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^1H - and ^{13}C -NMR Study of Naphtho[2,1-b]thiophene and Naphtho[2,1-b]furan Derivatives

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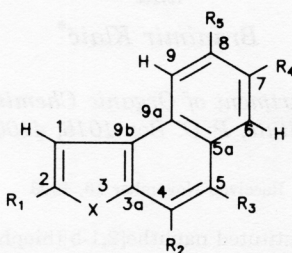
A series of four substituted naphtho[2,1-b]thiophenes **1–4** and a series of five substituted naphtho[2,1-b] furans **5–9** have been studied using one- and two-dimensional ^1H - and ^{13}C -NMR methods. Chemical shifts of protons could not be assigned on the basis of the homonuclear correlation (COSY) spectra only, but two-dimensional nuclear Overhauser (NOESY) spectroscopy had to be used. The cross-peak between H1 and H9 enabled unequivocal assignment of the H6-H9 four proton spin system. On the bases of NOE measurements of the naphtho[2,1-b]thiophene **3**, it was possible to estimate the interatom distances between H1 and H9 protons of 209 pm, and between H1 and H2 of 244 pm, respectively. Chemical shifts of substituted carbons were assigned using two-dimensional $^1\text{H}/^{13}\text{C}$ heteronuclear correlation (HETCOR) spectra. The substitution effect and the effect of solvent on the chemical shifts of the furan and thiophene analogues are reported, and the coupling constants $^nJ_{\text{H,H}}$ were determined.

INTRODUCTION

The naphtho[2,1-b]thiophenes are particularly interesting polycondensated heteroaromatic compounds because their derivatives with the cationic side chain in the 4-position exhibit interesting DNA-binding properties.^{1,2} These compounds were shown

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to intercalate with DNA. From most of the known intercalators, only the tilorone^{3,4} and the naphtho[2,1-b]thiophene^{1,2} class have been reported to show some pronounced A-T binding specificity. The relationship between the structure of intercalators, their binding strength and selectivity of their interactions with specific base pairs is fundamental to the understanding of small molecule-nucleic acid interactions, but factors that control their base-pair selectivity are not well known. Several factors influence the binding strength of intercalators, including the shape and size of the planar aromatic ring and electronic properties of the ring.^{5,6} It has been shown that it is possible to design intercalators that exhibit high A-T base pair binding selectivity, which can lead to a new understanding of specific base-pair interactions. The reported A-T specific intercalators include one with the naphtho[2,1-b]thiophene system, as the intercalating aromatic ring.⁷⁻⁹ Naphtho[2,1-b]thiophene-4-carboxylic acid is the key intermediate in the preparation of water soluble derivatives with intercalating properties. Although the syntheses of naphtho[2,1-b]thiophene-4-carboxylic and -5-carboxylic acid derivatives and analogous naphtho[2,1-b]furan-5-carboxy derivatives (Scheme I) have been described,¹⁰⁻¹³ there is little information about their ¹H- and ¹³C-NMR spectra.



Compound	X	R ₁	R ₂	R ₃	R ₄	R ₅
1	S	CHO	H	COOCH ₃	H	H
2	S	H	H	COOCH ₃	H	H
3	S	H	H	COOH	H	H
4	S	H	COOCH ₃	H	H	H
5	O	CHO	H	COOCH ₃	H	H
6	O	H	H	COOCH ₃	H	H
7	O	H	H	COOH	H	H
8	O	H	H	COOH	H	CH ₃
9	O	H	H	COOCH ₃	OCH ₃	H

Scheme I

In this paper, we report the total assignment of ¹H- and ¹³C-NMR spectra of naphtho[2,1-b]thiophene 1-4 and naphtho[2,1-b]furan derivatives 5-9. The spectra were investigated from the point of view of substituent effects. The effect of solvent on the chemical shifts was studied in polar deuteromethylsulfoxide and polar deuteriochloroform. The coupling constants ⁿJ_{H,H} were also determined.

EXPERIMENTAL

Material

Methyl-2-formylnaphtho[2,1-b]thiophene-5-carboxylate (**1**),¹⁰ methyl naphtho[2,1-b]thiophene-5-carboxylate (**2**),¹⁰ naphtho[2,1-b]thiophene-5-carboxylic acid (**3**),¹¹ methyl 2-formylnaphtho[2,1-b]furan-5-carboxylate (**5**),¹⁰ methyl naphtho[2,1-b]furan-5-carboxylate, (**6**),¹⁰ naphtho[2,1-b]furan-5-carboxylic acid (**7**),¹² and 8-methylnaphtho[2,1-b]furan-5-carboxylic acid (**8**),¹³ were synthesized by the described procedures.

Methyl naphtho[2,1-b]thiophene-4-carboxylate (4)

Naphtho[2,1-b]thiophene-4-carboxylic acid¹¹ (2.28 g, 10 mmol) was dissolved in absolute methanol (50 ml) to which concentrated sulfuric acid (0.5 ml) was added and refluxed for 7 hours. The cooled reaction mixture was poured onto 100 g of crushed ice, crystallized ester was recrystallized from methanol, yielding 1.89 g (78%) of **4**; m.p. 132–135 °C; IR (KBr): 1710 (COOCH₃) cm⁻¹.

Anal. Calcd. for C₁₄H₁₀O₂S: C 69.42, H 4.13%; found: C 69.49; H 4.03%

Methyl 7-methoxynaphtho[2,1-b]furan-5-carboxylate (9)

The methyl ester **9** was synthesized in a manner similar to the preparation of **4**, by 6 hours heating of 7-methoxynaphtho[2,1-b]furan-5-carboxylic acid¹³ (2.42 g, 10 mmol) dissolved in absolute methanol (50 ml) to which concentrated sulfuric acid (0.5 ml) was added. Recrystallized product (methanol) 1.79 g, (70%) was obtained; m.p. 64–66 °C; IR (KBr): 1705 (COOCH₃) cm⁻¹.

Anal. Calcd. for C₁₅H₁₂O₄: C 70.31; H 4.69%; found: C 70.19; H 4.63%.

NMR Techniques

The one- and two-dimensional NMR spectra were recorded at 30 ± 1 °C with a Varian Gemini 300 spectrometer operating at 300.1 (¹H) and 75.0 (¹³C) MHz, respectively. Typically, each one-dimensional ¹H-NMR spectrum was collected using a single 30° (5 μs) pulse, 1 s relaxation delay time, with the acquisition time 4.0 s, and a total sweep width of 3000 Hz sampled with 24k points. Data processing employed a Lorentz linebroadening factor of 0.25 Hz. Using these conditions, the experimental error of the measured coupling constants was ± 0.09 Hz. One-dimensional ¹³C-NMR spectra were acquired using a single 90° (15 μs) pulse, 1 s relaxation delay time, acquisition time 0.8 s, and a total sweep width of 18000 Hz sampled with 30k points. Data processing employed a Lorentz linebroadening factor of 1.25 Hz. The spectra were referenced to internal TMS, or to the residual DMSO signal (2.51 or 39.6 ppm, respectively). Concentrations of samples used for ¹H-spectra were approx. 10 mM, and 100 mM for ¹³C-NMR spectra.

Two-dimensional experiments: COSY,^{14,15} NOESY¹⁶⁻¹⁸ and HETCOR^{19,20} were performed using standard pulse sequences of the Varian Gemini software package. The COSY spectra were obtained in the magnitude mode, whereas NOESY spectra were obtained in the phase-sensitive mode.²¹ The COSY and NOESY experiments had 1024 points in the F2 dimension and 256 slices in F1, which were zero-filled to 1024 points. Each slice was obtained using 16 scans, a relaxation delay of 1 s, and a spectral width of 3000 Hz. The resolution in both domains was 6.0 Hz/point. The NOESY employed a mixing time of 600 ms.

The HETCOR experiment had 2048 points in F2 dimension and 256 slices in F1, which were zero-filled to 512 points. Each slice was obtained using 128 scans, a relaxation delay of 1 s, and the spectral width was 13600 Hz in F2, and 2700 Hz in F1 domains, respectively. The resolution in F2 is 13.3 Hz/point, and 10.5 Hz/point in the F1 dimension. The protons were decoupled by Waltz-16 modulation.

RESULTS AND DISCUSSION

As the starting point for the assignment of the proton NMR spectra of 1–7, it is reasonable to expect that the H6-H9 protons constitute an ABMX spin system. The H1-H2 spin system of compounds 2–4 and 6–9 would be assumed to appear as an AX rather than as an AB spin system because of the 2,3-fusion of the thiophene or furan ring to the naphthalene ring. Other protons in 1–9 are isolated, or constitute AX spin systems like H6-H7 in 8, or H8-H9 in 9. No individual assignments were possible within ABMX spin systems solely on the basis of the connectivities observed in the COSY spectra (Figure 1). Which proton of these H6-H9 four spin systems in naphtho[2,1-b]thiophene and naphtho[2,1-b]furan derivatives 1–7 falls in a lower field was distinguished on the basis of the NOESY spectra (Figure 2 and 3). In each NOESY spectrum, the NOE interaction between H1 and H9 was observed. This enabled full assignment of naphtho[2,1-b]thiophene and naphtho[2,1-b]furan protons from the COSY spectra. The corresponding chemical shifts are listed in Table I.

It can be seen that the H2 protons of the thiophene series (2–4) are more shielded than H1. This is an opposite effect to that observed for the smaller analogous com-

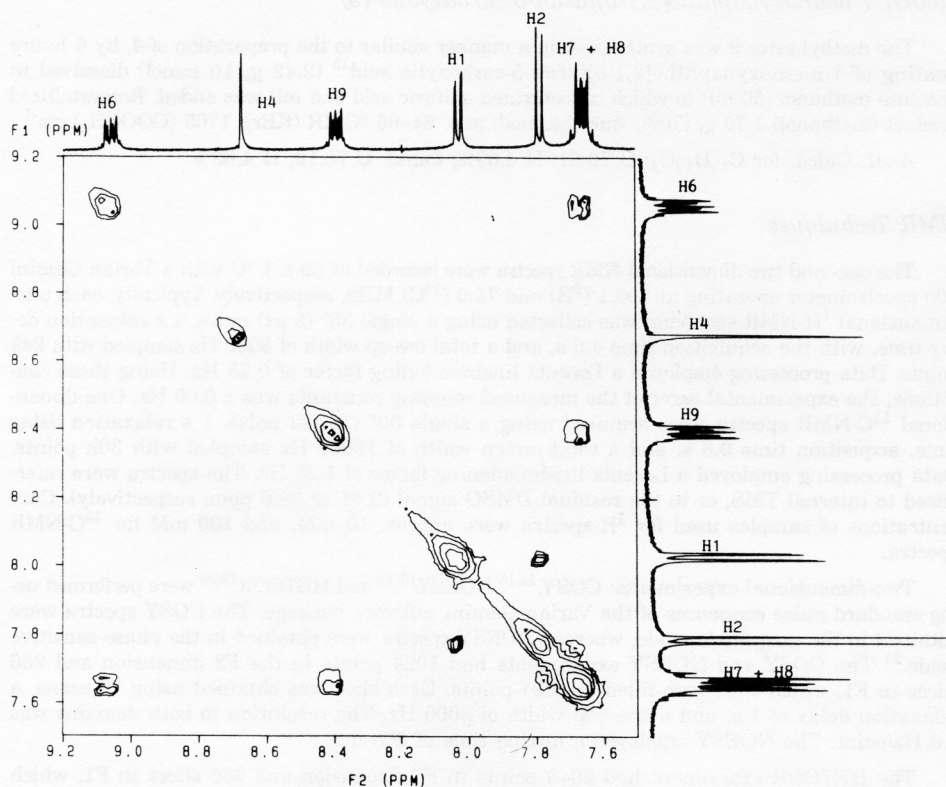


Figure 1. The COSY spectrum (magnitude mode) of methyl naphtho[2,1-b]thiophene-5-carboxylate (2) in deuteriochloroform, 10 mM, 30 °C. Assignments of protons are given in both projections.

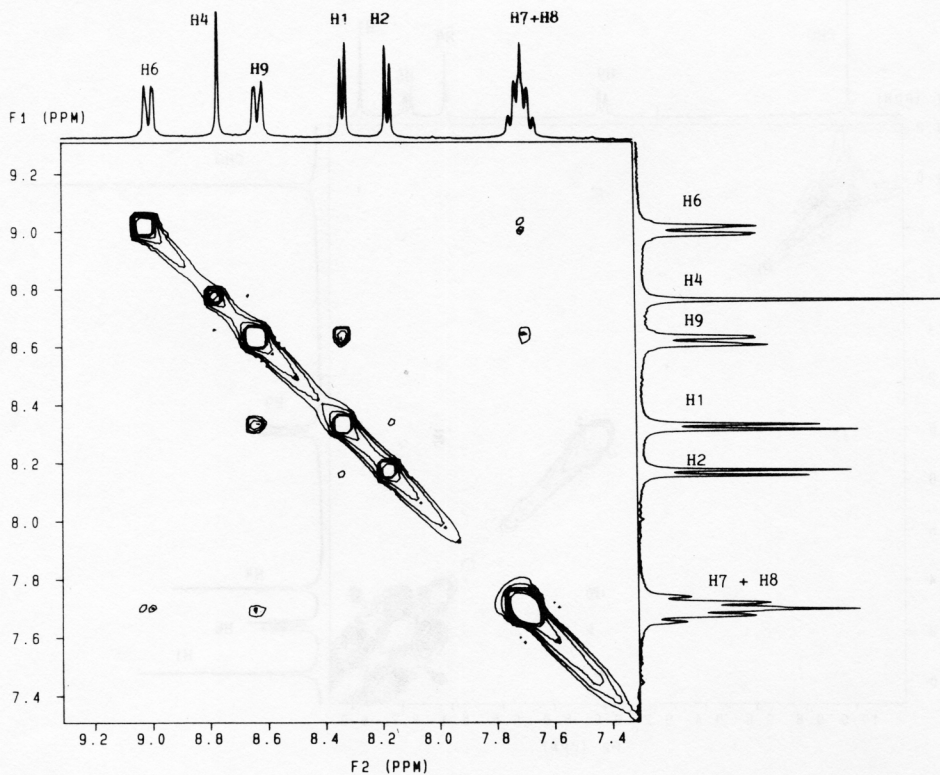


Figure 2. The NOESY spectrum (phase sensitive mode) of naphtho[2,1-b] thiophene-5-carboxylic acid (**3**) in deuteromethylsulfoxide, 10 mM, 30 °C, mixing time, $t_m = 600$ ms. Assignments of protons are given in both projections.

pond, benzothiophene,²² but does agree well with the reported data on unsubstituted naphtho[2,1-b]thiophene²² and on the bigger analogue, phenanthro[3,4-b] thiophene.²³ The sequence of chemical shifts of the four protons ABMX system in **1-4** is the same: $\delta_6 > \delta_9 > \delta_8 > \delta_7$, which does not agree with the corresponding four protons spin system (H8-H11) in phenanthro[3,4-b]thiophene,²³ but agrees with chemical shifts of the corresponding (H4-H7) protons of benzothiophene.²⁴ The situation regarding naphtho[2,1-b]furan derivatives **6-9** is quite different; in the AX spin system consisting of H1-H2 protons, the signals of H2 fall in a lower field than H1, and it is the same as in the case of the smaller analogue, benzofuran.²⁵ The sequence of the four proton ABMX systems in the furan series of **5-7** is different from the sequence observed in [2,1-b]thiophene derivatives: $\delta_9 > \delta_6 > \delta_8 > \delta_7$.

Substitution of the sulphur atom by oxygen causes a large upfield shift of the H1 and H6 atoms and a significant downfield shift of the H9 proton (Table II, **1-5** and **2-6**). The influence on the chemical shift of the closest neighbour, H2, is negligible ($\Delta\delta = -0.085$ ppm). Comparison of chemical shifts of thiophene and furan de-

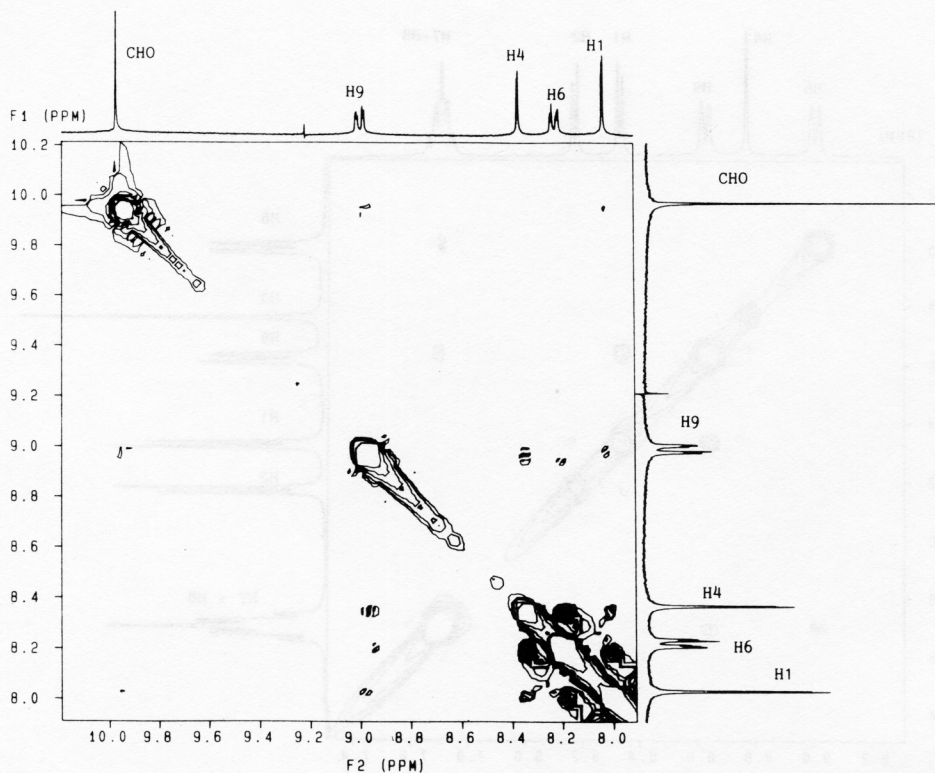


Figure 3. The NOESY spectrum (phase sensitive mode) of methyl 2-formylnaphtho[2,1-b]furan-5-carboxylate (**5**) in deuteriochloroform, 10 mM, 30 °C, mixing time, $t_m = 600$ ms. Assignments of protons are given in both projections.

TABLE I

¹H chemical shift data of naphtho[2,1-b]thiophene and naphtho[2,1-b]furan derivatives 1–9 in deuteriochloroform and deuteromethylsulfoxide at 300 MHz, 30 °C

Proton(s)	1	2	3	4	5	6	7	7	8	8	9
Solvent	CDCl ₃	CDCl ₃	DMSO	CDCl ₃	CDCl ₃	CDCl ₃	CDCl ₃	DMSO	CDCl ₃	DMSO	CDCl ₃
H-1	8.589	8.031	8.350	8.010	8.033	7.291	7.635	7.710	7.300	7.652	7.214
H-2	–	7.789	8.192	7.716	–	7.874	7.929	8.320	7.903	8.278	7.850
H-4	8.653	8.678	8.789	–	8.370	8.422	8.610	8.429	8.541	8.347	8.456
H-5	–	–	–	8.585	–	–	–	–	–	–	–
H-6	8.982	9.060	9.033	8.355	8.224	8.187	8.209	8.417	9.095	8.929	8.662
H-7	7.701	7.655	7.702	7.568	7.684	7.591	7.659	7.644	7.476	7.470	–
H-8	7.728	7.672	7.746	7.695	7.710	7.626	7.858	7.690	–	–	7.288
H-9	8.402	8.398	8.647	8.034	8.994	9.053	9.304	9.032	7.975	8.179	8.054
COOCH ₃	4.054	4.043	–	4.071	4.055	4.018	–	–	–	–	4.009
CHO	10.211	–	–	–	9.974	–	–	–	–	–	–
OCH ₃	–	–	–	–	–	–	–	–	–	–	3.983
CH ₃	–	–	–	–	–	–	–	–	2.598	2.550	–

Using the H10-H11 bond distance (237 pm) in 1-methylphenanthro[3,4-b] thiophene, which was determined crystallographically,²³ as an orientation value for the H8-H9 interatomic distance of **3**, from the observed NOE effects between H8-H9, H1-H9 and H1-H2, the interatomic distance of approx. 209 and 244 pm, between H1-H9 and H1-H2, respectively, could be calculated. Construction of a Dreiding model of **3**, assuming a planar conformation as the starting point, shows the interatomic distances between H1 and H9 of 213 pm, and between H1 and H2 of 249 pm, respectively, which is in excellent agreement with the distances measured in solution by the NOE technique.

Coupling constants $^3J_{H_1,H_2}$ in thiophene series are approx. 5.5 Hz (Table III) and agree well with the corresponding constants in the smaller benzothiophene²² and in the bigger analogue phenanthro[3,4-b]thiophene.²⁸ The same constants in the furan series are 2.1 Hz, and are in good agreement with the published data for benzofuran.²⁵ Other »ortho« constants of thiophene derivatives, $^3J_{H_6,H_7}$ and $^3J_{H_8,H_9}$ are around 8 Hz, whereas $^3J_{H_7,H_8}$ are approx. 7 Hz. A similar situation is that of the corresponding coupling constants of furan derivatives; although the $^3J_{H_6,H_7}$ are slightly bigger, they are fairly typical of benzenoid derivatives.^{24,25,28} The two observed long range constants including the H1 proton, $^5J_{H_1,H_4}$ and $^5J_{H_1,H_9}$, are around 0.8 and 1.0 Hz, respectively, and they are well within the range of values observed for other polycyclic aromatics of 0.6-1.1 Hz.²⁹

TABLE III

Coupling constants ($^nJ_{H,H}$) of naphtho[2,1-b]thiophene and naphtho[2,1-b]furan derivatives **1-9** in deuteriochloroform and deuteromethylsulfoxide at 300 MHz, 30 °C

Coupling constant	1	2	3	4	5	6	7	7	8	8	9
Solvent	CDCl ₃	CDCl ₃	DMSO	CDCl ₃	CDCl ₃	CDCl ₃	CDCl ₃	DMSO	CDCl ₃	DMSO	CDCl ₃
$^3J_{H_1,H_2}$	—	5.43	5.43	5.59	—	2.05	1.99	2.13	2.13	2.06	2.07
$^3J_{H_6,H_7}$	8.23	8.03	8.07	8.25	7.92	7.88	8.88	8.80	8.93	8.81	—
$^3J_{H_7,H_8}$	6.96	7.81	6.74	7.03	7.26	7.03	7.05	6.85	—	—	—
$^3J_{H_8,H_9}$	8.06	7.83	8.02	8.08	7.77	8.08	7.59	8.13	—	—	8.97
$^4J_{H_6,H_8}$	1.80	1.81	1.51	1.14	1.64	1.75	1.83	1.68	—	—	2.55
$^4J_{H_7,H_9}$	1.90	1.57	1.59	1.32	2.10	2.05	1.68	1.62	1.70	n.o.	—
$^5J_{H_1,H_4}$	0.75	0.78	n.o.	n.o.	0.95	0.88	0.88	0.66	n.o.	0.80	0.85
$^5J_{H_1,H_9}$	1.07	n.o.	n.o.	n.o.	1.23	0.90	n.o.	n.o.	1.02	n.o.	n.o.
$^5J_{H_2,H_4}$	—	n.o.	n.o.	n.o.	n.o.	n.o.	n.o.	1.02	1.20	1.02	n.o.
$^3J_{H_6,H_9}$	0.80	1.11	n.o.	n.o.	0.81	1.20	n.o.	n.o.	0.61	n.o.	n.o.

n.o. = not observed

Assignment of the substituted carbons of naphtho[2,1-b] thiophene **2-4** and naphtho[2,1-b]furan derivatives **7-9** is based on the HETCOR spectra (Figure 4) and the chemical shift data are given in Table IV. Carbonyl or carboxyl groups are in the lowest field in all the compounds studied (approx. 168 ppm). Assignment of C3a and C9b atoms in naphtho[2,1-b]furan series was made by comparison with benzofuran

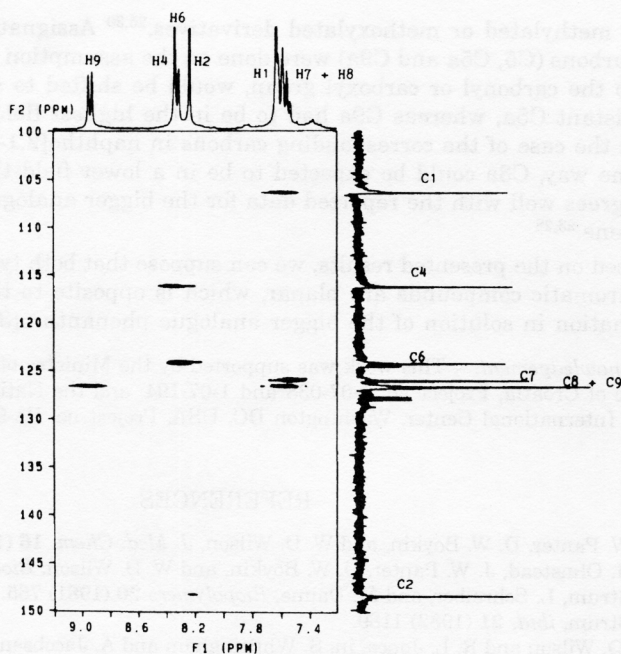


Figure 4. The two-dimensional $^1\text{H}/^{13}\text{C}$ heteronuclear correlation (HETCOR) spectrum of naphtho[2,1-b]furan-5-carboxylic acid (**7**) in deuteromethylsulfoxide, 100 mM, 30 °C. Assignments of protons and carbons are given in the corresponding projection.

TABLE IV

^{13}C chemical shift data of naphtho[2,1-b]thiophene **2-4** and naphtho[2,1-b]furan derivatives **7-9** in deuteriochloroform and deuteromethylsulfoxide at 75 MHz, 30 °C

Carbon	2	3	4	7	8	9
Solvent	CDCl_3	DMSO	CDCl_3	DMSO	DMSO	CDCl_3
C-1	121.84	122.82	121.41	106.47	106.28	105.68
C-2	129.32	131.19	130.26	148.26	147.91	146.72
C-3a	138.97	138.97	137.56	150.06	150.13	149.23
C-4	125.39	125.50	131.64	116.24	115.26	105.23
C-5	129.09	129.19	126.18	127.94	126.33	127.30
C-5a	128.33	128.28	130.59	126.79	125.99	122.45
C-6	123.50	124.42	124.02	124.28	123.30	118.20
C-7	126.19	126.74	129.43	126.04	126.44	157.60
C-8	126.19	126.48	129.43	126.67	134.14	116.84
C-9	126.33	126.48	129.56	126.67	127.94	124.50
C-9a	123.15	124.30	122.80	124.54	124.28	121.20
C-9b	134.96	135.22	135.69	127.68	127.82	129.68
CO	167.35	168.64	167.04	168.48	168.46	167.41
COOCH_3	51.77	—	52.71	—	—	51.51
CH_3	—	—	—	—	21.10	—
OCH_3	—	—	—	—	—	53.79

and its methylated or methoxylated derivatives.^{25,30} Assignations of the remaining three carbons (C5, C5a and C9a) were done on the assumption that C5, as the closest atom to the carbonyl or carboxyl group, would be shifted to a field lower than the more distant C5a, whereas C9a had to be in the highest field. The same logic was used in the case of the corresponding carbons in naphtho[2,1-b]thiophene series. In the same way, C3a could be expected to be in a lower field than C9b. This assignment agrees well with the reported data for the bigger analogue, phenanthro[3,4-b]-thiophene.^{23,28}

Based on the presented results, we can suppose that both types of polycondensated heteroaromatic compounds are planar, which is opposite to the pronounced helical conformation in solution of the bigger analogue phenanthro[3,4-b]thiophene.^{23,28}

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SAŽETAK

¹H- i ¹³C-NMR studija derivata nafto[2,1-b]tiofena i nafto[2,1-b]furana

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Niz od četiri supstituirana nafto[2,1-b]tiofena **1–4** i pet supstituiranih nafto[2,1-b]furana **5–9** proučavani su s pomoću jedno- i dvo-dimenzijskih metoda ¹H- i ¹³C-NMR spektroskopije. Kemijski pomaci protona nisu se mogli asignirati samo na temelju homonuklearnih korelacijskih (COSY) spektara, već je trebalo uporabiti dvo-dimenzijsku nuklearnu Overhauserovu (NOESY) spektroskopiju. Opažanje interakcijskog signala između H1 i H9 omogućilo je nedvojbenu asignaciju spinskog sustava sastavljenoga od četiri protona (H6-H9). Na temelju mjerenja NOE efekta mogu se u nafto[2,1-b]tiofenu **3** odrediti međuatomske udaljenosti između H1 i H9 (209 pm), odnosno između H1 i H2 (244 pm). Kemijski pomaci supstituiranih ugljika asignirani su s pomoću dvodimenzijskog ¹H/¹³C heteronuklearnog korelacijskog (HETCOR) spektra. Promatranjima su supstitucijski efekti i efekti otapala na kemijski pomak analoga furana i tiofena, a k tome su određene konstante sprege ⁿJ_{H,H}.