Tetrahedron. Vol. 29, pp 3939 to 3942. Pergamon Press 1973. Printed in Great Britain

THE NUCLEAR MAGNETIC RESONANCE SPECTRA OF PYRAZINES—II

THE INFLUENCE OF SIDE-CHAIN ALKYL SUBSTITUTION ON THE BENZYLIC COUPLING CONSTANTS

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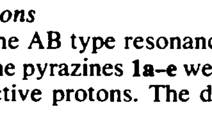
(*Received in the UK* 1 *June* 1973; *Accepted for publication* 13 *July* 1973)

Abstract—The benzylic coupling constants ^5J_m and ^6J_p for a series of 2-alkyl-3-methoxypyrazines, in which the size of the 2-alkyl group is progressively increased, are reported and discussed. ^5J_m remains virtually constant, while ^6J_p falls steadily with increasing alkyl group size. These effects are largely attributed to variations in the time-averaged orientation of the benzylic protons and are consistent with the generally accepted mechanisms for meta and para benzylic coupling. The results illustrate the importance of taking conformational aspects into account when attempting to use benzylic coupling constants derived from substituted side-chains in making structural assignments.

In previous publications[1,2] the "benzylic" coupling of ring protons to the ring Me protons in a number of substituted methylpyrazines was reported and discussed. From our results, and those of Bothner-By and Cox[3,4] it was apparent that a knowledge of the relative magnitudes of the benzylic coupling constants would allow, for example, the assignment of the chemical shifts of the ring protons in certain pyrazines even when protonated or complexed via the N atoms. For 2-Me-3-substituted or 2-Me-5-substituted derivatives this would involve comparison of the magnitudes of the well differentiated coupling constants ^5J_m and ^6J_p($^6J_p \sim 2 \times {^5J_m}$), or ^5J_m and ^4J_o ($^4J_o \sim 2 \times {^5J_m}$). However, since ^4J_o and ^6J_p are similar in magnitude (and sign)[2], uncertainties might arise in assigning 2-Me-6-substituted pyrazines in this way. Similarly, measurement of the benzylic coupling constant should, in principle, allow one to decide between possible alternative pairs of structures of type **a** and **b**, or **a** and **c**, for example, but a decision on the above basis between pairs of structures of type **b** and **c** would be more difficult.

When other groups are substituted for one or two of the ring Me group H atoms, however, the relative magnitudes of the benzylic coupling constants may undergo a considerable change. For example, the values of ^5J_m and ^6J_p (Fig 1 and table 1) for 2-isopropyl-3-methoxypyrazine are observed to be virtually identical (0·32 Hz, 0·31 Hz), whereas for 2-methyl-3-methoxypyrazine the corresponding magnitudes are 0·29 Hz and 0·71 Hz respectively. In this paper the values of the coupling constants ^5J_m and ^6J_p are reported and discussed for a series of 2-alkyl-3-methoxypyrazines in which the protons on the ring Me group of 2-Me-3-methoxypyrazine were progressively substituted, giving the sequence 2-Me, 2-Etl, 2-Et, 2-s-Bu and 2-(1-ethylpropyl)-3-methoxypyrazine (**1a–e**).

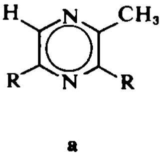


1 X = OMe **2** X = H
a: $R_1 = R_2 = H$
b: $R_1 = H, R_2 = Me$
c: $R_1 = Me, R_2 = Me$
d: $R_1 = Me, R_2 = Et$
e: $R_1 = Et, R_2 = Et$

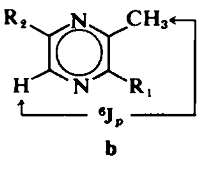
RESULTS

(i) *Assignment of the chemical shifts of the ring protons*

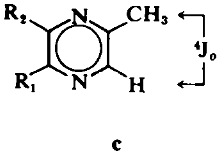
The AB type resonances of the two ring protons of the pyrazines **1a–e** were first assigned to their respective protons. The difference in chemical shift



a



b



c

Table 1

Pyrazine	$\|^5J_m\|$/Hz	$\|^6J_p\|$/Hz	Δ^a/p.p.m.
2-Methyl-3-methoxy	0·29±0·02	0·71±0·02	−0·12
2-Ethyl-3-methoxy	0·30±0·02	0·60±0·02	−0·04
2-Isopropyl-3-methoxy	0·32±0·02	0·31±0·02	+0·24
2-s-Butyl-3-methoxy	0·32±0·02	0·18±0·02	+0·33
2-(1-Ethylpropyl)-3-methoxy	0·33±0·02	0·08±0·03[b]	+0·43

[a] See definition in text.
[b] Not completely resolved, estimate from line width.

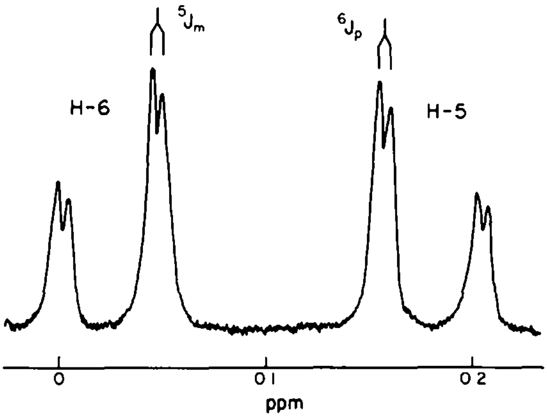


Fig. 1. Aromatic proton spectrum of 2-isopropyl-3-methoxypyrazine.

between A and B, δAB, increases in a regular manner from **1a** to **1e**, and, since δA and δB have previously been assigned by deuterium substitution[2] for **1a**, it appeared likely that these parameters could be assigned by analogy in cases **1b–e**. Estimated chemical shifts for the 5- and 6-protons were obtained by summation of the separate shifts for these protons (from pyrazine reference) observed in the spectra of methoxypyrazine and of the parent alkylpyrazines (**2b–e**), as previously described for substituted methylpyrazines.[2] The estimated shifts confirmed the assumption that the 5- and 6-proton resonances do not cross over in going from Me to the higher alkyl substituents.

(ii) *Measurement of the benzylic coupling constants ^5J_m and ^6J_p*

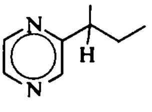
Values obtained for the coupling constants ^5J_m and ^6J_p are given in Table 1. Those for the first member of the series, 2-methyl-3-methoxypyrazine were reported previously.[2] For the remaining homologues the coupling constants were obtained from the splittings of the ring proton signals, except that in the case of 2-ethyl-3-methoxypyrazine, the splitting (triplet) due to the small coupling ^5J_m could not be fully resolved, but appeared to be about 0·3 Hz. In this case, therefore, the methylene signals of the Et group were simulated as the B_2 part of an A_3B_2XY system using suitable values for J_{BX} and J_{BY} in 0·02 Hz increments. Comparison with the observed methylene group spectrum gave the best fit for ^5J_m and ^6J_p with the values +0·30 Hz and −0·60 Hz respectively. The spectra of the isopropyl, s-Bu and 1-ethylpropyl derivatives could be satisfactorily treated by first-order analysis.

DISCUSSION

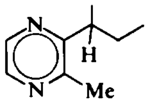
Substitution of the α side-chain C atom of the pyrazines could conceivably affect the magnitudes of the benzylic coupling constants (a) by a substituent electronegativity effect, and (b) by causing variations in the time-averaged orientation of the remaining α-protons with respect to the pyrazine ring. The first of these possibilities is not expected to be a significant factor for the small changes in electronegativity involved in successive substitution of methyl groups. For example, the plot of substituent electronegativity against ^6J_p obtained for substituted toluene derivatives by Janzen and Schaefer[5] suggests only a small reduction (of the order 5%) in ^6J_p on substitution of Me for H. For the pyrazines discussed here, therefore, this effect is unlikely to cause the quite significant fall in ^6J_p which is observed as the side-chain substitution is increased. In any case, after 2-isopropyl-3-methoxypyrazine, the substitution in traversing the series is no longer at the α-carbon atom, but a large change in ^6J_p is nevertheless still observed on going from isopropyl to s-Bu, and again on going from s-Bu to 1-ethylpropyl.

The observed effects on ^6J_p are thus attributed largely to differences between homologues in the time-averaged orientation of the side-chain α-protons with respect to the plane of the ring. Since there is evidence[2] to suggest that ^6J_p is π-electron transmitted, a theoretical dependence on $\sin^2\theta$ (where θ is the rotational angle between the C—H plane and the ring plane) discussed for the σ-π-interaction mechanism[6] is expected to apply. On the basis of this mechanism the π-electron transmitted coupling will be zero for the in-plane conformation of a side-chain proton, and at a maximum when it is at 90° to the plane. The behaviour of ^6J_p in the present series of compounds is consistent with this picture, as the increasing size of the side-chain substituents would be expected to favour an approach of the time-averaged α-proton orientation towards the in-plane conformation on simple steric grounds.

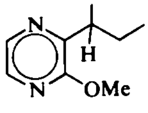
It is interesting in this context also to observe the behaviour of the chemical shift of the side-chain α-protons in the series of compounds **1a–e**. A contribution to the deshielding of these protons from the electrostatic effect of the OMe substituent might be expected,[7] but a gradual reduction in the angle θ would also be expected to be accompanied by a decrease in shielding due to the anisotropy of the aromatic ring system. In fact, a significant proportion of the shift is presumably due to the anisotropy of the pyrazine ring system since both Me and OMe groups, when substituted in the 3-position of 2-*s*-butylpyrazine, give rise to significant downfield shifts of the side-chain methine proton.



δ methine 2·81



2·96



3·13

In the series of compounds **1a–e**, the chemical shifts of the side-chain α-protons were compared by referencing each shift to that of the parent 2-alkyl compound **2a–e**, to avoid the effects on the chemical shift of increasing alkyl chain length other than those due to conformational orientation. The chemical shift difference Δ so obtained

$$\Delta_{\alpha\text{-proton}} = \delta(\text{2-alkyl-3-methoxypyrazine}) - \delta(\text{2-alkylpyrazine})$$

increases with increasing size of alkyl substituent (Table 1 and Fig 2) in accordance with the expectation of decreasing θ with increasing alkyl group size.

In comparison with the para benzylic coupling it is known that the mechanism of the meta benzylic coupling has a contribution due to σ-coupling.[2] It is significant, therefore, that the results in Table 1 show that while ^6J_p undergoes a steady decrease with increasing side-chain substitution, ^5J_m stays virtually constant. Schaefer *et al.*[8] have commented on the fact that ^5J_m in certain toluene derivatives, and in benzaldehyde, has the same value within experimental error. Since σ-coupling is expected to be at a maximum for the planar zig-zag path, and π-coupling to be at a maximum when the side-chain C—H bond is at 90° to the plane, these authors have suggested that the σ- and π-contributions might conceivably compensate each other in such a way as to lead to similar magnitudes for ^5J_m in the examples given. The constancy of the ^5J_m values for the pyrazines in Table 1 supports the idea of compensating σ- and π-mechanisms. Thus for 2-(1-ethylpropyl)-3-methoxypyrazine, the negligible π-interaction coupling on the evidence of the very small value for ^6J_p suggests the possibility that ^5J_m for this compound is almost entirely σ-electron transmitted. The best path for σ-electron coupling is the zig-zag conformation represented by the five bond coupling path in **3**, and it seems likely that the presence of the OMe substituent at the 3-position would lead to the conformation of **3** being preferred to that of **4**. In fact, it has been shown for certain toluene and aniline derivatives that the five bond path of the type represented in **4** leads to essentially zero meta benzylic coupling.[9,10]

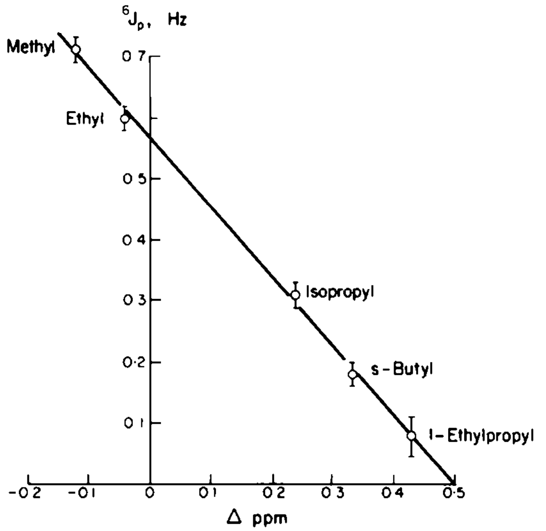
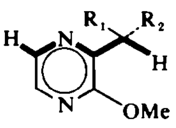


Fig. 2. Plot of para benzylic coupling constant ^6J_p for 2-alkyl-3-methoxypyrazines against chemical shift difference Δ.



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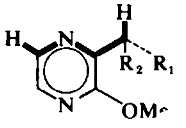

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In spite of the relative invariability of ^5J_m it will be seen that the results discussed in this paper demonstrate that the use for structural assignments of benzylic coupling constants derived from substituted side-chains, must be accompanied at least by careful consideration of conformational behaviour. In many cases, close models might well be necessary. For highly electronegative substituents the electronegativity factor will obviously also have to be taken into account.

EXPERIMENTAL

NMR measurements. All measurements were obtained at 60 MHz for CCl_4 solns with the instrumentation, and under the conditions, previously described.[2] Simulations of the A_3B_2XY spin system were carried out on a Varian 620i computer using the programme SIMEQ. Analytical

GLC was performed on a Pye 104 instrument with 9 ft. glass columns packed with Apiezon L on Chromosorb G, FFAP on Chromosorb G, or ethylene glycol adipate (EGA) on Chromosorb G. Preparative GLC was performed on a 20 ft. column of EGA on Chromosorb G. All solvents were reagent grade or better. The preparation of most of the compounds here mentioned has been described previously.[11]

2-Ethyl-3-methylpyrazine. This material was prepared in 55% overall yield by the condensation of ethylene diamine with 2,3-pentadione,[12] followed by dehydrogenation of the dihydropyrazine over copper chromite.[13]

2-s-Butyl-3-methylpyrazine. The alkylation of 2-ethyl-3-methylpyrazine with ethylbromide was carried out as previously described.[14] The product was isolated in 25% yield by fractionation through a spinning band column.

Acknowledgements—The authors wish to thank Mr. D. J. Frost of the Unilever Research Laboratory, Vlaardingen, Netherlands, for carrying out the simulation on the A_3B_2XY system, Mr. I. M. Payne for assistance with the synthesis of the compounds and Dr. G. Riezebos for his interest and encouragement.

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