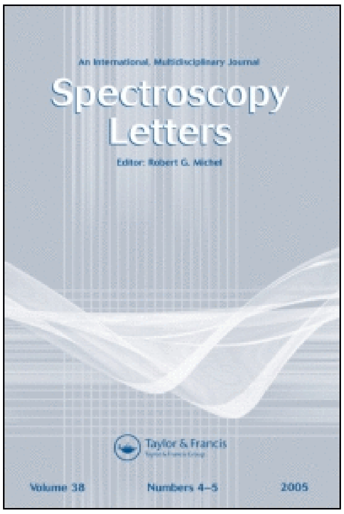


Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

^{13}C NMR in the Structural Assignment of Fused Furoxans

Leslie W. Deady[a]; Nurul H. Quazi[a]
[a] School of Chemistry, La Trobe University, Victoria, Australia

To cite this Article Deady, Leslie W. and Quazi, Nurul H.(1995) '^{13}C NMR in the Structural Assignment of Fused Furoxans', Spectroscopy Letters, 28: 7, 1033 — 1040
To link to this Article: DOI: 10.1080/00387019508009443
URL: http://dx.doi.org/10.1080/00387019508009443

SPECTROSCOPY LETTERS, 28(7), 1033-1040 (1995)

^{13}C NMR IN THE STRUCTURAL ASSIGNMENT OF FUSED FUROXANS

Key words: ^{13}C NMR Spectroscopy, benzofuroxans, pyridofuroxan, isoquinolinofuroxan.

Leslie W. Deady and Nurul H. Quazi

School of Chemistry, La Trobe University, Bundoora, Victoria 3083, Australia

ABSTRACT

The chemical shifts and multiplicities of the two bridgehead carbons in the ^{13}C NMR spectra of various fused furoxans are shown to provide a general method for assigning structure in these tautomeric systems.

INTRODUCTION

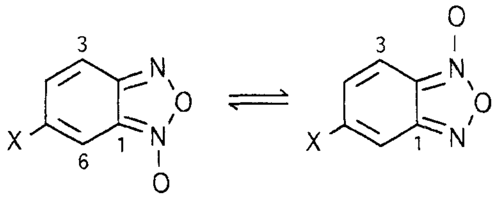
Furoxans represent a classic case of interconverting tautomers even though, in some substituted cases, the equilibrium may be such that only one isomer is detectable. Quite early in its development, ^1H NMR was used to assign the structure of the predominant tautomer in substituted benzofuroxans **1**.

Thus, the rapidly interconverting (at room temperature) **1c**/**2c** was shown to contain 70% **1c** at -31°.[1] Such analysis depended on some differential small chemical shifts in quite complex spectra. Notably, it was found that the proton *peri* to the N-oxide was shifted upfield by *c.* 0.25 ppm relative to the same proton in the isomeric oxide.[2] We recently synthesized some compounds in series **7**/**8** (the methyl derivative has been chosen as the example here) where there is no equivalent *peri* proton and ^{1}H NMR was not able to provide an unequivocal answer. Structure **8** for this compound at 24° was assigned by reference to the findings for simpler analogs such as **5**.[3] A possible *c.* 5% of isomer **7** was inferred from a second, slightly shifted methyl signal. In this report, we show that ^{13}C NMR is a more powerful and general technique for making these assignments.

Since the first ^{13}C NMR data for benzofuroxans were published,[4] there have been occasional references to other derivatives.[5,6] However, the substantial chemical shift difference between the two bridgehead carbons in a benzofuroxan compared to the situation in the benzofurazan parent **3** does not appear to have been generally applied to this isomer structure problem in fused furoxans. The upfield shift for C1[7] (e.g., 35 ppm for **1 a** with respect to **3**), while C2 is hardly altered, is a powerful pointer which can be simply used to establish isomer structure in fused furoxans. Depending on structure, the assignment of the two bridgehead carbons can be made from chemical shift or long-range coupling data, as shown by the results presented below.

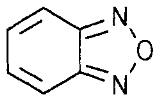
RESULTS AND DISCUSSION

For **1 b**,**c**/**2 b**,**c** and **4**/**5**, the assignments of the CH and quaternary carbons to the two isomers were made from relative peak heights, by inspection of the uncoupled spectra. The only complicating factor was



1 2

a X = H
b X = Cl
c X = NO_2



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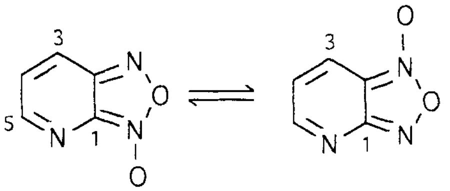
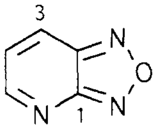


4 5



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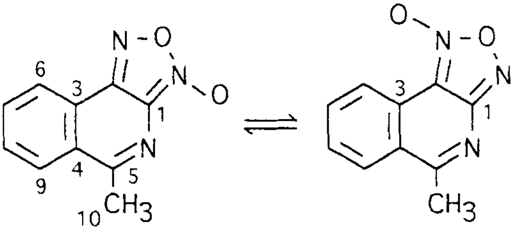
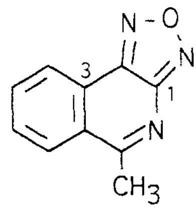


7 8



9

that, in the nitro case, C5 was close to **1c**-C2/**2c**-C1. Then, the bridgehead carbons within each were distinguished from their proton-coupled carbon spectra, by their different states of long-range coupling.

Using **1b**/**2b** as the example, the downfield peak in the major isomer (**1b**-C2 or **2b**-C1) was assigned to the latter (60% from ^{1}H NMR integration) from it being a doublet ($^3J_{C\text{-}H}$ = 5.8 Hz) by coupling only with H3. Likewise, the upfield signal in the minor isomer (**1b**-C1) was also a doublet ($^3J_{C\text{-}H}$ = 6.8 Hz). The remaining bridgehead carbons had more complex splitting patterns through three-bond coupling to two protons. The same analysis when applied to **1c/2c** showed that the major isomer, **1c** (67% from ^{1}H NMR integration), was opposite to that in the chloro case. These assignments agree with those based on ^{1}H NMR experiments.[1,8]

To complete these analyses, the CH carbons were also assigned — C4 from chemical shift (by analogy with **1a**) and C3 was distinguished from C6 by the absence of three-bond coupling for the former.

For **4/5** where two sets of signals were also evident at -32°C, C2 was similarly differentiated from C1 by the lesser three-bond coupling of the former (only to H4) and this was the upfield signal in the major isomer, i.e, **5** (90% from ^{1}H NMR integration). The spectrum of the previously unreported pyrido[2,3-*c*]furazan **6** was also recorded to confirm that the analysis of **4/5** gave sensible shifts with respect to those of **6**. The assignments of the three H bound carbons were made from selective proton decoupled carbon spectra.

Inspection of the results in Table 1 for **1/2** and **4/5** shows a consistent shift pattern similar to the effect noted in the ^{1}H spectra, in which the signal for the carbon *peri* to the N-oxide is shifted *c.* 5 ppm upfield with respect to the same carbon in the isomeric oxide.

In the spectrum of **9**, C1 and C2 were assigned by reference to **6**, and C1 showed no long-range coupling while C2 had three-bond coupling to H6 ($^3J_{C\text{-}H}$ = 4.0 Hz). In the N-oxide, where essentially only one form was present at 24°, the equivalent singlet for the quaternary carbon C1 was only slightly changed while the doublet for C2 ($^3J_{C\text{-}H}$ =

TABLE 1

^{13}C NMR Data[a]

Compound	C1	C2	C3	C4	C5	C6
1 a[b]	113.7	152.2	117.3	132.3	128.0	112.1
1 b	114.1	150.9	119.2	134.5	134.7	111.1
1 c	113.7	151.7	120.3	126.4	146.7	113.1
2 b	152.1	113.0	114.1	130.9	138.7	116.1
2 c	151.1	114.5	115.6	122.6	150.4	116.9
3[b]	148.6	148.6	115.8	131.2	131.2	115.8
4	124.6	146.8	126.9	128.0	156.0	-
5	158.6	108.3	122.3	124.6	160.3	-
6	158.4	142.7	125.3	126.6	159.1	-
8[c]	157.2	104.0	120.3	126.7	171.4	-
9[d]	155.8	141.2	121.7	127.2	170.5	-

[a] At -32°C in $CDCl_3$, except **8**, **9** (24°C, in DMSO-d_6) [b] From ref 4, in $CDCl_3$ [c] 122.3(C6), 133.9(C7), 131.1(C8), 128.8(C9), 24.3(C10)
[d] 124.4(C6), 133.0(C7), 131.5(C8), 128.3(C9), 23.3(C10)

4.0 Hz) was now shifted upfield by 37.4 ppm relative to **9**. Thus the compound exists as tautomer **8**, confirming the conclusion made earlier.[3]

For a complete analysis, the remaining carbons were assigned as follows: The lowest field signal was due to C5 (from isoquinoline data[9]). The hydrogen-linked carbons 6-9 were assigned from the proton-detected HMQC 2D spectrum. (The proton signals were assigned from the DGF-COSY 2D spectrum). The other bridgehead carbons 3,4 were assigned by noting the change in signal for the latter from broad singlet in the fully coupled spectrum to a triplet ($^3J_{C\text{-}H}$ to H6,8) when the methyl protons were irradiated.

These results demonstrate that 1D ^{13}C NMR provides a simple general method for assigning structures to tautomeric fused furoxans.

EXPERIMENTAL

Compounds

A solution of 2-amino-3-nitropyridine (1.0 g) and iodosobenzene diacetate (3.0 g) in acetone (75 ml) was heated under reflux for 1 h. The acetone was removed and the oily residue was extracted repeatedly with hot light petroleum (b.p. 90-110°C) to give the pyridofuroxans **4**/**5** (0.9 g, 91%), m.p. 51-52° (lit [10] m.p. 52-53°C). ^1H NMR ($CDCl_3$) δ **5** 7.30, dd, J 9.2, 3.8 Hz, H4; 7.87, dd, J 9.0, 1.4 Hz, H3; 8.88, dd, J 3.8, 1.4 Hz, H5. δ **4** 7.46, dd, J 9.2, 3.8 Hz, H4; 8.11, dd, J 9.0, 1.1 Hz, H3; 8.68, dd, J 3.8, 1.1 Hz, H5.

In a similar manner were prepared the nitro **1b**/**2b**, m.p. 67°C (lit [11] m.p. 67°C) and chloro **1c**/**2c**, m.p. 48°C (lit [11] m.p. 48°C) benzofuroxans.

Compounds **7**/**8** and **9** were available from previous work.[3]

A solution of the furoxan **5** (2.0 g) in trimethyl phosphite (5 ml) was heated at 100°C for 1 min., then cooled immediately in an ice-bath. Most of the trimethyl phosphite was removed by distillation at 1 mm/Hg. Water was added to the dark brown residue and the mixture was extracted with ether (3 x 30 ml). The ether was dried and evaporated and the residue was recrystallized from light petroleum (b.p. 40-60°C) to give pyrido[2,3-

c]furazan **6** (0.7 g, 40%), m.p. 28-30°. ^{1}H NMR (CDCl$_3$) δ 7.40, dd, J 9.0, 3.7 Hz, H4; 8.25, dd, J 9.0, 1.4 Hz, H3; 8.97, dd, J 3.7, 1.4 Hz, H5.

Spectra

Nmr spectra were recorded on a Bruker AM-300 spectrometer (^{1}H at 300.13 MHz and ^{13}C at 75.47 MHz). The DQF-COSY[12] experiment was applied using F2 spectral width 3597.122 Hz and 512 t_1 increments were collected with 32 scans and zero-filling in the *F1* dimension to produce 1K x 1K real data matrix. The data were processed using unshifted sine-bell windows in both time domains and symmetrized.

The proton detected one bond (^{1}H-^{13}C) heteronuclear correlation (HMQC) experiments[13] used spectral widths of 3311.26 Hz (proton) and 15151.52 Hz (carbon). With 32 scans each, 512 t_1 increments were acquired for the second dimension. Square sine bell window functions were applied, over 1024 complex data points in the *F2* dimension (60° shifted), and 512 real data points in the *F1* dimension (90° shifted). Data were zero filled to 1K x 1K real matrices and phased.

ACKNOWLEDGMENT

We thank Dr M. Sadek for recording the 2D NMR spectra.

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Date Received: April 27, 1995
Date Accepted: June 7, 1995