Carbon-13 Nuclear Magnetic Resonance Studies of Piperidine and Piperazine Compounds. Part I. Empirical Substituent Parameters for *C*-Methyl and *N*-Methyl Groups

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The carbon-13 chemical shifts of a number of piperidine and piperazine compounds have been measured. Substituent parameters have been derived, for methyl groups bonded to carbon and nitrogen, from the symmetrically substituted compounds and used to predict results for unsymmetrical compounds in good agreement with experimental values.

The carbon-13 magnetic resonance spectra of a number of methylcyclohexanes have been studied and analysed in terms of methyl substituent parameters derived for the molecules in their known steric conformations.[1] The completeness of that work was made possible because of the extensive thermodynamic data available for the methylcyclohexanes relating to their conformational barriers.

The emphasis in this paper has been placed on substituted piperidines and piperazine molecules for which thermodynamic data available is limited.[2,3] Previous studies have been restricted to proton resonance [2,4,5] and conformational studies have been mainly concerned with determining, qualitatively, the predominant conformer. The carbon-13 chemical shifts measured are weighted averages because of the rapid ring inversion involving a chair–chair equilibrium in most cases. Nitrogen inversion has been shown to be very rapid for those cases where the *N*-substituents are H, Me, Et, and Pr^i.[5]

The change in chemical shifts in going from one compound to another can be ascribed mainly to differences in charge polarisation [6] and steric interactions [1] if it is assumed that the conformational equilibrium is not drastically changed between molecules with methyl substituents at different positions in the ring. Substituent parameters have been used, successfully, to describe the effect of methyl groups in cyclohexanes [1] and similar parameters have been derived here. These parameters have been applied in predictions of carbon-13 chemical shifts in the less symmetrical molecules studied and the agreement with the experimental data has proved good in all cases except those where large steric interactions between substituent groups are expected.

RESULTS

The carbon-13 chemical shift data for the compounds studied are shown in Tables 1 and 2. Correlations of the assignments made in related molecules are shown schematically in Figures 1 and 2. The empirical substituent parameters are listed in Table 3. Δ_O^α Indicates the chemical shift of a carbon directly bonded (α) to a methyl group relative to the corresponding carbon nucleus in piperidine or piperazine. Δ_N^β Is the substituent parameter predicting the effect of a methyl group directly bonded to nitrogen on a carbon nucleus also bonded to nitrogen (other than the methyl carbon). Δ_N^δ Predicts the effect of the *N*-Me substituent on carbon nucleus three bonds removed from the nitrogen (Me–N–C$^\beta$–C$^\gamma$–C$^\delta$). The chemical shifts predicted using the substituent parameters are compared with the experimental results in Table 4.

Assignment of Experimentally Observed Lines.—The experimentally observed lines have been assigned to the carbon atoms in each molecule on the basis of: (*a*) relative intensities,[1] (*b*) chemical inductive effects,[7] (*c*) empirical parameters (this work), and (*d*) off-resonance experiments.[8]

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[1] D. K. Palling and D. M. Grant, *J. Amer. Chem. Soc.*, 1967, **89**, 6612.

[2] R. G. Lett, L. Petrakis, A. F. Ellis, and R. K. Jensen, *J. Phys. Chem.*, 1970, **74**, 2816.

[3] R. K. Harris and R. A. Spragg, *J. Chem. Soc.* (*B*), 1968, 684; M. L. Stien, G. Chiurdazlin, R. Ottinger, J. Reisse, and H. Christol, *Tetrahedron*, 1971, **27**, 411.

[4] H. Booth, *Progr. N.M.R. Spectroscopy*, 1969, **5**, 54, and references therein.

[5] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 1222; R. A. Y. Jones, A. R. Katritzky, A. C. Richards, R. J. Wyatt, R. J. Bishop, and L. E. Sutton, *J. Chem. Soc.* (*B*), 1970, 127.

[6] B. V. Cheney and D. M. Grant, *J. Amer. Chem. Soc.*, 1967, **89**, 5319.

[7] J. B. Stothers, *Quart. Rev.*, 1965, **19**, 144.

[8] E. G. Paul and D. M. Grant, *J. Amer. Chem. Soc.*, 1964, **86**, 2977.

TABLE 1

Piperidine carbon-13 chemical shifts * (p.p.m. from cyclohexane) †

Piperidines	C-2	C-3	C-4	C-5	C-6	Me	Other
Piperidine	−20·4	−0·4	1·6	−0·4	−20·4	—	
2-Methyl	−25·5	−8·0	1·7	0·5	−20·4	4·0	
3-Methyl	−27·1	−7·2	−5·2	0·0	−19·9	7·4	
N-Methyl	−29·5	0·9	2·9	0·9	−29·5	−19·6	
2,6-Dimethyl	−25·5	−7·4	1·8	−7·4	−25·5	3·76	
4-Methyl	−20·0	−8·9	−4·8	−8·9	−20·0	4·3	
4-Hydroxy-*N*-methyl	−26·5	−7·5	−3·9	−7·5	−26·5	−19·5	
2,2,6,6-Tetramethyl	−22·4	−11·6	8·5	−11·6	−22·4	−5·2	
2-Ethyl	−31·8	−5·9	1·5	0	−21·3	16·7	−3·5
N-Ethyl	−27·4	0·7	2·1	0·7	−27·4	14·6	−26·0 [a]
N-(2-Hydroxyethyl)	−28·0	+1·1	+2·4	+1·1	−28·0	C-8 −34·6	C-7 −31·6
1,2-Dimethyl	−32·3	−7·9	+2·1	+0·6	−30·0	*N*-Me 15·9	*C*-Me +6·8

* Neat liquid with cyclohexane internal reference (~10%) at 21 °C. † Error ±0·2 p.p.m., 27·5 p.p.m. downfield from TMS.

[a] Ethyl methylene (C-7) signal.

TABLE 2

Piperazine carbon-13 chemical shifts (p.p.m. from cyclohexane)

Piperazines	C-2	C-3	C-5	C-6	C-Me	1-Me	4-Me
Piperazine	−20·4	−20·4	−20·4	−20·4			
2-Methyl	−24·9	−27·0	−20·5 −19·5		6·9		
N-Methyl	−29·5	−19·4	−19·4	−29·5	−20·0		
2,5-Dimethyl	−24·2	−28·0	−24·2	−28·0	7·3		
2,6-Dimethyl	−26·4	−25·3	−25·3	−26·4	7·0		
1,2,4-Trimethyl	−36·0	−30·4	−28·5 −28·8		9·7	−15·4	−18·9
N-(2-Hydroxyethyl)	−28·0	−18·9	−18·9	−28·0		−34·5(C-8)	−31·5(C-7) [a]
NN'-Dimethyl	−28·2	−28·2	−28·2	−28·2			

[a] C-7 is the carbon bonded to nitrogen.

It has been found that, as the decoupling power was reduced, lines in the spectrum broadened at different rates and provided a useful initial pointer to the assignments made. The methylene carbon signals (CH_2) broadened more rapidly than those of the methine carbons ($-CH=$) in 2-methylpiperazine and 1,2,4-trimethylpiperazine.

Symmetrical Piperidines.—The empirical parameters have been derived from symmetrical piperidines where there was no ambiguity in assignment. The signals arising from the carbon nuclei in 4-methyl-, *N*-methyl-, and 2,6-dimethyl-piperidines were unambiguously assigned by taking account of the relative intensities arising from the symmetry the molecules possess. 4-Hydroxy-*N*-methylpiperidine presented a slight anomaly in that the 2 and 6 carbon nuclei signals appeared upfield relative to *N*-methylpiperidine by 3 p.p.m. It has been claimed that no intramolecular H-bonding occurs in 4-hydroxy-*N*-methylpiperidine and that therefore the boat form is unlikely.[9] However a contribution from the boat conformation would influence the chemical shifts although, *a priori*, it is not possible to assess the quantitative effect of such a contribution.

The lowest field signal in *N*-(2-hydroxyethyl)piperidine has been assigned to the carbon bonded to oxygen.[7] The carbon nucleus labelled 7 appeared at lower field than the 2 and 6 carbon nuclei because of its proximity to the oxygen atom which exerts an inductive effect manifested as a 5·6 p.p.m. downfield chemical shift.

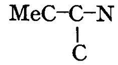
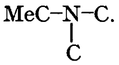
The methyl group carbons of *N*-ethyl- and 2-ethylpiperidines have been assigned to high-field signals at 14·6 and 16·7 p.p.m. respectively from cyclohexane. This difference reflects the distinction between the methyl carbon in  $MeC{-}\underset{|\atop C}{C}{-}N$ and  $MeC{-}\underset{|\atop C}{N}{-}C$. It can be broken down into two parts, the first inductive and the second steric (1,4-effect), but it is not possible to separate these effects with the existing data. A study of molecular models indicated that 2,2,6,6-tetramethylpiperidine is distorted because of steric interaction between methyl

TABLE 3

Empirical shift parameters (in p.p.m.) for *C*-methyl and *N*-methyl groups

(*a*)	* 4-Methylpiperidine	C-4	$\Delta_{C}{}^{\alpha} = -6{\cdot}4$
		C-3 and C-5	$\Delta_{C}{}^{\beta} = -8{\cdot}5$
		C-2 and C-6	$\Delta_{C}{}^{\gamma} = +0{\cdot}4$
(*b*)	* *N*-Methylpiperidine	C-2 and C-6	$\Delta_{N}{}^{\beta} = -9{\cdot}1$
		C-3 and C-5	$\Delta_{N}{}^{\gamma} = +1{\cdot}3$
		C-4	$\Delta_{N}{}^{\delta} = +1{\cdot}2$

(*c*) * 2,6-Dimethylpiperidine—use of parameters.

	Predicted	Observed
C-2 and C-6	$\Delta_{C}{}^{\alpha} + \Delta_{C}{}^{\gamma} = -6{\cdot}0$	−5·5
C-3 and C-5	$\Delta_{C}{}^{\beta} + \Delta_{C}{}^{\delta} = -8{\cdot}1$	−7·0
C-4	$\Delta_{C}{}^{\gamma} + \Delta_{C}{}^{\gamma} = 0{\cdot}8$	+0·2

(*d*) 2-Ethylpiperidine.

C-7 $\delta\nu(N\text{-}CH_2{-}) - \delta\nu(N\text{-Me}) = -6{\cdot}4$

Predicted	Observed
$\delta\nu$(*C*-Me in 2 Me-piperidine) $4{\cdot}0 + (-6{\cdot}4) = -2{\cdot}4$	−3·5

C-3 $\Delta_{N\cdot Et}{}^{\beta} - \Delta_{N\cdot Me}{}^{\beta} = +2{\cdot}1$

Predicted	Observed
$-8{\cdot}0 + 2{\cdot}1 = -5{\cdot}9$	−5·9

* With respect to piperidine.

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[9] R. E. Lyle, *J. Org. Chem.*, 1957, **22**, 1280.

groups.[10] The apparent C_{2v} symmetry suggested by the observed spectrum indicated further that ring ' motion ' averages the environments of the four methyl group carbons to give a single resonance line. This line appeared at much lower field relative to 2,6-dimethylpiperidine unlike the upfield shift of the geminal methyl carbons in 1,1-dimethylcyclohexane.[1] This result reflects the methyl group interactions across the ring.[10]

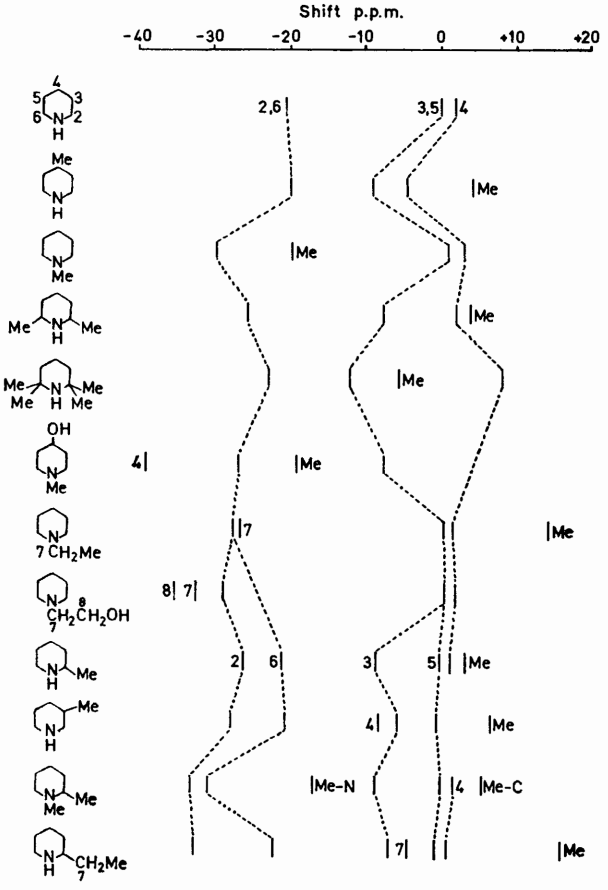

FIGURE 1 Piperidine ^{13}C chemical shifts in p.p.m. from cyclohexane

Unsymmetrical Piperidines.—The unsymmetrical piperidines studied presented the greatest difficulty in assignment. The ambiguity has been resolved where possible using off-resonance experimental data and undecoupled spectral data accumulated using a computer.[11] Such data has allowed the clear distinction between the methine and methylene carbon nuclei of the ring but does not not distinguish between carbons 4 and 5 of 2-methylpiperidine, for example. The empirical substituent parameters have been used in such cases and the agreement in general was good, as shown in Table 4. Some doubt must still exist however in, for example, the distinction between carbons 4 and 5 of 2-methylpiperidine where a reversal of the assignment still leaves predicted and observed values within 2·2 p.p.m. of one another. The maximum difference (2·2 p.p.m.) between observed and predicted values occurs in 3-methylpiperidine for the 4 carbon nucleus but there ambiguity has been resolved by the off-resonance experiments.

The spectrum of 2-ethylpiperidine was particularly difficult to interpret because of the limited data available for cross-referencing. The assignments made have been based on direct comparisons with other molecules with the emphasis on 2-methylpiperidine. The distinction between carbons 3 and 7 has been made using a comparison between methyl and *N*-methylene shifts of *N*-methyl- and *N*-ethylpiperidines respectively (*N*-Me of *N*-methylpiperidine 19·6 p.p.m.; *N*-CH_2 of *N*-ethylpiperidine 26·0 p.p.m.).

The difference of $-6·4$ p.p.m. ($CH_3 - CH_2$) was used to predict the position of the ethyl methylene carbon resonance of 2-ethylpiperidine from 2-methylpiperidine [Me of 2-methylpiperidine $+4·0$ p.p.m.; (Et)CH_2 of 2-ethylpiperidine $+4·00 - 6·4 = -2·4$].

The observed line at $-3·5$ p.p.m. has been assigned to the ethyl methylene carbon nucleus and that at $-5·9$ p.p.m. to carbon 3 of the ring. The overall similarity between the ring carbon chemical shifts for 2-methyl- and 2-ethylpiperidines suggests that ethyl substituent parameters exist which are similar to the methyl parameters with the exception of the directly bonded carbon. A similar effect has been observed in ethylbenzene as compared with toluene.[12]

Symmetrical Piperazines.—The assignments for piperazine, and *NN'*-dimethylpiperazine were straightforward. The 2 and 6 carbon signals of *N*-methylpiperazine were observed at lower field than the 3 and 5 carbon signals as predicted using the Δ_N^{β} and Δ_N^{γ} parameters. An exact correspondence was observed between the chemical

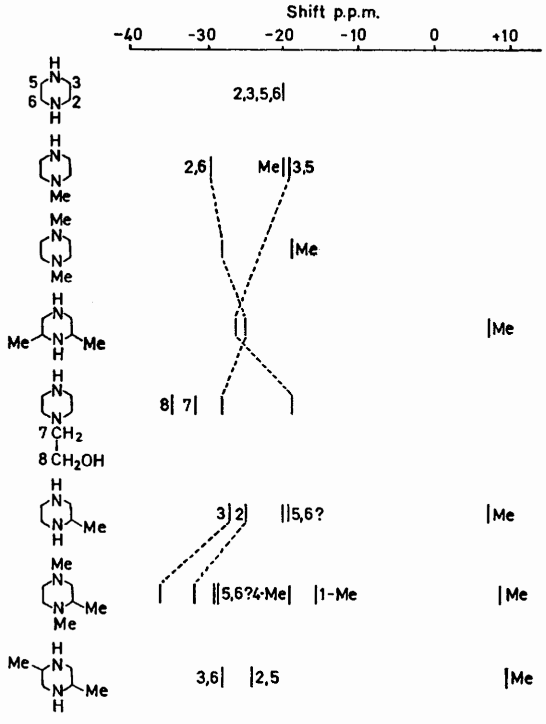

FIGURE 2 Piperazine ^{13}C chemical shifts in p.p.m. from cyclohexane

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[10] N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.*, 1961, **83**, 2145.

[11] R. G. Jones, P. Partington, B. W. Ready, and T. Trill, *J. Phys* (*E*), in the press.

[12] R. G. Jones and P. Partington, unpublished results.

TABLE 4

C-13 Chemical shifts from observed spectra compared with values calculated by empirical parameters, in piperidines and piperazines

Piperidines		C-2	C-3	C-4	C-5	C-6	C-7
2-Methyl	Predicted	−26·8	−9·0	+2·0	−0·4	−20·0	
	Observed	−25·5	−8·0	+1·7	+0·5	−20·4	
3-Methyl	Predicted	−28·9	−9·0	−7·4	0·0	−20·4	
	Observed	−27·1	−7·2	−5·2	0·0	−19·9	
1,2-Dimethyl	Predicted	−35·9	−7·7	+3·2	+0·9	−29·1	
	Observed	−32·3	−7·9	+2·2	+0·6	−30·0	
2,6-Dimethyl	Predicted	−26·4	−7·2	+3·8	−7·2	−26·4	
	Observed	−25·5	−7·4	+1·8	−7·4	−25·5	
2,2,6,6-Tetramethyl *	Predicted	−32·4	−17·4	+3·2	−17·4	−32·4	
	Observed	−22·4	−11·6	+8·5	−11·6	−22·4	
2-Ethyl †	Predicted		−5·9				−2·4
	Observed	−31·8	−5·9	+1·5	0·0	−21·3	−3·5

Piperazines		C-2	C-3	C-5	C-6
2,5-Dimethyl	Predicted	−26·8	−28·4	−26·8	−28·4
	Observed	−24·2	−28·0	−24·2	−28·0
2-Methyl	Predicted	−26·8	−28·9	−20·4	−20·0
	Observed	−24·9	−27·0	−20·5	−19·5
2,6-Dimethyl	Predicted	−26·4	−28·9	−28·9	−26·4
	Observed	−25·3	−26·4	−26·4	−25·3
1,2,4-Trimethyl	Predicted	−34·2	−36·7	−27·2	−27·8
	Observed	−30·4	−36·0	−28·5 −28·8	

* Distortion of ring expected due to large steric interactions by the methyl groups. † Insufficient data on ethyl derivatives for meaningful predictions.

shifts of 2, 6, 7, and 8 carbons of *N*-(2-hydroxyethyl)-piperidine and -piperazine, making the remaining assignment of 3 and 5 carbon signals in the piperazine compound trivial. The 2,6 and 3,5 carbons of 2,6-dimethylpiperazine gave rise to two observed lines close together at 25·3 and 26·4 p.p.m. from cyclohexane. The empirical parameters have been used to predict the results and off-resonance experiments used to confirm the assignment.

Three lines were observed in the spectrum of 2,5-dimethylpiperazine although the compound was supplied as a mixture of *cis*- and *trans*-isomers. The empirical parameters predicted that the line at lowest field arose from the 3 and 6 carbon atoms and the signal at highest field was assigned to the methyl carbon nuclei.

Unsymmetrical Piperazines.—An attempt has been made to assign the observed lines in the spectrum of 2-methylpiperazine using the empirical substituent parameters. The agreement is reasonable for the 2 and 3 carbon nuclei but the 5 and 6 lines are close together so that it is not possible to distinguish between them.

The chemical shifts predicted for 1,2,4-trimethylpiperazine agree reasonably closely with the observed shifts except for the 2 carbon and as above it is not possible to distinguish between carbons 5 and 6. The poor agreement in the case of the 2 carbon probably arises from the steric interaction of the methyl directly bonded to carbon 2 and the other two methyl groups in the molecule.

CONCLUSIONS

Empirical substituent parameters derived from *N*-methyl-, 4-methyl-, and 2,6-dimethyl-piperidine molecules provide a reasonably consistent basis for the prediction of carbon-13 chemical shifts in piperidine compounds provided that conformational equilibrium is not seriously distorted by steric crowding. Application of these results to piperazine molecules does give fair agreement again in the non-strained cases but it is considered inadvisable to stretch the predictions too far. It is expected that an improved set of parameters would result from a more extensive knowledge of the thermodynamic parameters for these molecules. Clearly, carbon-13 magnetic resonance has been shown yet again to be a very useful tool in studying stereochemical effects.

EXPERIMENTAL

The carbon-13 chemical-shift data have been measured from single-scan spectra of the neat liquids in 8 mm-sample tubes using the JEOL C60HL high-resolution n.m.r. spectrometer operating in a field–frequency sweep mode and employing noise modulated irradiation for decoupling the protons. A small amount of cyclohexane (up to 10%) was added as internal reference. Experiments carried out to check for solvent dependence showed that the addition of cyclohexane did not change the internal chemical shifts. A computer[11] was used for accumulating the spectra in off-resonance experiments when necessary.

The compounds were used as supplied by the manufacturer, without further purification. Some of the compounds which were solids were heated above their melting point in the probe.

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