CHARGE calculations a value of about one-third that of benzene was obtained. This was confirmed by the GIAO calculations. These involved calculating the chemical shift of a methane proton situated above the face of the ring so that the effect of the ring current could be calculated (Fig. 8). This method was also used to confirm that no ring current was present for maleic anhydride.

The ring current of a pyrone ring can now be compared with that of a benzene ring from the GIAO calculations.

In the example shown, the chemical shift of the proton on top of the ring is −1.3 ppm for pyrone and −3.4 for benzene. Hence there is excellent agreement between the GIAO result and the ring current found in CHARGE.

Note, however, that the pyrone ring also contains the ester functionality. The calculations show that the protons on the carbonyl side of the molecule are less deshielded (−0.6 ppm) than that on the other side (0.9 ppm). This means that a direct correlation of the *ab initio*-calculated chemical shifts to the ring current coefficients of Eqn (5) cannot be made. The method does, however, serve as a very useful guide to the existence of ring currents in polar systems.

The wealth of data used here in the parameterization of the ester group and the versatility of the CHARGE model has produced a very accurate model for the calculation of the ^{1}H chemical shifts of esters. The calculated − observed shifts over the 100 protons used for the parameterization gave an average error of 0.09 ppm (0.1 ppm for all the 150 protons included in the study!) and a correlation coefficient (r^2) of 0.995 when all compounds are included (see also Fig. 9). The largest error is found for the hydroxyl proton, as observed previously.[18]

The model can now be used with confidence to predict the effect of the ester group on the ^{1}H chemical shifts in any chemical environment. This is demonstrated by Fig. 10, where the calculated ^{1}H NMR spectrum of **23** is given using ^{1}H chemical shifts and H,H coupling constants from the CHARGE routine. Although this molecule was not included in the parameterization of any of the derived effects, the comparison with the observed spectrum is excellent.

Conformation analysis of vinyl esters

The CHARGE program can now predict the ^{1}H chemical shifts of organic esters. The program can also be used to solve conformational problems, as follows.
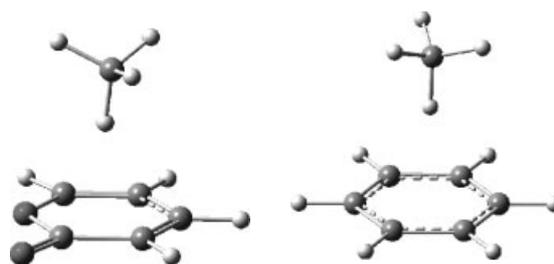
Figure 8. Modelling comparison of ring current effects on ^{1}H NMR chemical shifts.
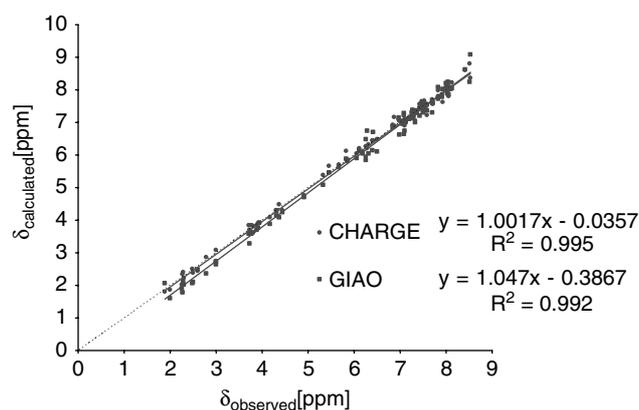
Figure 9. Plot of observed (CDCl$_3$) vs calculated (circles for CHARGE and squares for GIAO) chemical shifts.
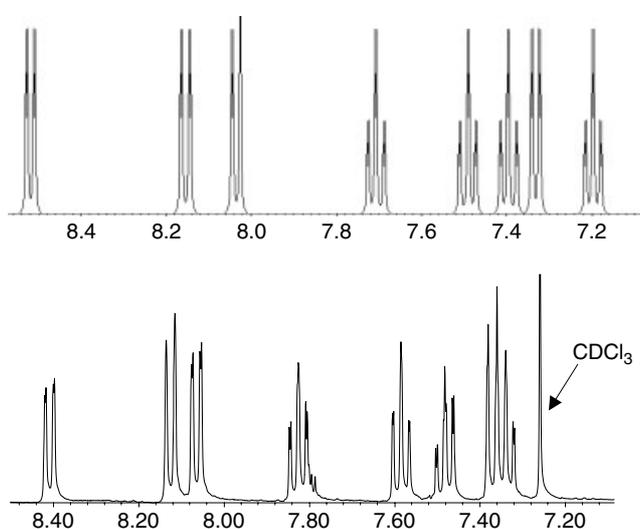
Figure 10. Experimental (bottom) and calculated (from NMRPredict[50]) ^{1}H NMR spectrum of benzochromen-6-one (**23**).

Figure 11. Conformers of methyl acrylate (R = H) and methyl crotonate (R = CH$_3$).

of the *cis* and *trans* isomers (Fig. 10) were obtained from the Gaussian program. The chemical shifts of the individual conformers are then given by CHARGE and GIAO and the averaged chemical shift, based on the populations of the *cis* and *trans* isomers obtained for methyl acrylate and methyl crotonate. The r.m.s. error of the observed vs calculated shifts is plotted against the *cis* conformer population in Fig. 12. Using CHARGE gives a lower r.m.s. error when the averaged chemical shifts are used. The optimized r.m.s. error of the averaged chemical shifts from CHARGE is at 90% *cis* conformer population for methyl acrylate, in good agreement with the 66% *cis* conformer found experimentally. For methyl crotonate the lowest r.m.s. error is found at 60% *cis* conformation, which again is in good agreement with the experimental data, cf. 75% *cis* from LIS experimental data.

It is of interest that the GIAO calculations in these cases cannot be used in terms of absolute chemical shifts in solution. The results suggest that the compounds are only in the *trans* conformation, which is not compatible with the experimental data.

Finally, the GMMX Monte Carlo routine in PCModel was used to obtain all possible conformers of these molecules. As expected, the analysis found both conformers (*cis/trans*) and their energies. The results are shown in Table 4. There is very good agreement between the different energy calculations and the use of CHARGE, which suggests that this combined technique may be very significant in predicting the chemical shifts of conformationally mobile compounds and for automation purposes.

Vinyl esters rapidly interconvert on the NMR time-scale between the two low-energy conformations *s-trans* and *s-cis* (Fig. 11). As the molecule is interconverting between these forms, one cannot correlate the observed chemical shifts with those calculated for either conformer. However, CHARGE can be used to determine the conformer populations, given that the conformers are known. Similarly, *ab initio*-calculated chemical shifts can be used in principle to find the populations. Finally, molecular dynamics may be used to search conformational space to display multiple minimum energy conformations.[48,63,64] The population of the conformers can then be obtained based on their relative energies. These can also be compared with *ab initio* energy calculations.

In a gas diffraction study[65] of methyl acrylate (**15**), the interconverting conformer populations were found to be 66 : 33 in favour of the *cis* conformer (Fig. 10). Similarly, a study using LIS reagents (F. Sancassan, personal communication, 2004) showed that methyl crotonate (**16**) is 75% in the *cis* conformation.

In order to determine the populations from the CHARGE and GIAO calculations, the minimum energy conformation

Figure 12. R.m.s. error of population averaged chemical shifts of methyl acrylate (M-A) and methyl crotonate (M-C) as calculated by CHARGE and GIAO against increasing *cis* conformer population.

MRC

Table 4. Conformer populations of methyl acrylate and crotonate

Method	*cis* population (%)	
	Methyl acrylate	Methyl crotonate
B3LYP/6−31G**	78	94
MMFF94	72	74
MMX	54	58
CHARGE	90	60
GIAO	0	0
Experimental	66	75

DISCUSSION

It is of some interest to compare the values of the carbonyl anisotropies obtained here with those found for other carbonyl groups and these are compiled in Table 5, together with, where quoted, the oxygen steric coefficient. These include both early and more recent studies. Spectrometer and molecular geometry limitations were a significant factor in the early studies. Modern spectrometers plus *ab initio* programs[27] which give generally reliable geometries have removed most of the earlier difficulties.

Schneider *et al.*[66] noted that the protons in vicinity of the group of interest were poorly predicted and a limit of 3 Å was suggested to avoid the large effects observed. The model used here overcomes this problem by only using through-space effects (steric, electric field and anisotropy) when more than three bonds away from the substituent, although in some cases (e.g. **13**, **14**, **21**, **22** and **23)** protons are further than three bonds away but still closer than 3 Å.

The data from the different studies in Table 5 should be compared with caution as different models have been used to derive these numbers. For example, if only the magnetic anisotropy term is used this value will differ from a model including also a steric term, which in turn will differ from a model adding also the electric field effect. Also, the basis of the parameterization is of crucial importance. The planarity of aromatic compounds provides many cases where protons are very close to functional groups more than three bonds away. This can be seen in the fairly large parallel anisotropies derived by investigations using only aliphatic compounds.

Table 5. Carbonyl anisotropies $\Delta\chi(\times10^{-30}$ cm^3 molecule^{-1}) and oxygen steric coefficients a_s (Å^6)

Compound	Ref.	$\Delta\chi_{parl}$	$\Delta\chi_{perp}$	a_s
Ketones	10	13.5	−12.2	
Ketones	11, 12	21	−6	
Ketones	66	24	−12	
Alkyl ketones	17	22.7	−14.8	67.9
Aryl ketones	18	6.4	−11.9	38.4
Amides	15	4	−9	
Amides	19	12.6	−14.2	
Alkyl amides	20	13.5	−21.2	60.0
Aryl amides	20	10.5	−7.3	62.4
Esters	This work	10.1	−17.1	85.0

However, there is general agreement on the reduction in the anisotropy on conjugation of the carbonyl in aromatic compounds, amides or ethers. Note that the anisotropy values given by Packer *et al.*[19] are from *ab initio* calculations on formaldehyde, hence they should be compared with the data for alkyl ketones in Table 5.

The GIAO calculations performed gave reasonable results (r.m.s. error of 0.2 ppm and correlation coefficient $r^2 = 0.992$). However, large discrepancies are present for protons close to the electronegative oxygens, the largest error being 0.5 ppm for H10 of **24**. Similar errors were found for halogen compounds.[1] This may be related to the large steric hindrance produced by use of more restricted basis sets as seen for **14**. These calculations may be improved by using alternative basis sets or theories, but this is beyond the scope of this study.

CONCLUSIONS

A semiempirical model (CHARGE) including electric field, anisotropy and steric effects was used to investigate the ^{1}H chemical shifts produced by the ester group. The derivation of a realistic electric field, thorough implementation of the π system to the Hückel model, together with the parameterization of the existing ring current, anisotropy, steric and charge models produces a model which accurately describes the substituent effects of this group. The model was parameterized using experimental data from 24 compounds including 150 protons and the experimental data were reproduced with an r.m.s. error of 0.1 ppm for all the shifts.

The conformations of phenyl acetate and methyl anthracene-9-carboxylate in solution were obtained by LIS techniques and *ab initio* calculations. The CHARGE model was used to derive the conformer populations of methyl acrylate and methyl crotonate from their observed averaged chemical shifts and the results were compared with Monte Carlo simulations using molecular mechanics and *ab initio* calculations.

The GIAO method was used for chemical shift calculations. The method agreed well with the experimental data, producing an r.m.s. error of 0.2 ppm for the compounds investigated here, although large discrepancies were found for protons close to electronegative atoms.

Overall, the semiempirical calculations produce more reliable results and are more likely to agree with experimental data once parameterized thoroughly. This, together with the swiftness of these calculations, makes them a useful tool for routine use in analysis of chemical shifts.

REFERENCES

1. Abraham RJ, Mobli M, Smith RJ. *Magn. Reson. Chem.* 2004; **42**: 436.
2. Cotton S. http://www.chm.bris.ac.uk/motm/ethylacetate/ ethylacetateh.htm, Bristol University, 2004.
3. Abraham RJ, Fisher J, Loftus P. *Introduction to NMR Spectroscopy* (2nd edn). Wiley: Chichester, 1988.
4. Narayanan CR, Iyer KN. *Tetrahedron* 1965; **42**: 3741.
5. Narayanan CR, Parkar MS. *Indian J. Chem.* 1971; **9**: 1019.
6. Jackman LM. *Nuclear Magnetic Resonance Spectroscopy* (1st edn). Pergamon Press: Oxford, 1959.

7. Jackman LM, Sternhell S. *Nuclear Magnetic Resonance Spectroscopy* (2nd edn). Pergamon Press: Oxford, 1969.
8. Narashiman PT, Rogers MT. *J. Phys. Chem.* 1959; **63**: 1388.
9. Bothner-By AA, Pople JA. *Annu. Rev. Phys. Chem.* 1965; **16**: 43.
10. Zürcher RF. *Prog. Magn. Reson. Spectrosc.* 1967; **2**: 205.
11. ApSimon JW, Demarco PV, Mathieson DW. *Tetrahedron* 1970; **26**: 119.
12. ApSimon JW, Beierbeck H. *Can. J. Chem.* 1971; **49**: 1328.
13. Toyne KJ. *Tetrahedron* 1973; **29**: 3889.
14. Williamson MP, Asakura T. *J. Magn. Reson.* 1991; **94**: 557.
15. Williamson MP, Asakura T. *J. Magn. Reson. B* 1993; **101**: 63.
16. Hunter CA, Packer MJ. *Chem. Eur. J.* 1999; **5**: 1891.
17. Abraham RJ, Ainger NJ. *J. Chem. Soc. Perkin Trans. 2* 1999; 441.
18. Abraham RJ, Mobli M, Smith RJ. *Magn. Reson. Chem.* 2003; **41**: 26.
19. Packer MJ, Zonta C, Hunter CA. *J. Magn. Reson.* 2003; **162**: 102.
20. Perez M. PhD Thesis, University of Liverpool, 2004.
21. Abraham RJ, Canton M, Edgar M, Grant GH, Haworth IS, Hudson BD, Mobli M, Perez M, Smith PE, Reid M, Warne MA. *CHARGE7*. University of Liverpool: Liverpool, 2004.
22. Pulay P, Hinton JF. In *Encyclopedia of Nuclear Magnetic Resonance*, Grant DM, Harris RK (eds), Wiley: New York, 1995; 4334.
23. Lampert H, Mikenda W, Karpfen A, Kählig H. *J. Phys. Chem. A* 1997; **101**: 9610.
24. Colombo D, Ferraboschi P, Ronchetti F, Toma L. *Magn. Reson. Chem.* 2002; **40**: 581.
25. Bednarek E, Dobrowolski JC, Kamienska-Trela K. *J. Mol. Struct.* 2003; **651−653**: 719.
26. Foresman JB, Frisch A. *Exploring Chemistry with Electronic Structure Methods* (2nd edn). Gaussian: Pittsburgh, PA, 1996.
27. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Baboul AG, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA. *GAUSSIAN 98, Revision A9*. Gaussian: Pittsburg, PA, 1998.
28. Jones GIL, Owen NL. *J. Mol. Struct.* 1973; **18**: 1.
29. Blom CE, Gunthard H. *Chem. Phys. Lett.* 1981; **84**: 267.
30. Öki M, Nakanishi H. *Bull. Chem. Soc. Jpn.* 1970; **43**: 2558.
31. Jung ME, Gervay J. *Tetrahedron Lett.* 1990; **31**: 4685.
32. Wiberg KB, Laidig KE. *J. Am. Chem. Soc.* 1987; **109**: 5935.
33. Larson JR, Epiotis ND, Bernardi F. *J. Am. Chem. Soc.* 1978; **100**: 5713.
34. Mark H, Baker T, Noe E. *J. Am. Chem. Soc.* 1989; **111**: 6551.

35. Pawar DM, Khalil AA, Hooks DR, Collins K, Elliott T, Stafford J, Smith L, Noe EA. *J. Am. Chem. Soc.* 1998; **120**: 2108.
36. Abraham RJ. *Prog. Nucl. Magn. Reson. Spectrosc.* 1999; **35**: 85.
37. McConnell HM. *J. Chem. Phys.* 1957; **27**: 1.
38. Pauling L. *J. Chem. Phys.* 1936; **4**: 673.
39. Abraham RJ, Smith PE. *J. Comput. Chem.* 1987; **9**: 288.
40. Abraham RJ, Smith PE. *J. Comput.-Aided Mol. Des.* 1989; **3**: 175.
41. Abraham RJ, Reid M. *J. Chem. Soc. Perkin Trans. 2* 2002; 1081.
42. Abraham RJ, Reid M. *Magn. Reson. Chem.* 2000; **38**: 570.
43. McClellan AL. *Tables of Experimental Dipole Moments*, vol. 3. Rahara Enterprises: El Cerrito, CA, 1989.
44. Chong YS, Huang HH. *J. Chem. Soc. Perkin Trans. 2* 1986; 1875.
45. Caswell LR, Soo LY, Lee DH, Fowler RG, Campbell JB. *J. Org. Chem.* 1974; **39**: 15 427.
46. Alonso JL, Pastrana MR, Pelaez J, Arauzo A. *Spectrochim. Acta* 1983; **39**: 215.
47. Kuo SS. *Computer Applications of Numerical Methods. Chapter 8.* Addison Wesley: London, 1972.
48. *PC Model 7.0.* Serena Software: Bloomington, IN, 1998.
49. Abraham RJ, Sancassan F. In *Encyclopedia of Nuclear Magnetic Resonance*, Grant DM, Harris RK (eds). Wiley: Chichester, 2002; 578.
50. Modgraph Consultants. *NMRPredict*. http://www.modgraph.co.uk/, 2004.
51. Abraham RJ, Angiolini S, Edgar M, Sancassan F. *J. Chem. Soc. Perkin Trans. 2* 1995; 1973.
52. Abraham RJ, Ghersi A, Pertillo G, Sancassan F. *J. Chem. Soc. Perkin Trans. 2* 1997; 1279.
53. Pouchert CJ, Behnke J. *The Aldirch Library of ^{13}C and ^{1}H FT NMR Spectra* (1st edn). Aldrich Chemical: Milwaukee, WI, 1993.
54. Shi M. *J. Chem. Res. (S)* 1998; 592.
55. Imagawa T, Haneda A, Kawanisi M. *Org. Magn. Reson.* 1980; **13**: 244.
56. Minami I, Tsuji J. *Tetrahedron* 1987; **43**: 3903.
57. Choudhury PK, Foubelo F, Yus M. *Tetrahedron* 1999; **55**: 10 779.
58. Moriarty RM, Vaid RK, Hokins TE, Vaid BK, Prakash O. *Tetrahedron* 1990; **31**: 197.
59. Mori M, Washioka Y, Urayama T, Yoshiura K, Chiba K, Ban Y. *J. Org. Chem.* 1983; **48**: 4058.
60. Bartle KD, Smith JAS. *Spectrochim. Acta, Part A* 1967; **23**: 1715.
61. Harvey RG, Cortez C, Ananthanarayan TP, Schmolka S. *J. Org. Chem.* 1988; **53**: 3936.
62. Heller E, Schmidt GMJ. *Isr. J. Chem.* 1971; **9**: 449.
63. Saunders M, Houk KN, Wu Y, Still WC, Lipton M, Chang G, Guida WC. *J. Am. Chem. Soc.* 1990; **112**: 1419.
64. Howard AE, Kollman PA. *J. Med. Chem.* 1988; **31**: 1669.
65. Egawa T, Maekawa S, Fujiwara H, Takeuchi H, Konaka S. *J. Mol. Struct.* 1995; **352−353**: 193.
66. Schneider HJ, Buchheit U, Becker N, Schmidt G, Siehl U. *J. Am. Chem. Soc.* 1985; **107**: 7027.