MAGNETIC RESONANCE IN CHEMISTRY, VOL. 36, 449–453 (1998)

Note

Complete Assignment of the ^{1}H and ^{13}C NMR Spectra of 2-Phenyl-3*H*-naphtho[2,1-*b*][1,4]oxazin-3-one, 2-*p*-Methoxyphenylnaphtho[1,2-*d*]oxazole and 2-Phenylnaphtho[1,2-*d*]oxazole. Concerted Use of One- and Two-Dimensional NMR Techniques

Amelia Márquez,[1] Claudio Saitz,[1]* Alvaro Cañete,[1] Hernán Rodríguez[1] and Carolina Jullian[2]

[1] Laboratorio de Mecanismos de Reacción, Departamento de Química Orgánica y Físico-Química, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Casilla 233, Santiago 1, Chile
[2] CEPEDEQ, Centro de Estudios Para el Desarrollo de la Química, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Casilla 233, Santiago 1, Chile

Received 16 September 1997; revised 5 January 1998; accepted 22 January 1998

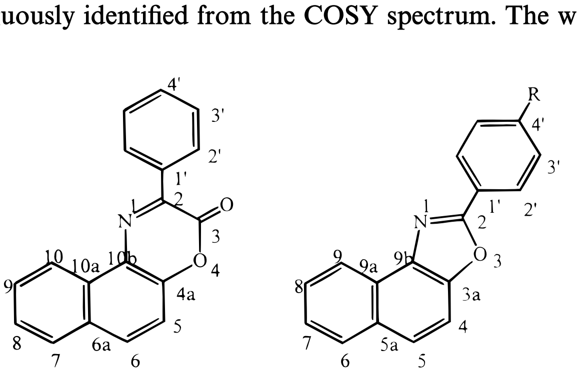
ABSTRACT: The ^{1}H and ^{13}C NMR spectra of 2-phenyl-3*H*-naphtho[2,1-*b*][1,4]oxazin-3-one, 2-*p*-methoxyphenylnaphtho[1,2-*d*]oxazole and 2-phenylnaphtho[1,2-*d*]oxazole were totally assigned using a combination of one- and two-dimensional NMR techniques. In addition to correlation of the proton signals by a COSY spectrum and one-bond heteronuclear correlation, complete assignment of the ^{1}H and ^{13}C NMR spectra of these heterocyclic compounds required the application of long-range CH coupling information, particularly for quaternary resonance assignments and for orientations of individual spin systems relative to one another. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; 2-phenylnaphthoxazinone; 2-phenylnaphthooxazole

INTRODUCTION

We have been interested in the synthesis of heterocyclic ring systems via 1,3-dipolar cycloaddition reactions.[1–3] Recently, we reported the formation of 2-phenyl-3*H*-naphtho[2,1-*b*][1,4]oxazin-3-one(**1**),2-phenylnaphtho[1,2-*d*]oxazole (**2**) and 2-*p*-methoxyphenylnaphtho[1,2-*d*]oxazole (**3**) (Fig. 1), through the reaction between 2-*p*-methoxyphenyl-4-phenyl-Δ^2-oxazolin-5-one and 1-nitroso-2-naphthol.[4] In this paper, we describe the complete chemical shift assignment of the ^{1}H and ^{13}C spectra of **1**, **2** and **3** through the concerted application of a variety of one- and two-dimensional techniques: COSY,[5] ^{1}H-detected one-bond (C–H) heteronuclear multiple quantum coherence (HMQC)[6] and long-range two- and three-bond C–H heteronuclear multiple bond connectivity (HMBC).[7] The inverse-detected heteronuclear shift correlation efficiency was significantly augmented by the incorporation of pulsed field gradients[8] (PFG). Phase-cycling requirements for t_1 noise suppression in gradient-enhanced experiments are, for the most part, obviated, making it feasible to acquire data in one or a few transient per t_1 increment. The benefits acquired by ^{1}H–^{13}C correlation (using GHMQC and GHMBC) are well documented.[9] In the process of making these assignments, COSY-90 and GHMQC were supplemented with GHMBC experiments.

Each of these compounds contains one two-spin system and one four-spin system and they can be unambiguously identified from the COSY spectrum. The well



1

2 R = H
3 R = OMe

Figure 1.

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* *Correspondence to*: C. Saitz, Laboratorio de Mecanismos de Reacción, Departamento de Química Orgánica y Físico-Química, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Casilla 233, Santiago 1, Chile.

Contract/grant sponsor: FONDECYT; *Contract/grant number*: 1940446.
Contract/grant sponsor: DTI; *Contract*/grant number: Q 3336-9323 Universidad de Chile.
Contract/grant sponsor: Fundacion Andes; *Contract/grant number*: C-12449.

CCC 0749-1581/98/060449–05 $17.50

resolved ^{13}C NMR spectrum establishes direct heteronuclear correlations from the HMQC spectrum, but complete unequivocal assignment of the spectrum is not possible without the concerted use of the HMQC and HMBC techniques. The two-spin system may be assigned from the observed vicinal couplings, from substituent group effects on the chemical shifts[10] and by comparison with other described naphthoxazoles.[11] These spin systems correspond to H-5 and H-6 in the oxazinone and H-4 and H-5 in the oxazole structures, and they serve as the entry point for spectral interpretation.

RESULTS AND DISCUSSION

Compound 1

The 2D ^{1}H homonuclear COSY spectrum (Fig. 2) showed the expected two-spin system as two doublets resonating at 7.37 and 7.90 ppm. The doublet at 7.90 ppm corresponds to H-6 and that at 7.37 corresponds to H-5, on the basis of their vicinal coupling constant ($J = 9$ Hz) and the chemical shifts. The spectrum also showed a four-spin system, in which the more deshielded doublet (δ 8.84) corresponds to the H-10 proton. This is the signal resonating far downfield; H-10 is first deshielded by its own aromatic system and then shifted further downfield by the deshielding effects of the oxazinone ring. Furthermore, in the contour plot of the COSY spectrum, the off-diagonal peaks establish the connectivities between all pairs of mutually coupled protons. Thus, the complete analysis for the heterocyclic ring of the naphthoxazinone could be made unambiguously. The aromatic resonance H-10 shows correlation peaks with the proton resonating at δ 7.65 (H-9, apparent triplet). H-9 also exhibits correlation with the aromatic proton located at δ 7.53 (other apparent triplet), which was therefore assigned to H-8. This latter resonance of the four-spin system, in turn, is correlated with the proton at δ 7.83, which can be ascribed to H-7. The other spin system corresponds to the phenyl group. The multiplet at 8.46 ppm corresponds to the two protons located at the *ortho* position (H-2′) and the other multiplet at 7.49 corresponds to the two H-3′ and one H-4′ protons.

The complete ^{1}H and ^{13}C NMR chemical shift assignments for **1** were deduced from the concerted application of ^{1}H-detected 'one-bond' and long-range (C,H) correlation experiments. The one-bond proton–carbon chemical shift correlation was established using the HMQC sequence; all the 'one-bond' (C,H) connectivities found between the pairs of mutually coupled atoms are given in Table 1. The assignments of quaternary carbons were obtained from the analysis of long-range correlations responses over three bonds using the HMBC technique. All these long-range correlations are presented in Table 1.

The HMBC spectrum (Fig. 3) shows long-range correlations between H-10 and three carbon resonances. Examining the structure of **1**, we can identify the resonance corresponding to C-8, and two quaternary carbons C-6a and C-10b. Both quaternary carbons correlate long-range with H-10 and H-5, but only C-6a correlates in addition with H-8. Also, the quaternary C-6a corresponds to the signal resonating at 131.48 ppm which correlates long-range with H-10, H-8 and H-5. H-6 correlates long-range with two quaternary carbons resonating at 145.19 and 130.91 ppm and with a protonated carbon at 128.48 ppm in the HMBC spectrum. By examining the structure of naphthoxazinone **1**, H-6 correlates long-range with quaternary carbons C-4a and C-10a. The resonance at 145.19 ppm is assigned to C-4a, because it has only one three-bond connectivity, as expected. Therefore, the carbon resonating at 130.91 ppm must be C-10a; this carbon is also long-range connected with H-7 and with the doublet of

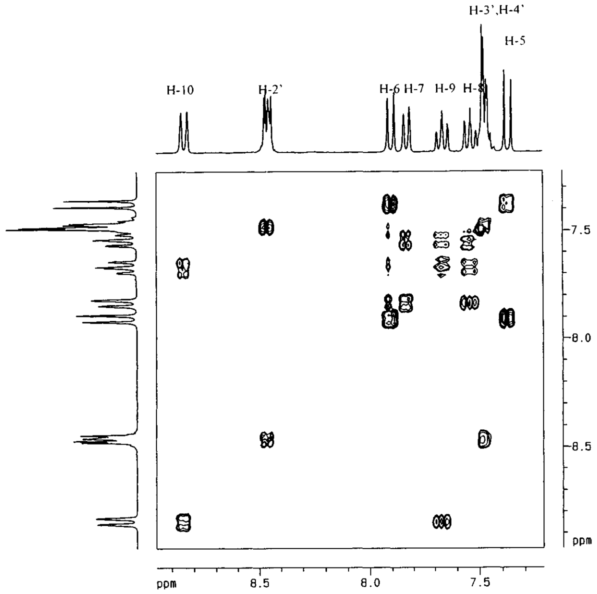

Figure 2. COSY spectrum of 2-Phenyl-naphtho[2,1-b]-[1, 4]oxazin-3-one (**1**).

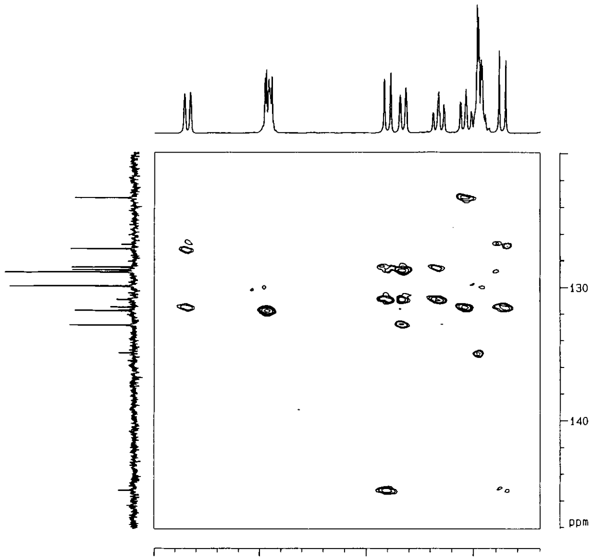

Figure 3. HMBC spectrum of 2-Phenyl-naphtho[2,1-b]-[1,4]oxazin-3-one (**1**)

Table 1. ^{1}H and ^{13}C NMR of 2-phenyl-3*H*-naphtho[2,1-*b*][1,4]oxazin-3-one (**1**)

Carbon No.	Chemical shift^{a}, δ [H–X, multiplicity, *J*(H,H)(Hz)]	^{13}C^{a}	HMQC ^{1}J(C,H)	Protons showing HMBC correlation [coupling]^{3}J(C,H)
2		148.83		
3		162.74		
4a		145.19		6
5	7.37 [H-5, d, *J*(5,6) = 9.0]	116.10	+	
6	7.90 [H-6, d, *J*(6,5) = 9.0]	132.84	+	7
6a		131.48		5, 8, 10
7	7.83 [H-7, d, *J*(7,8) = 8.1]	128.48	+	6, 9
8	7.53 [H-8, dd, *J*(8,7) = 8.1, *J*(8,9) = 8.3]	127.11	+	10
9	7.65 [H-9, dd, *J*(9,10) = 8.35, *J*(9,8) = 8.3]	128.67	+	7
10	8.84 [H-10, d, *J*(10,9) = 8.35]	123.30	+	8
10a		130.91		6, 7, 9
10b		126.79		5, 10
1′		134.92		3′
2′	8.46	129.89	+	4′
3′	7.49	128.83	+	
4′	7.49	131.74	+	2′

[a] In ppm from TMS.

doublets resonating at 7.65 ppm (H-9). The proton resonating at 7.49 ppm is one-bond connected with the carbon resonating at 129.89 ppm (C-2′), and it is also long-range coupled to the quaternary carbon resonating at 134.92 ppm, hence this carbon is assigned unambiguously as C-1′. The assignment of the other quaternary carbon resonance was straightforward. The quaternary carbon resonating at 148.83 ppm is assigned as C-2, and the downfield carbon corresponds to the carbonyl group at 162.74 ppm.

Compound 2

The structure of **2** is analogous to that of **1** except that it does not contain a carbonyl group. In the COSY spectrum (not shown), the expected two-spin AB system appears as a pair of doublets at 7.80 and 7.71 ppm. The four-spin system was also observed, but in this case the triplet of H-7 overlapped with the *meta* and *para* protons from the phenyl group. With the HMQC (not shown), we assigned the carbon signals and we could distinguish between C-7, C-3′ and C-4′.

In a fashion analogous to compound **1**, the HMBC spectrum shows long-range correlations between H-9 (δ 8.61 ppm), the most deshielded proton, and three carbon resonances (Table 2). Two of these are quaternary carbons. Examining the structure of **2**, these quaternary carbons corresponds to C-9b and C-5a. Both correlate with H-9 and H-4, but only C-5a is also correlated with H-7. The spectrum also shows that the quaternary carbon at 131.65 ppm correlates with three protons, H-9, H-4 and H-7. Also, the quaternary carbon C-9b corresponds to the signal resonating at 137.63 ppm.

Table 2. ^{1}H and ^{13}C NMR of 2-phenylnaphtho[1,2-*d*]oxazole (**2**)

Carbon No.	Chemical shift^{a}, δ [H–X, multiplicity, *J*(H,H) (Hz)]	^{13}C^{a}	HMQC ^{1}J(C,H)	Protons showing HMBC correlation [coupling]^{3}J(C,H)
2		162.33		2′
3a		148.04		5
4	7.71 [H-4, d, *J*(4,5) = 8.9]	110.81	+	
5	7.80 [H-5, d, *J*(5,4) = 8.9]	125.98	+	6
5a		131.23		4, 5, 7, 9
6	7.98 [H-6, d, *J*(6,7) = 8.1]	128.56	+	5, 8
7	7.58 [H-7, dd, *J*(7,6) = 8.1, *J*(7,8) = 8.3]	125.35	+	9
8	7.68 [H-8, dd, *J*(8,7) = 8.3, *J*(8,9) = 8.16]	126.95	+	6
9	8.61 [H-9, d, *J*(9,8) = 8.16]	122.27	+	7
9a		126.59		5, 6, 8
9b		137.63		4, 9
1′		127.55		3′
2′	8.36	127.34	+	4′
3′	7.69	128.88	+	4′
4′	7.69	131.04	+	2′, 3′

[a] In ppm from TMS.

The proton H-5 correlates long-range with four carbons, three of them quaternary carbons which correspond to C-3a, C-9a and C-5a. The quaternary carbon resonating at 148.04 ppm is assigned as C-3a; it exhibits a sole long-range coupling in the HMBC spectrum to H-5. The quaternary carbon resonating at 126.59 ppm correlates long-range with H-8 and H-6 and can thus be assigned as C-9a. In the phenyl group, H-2′ correlates long-range with three carbon signals. One of them corresponds to a quaternary carbon, resonating at 162.00 ppm, and is assigned to C-2.

Compound 3

The structure of **3** is similar to that of **2**, except that this compound is methoxy substituted at C-4′, so in the COSY spectrum (not shown) a symmetrical AX system ($J = 8.84$ Hz) appears. The H-3′ aromatic protons are shifted upfield at 7.04 ppm; this assignment is on the basis of the substituent effect[10] and coupling interaction. Hence in this case, we can observe the upfield double doublet at 7.53 ppm (H-7), which in the oxazole **2** was obscured by the H′-3 and H′-4 resonances. The HMBC spectrum shows basically the same long-range correlations for the heterocyclic portion as those observed for **2** (Table 3). The replacement of H-4′ by a methoxy group is mainly reflected in the chemical shift changes of C-4′, C-3′, C-2′ and C-1′, as stated in the literature.[10b] The assignments of C-3′ and C-2′ were established using the HMQC and those of C-1′ and C-4′ using the HMBC spectrum.

EXPERIMENTAL

Proton and carbon NMR spectra were acquired using a Bruker Avance DRX 300 spectrometer operating at a proton frequency of 300.13 and 75.47 MHz, respectively. All measurements were performed at a probe temperature of 300 K using solutions of **1**, **2** and **3** in CDCl$_3$ (10–20 mg ml^{-1}) containing tetramethylsilane (TMS) as an internal standard. All two-dimensional spectra were acquired with a Bruker inverse 5 mm Z-gradient probe. The one-dimensional carbon spectrum was obtained with a spectral width of 2500 Hz with 2 s between transients, and the 90° pulse was 10 μs. The homonuclear ^{1}H–^{1}H shift-correlated 2D spectra were obtained using standard Bruker software (COSY90). The spectral widths were 1800 Hz. The spectra were collected as 512 × 512 blocks of data and were processed by sinusoidal multiplication in each dimension, followed by symmetrization of the final data matrix. Other parameters were as follows: number of increments in t_1, 256; number of scans, 8; and relaxation delay, 2 s. The HMQC spectra were measured using standard Bruker software (inv4gstp). These spectra were collected with 512 × 512 data points, a data acquisition of 8 scans × F and 256 increments in t_1. Spectral widths of 1800 and 3200 Hz were employed in the F_2 (^{1}H) and F_1 (^{13}C) domains, respectively. Data were processed using Qsine functions for weighting in both dimensions. The HMBC spectra were obtained using the inv4gslplrnd pulse sequence in the Bruker software. The spectral widths were 1800 Hz (F_2) and 5000 Hz (F_1) and the delays Δ_1 and Δ_2 were set to 3.45 and 65 ms, respectively. Data were processed using an exponential window in F_2 with lb = 5 Hz and a Qsine window in F_1.

CONCLUSION

The structure of three heterocyclic compounds could be analyzed using 2D heteronuclear NMR spectra associated with the measurements of HMQC and HMBC connectivities. The latter technique allows complete and unambiguous assignments of the aromatic proton and

Table 3. ^{1}H and ^{13}C NMR of 2-*p*-methoxyphenylnaphtho[1,2-*d*]oxazole (**3**)

Carbon No.	Chemical shift,[a] δ [H–X, multiplicity, J(H,H) (Hz)]	^{13}C[a]	HMQC ^1J(C,H)	Protons showing HMBC correlation [coupling]^3J(C,H)
2		162.53		2′
3a		147.86		5
4	7.70 [H-4, d, $J(4,5) = 8.88$]	110.75	+	
5	7.77 [H-5, d. $J(5,4) = 8.88$]	125.41	+	6
5a		131.21		4, 5, 7, 9
6	8.10 [H-6, d, $J(6,7) = 8.18$]	128.55	+	5, 8
7	7.53 [H-7, dd. $J(7,6) = 8.18$, $J(7,8) = 8.3$]	125.22	+	9
8	7.65 [H-8, dd, $J(8,7) = 8.3$, $J(8,9) = 8.2$]	126.80	+	6
9	8.57 [H-9, d, $J(9,8) = 8.2$]	122.27	+	7
9a		126.47		5, 6, 8
9b		137.67		4, 9
1′		120.20		3′
2′	8.26 [H-2′, d, $J(2′,3′) = 8.84$]	129.09	+	2′
3′	7.04 [H-3′, d, $J(2′,3′) = 8.84$]	114.36	+	3′
4′		162.01		2′, 3′
p-OMe	3.89 [s, 3H]	55.41		

[a] In ppm from TMS.

carbon signals, which are particularly complex in these naphthoxazinone and naphthoxazole derivatives.

Acknowledgements

We thank the FONDECYT, Project 1940446, DTI, Project Q 3336-9323 Universidad de Chile, and the Fundacion Andes, Project C-12449, for financial support and the CEPEDEQ (Centro Para el Desarrollo de la Química), Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, for the use of NMR equipment. We also gratefully acknowledge Dr Verónica Armstrong for useful suggestions during the preparation of the manuscript.

REFERENCES

1. H. Rodríguez, H. Pavez, A. Márquez and P. Navarrete, *Tetrahedron* **38**, 23 (1983).
2. H. Pavez, A. Márquez, P. Navarrete, S. Tzichinovsky and H. Rodríguez, *Tetrahedron* **43**, 2223 (1987).
3. A. Márquez, H. Rodríguez, J. Medina and K. K. Cheung, *Synth. Commun.* **23**, 1321 (1993).
4. C. Saitz, A. Cañete, A. Márquez, L. Muñoz and H. Rodríguez, *Bol. Soc. Chil. Quím.* **41**, 295 (1996).
5. K. Nagayama, A. Kumar, K. Wüthrich and R. R. Ernst, *J. Magn. Reson.* **40**, 321 (1980).
6. A. Bax and S. Subramanian, *J. Magn. Reson.* **65**, 565 (1986).
7. A. Bax and M. F. Summers, *J. Am. Chem. Soc.* **108**, 2093 (1986).
8. R. E. Hurd, *J. Magn. Reson.* **87**, 422 (1990).
9. S. Braun, H. O. Kalinowski and S. Berger, *100 and More Basic NMR Experiments: A Practical Course*, pp. 244–390. Verlag Chemie, Weinhem, (1996).
10. (a) E. Pretsch, T. Clerc, J. Seibl and W. Simon, in *Tables of Spectral Data for Structure Determination of Organic Compound*, 2nd ed., edited by F. L. Boschke, W. Fresenius, J. F. K. Huber, E. Pungor, G. A. Reichnitz, W. Simon and T. West. pp. H265–H290. Springer, New York (1989); (b) E. Breitmaier and W. Voelter, *Carbon-13 NMR Spectroscopy*, 3rd ed., p. 260, VCH, Weinhein (1987).
11. A. R. Katritzky, B. Rashwal, S. Rashwal, D. Macomber and T. P. Smith, *J. Heterocycl. Chem.* **30**, 135 (1993).