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NMR Studies of N-Nitrosamines

Part II. Saturated Cyclic Mononitrosamines; The Diamagnetic Anisotropy of the N=O Group*

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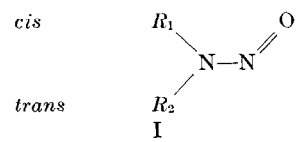
A number of alicyclic N-nitrosamines have been studied in order to discover the conformational effect of the nitroso group and to obtain data about its long-range shielding effect. It is found that a methyl group *cis* to the nitroso group exhibits a strong preference to adopt an axial position, in contrast to the situation in the absence of the nitroso group. Chemical shift data for pairs of β protons and methyl groups, corrected for electric field effects, give diamagnetic susceptibility anisotropies of $(29 \pm 10) \times 10^{-30}$ and $(102 \pm 15) \times 10^{-30}$ cm^3 mol^{-1} with respect to the susceptibility in the direction of the N=O bond. The effect is thus one of deshielding everywhere in the plane of the N—N=O group, being a maximum in the N=O bond direction. Electric field effects alter this situation substantially only for α-equatorial protons.

INTRODUCTION

It has been known for some time that unsymmetrical N-nitrosamines exhibit isomerism due to restricted rotation about the nitrogen–nitrogen bond (*1*). The stable forms are those in which the NNO group and the α-carbon atoms are coplanar (I). The room temperature NMR spectra of dialkyl nitrosamines show separate resonances from groups *cis* and *trans* to the nitroso group. The original workers assigned the high field resonance in the spectrum of dimethyl nitrosamine to the methyl group *trans* to the nitroso group but this assignment was reversed by later work (*2*, *3*) in which isomer ratios in unsymmetrical nitrosamines and solvent effects were investigated.



I

Karabatsos and Taller (*3*) found a considerable variation in the chemical shift differences between protons *cis* and *trans* to the nitroso group in dialkyl

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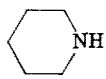
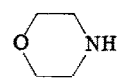
nitrosamines and attributed this to differences in the conformations adopted by the alkyl groups. The spectra of the dialkyl compounds contain insufficient information to determine both the conformations of the alkyl groups and the form of the anisotropic shielding by the N-nitroso group. We have examined the NMR spectra of a number of cyclic N-nitrosamines since in some cases there is no such difficulty. The aims of this study were to investigate the effects of steric interaction between the nitroso group and neighboring ring substituents on the ring conformation, and to relate the chemical shift differences observed between *cis* and *trans* protons to the molecular geometry. We have attempted to describe these chemical shift effects in terms of simple models of bond magnetic anisotropy and bond electric dipoles.

There are a few reports in the literature of NMR data for cyclic N-nitrosamines (*4–6*) but these mostly refer to compounds of uncertain conformation. Most of the compounds we have studied are derivatives of six-membered ring systems, piperidine II, piperazine III, and morpholine IV, in which the molecular geometry is fairly well understood.



II

III



IV

We have also studied two derivatives of the five-membered ring pyrrolidine.

EXPERIMENTAL

The following nitrosamines were prepared by treating the corresponding commercially available amine with sodium nitrite in the presence of hydrochloric acid (*7*); 1-nitrosopyrrolidine, 4-nitrosomorpholine,[1] 1-nitrosopiperidine, 1-nitrosohexamethyleneimine, 2-methyl-1-nitrosopiperidine, *cis*-2,6-dimethyl-4-nitrosomorpholine (present as the major component in a mixture with the *trans*-dimethylisomer).

2,6-Dimethylpiperidine, obtained from Koch–Light Laboratories Ltd., was also a mixture of *cis* and *trans* isomers. Nitrosation gave a yellow oil from which the nitroso derivative of the *cis* isomer crystallized on cooling in ice. The nitroso derivative of the *trans* isomer could not be completely separated, and its spectrum was studied using the *cis/trans* mixture with ca. 30% of the *trans* isomer.

1-*cis*-3,5-trimethyl-4-nitrosopiperazine was prepared from *cis*-3,5-dimethylpiperazine (Chemicals Procurement Laboratories Inc.) by partial conversion to 1-*cis*-3,5-trimethylpiperazine with methyl iodide, followed by nitrosation. The 1-methyl-4-nitroso derivative was separated from the 1,4-dinitroso derivative on an alumina column.

[1] Conventionally in some of the compounds studied the ring-nitrogen atom bearing the nitroso group is at position 1; in others it is at position 4.

1-Methyl-4-nitrosopiperazine was commercially available; 2,2,6,6-tetramethyl-1-nitrosopiperidine and 2,2,5,5-tetramethyl-1-nitroso pyrrolidine were provided by Mr. E. Lunt through the courtesy of May and Baker Ltd.

In all cases the absence of unexplained peaks in the NMR spectrum was taken as a sufficient indication of purity.

The spectra were obtained using three spectrometers: (a) Perkin–Elmer 40 Mc/sec instrument, (b) Perkin–Elmer R10 60 Mc/sec instrument with associated double resonance facilities, (c) Varian Associates HA-100 at 100 Mc/sec with double resonance and variable temperature facilities.

The nitrosamines were studied in solution in carbon tetrachloride at about 10% by volume, with tetramethylsilane as an internal reference. In some cases solutions in benzene were used to confirm the assignment of the spectra.

ANALYSIS OF SPECTRA

The prefixes α and β will be used throughout to describe ring positions adjacent to, and two bonds removed from the nitroso group, respectively.

In the spectra of the morpholine and piperazine derivatives the α and β protons *cis* to the nitroso group may be considered separately from the *trans* protons. Any cross-ring coupling between them occurs through at least four sigma bonds and is therefore small; in those cases in which it is observable it appears as a small splitting which may be treated on a first-order basis. In all other cases cross-ring coupling was neglected in analysis of the spectra. A typical spectrum is that of 1-*cis*-3,5-trimethyl-4-nitrosopiperazine (Fig. 1.)

The spectra of the piperidine derivatives are more complex, and in most cases the only information obtained is for the α positions. The resonance of the α protons occurs at about 2 ppm to low field of the β and γ protons, so that the approximate chemical shifts may be found. The chemical shifts of ring methyl groups may also be measured since the methyl resonance is readily identified, appearing either as an intense doublet, splitting 6.5–7 cps, for a $HCCH_3$ group or as a single line for a $C(CH_3)_2$ group where all six protons are equivalent. The methyl resonance usually occurs to high field of that from ring methylene protons.

In some cases double resonance experiments were used to simplify spectra, to determine which resonances were from protons coupled together, or to measure chemical shifts which could not be obtained directly. The assignment of resonances to protons *cis* and *trans* to the nitroso group was made on the basis of shift changes observed in benzene solutions, in which the upfield shift relative to carbon tetrachloride solutions is greater for *trans* protons than for *cis* protons (*3*). The chemical shifts for CCl_4 solutions are given in Table I.

In those cases in which a complete analysis was attempted (see Table I) use was made of the computer program LAOCOON II (*8*) in calculating trial spectra and obtaining the best parameters. For systems containing methyl groups trial

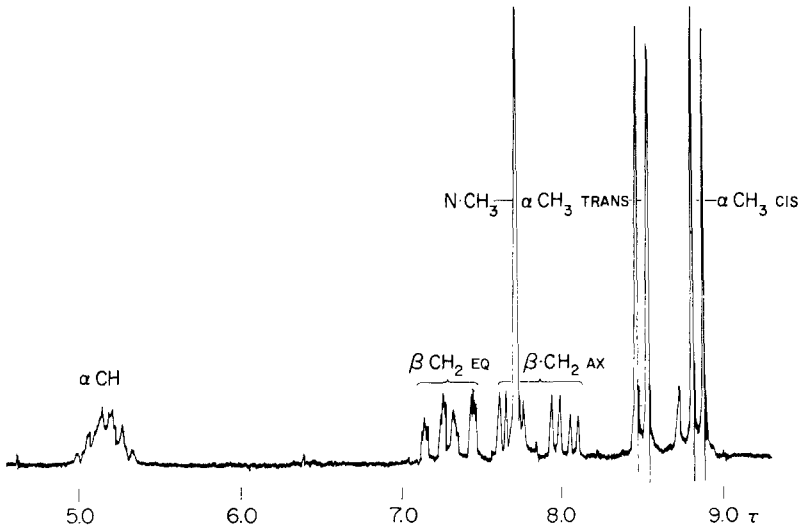


FIG. 1. 100 Mc/sec spectrum of 1-*cis*-3,5-trimethyl-4-nitrosopiperazine in CCl_4. Impurity at $\tau = 8.7$.

spectra were calculated using the program UEA NMR II (*9*) which is based on LAOCOON II Part I and incorporates magnetic equivalence factoring, allowing larger spin systems to be treated.

Those examples in which analysis of the spectra included features not already mentioned are described below.

(1) *Cis-2,6-dimethyl-4-nitrosomorpholine*

This compound was studied in a mixture with the *trans*-2,6-dimethyl isomer, there being about 30% of the latter present. Fortunately the spectrum of the *cis* isomer could be readily distinguished, only a few lines being overlapped by the *trans* isomer. The assignment was confirmed by comparison with a solution in benzene in which considerable chemical shift changes were observed (*3*). Trial spectra were calculated by treating each half of the molecule as the X_3ABC part of an X_3ABCDE system, so as to incorporate some cross-ring coupling.

(2) *1-Cis-3,5-trimethyl-4-nitrosopiperazine*

Complete analysis of this spectrum is difficult because of the small chemical shift difference between the methine protons. It did not prove possible to decouple both methyl groups simultaneously and in spectra with one methyl group decoupled the methine resonance is rather broad, probably because of coupling between the two methine protons. Trial spectra were calculated for a nine-spin system, corresponding to decoupling one methyl group, incorporating reasonable values for the coupling between the methine protons, and by comparison of

TABLE I

PROTON CHEMICAL SHIFTS IN 10% v/v SOLUTION IN CCl_4

Compound	NMR analysis	Position relative to nitroso group		Ring protons		Methyl groups	
				α	β	α	β
VII	[a] X_3ABC part of	*cis*	axial	7.831	6.663		
Cis-2,6-dimethyl-4-nitrosomorpholine	$X_3ABCDEF$		equatorial	5.202			8.81
		trans	ax	6.679	6.336		
			eq	5.411			8.73
VIII	[a] $X_3ABCDEF$	*cis*	ax		8.001	8.83	
Cis-1,3,5-trimethyl-4-nitrosopiperazine	[b] $ABCD$ part of $ABCDEF$		eq	5.21	7.378		
		trans	ax		7.667	8.49	
			eq	5.10	7.194		
IX	[b] $AA'BB'$	*cis*	ax ↔ eq	6.280	6.432		
4-Nitrosomorpholine		*trans*		5.786	6.188		
X	[c] $AA'BB'$	*cis*	ax ↔ eq	6.295	7.704		
1-Methyl-4-nitrosopiperazine		*trans*		5.806	7.447		
1-Nitrosopiperidine	[d]	*cis*	ax ↔ eq	6.31	8.48		
		trans		5.82	8.24		
2-Methyl-1-Nitrosopiperidine V	[d]	*cis*		4.88		9.29	
		trans		5.5 & 6.4			
2-Methyl-1-Nitrosopiperidine VI	[d]	*cis*		6.4			
		trans		5.45		8.86	
Cis-2,6-dimethyl-1-nitrosopiperidine XI	[d]	*cis*		5.0		8.92	
		trans		5.0		8.58	
Trans-2,6-dimethyl-1-nitrosopiperidine XII	[d]	*cis*		5.0		8.96	
		trans		6.1		8.37	
2,2,6,6-Tetramethyl-1-nitrosopiperidine	[d]	*cis*				8.66	
		trans				8.40	
1-Nitrosopyrrolidine	[d]	*cis*		6.60			
		trans		5.82			
2,2,5,5-Tetramethyl-1-nitrosopyrrolidine	[c] $AA'BB'$	*cis*			8.210	8.63	
		trans			8.120	8.45	
1-Nitrosoazetidine[e]	[d]	*cis*		5.83			
		trans		5.13			

[a] UEA NMR II.
[b] LAOCOON Pt. II.
[c] LAOCOON Pt. I.
[d] First order.
[e] Neat liquid (4).

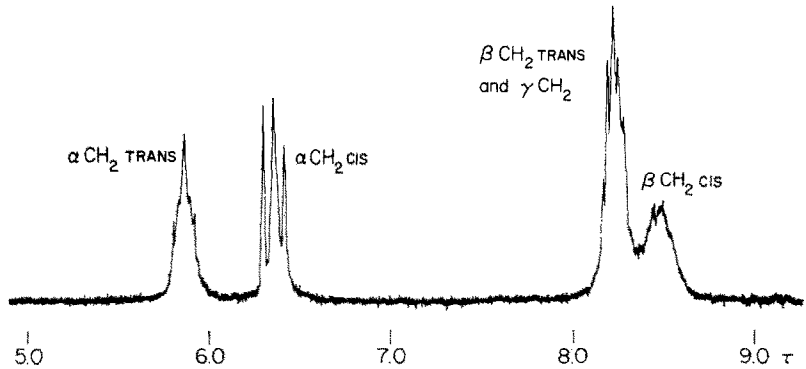


FIG. 2. 100 Mc/sec spectrum of 1-nitrosopiperidine in CCl_4

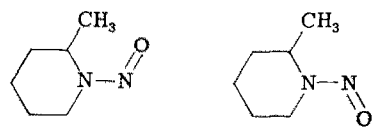
these with the observed spectra the chemical shifts of the methine protons were obtained.

(3) *1-Nitrosopiperidine*

There is a marked difference in apparent complexity between the resonances of the α-CH_2 protons (Fig. 2); the *cis* protons appearing as a broadened triplet while the *trans* protons give a much more complicated pattern. This is a result of coupling between the βCH_2 and γCH_2 protons. The chemical shift difference between the *cis* βCH_2 and γCH_2 protons, ca. 25 cps, is considerably larger than the coupling between them, so that the resonance of the α-CH_2 protons is apparently little affected by this coupling. The chemical shift difference between the *trans* βCH_2 and γCH_2 protons is much smaller, $\leqq 5$ cps, so that the resonance of the *trans* αCH_2 protons is more complicated. A similar difference in signal shape is observed between the *syn* and *anti* αCH_2 protons of phenyliminocyclohexane (*10*), and the explanation is probably the same as for 1-nitrosopiperidine, the spectra of the two compounds being very similar. An analogous explanation has been suggested to account for the appearance of the α-proton signals in alkyl fluorides (*11*).

(4) *2-Methyl-1-nitrosopiperidine*

This is the only compound studied which has two isomeric forms, V and VI, depending on the orientation of the nitroso group.



V VI

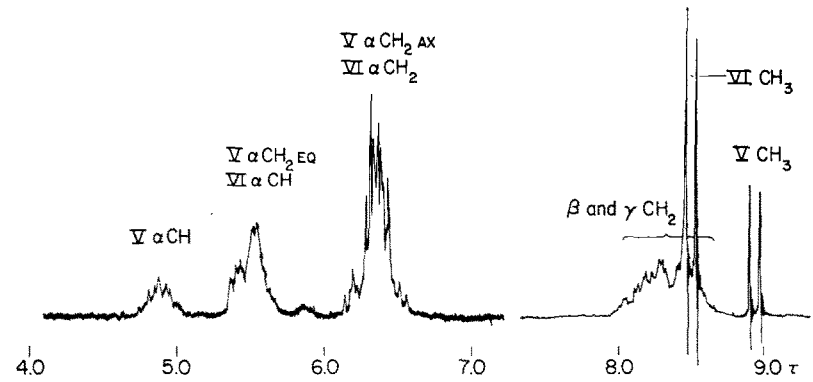


FIG. 3. 100 Mc/sec spectrum of 2-methyl-1-nitrosopiperidine in CCl_4. The amplification was reduced at ca. $\tau = 7.3$.

The spectrum (Fig. 3) is clearly that of a mixture of the two isomers; the observed bands could be assigned to their respective isomers from intensity ratios and double resonance experiments.

CONFORMATIONAL ANALYSIS

The expected ring conformation in the six-membered ring systems is basically a chair form. As the barriers to ring inversion in these compounds are probably similar to that in cyclohexane, the room temperature NMR spectra are weighted averages over the possible conformations. Interaction between the nitroso group and ring substituents may make the relative populations of the ring conformations different from those in the parent amines and may produce distortions from the chair form. In particular ring methyl groups in the parent amines preferentially adopt equatorial positions, but the situation is likely to be different for a methyl group α to a nitroso group, since equatorial substituents are very nearly coplanar with the NNO group for a chair conformation.

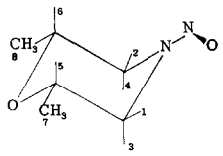
In the piperazine and morpholine derivatives information about the ring conformation is obtained from the vicinal coupling constants. For a fixed chair conformation there are three types of vicinal coupling constant: axial–axial, J_{aa}, axial–equatorial, J_{ae}, and equatorial–equatorial, J_{ee}. Typical values for these are in the range 9–11 cps for J_{aa} and 2–5 cps for J_{ae} and J_{ee} (*12*). If the ring conformation is rapidly inverting between two *equivalent* chair forms there are two possible vicinal coupling constants, $\frac{1}{2}(J_{aa} + J_{ee})$, ca. 7 cps, and $\frac{1}{2}(J_{ae} + J_{ea})$, ca. 3–4 cps.

1. *Cis-2,6-Dimethyl-4-nitrosomorpholine*

This compound exists predominantly in the conformation with both methyl groups equatorial (VII). The vicinal coupling constants (Table II) are very

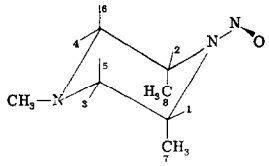
TABLE II

CONFORMATIONS AND COUPLING CONSTANTS IN MORPHOLINE AND PIPERAZINE DERIVATIVES[a]



Fixed[b]

VII



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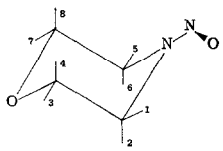
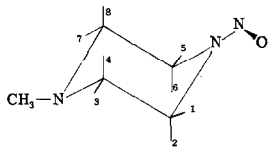
VIII



Inverting[b]

IX



Inverting[b]

X

VII	J_{13} J_{24}	^2J	13.2	13.0
	J_{15} J_{26}	$^3J_{ea}$	2.9	2.7
	J_{35} J_{46}	$^3J_{aa}$	10.7	10.7
	J_{57} J_{68}	$^3J_{HCH_3}$	6.15	6.2
	J_{12}	$^4J_{ee}$	1.4	
	J_{34}	$^4J_{aa}$	1.0	
VIII	J_{35} J_{46}	^2J	11.6	11.4
	J_{15} J_{26}	$^3J_{ea}$	4.8	4.4
	J_{13} J_{24}	$^3J_{ee}$	1.15	1.2
	J_{17} J_{28}	$^3J_{HCH_3}$	7.2	7.2
	J_{57} J_{68}	$^4J_{HCH_3}$	0.6	0.6
	J_{34}	$^4J_{ee}$	2.2	
IX	J_{12}^c, J_{34}^c	^2J	10.8, 8.8	
	J_{56}, J_{78}	^2J	10.9, 9.1	
	$J_{13} = J_{24}$ $J_{57} = J_{68}$	$\frac{1}{2}(^3J_{aa} + {}^3J_{ee})$	6.5	6.65
	$J_{14} = J_{23}$ $J_{58} = J_{67}$	$\frac{1}{2}(^3J_{ea} + {}^3J_{ae})$	3.8	3.4
X	J_{12}, J_{34}	^2J	11.5, 9.5	
	J_{56}, J_{78}	^2J	11.6, 10.0	
	$J_{13} = J_{24}$ $J_{57} = J_{68}$	$\frac{1}{2}(^3J_{aa} + {}^3J_{ee})$	7.0	6.95
	$J_{14} = J_{23}$ $J_{58} = J_{67}$	$\frac{1}{2}(^3J_{ea} + {}^3J_{ae})$	4.0	3.6

[a] In most cases the spectral analysis indicated that geminal and vicinal coupling constants were opposite in sign; in the remaining cases this was assumed. The relative signs of the long-range coupling constants are unknown.

[b] The term fixed is intended to imply that the inversion equilibrium lies heavily towards the conformation indicated; the term inverting implies that the isomers are equivalent.

[c] Not distinguished by analysis of the spectrum.

close to the values observed in the parent amine by Booth (*13*) (J_{aa} = 10.3 cps, J_{ae} = 2.1 cps). This suggests that the ring conformation is not greatly distorted from a chair form.

2. *1-Cis-3,5-Trimethyl-4-nitrosopiperazine* (*VIII*)

The vicinal coupling constants in this molecule are similar for protons *cis* and *trans* to the nitroso group. These indicate clearly that the ring conformation is basically a chair with the methyl groups *axial*, the vicinal coupling constants for such a conformation being J_{ae} and J_{ee}.

This is surprising since the repulsive interaction between two axial methyl groups is about 5.5 kcal/mole (*14*), but inspection of models shows that the chair conformation with both methyl groups equational is impossible without the N-nitroso group becoming nonplanar. The barrier to rotation of an N-nitroso group is greater than 20 kcal/mole (*1*), so that the delocalization energy associated with planarity of the N-nitroso group is the dominant factor in determining the conformation.

The interaction between the methyl groups is expected to produce some distortion by which the distance between them is increased. Such a distortion would alter the dihedral angles between vicinal CH bonds from those in an ideal chair form, decreasing the axial–equatorial angle and increasing the equatorial–equatorial angle. This would tend to increase J_{ae} and decrease J_{ee} (*15*) and the observed values show some evidence of this. The chemical shift difference between α-protons *cis* and *trans* to the nitroso group also shows some evidence of distortion, the value (for the equatorial position) being 0.11 ppm with the *cis* proton to high field, compared with 0.21 ppm with the *cis* proton to low field for the corresponding position in the *cis*-2,6-dimethylmorpholine derivative. For the β-positions however the shift difference between the axial protons, 0.33 ppm, is the same as for the β-axial protons in the dimethylmorpholine derivative, and the average for axial and equatorial positions, 0.26 ppm, is very close to that observed in 1-methyl-4-nitrosopiperazine and N-nitroso-morpholine.

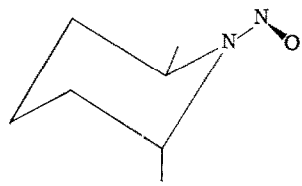
3. *1-Methyl-4-nitrosopiperazine and N-nitrosomorpholine*

Both compounds give spectra as expected for rapidly inverting chair conformations with equal populations. The spectrum of the piperazine derivative was also recorded at −60°C but although the signal from the α-proton *cis* to the nitroso group was greatly broadened, the spectrum corresponding to a fixed chair form was not obtained.

4. *N-Nitrosopiperidines*

The conformations of these can be assigned only from the chemical shift data since no vicinal coupling constants can be measured. In *cis*-2,6-dimethyl-1-nitrosopiperidine (XI) the *cis/trans* chemical shift differences observed for the

α-methyl and α-methine protons are very similar to those in the *cis*-2,6-dimethylpiperazine derivative. This indicates that the two compounds have similar conformations, that is again both methyl groups are axial. The expected conformation for the *trans*-2,6-dimethyl isomer is that in which the methyl group *cis* to the nitroso group is axial, the other methyl group being equatorial (XII). The chemical shifts of the α-methine protons are consistent with this conformation, the resonance of the *cis* proton, which is equatorial, being at 1.1 ppm to low field of the *trans* proton, which is axial



XII

As pointed out above there are two isomers (V and VI) of the 2-methyl derivative depending on the orientation of the methyl group. Integration shows there to be about 27 % of the isomer with the methyl group *cis* to the nitroso group (V) and about 73 % of the *trans* isomer (VI). The *cis* isomer is expected to exist predominantly in the conformation with the methyl group axial and this is confirmed by the chemical shifts of the α-protons. The two α-CH_2 protons give separate resonances at 5.5 and 6.4τ, these being assigned to the equatorial and axial protons, respectively; the α-methine proton is at very low field as expected for the equatorial position. The *trans* isomer shows an unexpected feature in that only one signal is observed for the α-CH_2 protons, the chemical shift difference between axial and equatorial protons being less than 0.1 ppm. If the ring were in a fixed conformation a large axial/equatorial chemical shift difference would be expected; for the corresponding protons in 4-nitroso-*cis*-2,6-dimethylmorpholine the shift difference is 2.6 ppm. The effect of the methyl group on the methylene chemical shifts is probably much smaller than that of the nitroso group, reducing the axial/equatorial shift difference by less than 0.2 ppm (*16*), so that the observed small chemical shift difference between the α-methylene protons is unlikely to arise from cancellation of the effects of the methyl group and the N-nitroso group in a fixed conformation. The ring is therefore not predominantly in one conformation but the relative populations of the inversion isomers cannot be obtained accurately. Consideration of the α-methylene and α-methine chemical shifts suggests that there is at least 50 % of the isomer with the methyl group axial. This is considerably different from the situation in methyl cyclohexane in which the methyl group is more than 90 % equatorial.

The ring conformation in 2,2,6,6-tetramethyl-1-nitrosopiperidine must be

considerably distorted from a simple chair by interaction between the nitroso group and the methyl groups. However the chemical shift data do not give any information about the conformation adopted.

COUPLING CONSTANTS (TABLE II)

Geminal Coupling Constants

The spectra of N-nitrosomorpholine and 1-methyl-4-nitrosopiperazine do not yield accurate values for the geminal coupling constants since they are $AA'BB'$ spectra of the type discussed by Abraham and Pachler (*17*), from which only the difference between the geminal coupling constants is obtained exactly. The value found between protons α to a nitroso group, -13.1 cps in VII, is larger than that for protons α to a N-methyl group, -11.5 cps in VIII, probably due to the partial π-character of the N=N bond (*18*).

Vicinal Coupling Constants

The values found for vicinal coupling constants in these compounds are generally similar to those in the parent amines, (*13*, *19*). The variations observed depend on the dihedral angle between the carbon–hydrogen bonds, and on the electronegativity and orientation of the ring substituents (*20*). It is not possible to separate these effects here since the magnitude of the variations in dihedral angle is not known. However the low values for $^3J_{ee}$ in VIII are consistent with the suggestion by Booth (*20*) that electronegative substituents (in this case the ring nitrogen atoms) have a maximum effect when *trans* to the coupling protons.

Coupling to Methyl Groups

There is some evidence that coupling between methine and methyl protons is larger for axial than for equatorial methyl groups (*19*, *21*); this would be expected if steric interactions produce a distortion reducing the angles between the carbon–carbon bond and the carbon–hydrogen bonds (*15*). The coupling between the methine and methyl protons in VIII, where the methyl groups are axial, is 7.2 cps which is much larger than that in VII, 6.2 cps, where the methyl groups are equatorial. In the piperidine derivatives the splitting of the methyl doublet is smaller for an equatorial methyl group (6.4 cps for XI) than for an axial methyl group (6.8 cps for XII, V, and for the *cis*-methyl group of XI, and 7.2 cps for the *trans*-methyl group of XI). However, the observed splitting cannot in general be taken as the coupling constant to the methine proton since the effect of coupling to the rest of the spin system must be considered. Four-bond coupling to ring methyl groups also is found to be larger for axial than for equatorial methyl groups (*22*), and the only example observed in these compounds is the 0.6 cps coupling between the β-axial protons and the α-axial methyl groups in VIII.

Cross-ring Coupling Constants

We have observed a long-range coupling of 0.35 cps between the methyl groups groups of dimethylnitrosamine; this is rather smaller than that observed in acetone, 0.54 cps (*23*). Cross-ring couplings are observed in only two of the compounds studied, both having fixed conformations. In VIII a coupling of 2.2 cps between the β-equatorial protons is found. (The coupling between the β-axial protons is less than 0.4 cps.) This coupling is rather large (in fact it is larger than $^3J_{ee}$) but the intervening bonds between the equatorial protons have a planar configuration, for which the maximum long-range interaction is expected (*24*). The resonance of the α-methine protons in this molecule is not sufficiently well resolved to allow an estimate of the coupling between them. In VII there are long-range couplings between the α-protons, 1.4 cps between the α-equatorial protons and 1.0 cps between the α-axial protons; no long-range couplings are reported in the parent amine (*13*). These interactions occur through single bonds, but the ring nitrogen atom is effectively sp^2 hybridized so that the coupling mechanism may be different from that in fully saturated systems. There is little data on the steric dependence of couplings in systems of this type, but Barfield (*25*) calculated that the indirect contribution to the coupling is a maximum for the all planar configuration. Since these long-range couplings appear as first-order splittings their signs are not obtained from analysis of the spectra.

The spectra of N-nitrosomorpholine and 1-methyl-4-nitrosopiperazine were both analyzed as two $AA'BB'$ spectra, cross-ring coupling being ignored. The effect of cross-ring coupling in these cases is not as simple as in the previous examples, since it cannot be treated on a first-order basis. We intend to investigate further the effect of small cross-ring couplings on the spectra of these and similar compounds.

LONG-RANGE SHIELDING BY THE NITROSO GROUP

In the cyclic compounds studied here, the close similarity between vicinal coupling constants for protons *cis* and *trans* to the nitroso group indicates that the ring conformations are not twisted appreciably so that the environments of *cis* and *trans* protons are identical except for the difference in position relative to the nitroso group. The chemical shift difference between *cis* and *trans* protons is therefore a direct measurement of the long-range shielding effect of the nitroso group, inductive effects and any contribution from the anisotropy of other groups being eliminated. Any intermolecular or solvent interactions are taken to be small since the chemical shift differences are measured in dilute (ca. 10% v/v) solution in CCl_4 and show little change from those in the neat liquids.

It has been shown (*2*, *3*) that in dialkyl nitrosamines α-methyl and α-methylene protons appear at higher field when *cis* than when *trans* to the nitroso group, the assignment being based on isomer ratios in unsymmetrical compounds and solvent shifts in aromatic solvents. In the only unsymmetrical

compound studied here, N-nitroso-2-methylpiperidine, we observe a similar isomer ratio to that in the equivalent acyclic compound, methyl ethylnitrosamine, and the pattern of chemical shifts for the α-CH_2 and α-methyl protons is similar to that in the acyclic compound. We conclude that for a rapidly inverting six-membered ring system the resonance of the α-methylene protons occurs at higher field for the *cis* protons than for the *trans* protons. This is confirmed by the shift changes observed in benzene solutions.

Using this assignment the *cis/trans* chemical shift differences for various positions in a six-membered ring are obtained as in the second column of Table III. The values for the α-positions are those for N-nitroso-*cis*-2,6-dimethylmorpholine in which distortions from a chair form are expected to be small; the average value, 0.47 ppm, is close to that observed in those cases with no ring substituents, 0.49 ppm. The values for the β-positions are from the dimethylmorpholine and dimethylpiperazine derivatives, the average value, 0.26 ppm, is similar to that in the unsubstituted compounds, 0.25 ppm. In these compounds the ring is assumed to adopt a chair conformation, distorted only by the presence of the amino nitrogen atom which is effectively sp^2 hybridized.

The value for the α-positions of a five-membered ring is that for N-nitrosopyrrolidine in which the ring conformation is not known. The most probable conformation is the "half-chair" as found in α-halocyclopentanones (*26*) which are similar in that the ring contains an sp^2 hybridized atom. The value for the β-positions is from N-nitroso-2,2,5,5-tetramethylpyrrolidine; inspection of models shows that the ring conformation must be very nearly planar, but the vicinal coupling constants between the β-protons, $J = J' = 7.2$ cps, suggest that the ring is puckered (*15*). The data for N-nitrosoazetidine are for the neat liquid (*4*) but we find little change in *cis/trans* chemical shift differences with dilution in CCl_4. The conformation of this compound must be effectively planar as in cyclobutanone (*27*).

The effect of the nitroso group on the shielding constant of any proton may be considered as having two components, one arising from the secondary magnetic field produced by the nitroso group, the other arising from its electric field. The secondary magnetic field produced by the nitroso group may be related to the anisotropy of the magnetic susceptibility of the N=O bond, using a point dipole approximation (*28*). The contribution of the anisotropy to a proton screening constant is given by

$$\Delta\sigma = \tfrac{1}{3}R^{-3}\{\Delta\chi_y(3\cos^2\theta_y - 1) + \Delta\chi_z(3\cos^2\theta_z - 1)\},$$

where $\Delta\chi_y = \chi_{xx} - \chi_{yy}$, $\Delta\chi_z = \chi_{xx} - \chi_{zz}$, χ_{xx}, etc. being the principal components of the susceptibility of the N=O group, x being the NO bond direction, y being in the plane of the NNO group, and z being perpendicular to this plane; R is the distance from the point dipole to the proton, and θ_y, θ_z being the angles between the R direction and the y or z axis.

Chemical shift data for amides, similar to that obtained here for nitrosamines,

TABLE III

THE OBSERVED LONG-RANGE SHIELDING EFFECTS OF AN N-NITROSO GROUP, AND SOME CALCULATED ELECTRIC FIELD CONTRIBUTIONS

Position	$\Delta\tau_{obs}$[a]	Electric field contribution					
		Permanent dipole		Van der Waals		Total	
		B	M	B	M	B	M
6-Membered ring							
αCH equatorial	−0.209	−0.47	−0.56	−0.50	−0.37	−0.97	−0.93
αCH axial	+1.152	+0.11	+0.16	−0.05	−0.04	+0.06	+0.12
βCH equatorial	+0.184	+0.02	+0.03	−0.005	−0.004	+0.015	+0.026
βCH axial	+0.331	−0.01	−0.01	−0.02	−0.015	+0.03	−0.025
βCH_3 equatorial	+0.080	−0.01	−0.02	−0.006	−0.004	−0.016	−0.024
5-Membered ring							
αCH_2	+0.78	−0.22	−0.25	−0.20	−0.15	−0.42	−0.40
βCH_2	+0.090	−0.01	−0.01	−0.002	−0.0015	−0.01	−0.01
4-Membered ring							
αCH_2	+0.70	−0.04	−0.03	−0.08	−0.06	−0.12	−0.09

[a] $\Delta\tau_{obs} = \tau_{cis} - \tau_{trans}$

[b] B and M refer to calculations using the values of constants A and B derived by Buckingham (*30*) and Musher (*31*), respectively.

has been used to estimate the magnetic anisotropy of the carbonyl group (*29*, *30*). In order to obtain the magnetic anisotropy it is necessary to eliminate the electric field contribution to the observed chemical shifts by calculating this separately. The electric field due to the nitroso group cannot be calculated accurately, and we have therefore used a very simple model to estimate its importance.

The effect of an electric field on a proton screening constant is given by

$$\Delta\sigma = -AE_z - BE^2 \qquad (29)$$

where E_z is the component of the field along the bond direction. For the constants A and B we used two sets of values, those obtained by Buckingham (*31*), $A = -2 \times 10^{-12}$, $B = -1 \times 10^{-18}$, and those obtained by Musher (*32*), $A = -2.9 \times 10^{-12}$, $B = -7.4 \times 10^{-19}$. There are contributions from the permanent electric dipole of the bond and from the intramolecular Van der Waals interaction. The permanent dipole contribution was represented as due to point charges of 0.5 e on the oxygen atom and an equal positive charge on the nitrogen atom. The Van der Waals contribution at a distance r from the center of the bond is given by (*33*)

$$\langle E^2 \rangle = 3\alpha I / r^6,$$

where α is the bond polarizability, and I is the bond ionization potential. Neither

of these quantities has been determined experimentally and they were estimated by comparison with measured values in other systems; the values chosen were $\alpha = 5 \times 10^{-24}$ cm^3 (*34*), and $I = 10$ eV (*35*).

The geometry of the N-nitroso group is not known accurately; bond distances were taken as: $r_{N-N} = 1.30$ Å, $r_{N-O} = 1.30$ Å, and the NNO angle as 120°. Ring conformations were assumed as already described with normal bond lengths and angles (*36*). The ring conformation in 2,2,5,5-tetramethyl-1-nitrosopyrrolidine was treated as planar, the results are not significantly different for a puckered conformation.

The electric field contributions to *cis/trans* chemical shift differences were obtained as in Table III. The contribution from terms in E^2 always reduces the shielding of a *cis* proton relative to that of a *trans* proton, but the contribution from the E_z term due to the permanent dipole may have either sign. The total effect is found to be small for β-protons, but may be appreciable for α-protons, as illustrated in Fig. 4.

Magnetic anisotropy components were then calculated to fit the *cis/trans* shift differences for β and γ protons. The values for α protons were not used because the uncertainty in the electric field contribution is large for positions near the nitroso group. The calculations were performed for three positions of the point magnetic dipole; at the center of the N=O bond, and on the oxygen and nitrogen atoms of the nitroso group. The values of the anisotropy components obtained by a least squares fit of the data are given in Table IV. For the dipole position on the nitrogen atom the *cis/trans* shift difference is independent of $\Delta\chi_z$ and a value of $\Delta\chi_y$ only is obtained.

The mean errors in the calculated $\Delta\tau$ values and the mean values of the changes in the anisotropy components required individually to correct these errors are also given in Table IV. The mean errors for the dipole position on the nitrogen atom are considerably larger than for the other two dipole positions. The fit for

TABLE IV

MAGNETIC ANISOTROPY COMPONENTS CALCULATED FROM *Cis/Trans* CHEMICAL SHIFT DIFFERENCES FOR β AND γ PROTONS, IN UNITS OF 10^{-30} cm^3 mol^{-1}

Dipole position	$\Delta\tau$	$\Delta\chi_y$	$\Delta\chi_z$	$\delta(\Delta\tau)_{av}$[a]	$\delta(\Delta\chi_y)_{av}$[b]	$\delta(\Delta\chi_z)_{av}$[b]
Center of N=O	Observed	27.3	92.4	0.024	1.15	11.7
	Corrected	28.8	102.0	0.014	0.76	7.7
N atom of N=O	Observed	21.2	—	0.050	5.9	—
	Corrected	23.2	—	0.052	5.8	—
O atom of N=O	Observed	37.2	90.0	0.028	1.76	10.2
	Corrected	39.6	101.4	0.017	1.39	8.1

[a] $\delta(\Delta\tau)$: $|\Delta\tau_{calc} - \Delta\tau_{obs}|$ or $|\Delta\tau_{calc} - \Delta\tau_{corr}|$, in ppm.

[b] $\delta(\Delta\chi_y)$, $\delta(\Delta\chi_z)$: the change in $\Delta\chi_y$ or $\Delta\chi_z$ required to correct the error in $\Delta\tau_{calc}$ for a constant value of the other anisotropy component.

the dipole position at the bond center is better than that for the dipole position on the oxygen atom, and in both cases the application of an electric field correction slightly reduces the errors. In the expression for $\Delta\tau$ for each case considered here the coefficient of $\Delta\chi_y$ is considerably larger than that of $\Delta\chi_z$, so that the values of $\delta(\Delta\chi_y)$ are much smaller than those of $\delta(\Delta\chi_z)$. However, the value obtained for $\Delta\chi_y$ is much more dependent on the location of the dipole than is the value for $\Delta\chi_z$. The best values for the anisotropy components are taken as $\Delta\chi_y = (29 \pm 10) \times 10^{-30}$ cm^3 mol^{-1} and $\Delta\chi_z = (102 \pm 15) \times 10^{-30}$ cm^3 mol^{-1}. The choice of the location of the dipole is arbitrary, the best fit with the observed shift differences being obtained with the dipole at the center of the bond. The chemical shift data used are all for protons more than 3.5 Å from the N=O bond center, and the dependence of the calculated anisotropy values on the dipole location is much smaller than that found by Narasimhan and Rogers (*29*) for the C=O bond, using data for protons much nearer the bond center.

Cis/trans shift differences for α protons were calculated for a point dipole at the N=O bond center, using those values of the anisotropy components which gave the best fit with the corrected shift differences for β and γ protons. These values are given in Table V and Fig. 4, and it is clear that the agreement with

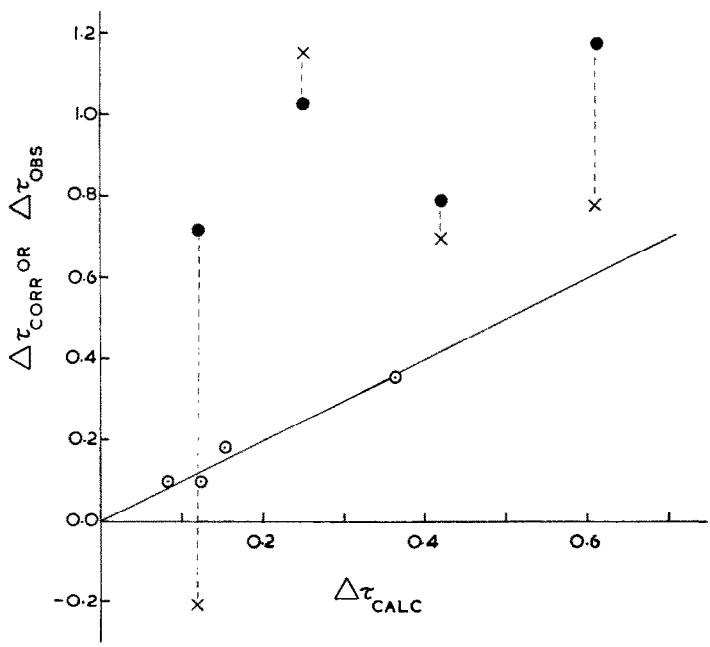


FIG. 4. $\Delta\tau$ values calculated for a point magnetic dipole at the center of the N=O bond using $\Delta\chi_y = 29 \times 10^{-30}$, $\Delta\chi_z = 102 \times 10^{-30}$ cm^3 mol^{-1}, plotted against $\Delta\tau$ values corrected for an electric field contribution. The observed $\Delta\tau$ values for α protons are also shown. ⊙, $\Delta\tau_{corr}$ for β and γ protons; ●, $\Delta\tau_{corr}$ for α protons; ×, $\Delta\tau_{obs}$ for α protons.

TABLE V

MAGNETIC ANISOTROPY CONTRIBUTION TO CHEMICAL SHIFT DIFFERENCES, CALCULATED USING $\Delta\chi_y = 28.8 \times 10^{-30}$ cm^3 mol^{-1}, $\Delta\chi_z = 102.0 \times 10^{-30}$ cm^3 mol^{-1}

Position	$\Delta\tau_{calc}$	$\Delta\tau_{obs}$	$\Delta\tau_{obs} - \Delta\tau_{elec}$[a]
β and γ Protons			
Six-membered ring			
β eq	0.153	0.184	0.164
β ax	0.364	0.331	0.359
β-CH_3 eq	0.124	0.080	0.100
Five-membered ring			
β-CH_2	0.084	0.090	0.100
α-Protons			
Six-membered ring			
α eq	0.12	−0.209	0.72
α ax	0.25	1.152	1.03
Five-membered ring			
α-CH_2	0.61	0.78	1.18
Four-membered ring			
α-CH_2	0.42	0.70	0.79

[a] $\Delta\tau_{elec}$ calculated using the values of A and B obtained by Musher (*32*).

the observed values and with the values obtained by subtracting an electric field contribution is very poor. No better agreement is obtained if the point dipole is located on the nitrogen atom or on the oxygen atom of the N=O group. The calculated shift differences are not very sensitive to the location of the point dipole, with the exception of the value for the α equatorial protons. The lack of agreement between calculated and observed values for α-protons indicates that the approximations used are not valid for positions near the nitroso group. The model used for the electric field contribution is very crude, but it is adequate for the β positions because the effect is relatively small and therefore need not be known very accurately. However, for the α positions the electric field contribution is likely to be more important and it must be known more exactly. The geometry of these systems is not known very precisely and because of the angular dependence of the various contributions to chemical shifts, the effect of a small charge in geometry on the calculated chemical shifts is greatest for positions near the nitroso group. The simple dipole models are not expected to hold at short distances, but insufficient is known about the electronic structure of the nitroso group to allow the use of more elaborate models.

DISCUSSION

The magnetic anisotropy contribution to the long-range shielding calculated with the anisotropy components derived here differs considerably from that pro-

posed by Brown and Hollis (*2*). They suggested a model in which positions along the bond direction are deshielded and positions perpendicular to the bond direction are shielded. We find that all positions in the plane of the NNO group are deshielded due to magnetic anisotropy, the effect being maximum along the bond direction and minimum perpendicular to it. The model of Brown and Hollis (*2*) retains some validity in the sense that in the plane of the nitroso group it is agreed that protons in the direction perpendicular to the N=O bond are shielded relative to those in the bond direction (but not in absolute terms.) The region experiencing shielding is contained by an elliptical cone with its axis perpendicular to the plane of the NNO group, and with the half angle in the plane containing the bond direction smaller than that in a perpendicular plane. This model is rather similar to that proposed by Jackman (*37*) for the carbonyl group in that the axis of maximum diamagnetic susceptibility is perpendicular to the nodal plane of the π-electron system. It is in principal possible to calculate the effect of the nitroso group at any position in space using the anisotropy values given here, together with the procedure for electric field corrections. However such calculations are only of limited use for the following reasons (apart from the errors in our values of $\Delta\chi_y$ and $\Delta\chi_z$):

(a) Since all inductive effects have been ignored only differences in chemical shift between protons in similar chemical groups may be calculated.

(b) Since all other bond anisotropies have been ignored, in particular those of the N—N bond, only pairs of protons in a symmetrical relationship to the N—N bond may be considered.

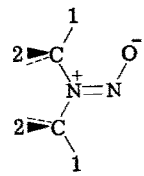
(c) The failure of our calculations for the α positions indicates that the point dipole models used are certainly not valid at short distances from the nitroso group (say, less than 3 Å).

It is worth pointing out that the data used in calculations of group anisotropies in amides (*29*, *30*) and oximes (*38*) are for α protons or for positions even closer to the group considered. As only a small amount of data was used for those calculations, their validity seems doubtful.

Even with the above restrictions however, the type of calculation used here is of use for many substituted N-nitrosamines and for pairs of rotational isomers of the unsymmetrical compounds. The magnetic anisotropy model derived here predicts that for all the positions considered, the protons *cis* to the nitroso group will be more shielded than *trans* protons. It is only the α equatorial positions in a six-membered ring that are observed not to conform to this pattern, and for this position the simple electric field model predicts a large low field shift for the *cis* proton. Qualitatively it would seem that the magnetic anisotropy contribution is dominant except at very short distances.

The chemical shift effects in dialkyl nitrosamines found by Karabatsos (*3*) may be explained on the basis of our results for the α-positions of a six-membered

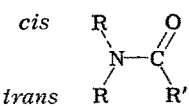
ring. It is assumed (*3*) that the alkyl groups adopt conformations in which the N—N double bond is eclipsed (XIII).

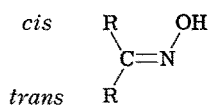


XIII

The positions in the plane of the nitroso group, 1, are equivalent to the equatorial positions in a six-membered ring, the out-of-plane positions, 2, are equivalent to axial positions. In the six-membered ring compounds the shift difference between *cis* and *trans* equatorial protons is 0.2 ppm with the *cis* proton to low field; between *cis* and *trans* axial protons the shift difference is 1.2 ppm with the *cis* proton to high field. The *cis/trans* shift difference for dimethylnitrosamine (and other alkylmethylnitrosamines) would be expected to be an average value $\frac{1}{3}(2\Delta\tau_{ax} + \Delta\tau_{eq}) = 0.71$ ppm. The observed values, 0.75 to 0.80 ppm, are in reasonable agreement with this. For other dialkylnitrosamines the *cis/trans* shift difference varies considerably, being 0.5–0.6 ppm for αCH_2 with the *cis* protons to high field, and 0.2–0.6 ppm for αCH with the *cis* proton to low field. This is also to be expected, since bulky substituents on the α carbon atom will tend to occupy the out-of-plane positions because of interaction with the nitroso group, so that in the series $—CH_3$, $—CH_2R$, $—CHR_2$ the α proton will spend an increasing proportion of its time in the in-plane positions. The position is complicated, however, by the possibility that the groups *cis* and *trans* to the nitroso group may adopt different conformations, and it is not possible to use chemical shift data to estimate conformer population quantitatively.

Dialkylamides (*39*, *40*) and ketoximes (*41*) both show similar patterns of *cis/trans* chemical shift difference to that observed in nitrosamines.





In dialkylformamides and acetamides the resonance of αCH_3 protons *cis* to the carbonyl group is at high field to that of *trans* protons, but for αCH_2 and αCH the *cis* protons are to low field. The chemical shift differences are much smaller than in nitrosamines (*38*, *39*). As in dialkylnitrosamines, this pattern is a result of differences in conformation between *cis* and *trans* groups as well as of anisotropic shielding by the C(:O)R group, but no data are available for cyclic amides to give detailed information about the shielding pattern. In the six-

membered ring system 4-*t*-butylcyclohexanone oxime the *cis/trans* shift differences for α equatorial and α axial protons are opposite in sign. The *cis* equatorial proton is to low field by 0.91 ppm; the *cis* axial proton is to high field by 0.34 ppm (*41*). However, we believe that future work aimed at obtaining bond anisotropies should use chemical shift values only for protons well removed from the anisotropic group in space.

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