MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. 2007; **45**: 749–757
Published online 19 July 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/mrc.2043

MRC

The prediction of ^{1}H chemical shifts in amines: a semiempirical and *ab initio* investigation†

Ernani A. Basso,[1] Gisele F. Gauze[1] and Raymond J. Abraham[2]*

[1] Chemistry Department, State University of Maringá, CEP-87020-900, Maringá, PR, Brazil
[2] Chemistry Department, The University of Liverpool, Liverpool L69 3BX, UK

Received 14 May 2007; Accepted 24 May 2007

Twenty one conformationally fixed amines and their *N*,*N*-dimethyl derivatives were obtained commercially or synthesized. These included *cis* and *trans* 4-*t*-butyl cyclohexylamine, 2-*exo* and 2-*endo* norbornylamine, 2-adamantylamine, 4-phenylpiperidine, 1-napthylamine and tetrahydro-1-napthylamine. The ^{1}H NMR spectra of these amines were measured in $CDCl_3$ solution, assigned and the ^{1}H chemical shifts given. This data was used to investigate the effect of the amino group on the ^{1}H chemical shifts in these molecules. These effects were analyzed using the CHARGE model. This calculates the electric field and steric effects of the amino group for protons more than three bonds removed, together with functions for the calculation of two-bond and three-bond effects. The rotational isomerism about the C–N bond of the amino group was investigated by *ab initio* calculations of the potential energy surface (PES) about this bond at the HF/3–21G level. The resulting conformers were then minimized at the B3LYP/6-311++G (d,p) level. These geometries were then used to calculate the ^{1}H chemical shifts in the above compounds by CHARGE and the *ab initio* gauge-invariant atomic orbital (GIAO) method at the B3LYP/6–311++G(d,p) level and the shifts were compared with those observed. The compounds investigated gave 170 ^{1}H chemical shifts ranging from 0.60 to 8.2 ppm. The rms errors (obs. – calc.) were *ca* 0.1 ppm (CHARGE) and *ca* 0.2 ppm (GIAO). Large deviations of *ca* 1.0 ppm were observed for the NH protons in the GIAO calculations. The complex spectra of alkyl and aryl amines can thus be successfully predicted by both *ab initio* and semiempirical methods except for the NH protons, for which the *ab initio* calculations are not sufficiently accurate. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H chemical shifts; amines; NMR prediction; GIAO; CHARGE

INTRODUCTION

Amines are one of the most important classes of organic compounds, being constituents of all alkaloids, amino acids, proteins, etc., and many other natural products. Also, many drugs are amines (e.g. amphetamines, morphine, nicotine, etc.). They are also versatile synthetic intermediates in organic and organometallic chemistry. Despite this common occurrence, there are few studies on the ^{1}H NMR chemical shifts of the amino group, and a definitive analysis of amino substituent chemical shifts (SCS) in ^{1}H spectra has not been performed to date. Zurcher's[1] pioneering investigation did not consider amines, probably because of lack of good data. Pretsch[2] reported literature data for some amines, mainly of attached methyl groups. More recently, Alkorta and Elguero[3] in their theoretical (GIAO) calculations of ^{1}H shieldings in amines gave literature data for the amines they investigated (methyl and ethylamine and some heterocyclic amines). They calculated the influence of the nitrogen lone pair on the ^{1}H chemical shifts and noted that it was a function of the ring size and the nitrogen substitution.

There are two possible reasons for the absence of any systematic investigation into amino chemical shifts. One is the strong basicity of alkyl amines. In a recent investigation, Abraham *et al*.[4] found that the ^{1}H shifts of the NH protons of aliphatic amines showed little consistency in either $CDCl_3$ or DMSO solvent and often the signals were too broad to be observed. They note that the NH_2^+ proton signals of dimethylamine hydrochloride occur at 9.2 ppm in $CDCl_3$ compared to those of the free base at *ca* 1 ppm,[5] and therefore traces of acid will produce large shifts for these protons and also broaden the signal owing to exchange. They suggested that this was the most probable reason for the lack of consistency of these shifts in either solvent and concluded that these protons are not suitable for diagnostic purposes. Other near protons would be expected to experience similar but much smaller effects because of protonation. Aryl amines are much less basic and we shall show that the chemical shifts of the NH protons in these compounds can be satisfactorily predicted once all the factors affecting their chemical shifts, including π contributions, are evaluated.

The other factor is simply the trivalent nature of the nitrogen atom. This gives additional degrees of freedom

*Correspondence to: Raymond J. Abraham, Chemistry Department, The University of Liverpool, PO Box 147, Liverpool L69 3BX, UK. E-mail: abrahamr@liv.ac.uk
†This is part 26 of ^{1}H Chemical Shifts in NMR series.

MRC

when compared to monovalent substituents. For example, the SCS of the amino group is dependent on the position of the lone pair.[3] In solution, the NH_2 group is usually not in a single orientation, but the precise populations of the different conformers are often unknown. For example, ethylamine has two distinct conformers with the lone pair *anti* or *gauche* to the C–C bond but the conformer energies in solution have not to our knowledge been measured accurately. Gas-phase *ab initio* calculations by Alkorta and Elguero[3] gave ethylamine as a 50 : 50 mixture but solvent effects were not considered. In more complex acyclic amines, the number of conformers is prohibitively large for any quantitative calculation.

For this reason we have investigated a variety of cyclic amines in which the carbon framework is in a rigid conformation (Fig. 1), and determined the orientation of the amino group by *ab initio* calculations. These molecules give rise to complex ^{1}H NMR spectra, which can, however, be completely assigned to give an ensemble of ^{1}H chemical shifts. This ensemble provides a stringent critique for any calculation of ^{1}H chemical shifts in these molecules and will be used to parameterize the CHARGE model for the amino group.

In previous parts of this series, the CHARGE program has been developed to provide a model capable of accurately predicting the ^{1}H chemical shifts of a variety of organic compounds in $CDCl_3$[6–8] and DMSO[4] solutions. This program consists of a neural-network-data-based approach for one-, two- and three-bond substituent effects plus a classical calculation of the long-range effects of substituents. This calculates the electric field, anisotropy and steric effect of the substituent plus, for conjugated systems, the effect of the π-electrons and for aromatics the ring-current shifts. The CHARGE program is available as part of NMRPredict,[9] a modeling ^{1}H and ^{13}C software package.

An alternative method of calculating NMR chemical shifts is by the *ab initio* gauge-invariant atomic orbital (GIAO)[10,11] method, in which the nuclear shielding tensor is calculated. This method has been used successfully in the calculation of heavy-atom chemical shifts. Pulay *et al*.[12] 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. An investigation by Lampert *et al*.[13] on phenol and benzaldehyde derivatives led to deviations of *ca* 0.5–1.0 ppm depending on the procedure and basis set used, and this may well represent the limit of accuracy of such calculations. Alkorta and Elguero[3] calculated amine shieldings at the GIAO/B3LYP/6–311++G** level but noted that their ^{1}H calculations were not as well correlated with the observed shifts as the analogous ^{13}C calculations. We use here an approach similar to that of Alkorta and Elguero in that the same density function theory and basis set will be used for the geometry optimization and GIAO calculations. The GIAO-derived chemical shifts will then be compared with the shifts from the CHARGE parameterization.

THEORY

As the theory has been given previously,[6–8] only a brief summary of the latest version (CHARGE8c) will be given here. The theory distinguishes between short-range substituent effects over one, two, and three bonds, which are attributed to the electronic effects of the substituents and long-range effects due to the electric fields, steric effects and anisotropy of the substituents.

The CHARGE scheme calculates the effects of neighboring atoms on the partial atomic charge of the atom under consideration on the basis of the classical concepts of inductive and resonance contributions. If we consider an atom I in a four-atom fragment, I-J-K-L, the partial atomic charge on I (q_I) is due to three effects. There is an α-effect from atom J, given by the difference in the electronegativity of atoms I and J and a β-effect from atom K proportional to both the electronegativity of atom K and the polarizability of atom I. There is 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 empirical parameters.

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

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

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, N, Cl, Br, I) interactions deshielding, according to a simple r^{-6} dependence, where a_S is the steric coefficient for any given atom.

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

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

The magnetic anisotropy of a bond with cylindrical symmetry (e.g. C≡C) is obtained from the appropriate McConnell[14] equation:

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

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

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

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

DOI: 10.1002/mrc

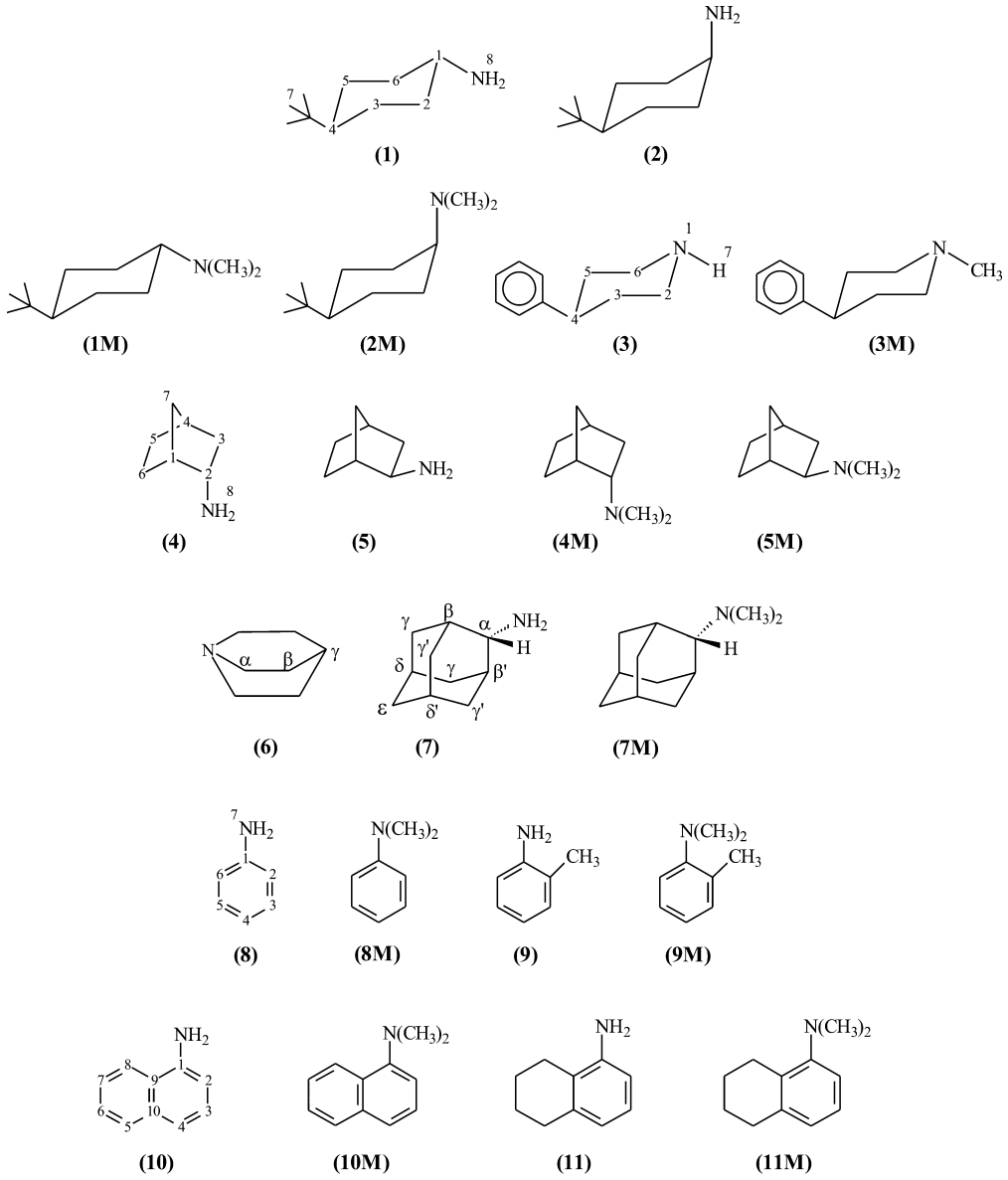

Figure 1. Amino compounds used for parameterization of CHARGE 177 × 203 mm (600 × 600 DPI).

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

The effect of the excess π-electron density at a given carbon atom on the proton chemical shifts of the neighboring protons is given by Eqn (5), where Δq_α and Δq_β are the excess π-electron density at the α- and β-carbon atoms, respectively. The π-electron densities are calculated using Huckel theory parameterized to reproduce the values obtained from *ab initio* calculations.[8]

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

For aromatic molecules, the effect of the aromatic ring current has to be included, and this is given by the equivalent dipole approximation (Eqn 6). In Eqn 6, R is the distance of the proton from the benzene ring center, 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.

$$\delta_{\text{rc}} = fc\ \mu(3\cos^2\theta - 1)/R^3 \tag{6}$$

The above contributions are added to Eqn (1) to give the calculated shift of Eqn (7).

$$\delta_{\text{total}} = \delta_{\text{charge}} + \delta_{\text{steric}} + \delta_{\text{anis}} + \delta_{\text{el}} + \delta_\pi + \delta_{\text{rc}} \tag{7}$$

APPLICATION TO AMINES

In the CHARGE routine, single bonds have been considered to be isotropic and the same assumption will be made here for the C–N and N–H bonds. The other terms in the CHARGE formulation (electric field, steric effects, π-effects and ring currents) all need to be considered. The electric field shift is given directly from the calculated partial atomic charges and these can be checked by comparison of the observed and calculated dipole moments. For methylamine,

DOI: 10.1002/mrc

MRC

dimethylamine, and trimethylamine, the observed *versus* calculated dipole moments are 1.33, 1.01, and 0.63 D[15] *versus* 1.32, 1.10, and 0.86 D, respectively. The agreement is such that the electric field term may be used directly. The nitrogen steric effect is given by Eqn 2, where the value of the steric coefficient a_S needs to be found. The aromatic ring current in substituted benzenes has been found in previous investigations to be the same as in benzene, and this will be assumed here for the amino benzenes. The effect of the π-electron density on the ring protons is given by Eqn 5, but the effect of the π-density on the nitrogen atom on the chemical shifts of the attached proton will require a different coefficient. There is also the influence of the nitrogen lone pair on the shielding of neighboring protons. This was not included explicitly for the analogous case of the oxygen atom in alcohols and ethers[6], being covered by the steric effect of the oxygen atom plus the α-, β- and γ-effects of the oxygen atom for the near protons. The same procedure will be used for the nitrogen atom of the amines considered.

Thus we need to evaluate the steric coefficient a_S (Eqn 2), π-electron coefficient (Eqn 5) and the α-, β- and γ-effects of the nitrogen atom on the chemical shifts of the near protons. These parameters were obtained from an iterative calculation on the observed shifts.

EXPERIMENTAL

Experimental details

All the amino (R═NH_2) compounds and solvents used were obtained commercially, as well were the dimethylamino compounds **8M, 9M** and **10M** (Fig. 1). The remaining dimethylamino derivatives were synthesized according to literature procedures, as follows.

The mixture of *cis* and *trans* 4-dimethylamino tert-butylcyclohexane isomers (**1M)** and **(2M)** and also *N*-methyl-4-phenyl piperidine (**3M)** were prepared through the method of Leuckart reductive alkylation,[16–18] using formaldehyde in the presence of formic acid. The 2-*endo*-dimethylaminonorbornane (**4M**) was obtained from selective reduction[19] of norcamphor, with sodium cyanohydridoborate ($NaBH_3CN$). A variation of this procedure[20] using just formaldehyde and the reductive agent ($NaBH_3CN$) was used to obtain the dimethylamino compounds (**5M)**, (**7M)** and (**11M),** as the Leuckart reaction did not work for these compounds.

Spectroscopy experiments

^1H 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. Compounds **1M, 2M, 3M, 4M,** and **10** gave complex, overlapping ^1H spectra at 400 MHz, and the ^1H spectra were obtained on a Bruker Avance spectrometer operating at 700.13 MHz. COSY, HMQC, and HMBC experiments were also performed as needed. The spectra were recorded in 20 mg cm^{-3} solutions in $CDCl_3$, with a probe temperature of *ca* 300 K and TMS as reference. To avoid the presence of residual HCl, all solutions were filtrated through columns of basic alumina before the spectra acquisition.

Computational methods

The geometries of all compounds used for parameterization (Fig. 1) were minimized using *ab initio* calculations with the Gaussian 03W program.[21] For all compounds the potential energy surfaces (PES) were constructed at the HF/3-21G level in order to determine the preferred amino group orientation. The stable conformers were then minimized at the B3LYP/6–311++G(d,p) level, and the GIAO calculations were performed using the recommended[22] B3LYP/6–31G(d,p) level. The chemical shifts were referenced to methane (minimized and calculated in the same manner) and converted to TMS using the experimental value of 0.23 ppm for methane.[23]

RESULTS AND DISCUSSION

Conformational analysis

The hydrocarbon fragments in the molecules studied were chosen as rigid structures; therefore only the rotational isomerism about the C–N bond needs to be determined. In order to determine the most stable rotamers for the amino group, we performed PES calculations by varying the C2–C1–N–H(C) dihedral angle with increments of 10° to all compounds where applicable. Although the nitrogen lone pair is not defined in either the *ab initio* or the CHARGE calculations, it is more convenient to describe the rotational isomerism about the H–C–N–R_2 (R = H, Me) bond in terms of the H–C–N-lone-pair dihedral angle (θ). For compounds **1, 1M,** and **2,** two populated rotamers were found, and the PES for each compound is shown in Fig. 2. Note that the energy is given relative to the more stable conformer in each case. In *trans*-4-*t*-butylcyclohexylamine (**1**) the gauche conformer ($\theta = 60^0$) is calculated to be slightly less stable (0.3 kcal mol^{-1}) than the *trans* ($\theta = 180^0$) conformer. The statistical weight of two for the *gauche* conformer results in almost equal populations of the two forms (*anti : gauche*, 45 : 55). In the dimethyl derivative (**1M**), the symmetric conformer is much more stable than the gauche by 1.7 kcal mol^{-1}. In *cis* 4-*t*-butylcyclohexylamine (**2**), the symmetric form ($\theta = 180°$) is more stable than the gauche conformer, with one hydrogen atom pointing into the ring ($\Delta E = 1.0$ kcal mol^{-1}), and is again the more populated form (77%). In the dimethyl derivative (**2M**), the methyl groups are too bulky to point into the ring and only the symmetric form is present. The conformations of piperidine derivatives analogous to (**3**) and (**3M**) have been determined previously. In piperidine and *N*-methyl piperidine, the N–H equatorial conformer is favored over the axial NH conformer by 0.4 and 3.0 kcal mol^{-1}, respectively.[24] The remaining compounds were found to have one major conformer. In both *endo* aminonorbornane (**4**) and the dimethyl derivative (**4M**), the stable conformer has the lone pair *anti* to the CH proton but in the corresponding *exo* compounds (**5**) and (**5M**) the lone pair is *anti* to the C_2–C_3 bond. Both 2-adamantanamine (**7**) and its dimethyl derivative (**7M**) exist in a symmetric conformation with the lone pair *anti* to the CH bond ($\theta = 180°$).

The *ab initio* calculations iterate to a planar nitrogen atom for aniline (**8**), *N*,*N*-dimethylaniline (**8M**) and *ortho*-toluidine (**9**), but in (**9M**) the nitrogen atom is pyramidal with one

DOI: 10.1002/mrc

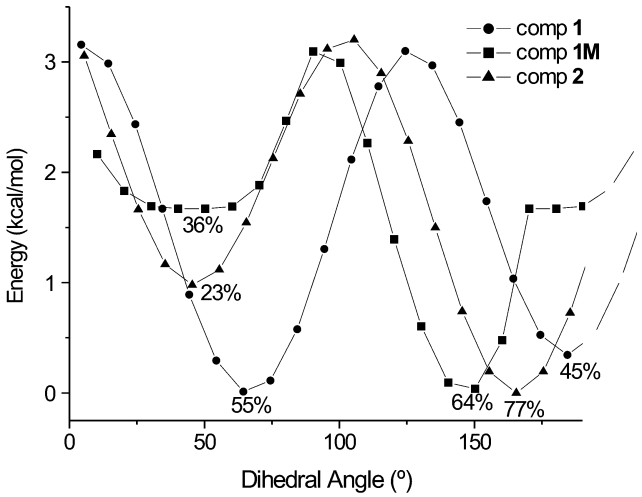

Figure 2. Potential energy surface of compounds **1, 1M,** and **2** about the C2–C1–N–H(C) dihedral angle. 101 × 76 mm (600 × 600 DPI).

methyl group at *ca* 90° to the phenyl ring. Interestingly the *ab initio* calculations give a nonplanar nitrogen atom for both the naphthalene derivatives (**10**) and (**10M**) and the tetrahydronapthalenes (**11**) and (**11M**).

Where the contribution of each rotamer was significant as in compounds **1, 1M, 2,** and **3,** the chemical shifts were calculated for each conformer and the final chemical shifts obtained from the weighted average. This procedure is necessary because for some protons the chemical shifts change by up to 0.5 ppm in the different conformers.

Proton chemical shift calculations

Effect of the π-density on the nitrogen atom on NH chemical shifts

The effect of the excess π-electron density at an aromatic carbon atom on the proton chemical shifts of the attached proton is given by Eqn (5), in which the coefficient for the attached proton was determined as 10 ppm/π electron.[23] In some current investigations on phenols,[25] it was found that the coefficient for the effect of π-electron on the oxygen atom on the OH proton was much larger (*ca* 40 ppm), and it is of interest to determine the analogous value for nitrogen. This can be obtained by comparing the NH proton shifts of some *para*-substituted anilines with the calculated π-densities at the nitrogen atom. The *para* substituent is sufficiently distant from the nitrogen atom so that the only factor affecting the NH shift is the π-electron density. This data is shown in Table 1 for a variety of *para*-substituted anilines. There is an excellent linear correlation between the shifts and the π-densities to give a coefficient of 42.8 ppm/π electron with an rms error of 0.142. The observed shifts and shifts calculated by CHARGE with the above coefficient inserted are shown in Table 1. The agreement clearly demonstrates the π-dependence of the shifts, but it is important to note that the coefficient depends on the π-calculation. The modified Huckel program detailed previously[6] is used here. This coefficient was included in the calculations of the NH proton chemical shifts of the aromatic amines in Table 3. It has no effect on the NH shifts of the aliphatic amines detailed here, as none of them are conjugated. The remaining parameters necessary for the calculation of the proton chemical shifts were obtained from an iterative calculation using the nonlinear least mean-square program CHAP8.[26] The coefficients *A* and *B* of the γ-effects (H–C–C–N and H–C–N–C) were determined with the nitrogen steric coefficient (a_S, Eqn 2), which equals 66.6 ppm/Å^6.

Table 1. NH_2 ^{1}H chemical shifts *versus* nitrogen π-electron excess for *para*-substituted anilines

		NH_2 Chemical Shift (ppm)	
Substituent	π-Electron excess (me)[c]	Obs.[a]	Cal.[b]
NMe_2	135	3.28	3.146
OEt	140	3.40	3.371
F	141	3.51	3.481
Me	145	3.48	3.585
Cl	149	3.63	3.739
Br	148	3.64	3.732
I	149	3.57	3.720
H	149	3.56	3.775
CF_3	152	3.90	3.920
CO_2Me	153	4.19	3.986
CN	158	4.30	4.202

[a] Data from Ref. 5.
[b] CHARGE program.
[c] Millielectrons.

CHARGE model versus GIAO calculations

The experimental and calculated proton chemical shifts of the aliphatic amines are presented in Table 2. The experimental chemical shifts range from *ca* 0.60 to 3.30δ and were predicted with the CHARGE model with an rms error of 0.108 ppm. The majority of the shifts show deviations of less than 0.1 ppm, showing excellent agreement between observed and calculated chemical shifts.

One of largest deviations of the calculated shifts is associated with the gamma substituent effect (N–C–C–H). This has large dihedral angle dependence. The norbornane derivatives and the 4-*t*-butylcyclohexane derivatives have very different dihedral angles (N–C–C–H) see Fig. 3 and this may be the reason for such deviations. The γ-effect has been parameterized using a simple (cos ϕ) term and this may not be adequate to fully account for this dihedral angle dependence.

The observed *versus* calculated proton chemical shifts for the aromatic amines are given in Table 3. The majority of the shifts were predicted to within 0.05 ppm, showing even better agreement than the aliphatic amines.

It is of some interest to compare the CHARGE model with the GIAO method. The data are also included in Tables 2 and 3. The GIAO calculations are, in general, less accurate than CHARGE calculations. In particular they gave all the amino proton chemical shifts significantly more shielded than the experimental value. The discrepancies between theory and experiment for these protons were so large that they were

DOI: 10.1002/mrc

Table 2. Experimental and calculated ^{1}H chemical shifts of aliphatic amines

Compound	Method	H1a	H1e	H2a/6a	H2e/6e	H3a/5a	H3e/5e	H4a	NR2	t-Bu			r.m.s
trans-4-*t*-Butylcyclohexylamine (**1**)	$CDCl_3$	2.551	–	1.033	1.885	1.033	1.755	0.962	1.100	0.842			–
	CHARGE	2.750	–	1.153	1.772	0.908	1.653	1.065	1.081	0.904			**0.124**
	GIAO	2.688	–	1.058	1.729	1.206	1.742	1.087	0.338	0.869			**0.113**
cis-4-*t*-Butylcyclohexylamine (**2**)	$CDCl_3$	–	3.148	1.535	1.654	1.274	1.525	0.962	1.100	0.859			–
	CHARGE	–	3.211	1.517	1.611	1.288	1.514	1.019	1.183	0.907			**0.041**
	GIAO	–	3.151	1.423	1.546	1.851	1.376	1.104	0.269	0.889			**0.239**
trans-4-*t*-Butyl-*N*,*N*-dimethylcyclohexylamine (**1M**)	$CDCl_3$	2.068	–	1.161	1.931	1.006	1.820	0.938	2.267	0.843			–
	CHARGE	2.109	–	1.063	1.637	0.893	1.650	1.056	2.335	0.905			**0.142**
	GIAO	2.074	–	1.227	1.822	1.169	1.801	1.069	2.115	0.872			**0.103**
cis-4-*t*-Butyl-*N*,*N*-dimethylcyclohexylamine (**2M**)	$CDCl_3$	–	1.945	1.296	2.005	1.324	1.431	1.032	2.205	0.847			–
	CHARGE	–	2.030	1.139	1.854	1.329	1.411	1.008	2.279	0.904			**0.090**
	GIAO	–	1.930	1.207	2.006	1.828	1.358	1.210	2.126	0.895			**0.196**
		H2a/6a	**H2e/6e**	**H3a/5a**	**H3e/5e**	**H4a**	**NR**	**orto**	**meta**	**para**			
trans-4-Phenylpiperidine (**3**)	$CDCl_3$	2.737	3.180	1.636	1.827	2.609	1.100	7.222	7.290	7.199			–
	CHARGE	2.720	3.155	1.680	1.921	2.589	1.217	7.212	7.313	7.186			**0.040**
	GIAO	2.407	2.582	1.435	1.192	1.845	0.385	6.971	6.994	6.913			**0.465**
trans-*N*-Methyl-4-phenylpiperidine (**3M**)	$CDCl_3$	2.040	2.969	1.820	1.820	2.465	2.317	7.209	7.271	7.166			–
	CHARGE	2.098	2.952	1.864	1.798	2.599	2.277	7.212	7.312	7.187			**0.056**
	GIAO	2.028	2.628	1.831	1.524	2.113	2.092	7.234	7.270	7.194			**0.205**
		H1	**H2**	**H3x**	**H3n**	**H4**	**H5x**	**H5n**	**H6x**	**H6n**	**H7a**	**H7s**	**NR_2**	
endo-2-Aminonorbornane (**4**)	$CDCl_3$	2.071	3.256	1.956	0.588	2.142	1.547	1.221	1.366	1.728	1.296	1.388	1.100	–
	CHARGE	2.287	3.192	1.983	0.564	2.186	1.541	1.269	1.349	1.780	1.187	1.149	1.088	**0.109**
	GIAO	1.920	3.401	1.667	0.700	2.055	1.482	1.289	1.129	2.494	1.313	1.344	0.266	**0.270**
exo-2-Aminonorbornane (**5**)	$CDCl_3$	1.927	2.806	1.026	1.635	2.208	1.419	1.046	1.464	1.079	1.097	1.469	1.100	–
	CHARGE	1.975	2.769	0.985	1.640	2.205	1.56	1.234	1.509	1.243	1.090	1.475	1.138	**0.090**
	GIAO	1.785	3.001	1.073	1.369	2.146	1.447	1.016	1.442	1.017	1.047	2.039	0.153	**0.206**

MRC

endo-2-*N*,*N*-Dimethylamino norbornane (**4M**)	$CDCl_3$	2.228	2.087	1.709	0.898	2.165	1.497	1.270	1.280	1.748	1.288	1.353	2.165	–
	CHARGE	2.484	1.977	1.569	0.709	2.199	1.530	1.278	1.118	2.065	1.177	1.158	2.267	**0.164**
	GIAO	1.863	2.019	1.363	0.649	1.795	1.222	1.007	0.976	2.012	1.026	1.090	1.768	**0.320**
exo-2-*N*,*N*-Dimethylamino norbornane (**5M**)	$CDCl_3$	2.346	1.811	1.378	1.354	2.242	1.445	1.077	1.495	1.077	1.053	1.470	2.171	–
	CHARGE	2.343	1.955	1.510	1.176	2.199	1.554	1.062	1.485	1.231	1.062	1.496	2.215	**0.106**
	GIAO	2.325	1.758	1.465	1.319	2.181	1.436	1.097	1.482	1.045	1.045	1.717	1.976	**0.081**
Compound	Method	**Hα**	**Hβ**	**Hγ**								**r.m.s**		
Quinulidine (**6**)	$CDCl_3$	2.854	1.531	1.735								–		
	CHARGE	2.836	1.663	1.802								**0.086**		
	GIAO	2.615	1.281	1.580								**0.229**		
		Hα	**Hβ/β′**	**Hγ′a**	**Hγ′e**	**Hγa**	**Hγe**	**Hδ′**	**Hδ**	**Hε**	**NR_2**			
2-Adamantanamine (**7**)	$CDCl_3$	2.982	1.720	1.731	1.847	1.979	1.527	1.786	1.822	1.717	1.419	–		
	CHARGE	3.082	1.881	1.592	1.631	2.123	1.459	1.923	1.929	1.664	1.294	**0.191**		
	GIAO	3.186	1.453	1.617	1.775	2.591	1.279	1.643	1.645	1.645	0.238	**0.236**		
2-*N*,*N*-Dimethyl adamantanamine (**7M**)	$CDCl_3$	1.870	2.051	1.667	1.848	2.043	1.435	1.809	1.790	1.709	2.216	–		
	CHARGE	2.263	2.029	1.601	1.615	2.226	1.336	1.920	1.927	1.664	2.288	**0.172**		
	GIAO	1.939	1.965	1.627	1.796	2.320	1.324	1.676	1.655	1.663	2.085	**0.127**		

Magn. Reson. Chem. 2007; **45**: 749–757
DOI: 10.1002/mrc

MRC

Table 3. Experimental and calculated ^{1}H chemical shifts of aromatic amines

Compound	Method	H2/6	H3/5	H4	NR_2					r.m.s
Aniline (**8**)	$CDCl_3$	6.635	7.127	6.733	3.500					–
	CHARGE	6.661	7.134	6.678	3.538					**0.035**
	GIAO	6.159	7.028	6.474	2.837					**0.318**
N,*N*-Dimethylaniline (**8M**)	$CDCl_3$	6.730	7.231	6.713	2.926					–
	CHARGE	6.651	7.124	6.669	2.726					**0.122**
	GIAO	6.402	7.172	6.662	2.923					**0.169**
		H3	**H4**	**H5**	**H6**	**CH_3**	**NR_2**			
o-Toluidine (**9**)	$CDCl_3$	7.021	6.683	7.010	6.625	2.128	3.488			–
	CHARGE	6.929	6.612	6.946	6.585	2.376	3.933			**0.060**
	GIAO	6.918	6.471	6.960	6.168	2.924	1.860			**0.260**
o-*N*,*N*-Dimethyltoluidine (**9M**)	$CDCl_3$	7.147	6.934	7.142	7.023	2.322	2.689			**0.047**
	CHARGE	7.090	6.990	7.076	6.980	2.325	2.715			**0.102**
	GIAO	7.189	6.959	7.121	6.927	2.192	2.507			
		H2	**H3**	**H4**	**H5**	**H6**	**H7**	**H8**	**NR_2**	
1-Aminonaphthalene (**10**)	$CDCl_3$	6.676	7.272	7.308	7.800	7.441	7.433	7.788	3.966	–
	CHARGE	6.530	7.212	6.937	7.718	7.465	7.333	8.107	3.973	**0.201**
	GIAO	6.503	7.257	7.125	7.647	7.425	7.400	7.732	3.236	**0.114**
1-*N*,*N*-Dimethylaminonaphthalene (**10M**)	$CDCl_3$	7.023	7.344	7.474	7.775	7.413	7.443	8.223	2.853	–
	CHARGE	7.047	7.384	7.433	7.807	7.493	7.431	8.422	2.848	**0.080**
	GIAO	7.024	7.365	7.398	7.702	7.466	7.509	8.369	2.729	**0.083**
5-amino-1,2,3,4-Tetrahydronaphthalene (**11**)	$CDCl_3$	6.449	6.901	6.512	2.704	1.723	1.826	2.398	3.475	–
	CHARGE	6.463	6.931	6.467	2.679	1.816	1.808	2.550	3.995	**0.072**
	GIAO	6.217	6.913	6.451	2.626	1.618	1.713	2.229	2.540	**0.129**
5-*N*,*N*-Dimethylamino-	$CDCl_3$	6.889	7.074	6.798	2.794	1.760	1.780	2.735	2.669	–
1,2,3,4-tetrahydronaphthalene (**11M**)	CHARGE	6.898	7.080	6.89	2.694	1.808	1.800	2.828	2.679	**0.061**
	GIAO	6.836	7.083	6.801	2.737	1.661	1.646	2.706	2.464	**0.098**

disregarded in the rms error calculations. The theoretical predictions for protons attached to the carbon chains do not show a regular behavior. Some of the predicted shifts were shielded and others were deshielded. Nevertheless the rms error values are only 0.096 for CHARGE and 0.187 for GIAO.

We also analyzed the model that produces the greatest number of hits closest to the observed chemical shifts. CHARGE produces the largest number of best hits (64%), while GIAO is better only in 32% of the hits.

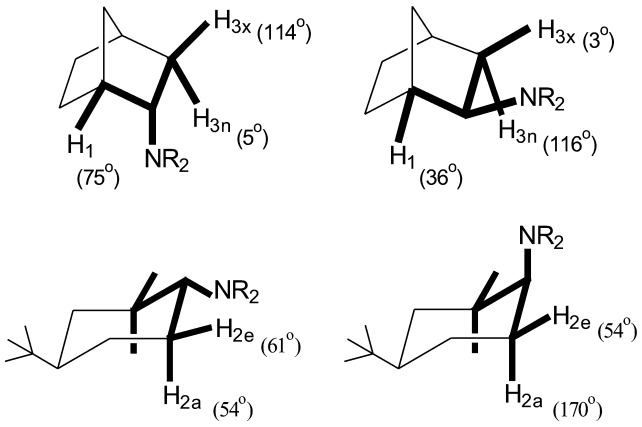

Figure 3. Structure and dihedral angle of amines derivatives (R = H, CH_3) of norbornane and 4-*t*-butylcyclohexane. 127 × 76 mm (600 × 600 DPI).

In conclusion the GIAO calculations yield reasonable results and could be improved by using alternative basis sets or theories, but this is beyond the scope of this study. Overall, the semiempirical calculations produce more reliable results and provide a rapid and useful tool for routine use in chemical shifts prediction.

Acknowledgements

We thank Dr Mehdi Mobli and GlaxoWellcome plc. for the 700 MHz spectra. The authors acknowledge Coordenação de Aperfeiçoamento de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for scholarships to G.F.G and E.A.B and a Leverhulme Emeritus Fellowship to R.J.A.

REFERENCES

1. Zurcher RF. *Prog. Nucl. Magn. Reson. Spectrosc.* 1967; **2**: 205.
2. Pretsch E, Simon W, Seibl J, Clerc T. In *Spectral Data for Structure Determination of Organic Compounds*, 2nd edn., Springer-Verlag: London, 1989.
3. Alkorta I, Elguero J. *Magn. Reson. Chem.* 2004; **42**: 955.
4. Abraham RJ, Byrne JJ, Griffiths L, Perez M. *Magn. Reson. Chem.* 2006; **44**: 491.
5. Pouchert CJ, Behnke J. *Aldrich Library of 13C and 1H FT NMR Spectra*. Aldrich Chemical Company: Milwaukee, 1993.
6. Abraham RJ. *Prog. Nucl. Magn. Reson. Spectrosc.* 1999; **35**: 85.
7. Abraham RJ, Griffiths L, Warne MA. *J. Chem. Soc., Perkin Trans. 2* 1998; 1751.
8. Abraham RJ, Bardsley B, Mobli M, Smith RJ. 2005; **43**: 3.
9. NMRPredict. http://www.modgrah.co.uk [accessed 2006], Modgraph Consultants Ltd. 1, Oakland View, Oaklands Welwyn, Herts, AL6, ORJ, UK.

10. Dodds JL, McWeeny R, Sadlej AJ. *Mol. Phys.* 1980; **41**: 1419.
11. Wolinski K, Hilton JF, Pulay P. *J. Am. Chem. Soc.* 1990; **112**: 8251.
12. Pulay P, Hinton JF. *Encyclopedia of Nuclear Magnetic Resonance*. Wiley: New York, 1995.
13. Lampert H, Mikenda W, Karpfen A, Kählig H. *J. Phys. Chem. A* 1997; **101**: 9610.
14. McConnell HM. *J. Chem. Phys.* 1957; **27**: 226.
15. McClellan AL. *Table of Experimental Dipole Moments Volume 3*. Rahara Enterprises: El Cerrito, CA, 1989.
16. Pine SH, Sanchez BL. *J. Org. Chem.* 1971; **36**: 829.
17. Meiners AF, Bolze C, Schorer AL, Morris FV. *J. Org. Chem.* 1958; **23**: 1122.
18. Moore ML. *Org. React.* 1948; **5**: 301.
19. Borch RF, Berstein MD, Durst HD. *J. Am. Chem. Soc.* 1971; **93**: 2897.
20. Borch RF, Hassid AI. *J. Org. Chem.* 1972; **37**: 1673.
21. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Piskorz IP, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA. *GAUSSIAN 03W (Revision 8.02)*. Gaussian: Pittsburgh, 2003.
22. Foresman JB, Frish AE. In *Exploring Chemistry with Electronic Structure Methods*, ed. Gaussian Inc: Pitsburg, 2nd edn., 1996.
23. Gunther H. *NMR Spectroscopy-An Introduction*. John Wiley & Sons: New York, 1980; 68.
24. Eliel EL, Wilen SH. *Stereochemistry of Organic Compounds*. Wiley: New York, 1994; 743.
25. Abraham RJ. Mobli M. unpublished work.
26. Kuo SS. *Computer Applications of Numerical Methods. cd. 8*. Addison Wesley: London, 1972; in.

DOI: 10.1002/mrc