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TAUTOMERISM IN *OH*-, *SH*-, AND NH_2-SUBSTITUTED PYRAZINES
- A CARBON-13 AND NITROGEN-15 NMR STUDY -[+]

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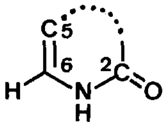
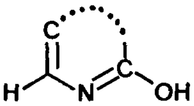
Abstract: It is shown that ^{13}C,^{1}H spin-spin coupling constants can be used to study heteroaromatic tautomerism. Results for the title compounds are supported by ^{15}N-NMR data.

NMR spin-spin coupling constants between carbon-13 and protons have recently been recognized as sensitive probes for the elucidation of protonation schemes in heterocyclic systems.1) The application of these parameters to problems of heteroaromatic tautomerism of the pyridone-hydroxypyridine type2) was thus indicated. Considering the tautomers A and B, on the basis of earlier results1,3) we expected especially the constants involving 6-H — i.e. $^{3}J(2,6)$ and $^{2}J(5,6)$ — to differ characteristically in both structures.

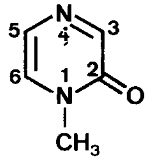


A

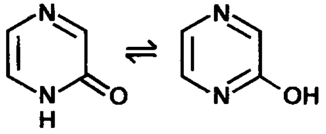


B

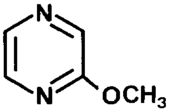
We now report data for suitable substituted pyrazines (**1** - **8**) as obtained from their 100.6 MHz ^{13}C-NMR spectra (solvent DMSO). At a B_o-field of 9.4 T, the ^{1}H spin systems of **1** - **8**4) are first order and the ^{13}C,^{1}H coupling constants can be measured directly. The results given in Table 1 indeed indicate that J(^{13}C,^{1}H) data are of value with respect to the analysis of A ⇌ B equilibria. In addition, recent advances in ^{15}N-NMR spectroscopy, where the sensitivity problem is now less severe through the use of high B_o fields and the INEPT pulse sequence5) made it desirable to investigate **1** - **8** using also this technique, especially since earlier ^{14}N-NMR results6) had shown that characteristic differences can be observed for the tautomeric structures A and B.



1



2a 2b



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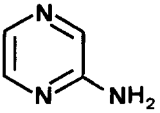

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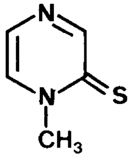

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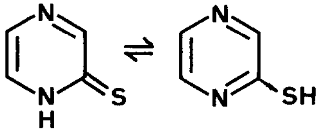
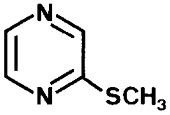


5a 5b



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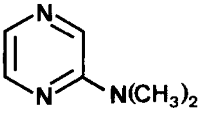


8

^{13}C-NMR Results

Considering the first set of compounds (1-3), with 1 and 3 as models for the tautomers 2a and 2b, respectively, it is immediately clear that for the OH-substituted system 2a is the dominating tautomer. Except for a methyl group effect on $^3J(2,6)$ the data for 1 and 2 agree closely, whereas those for the model system 3 differ considerably. The most pronounced changes are given in italics in Table 1.

In view of the exp. error of $\leqslant 0.2$ Hz it is also clear from the observed ^2J and ^3J values, however, that a certain percentage of 2b must be present. Using only

Table 1. ^{13}C,^{1}H spin-spin coupling constants of OH, SH-, and NH$_2$-substituted pyrazines (solvent DMSO-d$_6$; ν_o = 100.61 MHz)

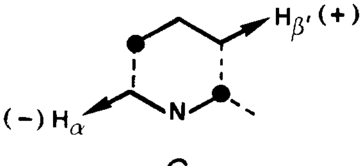
	1	2a/2b	3	4	5a/5b	6	7	8
$^1J(3,3)$	187.4	187.0	186.9	191.8	192.2	186.5	184.6[a]	183.2
$^1J(5,5)$	188.9	188.9	184.6	189.3	191.4	185.1	183.1	183.2
$^1J(6,6)$	183.1	182.9	183.1	186.5	186.9	184.2	178.2	178.7
$^2J(2,3)$	10.9	10.3	*6.6*	12.9	12.7	*9.8*	9.1	9.4
$^2J(5,6)$	5.0	5.4	*9.9*	5.7	5.5	*10.0*	9.7	9.7
$^2J(6,5)$	13.3	12.7	*11.5*	13.3	12.6	*11.2*	11.5	11.6
$^3J(2,6)$	4.8[b]	6.2	*10.6*	4.4[c]	5.4	*9.8*	9.1	9.4
$^3J(3,5)$	10.2	10.1	10.7	10.1	9.7	10.0	9.4[a]	9.9
$^3J(5,3)$	12.8	12.0	*9.9*	12.4	11.6	*10.0*	9.7	9.7
conc(M)	1.7	1.5	1.7	1.6	1.5	1.5	4.2	1.5

[a] in H_2O as solvent; [b] after correction for the CH_3-effect[7)] 5.6 Hz; [c] after correction for the CH_3-effect[7)] 5.2 Hz

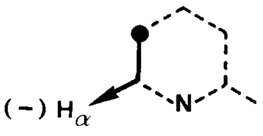
couplings that differ by more than 4 Hz in both model structures (1 and 3, respectively), one estimates a molar ratio 2a/2b of ~ 9:1. More exact determinations should be possible by reducing the exp. error and employing extrapolation to infinite dilution.

For the second set of compounds (4-6) with 4 and 6 as models for the tautomers 5a and 5b, respectively, a similar comparison establishes 5a as the dominating structure. Again, the presence of a few percent of the alternative structure 5b is indicated (~5%). Finally, the data found for 7 and 8 clearly establish the 2-amino-pyrazine structure for these systems, even in the absence of data for an imino tautomer.

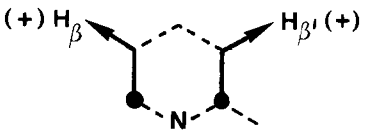
Comparing the model systems 1 and 3 as well as 4 and 6 it is interesting to note that practically all the long-range ^{13}C,^{1}H coupling constants are affected by the structural change. On the other hand, our data support Takeuchi's conclusion that the ^{1}J-values are less sensitive to this change.[3] As a *general rule* for the application of ^{13}C,^{1}H coupling constants to heteroaromatic tautomerism in six-membered nitrogen heterocycles we have summarized the consequences associated with the structural change B $\rightarrow$ A in diagrams C - E: *geminal and vicinal $^{13}C,^{1}H$ coupling constants involving H_α decrease and those involving H_β and $H_{\beta'}$ increase.*



C



D



E

^{15}N-NMR Results

The results of our ^{15}N-NMR measurements are shown in Table 2, where the close agreement between the N-1 screening constants observed for 2 and 5 with those of the model systems 1 and 4, respectively, again establishes the pyrazinone and thiopyrazinone structures (2a, 5a). On the other hand, σ(N-4) is not significant-

Table 2. ^{15}N screening constants σ (ppm) rel. to ext. CD_3NO_2 (solvent DMSO-d_6; ν_o = 40.53 MHz)

	1	2a/2b	3[a]	4	5a/5b	6[a]	7[a]	8[a]
N-1	211.8	198.3	101.6	180.1	179.7	63.7	106.6	104.3
N-4	38.9	35.6	38.6	58.3	51.2	47.8	45.9	45.4

[a] Ref. 8)

ly affected by the structural change. From the ^{14}N-NMR work[6] a methyl effect of ca. -3 ppm can be estimated for σ(N-1) in **1** and **4**. Correcting the experimental value for this amount and neglecting any methyl effect on σ(N-1) in **3** and **6**, it is again possible to derive the concentration of the second tautomer. The result is ~15% for **2b** and ~3% for **5b**, in fair agreement with the figures obtained above on the basis of the $^{13}C,^{1}H$ coupling constants. Our finding that the sulphur compound prefers the thiopyrazinone structure more strongly than the oxygen compound prefers the pyrazinone structure is in agreement with other observations.[9] Finally, the low-field absorption found for **7** and **8** again supports the 2-aminopyrazine structure.

Conclusions

We have shown that $^{13}C,^{1}H$ coupling constants as well as ^{15}N chemical shifts are sensitive probes for structural changes associated with heteroaromatic tautomerism of the pyrazinone-hydroxypyrazine type. Earlier indications by ^{1}H-NMR regarding the structure of **2** and **7**[4] are thus substantiated. An extension of such investigations to other heterocycles and other solvents is straightforward. Quantitative studies require suitable model compounds for the tautomeric structures involved, whereas for qualitative conclusions the parameters for both tautomers are sufficiently different to allow an interpretation even if model systems are not available.

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References and Notes:

\+ *Dedicated to Professor Dr. Klaus Weissermel on the occasion of his 60th birthday.*

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