Tetrahedron. Vol 32, pp 1065 to 1067 Pergamon Press 1976. Printed in Great Britain

^{14}N AND ^{13}C NMR OF TAUTOMERIC SYSTEMS OF HYDROXY-PYRIDINES

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(*Received in UK* 10 *November* 1975; *Accepted for publication* 9 *December* 1975)

Abstract—^{14}N NMR is shown to be an efficient method of investigation of the tautomeric equilibria in hydroxy-and related substituted pyridines. Large relative ^{14}N chemical shifts within tautomeric pairs estimated from N-Me and O-Me derivatives make possible quantitative determinations of the equilibria. Qualitative conclusions may be drawn from ^{14}N line widths as well as from ^{13}C and proton chemical shifts.

INTRODUCTION

Numerous methods have so far been employed for investigating the tautomeric equilibria in aza-aromatic ring systems. These involve UV and IR spectroscopy, X-ray methods dipole moments, basicity determination and proton NMR, and have been reviewed in detail by Katritzky and Lagowski.[1] Only qualitative estimations of the equilibrium constants were possible in these studies as well as in the more recent proton,[2,3] ^{13}C[3,4] and ^{14}N[5] NMR studies. However, the preliminary measurement of nitrogen chemical shifts[6b] indicated that the method may be well-suited to quantitative determinations.

RESULTS AND DISCUSSION

Usually large changes in nitrogen nuclear screening constants are observed upon tautomeric changes which directly involve N atoms. Since in most cases of such tautomeric equilibria the observed chemical shift is a weighted average of those of the individual tautomeric forms, it is necessary to obtain reasonable accurate estimates of the latter for quantitative determinations of the equilibria. One method employs measurements for model molecules where tautomerism has been made impossible by replacing H atoms with blocking groups (e.g. Me groups) and the estimation of corrections for the shifts resulting from such substitutions. The other approach is based on calculations of the shifts by empirical and theoretical methods and must be based on a considerable amount of experimental data that show good correlations with empirical additivity rules or nuclear screening constants calculated by various theoretical methods. Both of these approaches introduce uncertainties due to arbitrary assumptions which may critically affect the validity of quantitative estimations. However the former has a definite advantage if the tautomeric shifts are sufficiently large compared with the maximum reasonable limits of corrections for the shifts resulting from the Me substitution.

This is the case with the tautomeric equilibria exhibited by the hydroxy-pyridines. The data contained in Table 1 for N-Me and O-Me derivatives indicate that a difference of about 100–150 ppm in the screening constant for nitrogen is involved in a tautomeric shift of the type

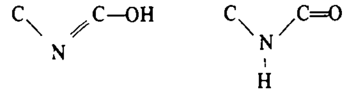


Table 1. ^{14}N NMR of hydroxy-pyridine derivatives

Compound	Solvent	Chemical shift[a] in ppm referred to CH_3NO_2			Half-height width in Hz		
		2-	3-	4-	2-	3-	4-
N-Methyl-2- or 4-pyridone and N-methyl-3-oxypyridyl betaine	Neat	+215±3	-	-	450±30	-	-
	Acetone 1:1 V/V	+213±2	-	+248±3	160±10	-	350±30
	Acetone 1:3 V/V	+215±2	-	+247±2	130±10	-	300±25
	Methanol 1:1 V/V	+213±2	+182±2	+239±3	200±15	75±3	400±30
	Methanol 1:3 V/V	+213±1	+179±1	+238±3	160±10	35±1	220±20
	Methanol:Acetone 1:1:2 V/V	-	+180±1	-	-	36±1	-
Hydroxy-pyridine, pyridone or 3-oxypyridyl betaine	Acetone 1:3 V/V	+208±2	+66±4[b]	+221±4[b]	150±10	500±50[b]	300±30[b]
	Methanol 1:1 V/V	+211±3	-	-	280±20	-	-
	Methanol 1:3 V/V	+210±2	+69±4	+225±3	180±10	700±60	350±30
	Methanol:Acetone 1:1:2 V/V	-	+68±4	-	-	600±60	-
Methoxy-pyridine	Neat	+109±3	+60±3	+89±4	360±30	700±50	1000±100
	Acetone 1:1 V/V	+112±2	+62±3	+91±4	280±20	320±30	600±50
	Acetone 1:3 V/V	+110±2	+63±3	+90±3	260±20	290±20	450±30
	Methanol 1:1 V/V	+113±3	+64±4	+92±4	350±30	700±50	1000±100
	Methanol 1:3 V/V	+117±2	+65±4	+93±4	320±20	660±40	950±80
	Methanol:Acetone 1:1:2 V/V	-	+63±4	-	-	600±40	-

a - Positive sign corresponds to a high field shift; b - Saturated solution in acetone.

So far, large shifts in such systems have been expected on the basis of preliminary ^{14}N measurements for 2-, 3- and 4-hydroxypyridines[6] but some of the data show appreciable experimental errors as compared with the measurements carried out in the present work and do not contain any information on the shifts of N-Me derivatives. If the averaged nitrogen chemical shift of the tautomeric equilibrium systems (δ_T) is measured together with those for the corresponding N-Me or O-Me derivatives (δ_{NMe} and δ_{OMe}, respectively) and if corrections for NMe → NH and OMe → OH substitutions (Δ_{NH} and Δ_{OH}, respectively) may be estimated then the mole fraction of the pyridine-type tautomer X is:

$$X = \frac{\delta_{NMe} + \Delta_{NH} - \delta_T}{\delta_{NMe} + \Delta_{NH} - \delta_{OMe} - \Delta_{OH}} \qquad (1)$$

The NMe → NH shift for 2- and 4-pyridines may be estimated from the shifts for amides[5]

in acetone, referred to nitromethane in ppm

$HCONH_2$	+274
$HCONHMe$	+272
$HCONMe_2$	+273

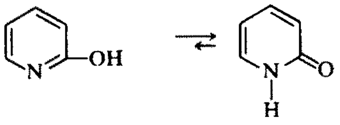
in chloroform, referred to nitromethane in ppm

$MeCONH_2$	+270
$MeCONHMe$	+269
$EtCONH_2$	+273
$EtCONHMe$	+270

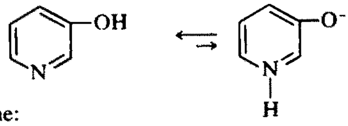
as about +1 ppm on the screening constant scale. Since the OMe → OH correction results from the substitution at a remote center, its numerical value should be negligible. The NMe → NH correction for the betaine tautomer of 3-hydroxypyridine should also be negligible, as can be seen from the ^{14}N shift measurement reported in the present work in methanol, 1:3 V/V, referred to nitromethane, chemical shifts in ppm and half-height width in Hz, respectively

Pyridinium iodide	+179 ± 1	32 ± 3
N-Methyl pyridinium iodide	+179 ± 1	24 ± 2
3-Hydroxy-N-methyl pyridinium iodide	+177 ± 1	24 ± 2

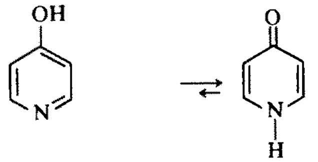
The results of ^{14}N NMR measurements (concentration 1:3 V/V) for hydroxy-pyridine systems (Table 1, eqn 1) gave the following estimates of the tautomeric equilibria in terms of mole fractions:



acetone	0.08 ± 0.04	0.92 ± 0.04
methanol	0.04 ± 0.04	0.96 ± 0.04



acetone: methanol 2:1 v/v	0.96 ± 0.03	0.04 ± 0.03
methanol	0.97 ± 0.03	0.03 ± 0.03



acetone	0.17 ± 0.04	0.83 ± 0.04
methanol	0.10 ± 0.04	0.90 ± 0.04

The uncertainities quoted for the mole fractions are maximum expected deviations calculated on basis of experimental errors (Table 1) and maximum expected errors in the estimation of N-Me and O-Me substitution corrections, ± 1 ppm in each case.

It is interesting that the quadrupolar relaxation times (and line widths) of ^{14}N exhibit large variations within the isomeric pairs and that the values observed for the tautomeric equilibria are close to those for the isomers which represent the prevailing tautomeric structures in the equilibria.

The ^{13}C and ^{1}H NMR data only give qualitative indications of the positions of the tautomeric equilibria, as may be inferred from the previously reported measurements[3] for a complete set of model compounds in DMSO solutions as well as from data obtained in the present work (Table 2) for acetone solutions which were also used for the ^{14}N measurements.

The relative ^{13}C shift differences between the isomeric pairs (N-Me and O-Me derivatives) are not very large (0.9–20.7 ppm) and the shifts for the equilibria between the NH and OH tautomers are frequently found outside the range set by the model compounds. Generally, the shifts for the carbon atoms which are appreciable affected (*ca.* 10–20 ppm) by the tautomeric changes show that the prevailing tautomers are those indicated by the ^{14}N shifts, but no quantitative conclusions may be drawn. The ^{13}C resonance signals of the corresponding $-\overset{|}{C}=O$ and $=\underset{|}{C}-OH$ groups which are characterized by large downfield shifts relative to the remaining ^{13}C resonances cannot yield even qualitative information in some cases.

Thus, it seems that nitrogen chemical shifts should be far superior to those of ^{13}C and ^{1}H chemical shifts as a source of information about tautomeric equilibria in aza-aromatic systems bearing hydroxy groups as substituents.

EXPERIMENTAL

The substances investigated were either commercially available products purified by conventional methods (all hydroxy-pyridines) or were prepared according to published procedures: 2-methoxypyridine,[7] 3-methoxy-pyridine,[8] 4-methoxy-pyridine,[9] N-methyl-2-pyridone,[10] N-methyl-3-oxypyridyl-betaine[11] and N-methyl-4-pyridone.[12]

The identity of all substances were checked by means of their proton NMR spectra.

The ^{14}N NMR spectra were measured at 4.3346 MHz (14.09 kG) and modulated with an audio-frequency of 2002 Hz. The spectrometer used was a Varian HA-60IL model operating at room (28°) temp in the field-sweep HR mode with 15 mm o.d. sample tubes without spinning. Nitromethane was employed as an internal reference compound and the shifts are expressed on the screening-constant scale, i.e. high-field shifts are taken as positive. In order to obtain a good signal-to-noise ratio, which was quite critical in a few cases, the spectra were digitized and transferred to a tape using a KART-2 automatic coordinatograph. In this form,

Table 2. ^{13}C NMR of hydroxy-pyridine derivatives

	Chemical shifts[a] in ppm referred to tetramethylsilane					
	C-2	C-3	C-4	C-5	C-6	CH_3
2-Derivatives						
N-Me[b]	-162.9	-120.4	-140.1	-105.4	-140.1	-37.1
O-H[c]	-165.0	-121.0	-142.3	-106.7	-136.2	-
O-Me[b]	-164.9	-111.4	-139.2	-117.3	-147.7	-53.3
△ (NMe-OMe)	+2.0	-9.0	-0.9	+11.9	+7.6	-
3-Derivatives						
N-Me[c]	-133.1	-170.6	-135.7	-127.3	-121.9	-47.3
O-H[c]	-138.7	-154.9	-123.2	-125.0	-141.2	-
O-Me[b]	-138.5	-156.6	-120.5	-124.5	-142.6	-55.7
△ (NMe-OMe)	+5.4	-14.0	-15.2	-2.8	+20.7	-
4-Derivatives						
N-Me[b]	-142.4	-118.2	-178.3	-118.2	-142.4	-43.3
O-H[c]	-141.6	-116.7	-176.4	-116.7	-141.6	-
O-Me[b]	-151.7	-110.6	-166.3	-110.6	-151.7	-55.5
△ (NMe-OMe)	+9.3	-7.6	-12.0	-7.6	+9.3	-

a - Negative indicates deshielding; b - In acetone 1:3 V/V; c - Saturated solution in acetone.

they were ready for recalibration and noise-averaging procedures in a computer system and subsequent line-shape fitting procedures. About 10–20 spectra were accumulated in each case to give satisfactory results for the concentrations and line widths involved. The data processing was performed on the ODRA-1204 computing system of the Polish Academy of Sciences.

The carbon and proton NMR spectra were measured in 1:3 V/V or saturated solns of acetone-d_6 with TMS as an internal standard.

The ^{13}C NMR spectra were obtained by PFT technique with a Bruker WH-90 spectrometer operating at 22.6364 MHz with a deuterium internal lock and proton noise-decoupling (6 μsec pulses repeated at 0.68 sec, 3000–100000 scans).

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