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CORRELATIONS OF N.M.R. SPECTRAL PARAMETERS WITH STRUCTURE: BENZYLIC COUPLING IN SUBSTITUTED PYRAZINES

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The recent isolation of pyrazines from various natural sources (1) has stimulated interest in the characterisation of this class of compound.(2) For simple di- and tri-substituted pyrazines the main problem of structure elucidation is often the determination of the relative positions of the substituent groups on the pyrazine ring. In this respect n.m.r. coupling constant data are especially helpful. The purpose of the present communication is to present our preliminary observations on the phenomenon of benzylic coupling in substituted pyrazines.

Summarised in the Table are the benzylic coupling constants for methylpyrazine and the three isomeric methoxy methylpyrazines, obtained by a first order analysis (at 60 MHz) of the splitting of the ring methyl signal.

Long Range Splittings of Methyl Proton Signal

Compound	Solvent	Coupling Constants (Hz)		
		$\lvert {}^4\underline{J}\ \text{ortho} \rvert$	$\lvert {}^5\underline{J}\ \text{meta} \rvert$	$\lvert {}^6\underline{J}\ \text{para} \rvert$
2-methylpyrazine	CCl_4 [a]	~0.6	0.29	~0.6
2-methoxy-3-methyl pyrazine	CCl_4 benzene-d_6	- -	0.22 0.25	0.65 0.66
2-methoxy-5-methyl pyrazine	CCl_4 DMSO-d_6	0.66 0.64	0.29 0.27	- -
2-methoxy-6-methyl pyrazine	benzene-d_6	0.66 or 0.74 [b]	-	0.74 or 0.66 [b]
	CCl_4	$\lvert {}^4\underline{J}_o \rvert + \lvert {}^6\underline{J}_p \rvert = 1.40$ [c]		

a With the addition of 0.025 molar equivalents of Eu $(DPM)_3$ (3).

b The alternative values were obtained by applying decoupling irradiation to the ring protons separately.

c The methyl signal approximates a 1:2:1 triplet.

The orders of magnitude of the constants are in accordance with a fairly well established pattern for benzylic coupling involving "free" rotating alkyl groups (4) (the absolute magnitudes are quite similar to corresponding values obtained for toluene(5) and substituted toluenes (6), for example). *Furthermore, the consistency of the values clearly reflects the previously observed* (7) *relative* insensitivity of benzylic coupling constants to substituent effects. The relationship $|{}^6\underline{J}_p| \sim |{}^4\underline{J}_o| > |{}^5\underline{J}_m|$ is therefore expected to be general for a much wider variety of substituted methylpyrazines. The results recorded in the Table are not in accordance with the interpretation of benzylic coupling ($|{}^5\underline{J}_m| > |{}^6\underline{J}_p|$ or $|{}^4\underline{J}_o|$) proposed by Cox and Bothner-By (8,9) for methylpyrazine and for a number of di- and tri-substituted pyrazines. Values given by these authors were probably based on a misinterpretation of the chemical shifts of the ring protons of the 2,3-disubstituted pyrazines, and of the ring methyl protons of the trisubstituted pyrazines.*

The correct assignment of the ring proton chemical shifts for disubstituted pyrazines (which is a prerequisite for determination of the benzylic couplings) is by no means a trivial problem. An unambiguous assignment was made possible for the 2,3- and 2,5-isomers listed in the Table by examination of the spectra of specifically ring deuterated derivatives. Details of the synthesis of these, and of the undeuterated compounds, will be given in a forthcoming publication.

Trisubstituted pyrazines possessing two methyl substituents pose an analogous problem of assignment. Although data for these compounds are not included here, the relation $|{}^4\underline{J}_o| > |{}^5\underline{J}_m|$ requires that, for the compounds listed in the earlier work (8), the *signal of the methyl group adjacent to the non-alkyl substituent is the one downfield of that* of the other methyl group. Our observation that the 2,3-methoxy and chloro methylpyrazines show downfield ring methyl shifts relative to those of the corresponding 2,6-isomers supports this assignment.

The absolute, as well as the relative, magnitudes of some of the coupling constants given in the Table require some comment, for it is evident that values derived from a first order analysis will be in error where the spin system concerned does not give rise to a first order spectrum. At 60MHz the spectrum of methylpyrazine in CCl_4 (or $CDCl_3$) shows evidence of a tightly coupled aromatic proton system, and the methyl group signal (X_3 part

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* It seems likely that the values for methylpyrazine were assigned by analogy.

of an $ABCX_3$ system) appears as a rather complex multiplet which is not readily interpretable. On addition of (approximately) 0.025 molar equivalents of Eu $(DPM)_3$ (3) the whole spectrum becomes capable of first order interpretation, the methyl signal now appearing as a triplet of doublets with the splittings recorded in the Table. Assignment of the smaller doublet splitting to $^5\underline{J}_m$ was readily achieved by irradiation at the frequency of the ring proton meta to the methyl group, whereupon the methyl signal collapsed to an approximate 1:2:1 triplet. A triplet with virtually identical splittings was observed for the methyl signal in the spectrum of 2-deutero-6-methylpyrazine. This latter observation indicates that $Eu(DPM)_3$ at the low concentration employed does not significantly affect the size of the nuclear couplings. Similarly, no difference could be observed in the ring methyl triplet splitting for 2-methoxy-6-methylpyrazine in the presence or absence of 0.025 molar equivalents of $Eu(DPM)_3$. While further work is required to establish the generality of these observations, it seems likely that (where applicable) the use of small concentrations of lanthanide DPM complexes may be of considerable value in enabling the determination of certain small long range couplings by first order analysis. Determination of the spectrum at high frequencies may not be a satisfactory alternative, since the present generation of 220/300 MHz instruments exhibit lower resolution (linewidth) performance than those at 60 or 100 MHz.

Although the ring protons and the ring methyl group of the 2,5- and 2,6-isomers of methoxy methylpyrazine can be considered to approximate to AMX_3 spin systems (for carbon tetrachloride and benzene solutions) the 2,3-isomer shows an ABX_3 system, the AB protons becoming more tightly coupled as the solvent series benzene-d_6 ⟶ carbon tetrachloride ⟶ DMSO-d_6 is traversed. While a first order interpretation of the X part of the spectrum is permissible for the benzene and carbon tetrachloride solutions without serious error, the same is not true for the DMSO-d_6 spectrum(or indeed, the DMSO spectrum (8)). In this latter solvent the methyl signal appears as (essentially) a doublet with a splitting of 0.4Hz. A solvent dependence of the coupling constants of the order implied by this change is not likely (cf. the results in the Table for 2-methoxy-5-methylpyrazine in carbon tetrachloride and DMSO-d_6). From a consideration of the ABX_3 analysis (10) the methyl splitting is $|\underline{J}_{AX} + \underline{J}_{BX}|$. The observed splittings for carbon tetrachloride and benzene solutions compared with the splittings for DMSO-d_6 solution therefore suggest that $\underline{J}_{AX}$ and $\underline{J}_{BX}$ (i.e. $^6\underline{J}_p$ and $^5\underline{J}_m$) are of opposite sign, as indeed they are for toluene (5) and 2-bromo-

5-chlorotoluene (6b).

A subsequent publication will discuss benzylic coupling in pyrazine derivatives which have one or more substituents at the benzylic carbon atom.

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