Long-range ^{13}C—^{1}H Coupling Constants. Part II.[1] Morpholine, *N*-Methylmorpholine, and 1-Methyl-4-piperidone

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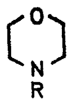
Single resonance ^{13}C Fourier transform n.m.r. spectra of the title compounds are described. It is shown that the pattern of fine splitting caused by long-range ^{13}C–^{1}H couplings together with the ^{1}J values provides a means of differentiating ^{13}C nuclei in the system $NCH_2{}^{13}CH_2X$, where X = $>$C=O, $>$NH, $>$NMe, or $>$O.

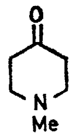
RECENTLY, determination of long-range ^{13}C–^{1}H coupling constants directly from single resonance ^{13}C n.m.r. spectra (either by CAT or by FT) has attracted some attention.[1,2] Basically, long-range ^{13}C–^{1}H coupling constants should be determined by complete iterative computer analysis.[2] However, if one needs to determine them for diagnostic purposes, *i.e.* to apply the coupling constants for unequivocal assignment of ^{13}C resonances of complex molecules, approximate constants determined by a first-order analysis are sufficient. Indeed, the usefulness of the analysis of fine splitting has been demonstrated in the case of cyano-pyridines,[1] hydroxypyridines,[3] and *ortho*-disubstituted benzenes.[4]

It is expected that the pattern analysis of the fine splitting can be extended to non-aromatic systems, and as an example, the analysis of fine splitting of the undecoupled ^{13}C n.m.r. spectra of morpholine (1),* 1-methylmorpholine (2), and 1-methyl-4-piperidone (3) was attempted.



(1) R = H

(2) R = Me



(3)

EXPERIMENTAL

^{13}C N.m.r. spectra were recorded with a Varian XL 100-FT instrument with proton-noise decoupling to assess chemical shifts and without to assess coupling constants. Conditions of measurement: (decoupled spectra) sweepwidth 5000 Hz with 4096 memory points, acquisition time 0·4 s, pulse width 25 μs, no. of pulses accumulated 200; (undecoupled spectra) sweepwidth 1000 Hz with 4096 memory points, acquisition time 2·0 s, pulse width 10 μs, no. of pulses accumulated 7500—8000. The solutions

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* In this paper morpholine is numbered with the nitrogen atom 1 to facilitate comparisons.

[1] Part I, Y. Takeuchi and N. Dennis, *J. Amer. Chem. Soc.*, 1974, **96**, 3657.

[2] M. Hansen and H. J. Jakobsen, *J. Magnetic Resonance*, 1973, **10**, 74.

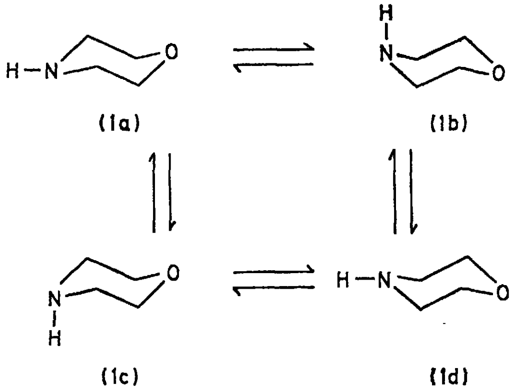
[3] U. Vögeli and W. von Philipsborn, *Org. Magnetic Resonance*, 1973, **5**, 551.

[4] H. Günther, H. Schmickler, and G. Jikeli, *J. Magnetic Resonance*, 1973, **11**, 344.

were prepared by adding $CDCl_3$ (1·5 ml) to the sample (2 ml).

RESULTS AND DISCUSSION

The essential difficulty associated with the analysis of the n.m.r. spectra of compounds such as (1) is the fact that because of rapid ring- and nitrogen-inversions the observed n.m.r. parameters are in fact the weighted average of all the possible conformers; in morpholine, for instance, a rapid equilibrium is established among the four conformers (1a—d). This study demonstrates that the average parameters have some diagnostic value as long as one realises their approximate nature.



Under the undecoupled conditions, each of the ring carbon nuclei of (1)—(3) gives a triplet (relative intensity 1 : 2 : 1) owing to two equal couplings with protons directly bonded to it, while the methyl carbon of (2) and (3) gives a quartet (relative intensity 1 : 3 : 3 : 1) owing to three equal couplings with the methyl protons. Each line further splits into a multiplet due to the long-range (*i.e.* through more than two bonds) couplings; the pattern and the width of the fine splitting seem to depend on the nature of the atom or the group of atoms adjacent to the carbon in question.

The chemical shifts were read directly from the decoupled spectra, and ^1J values [*] were estimated as the difference in Hz between the centres of the multiplets. The results are summarised in Table 1. The assignment is based on the larger ^1J values associated with the carbon nuclei adjacent to a heteroatom (>130 Hz), in particular to an oxygen atom (*ca.* 140 Hz).[†]

In principle, the fine splitting of the C(2)–C(6) signal of (1), for instance, should be analysed as an $A_2A'_2B_2B'_2X$ ($X = {}^{13}C$) spin system [‡] (or at least as an $A_2A'_2B_2X$ spin system if four-bond coupling constants are neglected [6]). In the light of the results obtained for pyridines,[1] it is anticipated that first-order analysis of the fine splitting will provide approximate average coupling constants which are sufficient for diagnostic purposes. If first-order analysis is allowed, and the contribution of ^4J is neglected, C(2)–C(6) and C(3)–C(5) resonances of (1) and C(3)–C(5) resonances of (2) and (3) should involve four couplings, *i.e.* couplings with two adjacent protons {*e.g.* two ^2J[C(2)–H(3)]} and two protons across the heteroatom or the carbonyl carbon {*e.g.* two ^3J[C(2)–H(6)]}. The fine splitting pattern will depend on the magnitude of the two coupling constants involved.

TABLE 1

Chemical shift (δ) and one-bond coupling constants (^1J) for (1)—(3)

	δ [a,b]			^1J/xz		
	C(2)–C(6)	C(3)–C(5)	Me	C(2)–C(6)	C(3)–C(5)	Me
(1)	45·8	67·2		132	140	
(2)	55·1	66·3	46·0	133	142	132
(3)	54·7	40·9	44·6	134	130	133
	(55·4)	(40·3)	(45·1)			

[a] In p.p.m. from the ^{13}C resonance of Me_4Si. [b] Values in parentheses are taken from A. J. Jones and M. M. A. Hassan, *J. Org. Chem.*, 1972, **37**, 2332.

First, which of the two coupling constants, ^2J or ^3J, is the larger should be determined. This is difficult because the observed coupling constants are in fact the averaged values while ^3J, the vicinal coupling constant, varies from 0 to 8 Hz depending on the torsional angle.[7] In this connection, the fine splitting observed for the methyl carbon of (2) and (3) is the most straightforward to analyse. Thus, if predominance of the equatorial methyl conformer is assumed,[8] the fine splitting should be a quintet [couplings with four equal protons, *e.g.* two H(2) and two H(6)] as is in fact observed (Figure). The apparent coupling constant (2 Hz) is rather small probably because of the averaging effect. If this assignment can be extended to the ^3J values associated with ring carbon nuclei of (1)—(3), ^3J are in the range 0—2·5 Hz while ^2J are in the range 3—5 Hz.

TABLE 2

Fine splitting pattern for the ring carbon nuclei of (1)—(3)

Pattern		J/Hz	Width of multiplet (Hz)
Triplet	$^2J \gg {}^3J \simeq 0$	C(3)–C(5) of (3) (3 Hz)	~6
Triplet with structure	$^2J \gg {}^3J > 0$	C(2)–C(6) of (1) (5, 1 Hz)	>10
		C(3)–C(5) of (1) (5, 2 Hz)	~10
Septet	$^2J \simeq 2 \times {}^3J$	C(3)–C(5) of (2) (5, 2·5 Hz)	~15
Sextet	$^2J \simeq {}^3J[C(2)–H_3C] \gg {}^3J[C(2)–H(6)]$	C(2)–C(6) of (2) and (3) (5, 1 Hz)	~25

Now it is possible to classify the observed splitting patterns according to the relative magnitude of ^2J and

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[*] In fact ^1J values for methylene carbons adjacent to nitrogen depend on the torsional angle between the nitrogen lone pair and the C–H bond involved, and two ^1J values can be obtained if the system is fixed.[5]

[†] Johnson and Jankowsky made an assignment different from the present study. They assigned the low-field peak to C(6) rather than C(3) or C(5): L. F. Johnson and W. C. Jankowski, 'Carbon-13 N.M.R. Spectra,' Wiley, New York, 1972, No. 202 (2-ethylpiperidine).

[‡] A small ^{13}C isotopic shift should also be taken into consideration.

[5] Y. Takeuchi, P. J. Chivers, and T. A. Crabb, *J.C.S. Chem. Comm.*, 1974, 210.

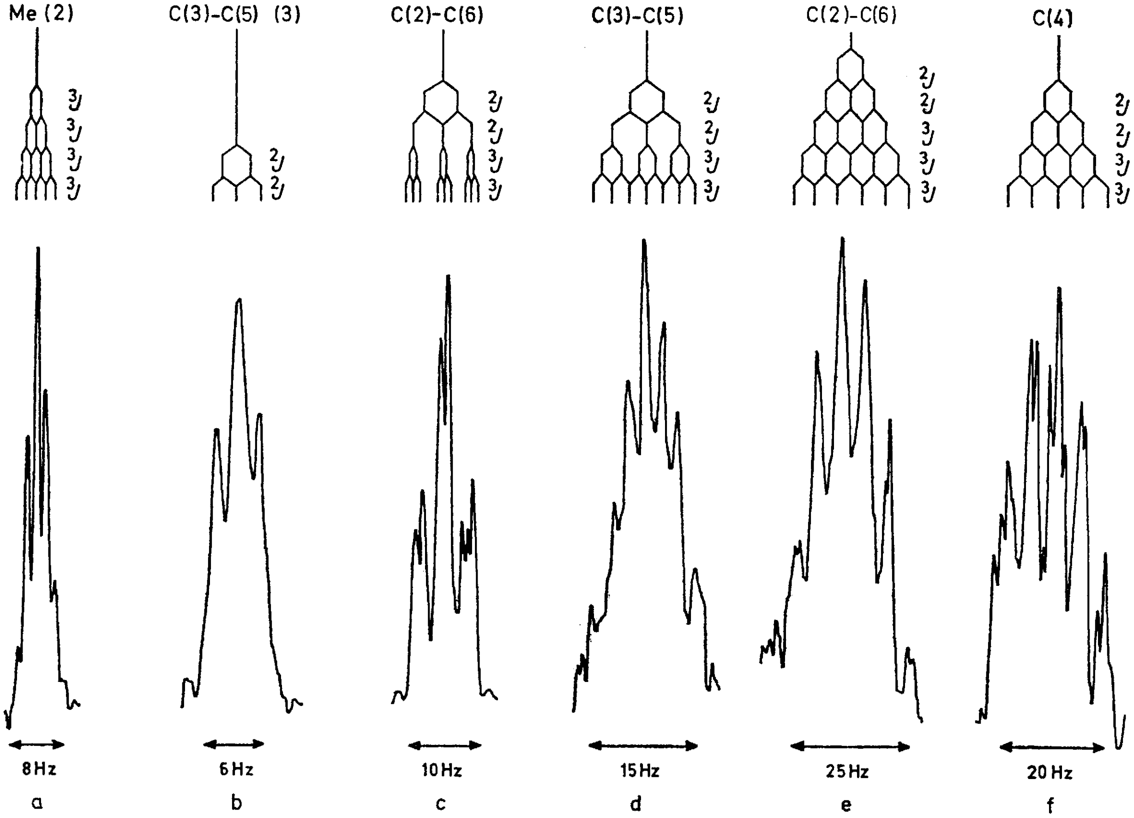
[6] J. B. Stothers, 'Carbon-13 N.M.R. Spectroscopy,' Academic Press, New York, 1972, ch. 10.

[7] L. T. J. Delbaere, M. N. G. James, and R. U. Lemieux, *J. Amer. Chem. Soc.*, 1973, **95**, 7866.

[8] For 1-methylpiperidine, the amount of the equatorial methyl conformer is estimated as 75%: I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.

^3J; the results are summarised in Table 2. In Figures b—d, examples of the patterns are given for various cases.

The fine splitting observed for C(2)–C(6) of (2) and (3) can be analysed as a sextet (Figure e). The most reasonable explanation is that the splitting involves five equal couplings (J 5 Hz). Two of them are due, by analogy with the ring carbon nuclei, to $^2J\{^2J[\text{C(2)–H(3)}]\}$, and the rest to the coupling with the three methyl protons. The reason why coupling with the methyl protons is larger than $^3J[\text{C(2)–H(6)}]$ is probably the difference in the net effect of averaging three rather than two protons. Larger ^3J values for the former case are reasonable in the light of the large ^3J for, *e.g.*, dimethyl ether (5·4 Hz).[6]



Fine splittings of ^{13}C resonances caused by long-range coupling

The fine splitting observed for C(4) of (3), which couples with four equal protons [two H(3) and two H(5)], is a quintet (5 Hz) (Figure f). This is not unexpected if ^3J is small (*ca.* 1 Hz).

In summary, analysis of the fine splitting pattern together with the magnitude of ^1J is valuable in identifying carbon nuclei adjacent to >C=O, >NH, >N–Me, and >O groups in complicated saturated heterocyclic compounds (Table 3).

Finally, the possibility of applying long-range ^{13}C–^{1}H coupling constants to conformational analysis of (2) was investigated. It is expected that at low temperature ring- and/or nitrogen-inversion is slowed down, and that the amount of the less stable axial methyl conformer will increase to some extent. The combined effect will affect the n.m.r. parameters, both chemical shifts and coupling constants, and from this change some information on the conformation could perhaps be obtained. Thus, the undecoupled spectrum of (2) was determined at −70°. Unfortunately, no significant change was observed for the fine splitting. This failure is due partly to the low ^3J values involved, and partly to very small conformational barriers for (2).[9]

TABLE 3

Fine splitting of ^{13}C resonances in $CH_2{}^{13}CH_2X$

X	Pattern	Width (Hz)	^1J/Hz
>C=O	Triplet	~6	130
>NH	Triplet [a]	~10	132—134
>NMe	Sextet	~25	132—134
>O	Triplet [a] or septet	~10 ~15	140

[a] Sometimes with structure.

A minor downfield shift (6 Hz or 0·25 p.p.m.) was, however, observed for the methyl carbon resonance though the shifts of the ring carbons remain unchanged. If this shift is ascribed to an increase in the

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[9] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 122.

less stable conformer, the axial methyl resonance is at lower field than the equatorial methyl one. This is contrary to observations of the methyl resonance for methylcyclohexane where the shift for the axial methyl is 6 p.p.m. to higher field than that for the equatorial methyl group.[10]

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[10] F. A. L. Anet, C. H. Bradley, and C. W. Buchanan, *J. Amer. Chem. Soc.*, 1971, **93**, 258.