Carbon-13 Nuclear Magnetic Resonance Studies of Piperidine and Piperazine Compounds. Part II.† Empirical Substituent Parameters for, and the Shielding Anisotropy of, the *N*-Nitroso-group

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The carbon-13 chemical shifts have been measured for a number of substituted nitroso-piperidines and -piperazines. Complete assignments have been made and substituent parameters derived which allow reasonably accurate prediction of the chemical shifts in the molecules studied. The theories available for calculating the effect of the electric field, generated by the presence of the polar NO group, on the chemical shifts have been applied in a critical way for these molecules. The possibility of alternative formulations of electric field effects has been suggested and the limitations of studying small numbers of molecules in this respect assessed.

THE effect of the shielding anisotropy of the nitroso-group upon proton chemical shifts has been the subject of recent papers.[1,2] It has been shown that proximate protons (within two bonds removed from the nitroso-group) *cis* to the nitroso-group are shielded and the *trans*-protons are deshielded in *N*-nitroso-dialkylamines, and any ambiguity can be clearly resolved using the methyl proton intensities to distinguish between possible geometric isomers.[3] A more detailed study of *N*-nitroso-piperidines and -piperazines has devoted much attention to the effect of the nitroso-group on the shielding constant of the protons and concluded that the calculations made were of limited use because of difficulty in finding an appropriate dipole model applicable to protons near to, and further removed from, the nitroso-group.[2] A further paper has emphasised the importance of the electric field of the carbonyl group in *NN*-disubstituted amides upon carbon-13 chemical shifts.[4] The electric field has also been suggested to be important for carbon nuclei proximate to a nitroso-group.[5]

We have undertaken a study of the carbon-13 chemical shift of *N*-nitroso-piperidines and -piperazines as a natural extension of the work which has been completed on the parent amines.[6] Further to the additive substituent parameters found for the *C*-methyl and *N*-methyl substituents [6] we have found that similar additive parameters can be used to predict the anisotropic shielding effects of the nitroso-group.

The agreement between the predicted and observed chemical shifts is generally good in strain-free molecules and provides some encouragment to look again at the problem of calculating the effects of magnetic anisotropy and electric field anisotropy of the nitroso-group in these molecules.

EXPERIMENTAL

The majority of chemical shifts were measured using a JEOL C60HL n.m.r. spectrometer operated at 15·08 MHz. The samples were contained in 8 mm o.d. n.m.r. tubes with small amounts of cyclohexane added as an internal reference. Many of the compounds studied were liquids but some were solid and those were dissolved in a minimum of chloroform. The magnetic field stability was maintained by an external lock using a water sample and, where necessary, spectrum accumulation was used to improve the signal : noise ratio employing a PDP8/I computer interfaced to the C60HL.[7] The carbon–proton coupling was eliminated by broad band irradiation of the protons in a field–frequency sweep experiment.

The spectra of the most difficult samples, which were mixtures of isomers, were obtained from the S.R.C. Fourier transform n.m.r. service.

RESULTS AND DISCUSSION

Assignment of the Carbon-13 Resonance Lines.—The assignments summarised in Table 1 were more obvious in some cases than others because the spectral lines were distinctly resolved and readily correlated with those of the parent amine. The distinction between carbon nuclei *cis* and *trans* to the nitroso-group was made assuming that the shielding anisotropy evaluated from proton studies [1] can be extended at least qualitatively to the carbon nucleus. The electric field effect may be expected to differ for carbon nuclei and protons because of the quite different paramagnetic contributions to the respective shielding constants.

Initial assignments made for *N*-nitroso- and *N*-nitroso-4-methyl-piperidine provided the basis for evaluation of piperidine nitroso-group substituent parameters which are shown in Table 2. Subsequent application of the substituent parameters in predicting the chemical shifts proved to be reasonably successful as shown in the Figure. The results shown were obtained by invoking the substituent parameters for methyl groups obtained from the parent amines except where the methyl group was *cis* to the NO group. In the latter case the parent amine conformation predominantly involves equatorial methyl groups. The *cis*-isomer of the *N*-nitroso-compound however adopts a configuration where the methyl group is axially oriented because of large steric interactions between the nitroso and the methyl group.[1] It was therefore necessary to use axial methyl substituent

† Part I, ref. 6.

[1] R. K. Harris and R. A. Spragg, *J. Mol. Spectroscopy*, 1967, **23**, 158.
[2] R. K. Harris and R. A. Spragg, *J. Mol. Spectroscopy*, 1969, **30**, 77.
[3] H. W. Brown and D. P. Hollis, *J. Mol. Spectroscopy*, 1964, **13**, 305.
[4] W. McFarlane, *Chem. Comm.*, 1970, 418.
[5] D. S. Pregosin and E. W. Randall, *Chem. Comm.*, 1971, 399.
[6] G. Ellis and R. G. Jones, *J.C.S. Perkin II*, 1972, 437.
[7] R. G. Jones, P. Partington, B. W. Ready, and T. Trill, *J. Phys. E Sci. Instruments*, 1972, **5**, 45.

TABLE 1

Carbon-13 chemical shifts of *N*-nitroso-piperidines and -piperazines †

N-Nitrosopiperidines	Orientation of NO group relative to C-2	Carbon nucleus 2	3	4	5	6	Me	Others
Piperidine	*cis*	39·0	25·5	24·7	27·2	50·8		
2-Methyl	*cis*	43·2	28·2	19·8	26·8	47·0	15·1	
	trans	56·6	33·7	25·6	22·0	37·7	18·6	
3-Methyl	*cis*	45·9	31·5	32·9	26·2	50·2	18·8	
	trans	56·8	33·1	32·9	24·5	39·5	19·1	
4-Methyl	*cis*	38·9	33·4	31·4	35·2	50·1	19·9	
syn-2,6-Dimethyl	*cis*	43·8	30·7	22·5	29·8	54·5	15·6 (*cis*) 18·7 (*trans*)	
Piperazines								
1,4-Dinitroso-	*cis,cis*	38·8	38·8		49·7	49·7		
	cis,trans	43·0	46·7		43·0	46·7		
1-Nitroso-4-(β-hydroxyethyl)-	*cis*	40·0	52·5		53·9	49·9		59·2 (α-CH_2) 60·0 (β-CH_2)
1-Nitroso-4-methyl-	*cis*	39·8	54·1		55·7	49·8	46·1	
2,6-dimethyl-1,4-dinitroso- *	*cis,cis*	42·7	45·1		53·7	51·4		
	cis,trans	46·4	52·1		48·0	51·3		

* Methyl groups equatorial. † P.p.m. to low field from tetramethylsilane.

parameters to predict the chemical shifts in *cis*-*N*-nitroso-2-methylpiperidine derivatives. The parameters derived by Dalling and Grant [8] provided better agreement than those given by Booth.[9]

TABLE 2

Substituent parameters (p.p.m.)

N-Nitroso- (I) and *N*-nitroso-4-methyl-piperidines (II) *

	(I)	(II)	Mean value †
α_{cis}	−8·6,	−8·9	−8·8
β_{cis}	−2·4,	−3·0	−2·7
α_{trans}	2·6,	2·9	2·8
β_{trans}	−0·7,	−1·0	−0·9
γ	−1·2,	−0·9	−1·1

1-Nitroso-4-methyl- (III) and 1-nitroso-4-(β-hydroxyethyl)-piperazines (IV) *

	(III)	(IV)	Mean value
α_{cis}	−7·1,	−6·9	−7·0
β_{cis}	−2·9,	−3·0	−3·0
α_{trans}	2·9,	3·0	3·0
β_{trans}	−1·3,	−1·6	−1·5
δ	−1·4,	0	−0·7

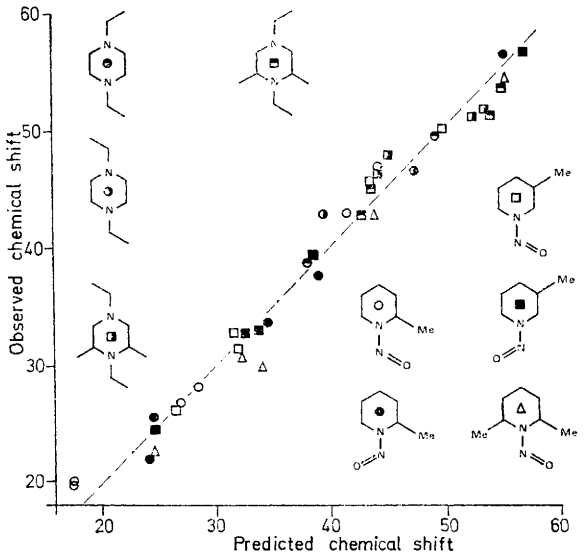
Booth's axial parameters

α_{axial}	+2·2
β	+4·8
γ	−6·2

* Derivatives used to calculate the parameters. † Negative value implies shielding effect.

The replacement of the C-4 in piperidine by the azomethine group and consequent change in bond lengths have an effect on the conformational equilibria of six-membered rings by changing the 1,3-diaxial interaction for methyl groups β to the second nitrogen. These effects are evident in the *N*-nitroso-substituent parameters derived from 1-nitroso-4-methyl- and 1-nitroso-4-(β-hydroxyethyl)-piperazine (Table 2). The mean of parameter values shown have been used to predict the chemical shifts for the other nitrosopiperazines (see Figure).

The *C*-methyl substituted compounds provided major problems in assignment because of isomerism. These were resolved using relative intensities and predictions of the chemical shifts relative to piperazine. It was found, for example, that the equatorial methyl substituent parameters generated predicted results in better agreement with the observed shifts than the axial parameters in *NN'*-dinitroso-2,6-dimethylpiperazine. A comparison of the methyl carbon chemical shift (15·1 p.p.m. from tetramethylsilane) in *cis*-2-methyl-*N*-nitroso-piperidine (unequivocally axial) with the corresponding carbon-13 shift (17·2 p.p.m.) in *cis,cis*-1,4-dinitroso-2,6-dimethylpiperazine suggests also that the contribution of an equatorial or some pseudo-equatorial configuration is significant.



Plot of observed against calculated ^{13}C chemical shifts for some piperidines and piperazines

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

[9] H. Booth and D. V. Griffiths, *J.C.S. Perkin II*, 1973, 842.

Magnetic Anisotropy and Electric Field Calculations.— Initially it was decided to restrict attention in the calculations to those nitrosamines which have a parent amine with a plane of symmetry passing through the nitrogen atom, at right angles to the molecular plane arising as a result of time averaging of the possible conformers. This limitation then allows the approximation that the differences in the chemical shifts of nuclei in the 2,6 and 3,5 pairs arise solely from the introduction of the nitroso-group. Furthermore electron-withdrawing effects of the nitroso-group have been assumed to be identical for the two carbon nuclei in each of the pairs mentioned. The difference in chemical shift can then be described by equation (1) where $\Delta\sigma_m$ takes account of

$$\Delta\sigma = \Delta\sigma_m + \Delta\sigma_E \qquad (1)$$

the magnetic anisotropy and $\Delta\sigma_E$ the electric field of the nitroso-group.

Magnetic anisotropy $\Delta\sigma_m$. The contribution of the magnetic field anisotropy to the screening of a nucleus at a distance R from a point magnetic dipole placed at the centre of the anisotropic bond in question can be calculated using McConnell's equation.[10] The limitations of using this formula arise from the point dipole approximation but other evidence suggests that this effect is small compared with electric field effects for carbon-13 nuclei.[4] The results of the calculations made for adopted planar skeletal configurations of the piperidines and piperazines are given in Table 3. The results have also been calculated for the azabicyclononane and pyrrolidine derivatives which serve as worthwhile test-molecules for the calculations that have been performed because they have different geometric structures.

Electric field effect on ^{13}C *chemical shifts.* A number of attempts have already been made to calculate the effect of electric fields on screening constants. Harris and Spragg [1] gave their attention to proton chemical shifts in *N*-nitrosopiperidines using the Buckingham [11] formulation for calculating the effect. The poor agreement with experimental data was ascribed to an inadequate electric field model. Models which have been set up have assumed equal and opposite charges on nitrogen and oxygen atoms of the NO group.[2,12,13] It is suggested here that such an arrangement is not necessarily required of a bond in an asymmetric molecule and arises purely from the approximation of bond dipole moments. The approach here has been to calculate the charge distribution in a representative molecule, *N*-nitrosodimethylamine, where an accurate structure is known.[14] The program CNDO/2 has been used for this purpose because it has provided good agreement with experimental molecular dipole moments.[15] Not surprisingly the charges on the nitrogen (+0·157|e|) and oxygen (−0·245|e|) have different magnitudes and are of opposite sign. They provide a new basis of a model for calculating electric fields without the assumption of a point dipole. The calculation of the resultant electric field at a given nucleus reduces simply to the vector addition of two components derived taking into account the possibly different distances from the nitrogen and oxygen as measured from models and checked against graphical representations of the molecules.

TABLE 3

Calculated chemical shift differences for carbon pairs in selected *N*-nitroso-derivatives

	1-Nitroso-piperidine		*trans*-1,4-Dinitroso-piperazine	*cis*-1,4-Dinitroso-piperazine	1-Nitroso-pyrrolidine		3-Nitroso-3-aza-bicyclo[3.2.2]nonane			
	2,6	3,5	2,6	2,6	2,5	3,4	2,4	1,5	6,7	
Experimental $\Delta\sigma$ §	11·8	1·7	3·7	10·9	4·5	1·4	11·4	0	0·2	
Magnetic anisotropy effect of the N=O group $\Delta\sigma_m$	1·4	0·4	−0·1	0·6	0·8	−0·1	1·4	0·4	0	
Buckingham [11] $\Delta\sigma_E = A\Sigma(E_{z1} - E_{z2}) + B(E_1^2 - E_2^2)$	*	*	9·4 ‡	15·7 ‡	†	†	†	†	†	$A = 32{\cdot}5 \times 10^{-15}$ $B = -13{\cdot}8 \times 10^{-24}$ E in N C^{-1}
Boden *et al.*[16] $\Delta\sigma_E = A(E_1^2 - E_2^2) + B(\langle E^2\rangle_1 - \langle E^2\rangle_2)$	*	*	4·4 †	11·0 †	6·1 ‡	1·2 ‡	11·8 ‡	0·9 ‡	0·4 ‡	$A = -11{\cdot}0 \times 10^{-24}$ $B = 34{\cdot}2 \times 10^{-17}$ E in N C^{-1}
Horsley and Sternlicht [17] $\Delta\sigma_E = A(E_{z1} - E_{z2})$	0·86 ‡	0·09 †	1·2 ‡	1·1 ‡	1·8 ‡	0·1 ‡	†	†	†	$A = 5{\cdot}1 \times 10^{-11}$ (c.g.s. units)
Ellis *et al.* (this work) $\Delta\delta_E = A(E_1 - E_2)^2 + B(\sqrt{E_1} - \sqrt{E_2})$	*	*	3·7 ‡	12·4 ‡	4·5 ‡	1·3 ‡	11·8 ‡	0	0·2 ‡	$A = 19{\cdot}3 \times 10^{-24}$ $B = -2{\cdot}2 \times 10^{-6}$ E in N C^{-1}

* Data used to derive A and B constants in each case. † Not calculated because results were poor for *cis*- and *trans*-1,4-dinitropiperazines. ‡ The differences given include the magnetic anisotropy correction. § C-6 Is at low field from C-2, and C-5 is at low field from C-3, *etc.*

[10] H. M. McConnell, *J. Chem. Phys.*, 1957, **27**, 226.
[11] A. D. Buckingham, *Canad. J. Chem.*, 1960, **38**, 300.
[12] R. Okazaki and N. Inamoto, *J. Chem. Soc.* (*B*), 1970, 1583.
[13] E. G. Sauer and T. Oja, *J. Chem. Phys.*, 1973, **58**, 2710.
[14] P. Rademacher, R. Stolevic, and W. Lüttke, *Angew. Chem.*, 1968, **7**, 806.
[15] J. R. Hoyland, 'Molecular Orbital Studies in Chemical Pharmacology,' Springer-Verlag, Berlin, 1971.

It has been shown that the shielding constant depends upon E_z, the electric field component along a C–H bond direction, and E^2, the square of the electric field intensity at the proton such that equation (2) holds where the

$$\Delta\sigma = -AE_z - BE^2 \quad (2)$$

constants A and B characterise the distortion of the electronic charge distribution along the bond direction and perpendicular to it respectively.[11] It has been implied that this formulation applies equally well to fluorine nuclei in σ F bonds and the effects of Van der Waal's forces between non-bonded atoms has been included to account for the *ortho*-effect in substituted fluorobenzenes.[16]

The effect of electric fields on carbon-13 chemical shifts has been debated for the case of a positive charge $+q$ introduced on an atom X in the CH_3X system.[17]

We have confined our attention to differential intramolecular effects in much the same way assuming that intermolecular effects, reaction field, *etc.*, will be the same for each carbon nucleus in a chosen pair. Our first attempts to predict separations of chemical shifts in the nitrosamines involved the format of the original equations for protons in carbon–hydrogen bonds.[11] The extension of the theory requires that the quadrivalence of carbon be taken fully into account since the polarisation along the C–X bonds will depend upon the X substituent or atom. It is assumed throughout that changes in the valence state of carbon can be taken account of through C–X bond parameters A_{CX} in equation (3). The B value is taken to be constant in the

$$\Delta\sigma_E = -\sum_X A_{CX}E_{CX} - BE^2 \quad (3)$$

series of compounds studied. The parameters required to describe the situation in *N*-nitrosopiperidine are A_{CN}, A_{CC}, A_{CH}, and B. However, the number of experimental parameters available is only two, the separations of signals in the pairs 2,6 and 3,5. It seemed prudent therefore to reduce the unknowns further by taking $A_{CH} = A_{CC} = A_{CN}$. This is not unreasonable if the electric field constants derived above are considered:[17] $A_{CH} = 3{\cdot}0 \times 10^{-11}$, $A_{CC} = 5{\cdot}1 \times 10^{-11}$, and $A_{CN} = 4{\cdot}5 \times 10^{-11}$ (c.g.s.). The values of the constants A and B derived here are then $A = 32{\cdot}55 \times 10^{-15}$ C N^{-1} and $B = -13{\cdot}81 \times 10^{-24}$ C^2 N^{-2}.

These values were used to predict the chemical shift separations in the *NN'*-dinitrosopiperazines and the agreement with the experimental results is poor even when the magnetic anisotropy effect is taken into account (see Table 3). It may be possible to improve this by taking into account different A_{CX} parameters but there is insufficient unique, experimental data available here to produce a complete set.

An attempt has also been made using the Horsley and Sternlicht approach [17] but with little success. The third approach invoked the Van der Waal's interaction proposed by Boden *et al.*,[16] and the electric field at the carbon nucleus [equation (4)]. The constants A and B are

$$\Delta\sigma = AE + B\langle E^2\rangle \quad (4)$$

assumed to retain the same values for carbon atoms with 2C,2H substituents and C,N,2H substituents. The application of this expression in a way similar to that described above (*i.e.* using the *N*-nitrosopiperidine to solve for A and B first) gives good agreement between predicted and experimental separations in the three chosen test-molecules. Omission of the AE term leads to poor agreement. The agreement achieved cannot be taken to be indicative of a convincing method of calculating electric field effects mainly because of the small number of molecules involved. A greater variety of suitable molecules is obviously needed but their availability is restricted by the symmetry requirements we have imposed. A totally empirical expression for the separation between two carbon nuclei was tested in a radically different approach [equation (5)]. The agreement obtained was better in particular for the small observed differences, with a 14% deviation in one case of the larger separations.

$$\Delta\sigma_1 - \Delta\sigma_2 = A(E_1 - E_2)^2 + B(\sqrt{E_1} - \sqrt{E_2}) \quad (5)$$

This agreement serves to underline the dangers of seeking to draw conclusions from an investigation of a small number of molecules. We feel that there may well be other expressions which can be fitted to the limited data of the 'symmetrical' compounds. The distinction between alternatives will only be made by increasing the experimental data used in testing the equations. We do not feel confident in extending the investigation to less symmetrical piperidine and piperazine compounds because in these cases no fundamentally new information is provided from the ring carbon chemical shifts when corrections for the substituent effects have been made.

[4/792 *Received*, 19*th February*, 1974]

[16] N. Boden, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, *Mol. Phys.*, 1964, **8**, 133.

[17] W. J. Horsley and H. Sternlicht, *J. Amer. Chem. Soc.*, 1968, **90**, 3738.