

Unambiguous Assignment of the ^1H - and ^{13}C -NMR Spectra of Propafenone and a Thiophene Analogue

Wolfgang Holzer

Institute of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria. Tel. (43)-1-4277-55123, Fax (43)-1-4277-9551, e-mail holzer@merian.pch.univie.ac.at

Dedicated to Professor *Wilhelm Fleischhacker* on the occasion of his 70th birthday

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Abstract: Full and unambiguous assignment of all ^1H - and ^{13}C -NMR resonances of the free bases as well as the hydrochloride salts of the antiarrhythmic agent propafenone and a thiophene analogue in different solutions ($\text{DMSO-}d_6$, CDCl_3) is reported.

Keywords: Propafenone, Antiarrhythmics, ^1H -NMR, ^{13}C -NMR

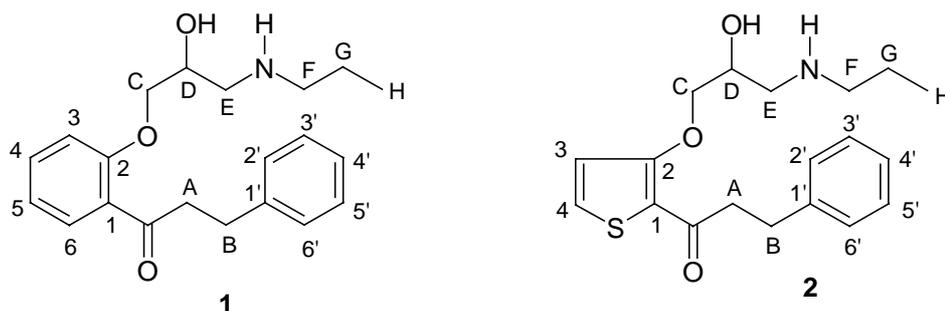
Introduction

Propafenone (**1**) is a class Ic antiarrhythmic drug with β -adrenoreceptor blocking and calcium antagonistic activity [1,2]. Moreover, **1** and related compounds have been identified to be highly effective modulators of multidrug resistance [3-5].

Although some NMR data of propafenone-like molecules have been reported [5-8] in most cases full assignments are missing and to the best of our knowledge no ^{13}C -NMR data for the parent compound **1** have been published. Thus, the present communication deals with the completely assigned ^1H - and ^{13}C -NMR spectra of propafenone and its thiophene analogue **2** [9], obtained by combined application of one and two-dimensional standard NMR techniques.

Results and Discussion

Complete and unambiguous assignments of all proton and carbons resonances were achieved on the basis of chemical shift considerations, coupling information (APT [10] and 'gated decoupled' ^{13}C -NMR spectra), and NOE-difference [11], COSY45 [12], HMQC [13], and 1D-TOCSY [14] spectra as well as on long-range INEPT experiments with selective excitation [15]. The numbering of atoms used in the discussion and in Tables 1 and 2 is given in the formulas of Scheme 1.



Scheme 1. Propafenone (**1**) and its Thiophene Analogue (**2**)

^1H -NMR Spectra

Whereas the aromatic region of the ^1H -NMR spectra of the investigated compounds is easy to interpret (AX-system for thiophene protons of **2**, four different signals of H-3, H-4, H-5, and H-6 of propafenone (**1**) - with the long-range coupling $^5J(\text{H-3}, \text{H-6})$ not resolved) the aliphatic part of the spectra is much more complex. Although - at first sight - the signal of protons H_B in some cases seem to have a pseudo-triplet structure, the nuclei attached to carbons A and B give rise to a spin-system consisting of four non-equivalent protons (ABMN), with the accurate coupling constants and chemical shifts not directly extractable from the higher order multiplets. Thus, in Table 1 only the centers of the signals due to protons A and B are given. The protons of the O-CH₂-CH(OH)-CH₂-N substructure formally establish an ABMXY spin-system, the chiral carbon center D causing more or less non-equivalence of the adjacent diastereotopic protons H_C and $\text{H}_{\text{C}'}$, as well as of H_E and $\text{H}_{\text{E}'}$ (see Figure 1 for **1**•HCl in DMSO-*d*₆). In DMSO-*d*₆ solutions, the signal due to H_D of **1**•HCl is additionally split by a vicinal coupling to the acidic OH proton. However, in many cases the corresponding chemical shifts and coupling constants of this substructure can be determined with sufficient accuracy. In principle, methylene protons $\text{H}_\text{F}/\text{H}_{\text{F}'}$ and $\text{H}_\text{G}/\text{H}_{\text{G}'}$ of the propylamino moiety are also non-equivalent, the signal of $\text{H}_\text{F}/\text{H}_{\text{F}'}$ showing more deviation from a first order pattern than that of $\text{H}_\text{G}/\text{H}_{\text{G}'}$ (Figure 1). Expectedly, hydrochloride salt formation in general leads to larger chemical shifts for the proton signals of the aminoalcohol moiety compared with those of the corresponding free bases.

¹³C-NMR Spectra

The ¹³C chemical shifts and some selected ¹³C, ¹H spin coupling constants are collected in Table 2. The data show a high degree of consistency, in nearly all cases the chemical shifts for carbons of the aminoalcohol chain (carbons C-H) are somewhat reduced when switching from the free bases to the hydrochloride salts (the opposite trend as observed for the corresponding ¹H chemical shifts). It should be mentioned that a good estimation of the ¹³C chemical shifts in **1** could be performed using the CSEARCH-program [16], the difference between the predicted (also given in Table 2) and observed values is less than 3.8 ppm for all carbon atoms.

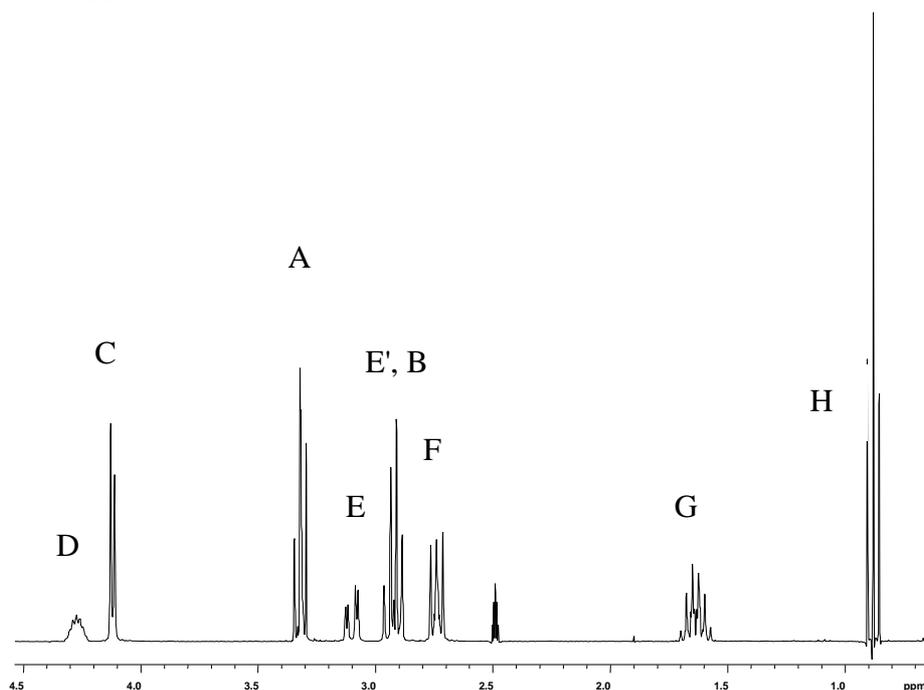


Figure 1. Aliphatic Part of the ¹H-NMR Spectrum of **1**•HCl (in DMSO-*d*₆ Solution)

Conclusions

We have presented the complete ¹H- and ¹³C-NMR chemical shifts of propafenone (**1**) and its thiophene analogue **2** as well as some selected spin-spin coupling constants.

Experimental

The NMR spectra were obtained using a Varian UnityPlus spectrometer (300 MHz for ¹H, 75 MHz for ¹³C) from DMSO-*d*₆ and CDCl₃ solutions (concentrations approximately 0.1 M, **1**•HCl in CDCl₃ had a much lower concentration due to solubility problems) at 28 °C. The center of the solvent signal was used as internal standard which was related to TMS with δ 7.26 ppm (¹H, CDCl₃), δ 2.49 ppm (¹H, DMSO-*d*₆), δ 77.0 ppm (¹³C, CDCl₃), and δ 39.5 ppm (¹³C, DMSO-*d*₆). The digital resolution was 0.2

Hz/data point for the ^1H -NMR spectra and 0.5 Hz/data point for the ^{13}C -NMR spectra. Propafenone hydrochloride was obtained from Sigma-Aldrich Chemical Company (USA), its thiophene analogue **2**•HCl was prepared according to the literature [9]. The corresponding free bases were obtained by treatment of aqueous solutions of the hydrochlorides with an excess of potassium carbonate and subsequent extraction with dichloromethane. The base **2** gave a satisfactory elemental analysis (calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_3\text{S}$: C 65.68; H 7.25; N 4.03. Found: C 65.52; H 7.21; N 3.93) and showed a melting point of 60 °C (the re-solidified product had a mp of 71 °C).

Table 1: ^1H - Chemical Shifts and Selected ^1H , ^1H -Coupling Constants

Compound	1		1 •HCl		2		2 •HCl	
	DMSO- d_6	CDCl_3	DMSO- d_6	CDCl_3	DMSO- d_6	CDCl_3	DMSO- d_6	CDCl_3
'aromatic' H-atoms'								
3	7.14	6.96	7.16	6.99	7.12	6.85	7.15	6.87
4	7.49	7.42	7.50	7.50	7.86	7.48	7.86	7.44
5	6.99	7.00	7.01	7.05	---	---	---	---
6	7.52	7.65	7.53	7.74	---	---	---	---
2',6'	7.22	7.24	7.21-7.28	7.21	7.24	7.25	7.23-7.30	7.24
3',5'	7.23	7.27	7.21-7.28	7.30	7.25	7.28	7.23-7.30	7.28
4'	7.15	7.17	7.15	7.20	7.16	7.18	7.15	7.15
'aliphatic' H-atoms								
A	3.33	3.33	3.33	3.32	3.21	3.23	3.22	3.13
B	2.90	3.03	2.91	3.01	2.90	3.02	2.92	2.99
C, C'	4.08, 4.01	4.06	4.14	4.20	4.19, 4.13	4.14, 4.13	4.26	4.27, 4.22
D	3.90	4.00	4.32	4.54	3.86	3.96	4.26	4.60
E, E'	2.64, 2.58	2.79, 2.69	3.11, 2.94	3.43, 3.14	2.61, 2.56	2.78, 2.69	3.11, 2.93	3.27, 3.13
F	2.41	2.53	2.74	2.94	2.39	2.51	2.74	2.88
G	1.37	1.49	1.66	1.97	1.36	1.46	1.65	1.88
H	0.83	0.91	0.87	1.01	0.83	0.91	0.88	0.96
NH and OH	*	2.70 (2H)	9.15 (2H), 5.96	9.40, 8.84, 1.65	4.99 (1 H)	2.15 (2H)	9.13 (2H), 5.90	9.28, 8.70

* Not unequivocally identified

Selected Coupling Constants

'aromatic' H: $^3\text{J}(3,4) = 7.8 \text{ Hz}$, $^4\text{J}(3,5) = 1.7 \text{ Hz}$, $^3\text{J}(4,5) = 7.8 \text{ Hz}$, $^4\text{J}(4,6) = 1.0 \text{ Hz}$, $^3\text{J}(5,6) = 8.4 \text{ Hz}$
 (**1**•HCl/ CDCl_3); $^3\text{J}(3,4) = 5.5 \text{ Hz}$ (**2** and **2**•HCl/ CDCl_3 and DMSO- d_6)

'aliphatic' H: $^2J(C,C') = 9.8$ Hz, $^3J(C,D) = 4.8$ Hz, $^3J(C',D) = 5.5$ Hz (**1**/DMSO- d_6)
 $^2J(C,C') = 9.7$ Hz, $^3J(C,D) = 4.3$ Hz, $^3J(C',D) = 5.2$ Hz (**2**•HCl/CDCl₃)
 $^3J(D,E) = 2.6 - 5.0$ Hz, $^3J(D,E') = 4.8 - 8.9$ Hz, $^2J(E,E') = 11.8 - 12.7$ Hz (all cases)
 $^3J(G,H) = 7.4 - 7.6$ Hz (all cases)
 $^3J(D,OH) = 4.8$ Hz (**1**•HCl/DMSO- d_6)

Table 2: ^{13}C -NMR Chemical Shifts and Selected ^{13}C , ^1H Coupling Constants

Compound	1			1•HCl		2		2•HCl		
	Solvent	DMSO- d_6	CDCl ₃	*	DMSO- d_6	CDCl ₃	DMSO- d_6	CDCl ₃	DMSO- d_6	CDCl ₃
sp^2 -hybridized C-atoms										
1		128.0	128.4	125.5	128.0	128.0	121.5	122.9	121.7	121.4
2		157.5	157.6	159.1	157.1	157.1	159.8	159.2	159.0	159.3
3		113.1	113.0	115.9	113.2	113.2	118.1	116.9	118.0	117.1
4		133.4	133.3	132.5	133.5	134.5	133.7	132.5	133.4	132.2
5		120.4	121.0	121.4	120.7	121.3	---	---	---	---
6		129.5	130.2	130.7	129.5	130.9	---	---	---	---
1'		141.3	141.5	140.7	141.3	141.0	141.3	141.6	141.2	141.2
2',6'		128.2	128.3	128.7	128.3	128.4	128.2	128.3	128.1	128.4
3',5'		128.1	128.3	128.4	128.2	128.6	128.1	128.3	128.0	128.5
4'		125.6	125.9	126.3	125.7	126.2	125.7	125.9	125.5	126.1
C=O		201.1	201.5	201.8	201.0	201.7	191.3	192.1	191.1	192.0
sp^3 -hybridized C-atoms										
A		44.5	45.1	41.3	44.4	43.4	42.1	43.1	41.9	43.0
B		29.7	30.2	30.6	29.7	30.2	29.5	30.1	29.3	30.1
C		71.2	71.4	72.0	70.4	71.5	74.4	74.0	73.4	74.2
D		67.9	67.8	69.3	64.8	64.8	68.1	67.7	64.8	65.0
E		52.3	51.8	52.4	49.8	51.6	52.1	51.5	48.7	51.5
F		51.2	51.6	52.3	48.8	50.7	51.3	51.5	48.7	50.6
G		22.5	23.1	23.1	18.7	19.4	22.7	23.2	18.5	19.3
H		11.6	11.6	11.9	10.9	11.2	11.7	11.6	10.7	11.1

* ^{13}C -NMR chemical shifts estimated by the CSEARCH-program [16] using neuronal network technology

Selected 2 and 2•HCl Coupling Constants

$^1J(\text{C4,H4}) = 171.7$ (2/DMSO- d_6), 169.7 (2/CDCl₃), 171.7 (2•HCl/DMSO- d_6), 170.7 (2•HCl/CDCl₃)

$^2J(\text{C4,H5}) = 4.5$ Hz (all cases); $^2J(\text{C5,H4}) = 4.5$ Hz (all cases)

$^1J(\text{C5,H5}) = 188.8$ (2/DMSO- d_6), 186.3 (2/CDCl₃), 188.9 (2•HCl/DMSO- d_6), 187.1 (2•HCl/CDCl₃)

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Sample Availability: Compound **2•HCl** is available from MDPI.

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