A Nuclear Magnetic Resonance and Molecular-modelling Study of Cyclohexylamine and Several *N*-Substituted Derivatives and their Hydrochloride Salts

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A ^{13}C n.m.r. study has been carried out on cyclohexylamine and 11 of its *N*-substituted derivatives along with the corresponding hydrochloride salts; all of the observed resonances were assigned. An empirical set of chemical shift differences ($\Delta\delta$) are suggested which allow the chemical shifts of this class of compound to be calculated with good agreement between the calculated and observed chemical values. Semiempirical charge calculations were carried out for all the compounds and the partial charge allocations related with the observed n.m.r. chemical shifts; the extent of correlation is discussed.

Cyclohexylamine and its *N*-substituted derivatives form an interesting group of alicyclic bases the differences in basicity and other properties of which have found use in various industrial applications ranging from intermediates in pharmaceuticals and dyes to catalysts in certain polymerisation processes. While the n.m.r. spectra of cyclohexylamine itself and other alicyclic amine compounds are well documented,[1–3] less attention has been paid to a variety of *N*-substituted derivatives. We decided therefore to study the ^{13}C n.m.r. of a range of *N*-substituted cyclohexylamine compounds and their corresponding hydrochloride salts and also the ^{14}N n.m.r. of the hydrochloride salts. One purpose of this study was to elucidate empirical chemical-shift rules for this class of compound. In addition, we have carried out computer-modelling calculations on all of the bases and their salts and the partial atomic charges have been calculated by two different methods. The aim of this exercise was to test the correlation between the measured n.m.r. chemical shifts and the calculated atomic charges and thereby give some comparative indication of the validity of the methods used for allocating the charges.

Experimental

The bases used were cyclohexylamine [entry (1) in Table 2] *N*,*N*-dimethylcyclohexylamine (2), *N*-ethylcyclohexylamine (3), *N*-isopropylcyclohexylamine (4), *N*-(2-hydroxyethyl)cyclohexylamine (5), *N*-phenylcyclohexylamine (6), *N*-(2-cyanoethyl)-cyclohexylamine (7), *N*-(3-aminopropyl)cyclohexylamine (8), *N*-methylcyclohexylamine (9), 2-cyclohexylamine-1-phenylethanol (10), *N*-cyclohexylpiperidine (11), and *N*-cyclohexylmorpholine (12). The bases were originally obtained from Abbot Laboratories (Development Division) and were purified by distillation prior to use and then used immediately. The hydrochlorides were prepared by the direct reaction of the bases (cooled in ice) with a slight excess of ice-cold conc. HCl. The salts were filtered off, washed with acetone on a Buchner funnel and then dried in a vacuum oven at 60 °C.

N.M.R. Measurements.—The ^{13}C broadband decoupled and off-resonance n.m.r. spectra of the compounds were measured on a Jeol FX90Q Fourier-transform n.m.r. spectrometer (^{13}C resonance at 22.5 MHz). The bases were measured in $CDCl_3$ as solvent and referenced relative to $SiMe_4$ at δ 0.0, while the hydrochloride salts were measured in water (using a D_2O capillary as the instrument lock) and were referenced relative to TSP † at δ 0.0. In all cases the spectra were measured over a spectral range of 4 500 Hz and acquired in 8K data points using a pulse angle of 30° and a pulse repetition time of 1 s. The accumulated spectra were zero-filled to 16K data points and an exponential broadening of 0.7 Hz applied prior to Fourier transformation. The ^{13}C resonances were assigned making use of the off-resonance spectra and the published data for cyclohexylamine.[1,4,5] The ^{14}N broadband decoupled n.m.r. spectra of the hydrochloride salts were measured at 6.43 MHz and were referenced relative to NH_4Cl in water (δ 0.0).

Molecular Modelling and Charge Allocation.—We have available to us a powerful suite of molecular modelling programs COSMIC (computational and structural manipulation in chemistry), the detailed contents of which have been described by its originators (Vinter *et al.*[6]). The package was run on a VAX 8300 computer using a Sigmex 5000 graphics terminal. The features of the software used by us were (*a*) the molecular-modelling facility, (*b*) the molecular-energy minimisation procedures (500 iterations were used or until the energy change between successive iterations was 0.0001 kcal mol^{-1}), (*c*) the CNDO/INDO program (this is an extensively rewritten version of an earlier program[7]), and (*d*) the addition of atomic charges by the Liverpool method[8–10] (which is a simpler and faster procedure than the CNDO method). The Liverpool method[8–10] is based upon an empirical breakdown of the transmission of charge into one-, two-, and three-bond additive contributions. The one-bond effect is proportional to the difference in electronegativities of the bonded atoms, and the two- and three-bonded effects are functions of the atomic electronegativity and polarizability. Using the derived charge contributions the calculated and observed dipole moments of halogenoalkanes, alcohols, amines, acids, ethers, amides, and amino acids show good agreement.[8–10] The molecular conformations included in the charge calculations were those depicted in structure (**III**).

Results and Discussion

The concept of chemical shift additivity which works so well with acyclic and also aromatic compounds can be extended to alicyclic compounds, but unfortunately a relatively simple and universal set of $\Delta\delta$ values is invariably too general to provide accurate chemical shift predictions for monocyclic and especi-

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† Sodium 3-(trimethylsilyl)tetradeuteriopropionate.

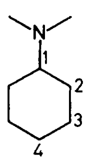
Table 1. ^{13}C Chemical shift differences (Δδ values) for cyclohexylamine derivatives.

	Δδ(ppm)
Ring cyclohexyl carbon	27.3
α-C atom	8.0
β-C atom (through C or N)	8.0
γ-C atom	−1.5
γ-C atom (through N or O)	0.0
C (tertiary)	−3.0
α-N	22.5
α-NH^{+}	28.0
β-N	6.0
β-NH^{+}	6.0
γ-N	−4.0
γ-NH^{+}	−0.3
δ-N	−3.0
δ-NH^{+}	0.0
α-O	43.0
β-O	8.0
γ-O	−5.0
α-Ph	22.1
β-Ph	9.3
α-CN	3.1
β-CN	2.4

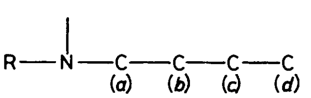
ally polycyclic systems. The reason for this is that each different ring system possesses unique features which lead to different Δδ values for the substituents. One approach to this problem is to use the parent hydrocarbon as a reference to which the effects of substituents, *other* than the ring atoms, are added. This approach has recently been recommended[1] and we have chosen to adopt this method in the present work.

The values of Δδ which have been used to calculate the chemical shifts of the cyclohexyl derivatives are given in Table 1. These are a combination of features from two main sources.[1,11] The values of Δδ for α- and β-carbon atoms are frequently given as different values for simple chemical shift additivity purposes, but we have chosen to make them the same (Table 1) for this work as has been suggested for alicyclic systems.[1]

The assignments and the values of the ^{13}C resonances are given in Table 2, with the numbering of the ring carbon atoms in the conventional manner (I) and those of the *N*-substituents as in structure (II). In Table 2 the calculated and observed chemical shifts are compared and can be seen to be in good agreement. In the majority of cases the agreement is within 2 ppm and is frequently better than this. However, there are some notable exceptions, namely the tertiary bases (entries 2, 9, 11, and 12) and their corresponding hydrochloride salts where for ring carbon atom 2 there is considerable difference between the observed and calculated shifts, the observed resonances being at lower frequency (*i.e.* upfield) on average of about 5.1 ppm for the bases, and an average low frequency (upfield) shift of 3.3 ppm for the salts (*i.e.*, −5.1 and −3.3 Δδ) compared to the calculated values. Since, for such cases, none of the other ring resonances are appreciably affected, the phenomenon is undoubtedly a gauche 'γ-effect' of the second of the two *N*-substituents in the tertiary base (and its salt) on C-2 in the ring, as compared with a secondary base. This effect is due to the perturbation of the electron density on the hydrogen atoms attached to C-2 by the two substituents on the *N*-atom (see structures **III** and **IV**), in the case of the tertiary bases as opposed to the secondary bases. This γ-effect also shows itself to some extent within the second R-substituent side chain at a γ-position relative to the ring C-2 atom. In addition there is a γ-effect within the side chain itself in the case of base (8) and its salt.



(I)



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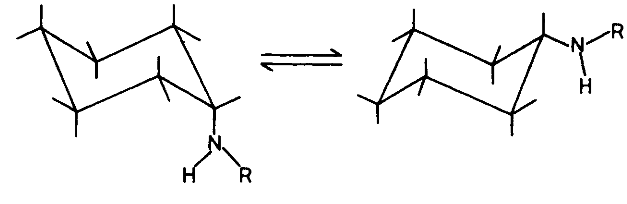
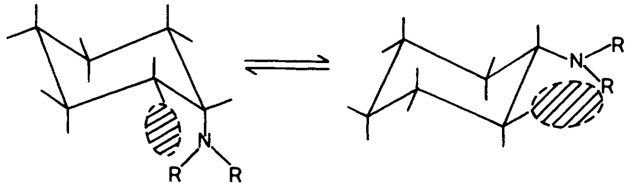


(III)



(IV)

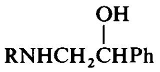
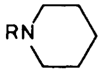
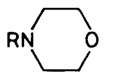
The protonation of the NH$_2$ group of amines frequently causes considerable low frequency (upfield) shifts for the adjacent carbon atoms particularly for the β-position relative to the protonated group.[12,13] The changes in ^{13}C resonances produced by protonation, calculated as $\delta_{salt} - \delta_{base} = \Delta_{sb}$ are given in Table 2. Here it can be seen that the situation is not the same as for acyclic bases, and the average Δ_{sb} values for the ring carbon atoms are given in Table 3 showing high frequency (downfield) shifts for C-1, C-3, and C-4, while for C-2 there is a low frequency shift for the primary and secondary amines. For the tertiary amines, however, protonation produces a high frequency shift for C-2 which, again, is a probable consequence of the γ-effect.

Thus, apart from the γ-effect for the C-2 atoms in the ring of the tertiary amines, the Δδ values given in Table 1 provide a reasonable approach to the calculation of chemical shifts for the *N*-substituted cyclohexylamine derivatives and their salts. If the γ-effect contributions of −5.1 ppm for the amines and −3.3 ppm for the salts are included, as discussed above, then the C-2 chemical shifts of the tertiary bases and their corresponding salts can also be accommodated.

In view of the upsurge in interest in computational chemistry and molecular modelling in recent years[14] it was of interest to us to attempt a correlation of the calculated partial atomic charges, obtained by the CNDO method[6] and the Liverpool method,[8–10] with the observed ^{13}C n.m.r. chemical shifts for the bases and also the salts. It was found that the CNDO method gave small negative charges (*ca.* −0.16 to −0.21) on the N-atoms of the bases with the rest of the negative charge being spread around the H-atoms, leaving the C-atoms positively charged. The protonated amines, *i.e.* the salts, when subjected to CNDO calculations were found to possess a small positive charge on the N-atom (a *change* of charge of *ca.* +0.25) and with the carbon atoms experiencing a small decrease in their positive charge compared to the corresponding amines.

In the case of the Liverpool method calculations for the amines, the charge on the N-atom was rather more negative than in the CNDO calculations (*ca.* −0.3 to −0.4) and the carbon atoms were correspondingly negatively charged with the hydrogen atoms being positively charged. Protonation of the N-atom produced a *change* in its atomic charge of about +0.6.

Table 2. Comparison of observed and calculated ^{13}C n.m.r. chemical shifts for cyclohexylamine derivatives.

Entry	Derivative (R = cyclohexyl)			Carbon atom							
				1	2	3	4	(*a*)	(*b*)	(*c*)	(*d*)
1	RNH_2	base	obs.	48.6	35.2	23.4	24.3				
			calc.	46.8	33.3	23.3	24.3				
		salt	obs.	53.7	33.5	27.0	27.4				
			calc.	52.3	33.3	27.0	27.4				
		$\delta_{salt} - \delta_{base} = \Delta_{sb}$		5.1	−1.7	3.6	3.1				
2	$RN(CH_3)_2$	base	obs.	62.2	27.4	23.8	24.9	39.8			
			calc.	62.8	33.3	23.3	24.3	38.5			
		salt	obs.	68.4	29.2	27.2	27.3	42.2			
			calc.	68.3	33.3	27.0	27.3	44.0			
		Δ_{sb}		6.2	1.8	3.4	2.4	2.4			
3	$RNHCH_2CH_3$	base	obs.	55.5	32.4	23.8	24.9	39.7	14.3		
			calc.	54.8	33.3	23.3	24.3	38.5	14.0		
		salt	obs.	59.7	32.0	27.0	27.7	42.8	14.0		
			calc.	60.3	33.3	27.0	27.3	44.0	14.0		
		Δ_{sb}		4.8	−0.4	3.2	2.8	3.1	−0.3		
4	$RNHCH(CH_3)_2$	base	obs.	52.3	33.1	24.2	25.2	43.5	22.3		
			calc.	54.8	33.3	23.3	24.3	43.5	22.0		
		salt	obs.	56.7	31.9	26.8	27.4	49.6	21.3		
			calc.	60.3	33.3	27.0	27.3	49.0	22.0		
		Δ_{sb}		4.4	−1.2	2.6	2.2	6.1	−1.0		
5	$RNH(CH_2)_2OH$	base	obs.	56.2	32.7	24.5	25.5	47.9	59.9		
			calc.	54.8	33.3	23.3	24.3	46.5	57.0		
		salt	obs.	60.3	31.9	27.1	27.6	49.2	60.1		
			calc.	60.3	33.3	27.0	27.3	52.0	57.0		
		Δ_{sb}		4.1	−0.8	2.6	2.1	1.3	0.2		
6	RNHPh	base	obs.	51.1	32.9	24.6	25.5	147.0	112.8	128.7	116.2
			calc.	56.1	33.3	23.3	24.3	148.5	115.0	129.5	118.5
		salt	obs.	56.2	32.0	26.8	27.4	131.2	126.0	132.9	131.2
			calc.	61.6	33.3	27.0	27.3	—	—	—	—
		Δ_{sb}		4.9	−0.9	2.2	1.9				
7	$RNH(CH_2)_2CN$	base	obs.	54.7	32.3	23.7	24.7	41.1	18.0		
			calc.	54.8	33.3	23.3	24.3	40.9	17.1		
		salt	obs.	60.8	31.9	27.0	27.6	43.2	33.6?		
			calc.	60.3	33.3	27.0	27.3	46.4	17.1		
		Δ_{sb}		6.1	−0.4	3.3	2.9	2.1	15.6		
8	$RNH(CH_2)_3NH_2$	base	obs.	55.2	32.0	23.3	24.6	42.8	32.7	39.0	
			calc.	54.8	33.3	23.3	24.3	42.5	28.0	34.5	
		salt	obs.	60.6	31.9	26.7	27.5	44.5?	27.1	40.0	
			calc.	60.3	33.3	27.0	27.3	52.0	28.0	44.0	
		Δ_{sb}		5.4	−0.1	3.4	2.9	1.7	−5.6	1.0	
9	 $\underset{\substack{\mid \\ CH_3}}{RNR}$	base	obs.	58.5	29.8	25.3	25.5	31.7			
			calc.	62.8	33.3	23.3	24.3	38.5			
		salt	obs.	65.0	32.0	27.4	29.2	34.9			
			calc.	71.3	33.3	27.0	27.3	44.0			
		Δ_{sb}		6.5	2.2	2.1	3.7	3.2			
10	 $RNHCH_2\overset{\substack{OH \\ \mid}}{C}HPh$	base	obs.	54.1	32.8	24.6	25.6	56.4	71.5		
			calc.	54.8	33.3	23.3	24.3	57.8	76.1		
		salt	obs.	61.1	32.0	27.3	27.6	63.5	72.3		
			calc.	60.3	33.3	27.0	27.3	63.3	76.1		
		Δ_{sb}		7.0	−0.8	2.6	2.0	7.1	0.8		
11		base	obs.	63.5	28.0	25.4	25.7	49.3	25.9	24.2	
			calc.	62.8	33.3	23.3	24.3	45.0	28.5	28.0	
		salt	obs.	68.8	29.4	27.3	27.3	52.7	27.6	24.5	
			calc.	68.3	33.3	27.0	27.3	50.5	28.5	32.0	
		Δ_{sb}		5.3	1.4	1.9	1.6	3.4	1.7	0.3	
12		base	obs.	62.5	27.8	24.6	25.3	48.6	66.1		
			calc.	62.8	33.3	23.3	24.3	46.5	65.0		
		salt	obs.	69.0	29.4	27.3	27.3	51.6	66.9		
			calc.	68.3	33.3	27.0	27.3	52.0	65.0		
		Δ_{sb}		6.5	1.6	2.7	2.0	3.0	0.8		

The various methods of allocation of partial atomic charges are well known to produce different values of charge. However, this in itself is not too important in many situations. What is crucial for their credibility is that the *trend* of charges within a given molecule follows the same direction for the various methods of calculation. This is the case for the partial charges obtained here by the CNDO and Liverpool methods. Although the signs of the charges on the carbon atoms are different, the trends for the various atoms within a given molecule parallel one another.

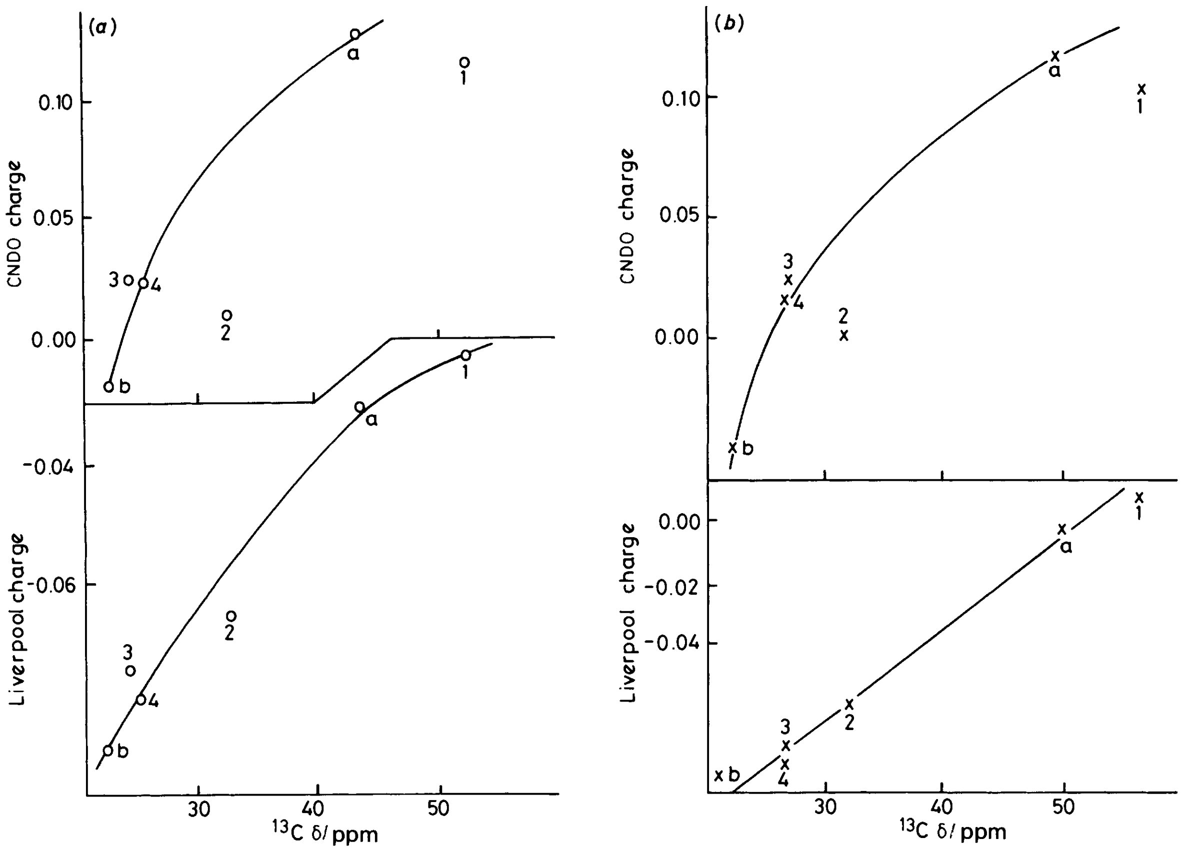


Figure 1. Atomic charge–chemical shift correlations for $RNHCH(CH_3)_2$, (*a*) base; (*b*) salt. The numbering and lettering of the points represent specific carbon atoms—see structures (I) and (II) in the text.

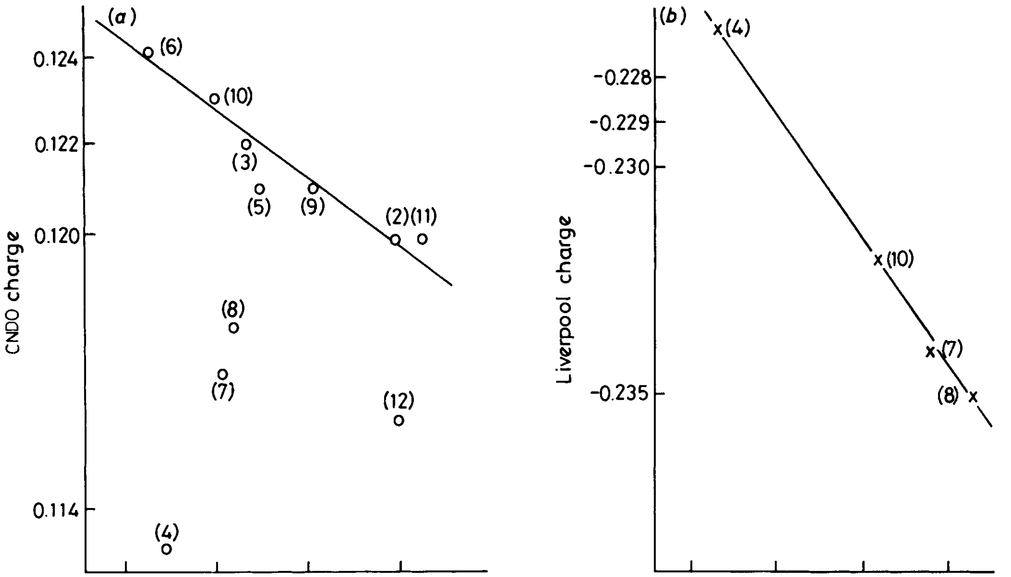


Figure 2. Correlation of charge on C-1 with chemical shift, (*a*) CNDO charges; (*b*) Liverpool charges. The numbered points represent particular compounds—see the Experimental section.

Plotted in Figure 1 are the ^{13}C n.m.r. data against the corresponding CNDO and Liverpool charges for *N*-isopropylcyclohexylamine and its hydrochloride salt. These graphs were entirely typical for the whole range of compounds studied. It can be seen that there is a correlation for both sets of calculations with the correlation being equally good for the Liverpool method of charge allocation, for which the computing time is considerably less than for the CNDO calculations.

A rather more rigorous test of the consistency of the partial charge calculations is to consider the whole range of compounds. The most profound effect of the *N*-substituent is felt at C-1 in the cyclohexane ring [and at C-(*a*) in the substituent itself].

Table 3. Effects of protonation on ^{13}C n.m.r. chemical shifts in cyclohexylamine-ring average Δ_{sb} values.

	Carbon atom			
	1	2	3	4
Δ_{sb} for primary amine	5.1	−1.7	3.6	3.1
Δ_{sb} for secondary amine	5.2	−0.7	2.8	2.4
Δ_{sb} for tertiary amine	6.1	1.9	2.5	2.4

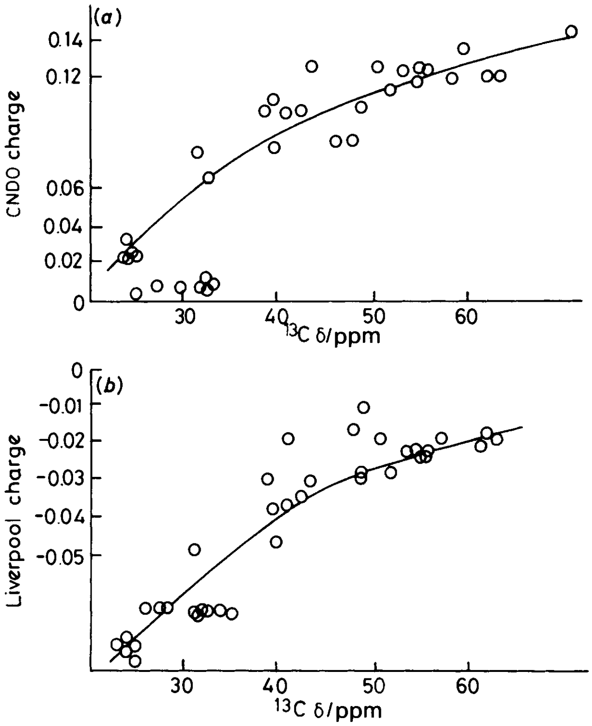


Figure 3. Charge *versus* chemical shift correlation for all C atoms in bases, (*a*) CNDO charges; (*b*) Liverpool charges.

Figure 2 shows the correlations for the CNDO and Liverpool charge allocations for C-1 as a function of ^{13}C chemical shift. Some of the points correlate quite reasonably, but others are widely off the correlation and it is not clear why this is.

Over a wider range one can of course consider *all* of the ^{13}C n.m.r. shifts for all of the carbon atoms of the whole series of compounds and the corresponding charge allocations. This will of course involve uncertainties due to the γ-effects which are not accommodated in the charge calculations. Figure 3 shows such plots for all the bases and, although there is a considerable spread of points and many points which have coincidental positions which are not represented, it can be seen that there is an overall trend. An extremely similar pair of graphs was obtained for the salts but is not presented here. Once again the Liverpool method of charge allocation does remarkably well in spite of its simplicity.

The calculated charges on the N-atom of the hydrochloride salts of the amines as a function of the ^{14}N chemical shifts are plotted in Figure 4. The data appear to fall into two distinct sets, namely those for the secondary amine salts and those for the tertiary amine salts. However, while the CNDO calculations do show a trend with the ^{14}N chemical shifts, the corresponding N-atom charges calculated by the Liverpool method are strangely relatively insensitive to the *N*-substituent.

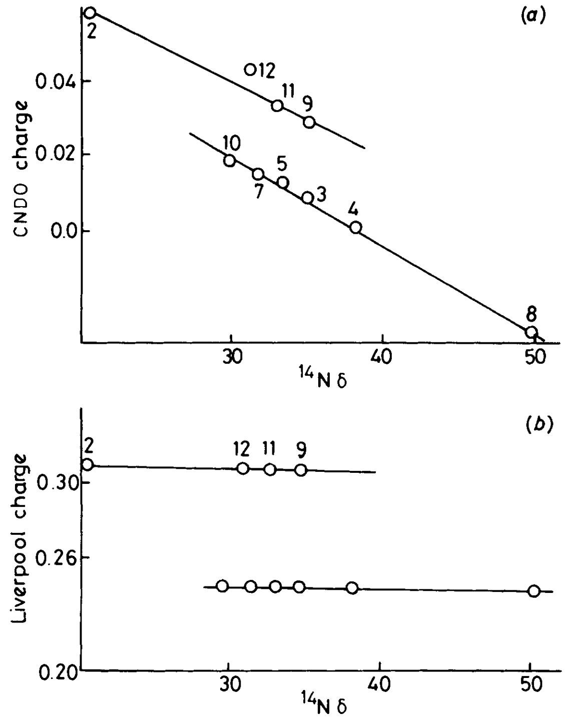


Figure 4. Charge *versus* chemical shift correlations (^{14}N) for salts, (*a*) CNDO charges; (*b*) Liverpool charges.

Acknowledgements

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References

1 J. K. Whitesell and M. A. Minton, 'Stereochemical Analysis of Alicyclic Compounds by C-13 NMR,' Chapman and Hall, London, New York, 1987.
2 Sadtler Standard Carbon-13 NMR Spectra, Sadtler Research Laboratories, Philadelphia, 1976–1982.
3 J. H. Schneider, N. Nguyen-ba, and F. Thomas, *Tetrahedron*, 1982, **38**, 2327.
4 L. F. Johnson and W. C. Janowski, 'C-13 NMR Spectra,' Wiley, London, New York, 1972.
5 T. Pehk and E. Lippmann, *Org. Magn. Reson.*, 1971, **3**, 679.
6 J. G. Vinter, A. Davis, and M. R. Saunders, *Journal of Computer-Aided Molecular Design*, 1987, **1**, 31.
7 J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory,' Mcgraw-Hill, New York, 1970.
8 R. J. Abraham, L. Griffiths, and P. J. Loftus, *J. Comput. Chem.*, 1982, **3**, 407.
9 R. J. Abraham and B. D. Hudson, *J. Comput. Chem.*, 1984, **5**, 562.
10 R. J. Abraham and B. D. Hudson, *J. Comput. Chem.*, 1985, **6**, 173.
11 H. Gunther, 'NMR Spectroscopy,' Wiley, Chichester, New York, 1980.
12 E. Breitmaier and W. Voelter, ^{13}C NMR Spectroscopy, 2nd edn., Verlag Chemie, Weinheim, New York, 1978.
13 J. G. Batchelor, J. H. Prestgard, R. J. Cushley, and S. R. Lipsky, *J. Am. Chem. Soc.*, 1973, **95**, 6358; J. G. Batchelor, J. Feeny, and G. C. K. Roberts, *J. Magn. Reson.*, 1975, **20**, 19; J. G. Batchelor, *J. Am. Chem. Soc.*, 1975, **97**, 3410.
14 See for example: 'Molecular Electronic Calculations—Methods and Applications,' Faraday Symposia of the Chemical Society, No. 19, 1984; J. Sadlej, 'Semi-Empirical Methods of Quantum Chemistry,'

translated by I. L. Cooper, Ellis-Horwood, Chichester, 1985; T. Clark, *Handbook of Computational Chemistry*, Wiley, New York, Chichester, Brisbane, Toronto, Singapore, 1985; J. G. Vinter, Molecular Modelling Systems, in 'Molecular Graphics and Drug Design,' eds. A. S. V. Burgen, G. C. K. Roberts, and M. S. Tute, Elsevier, Amsterdam, New York, Oxford, 1986.

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