ONE-BOND ^{13}C-^{1}H COUPLING CONSTANTS FOR SUBSTITUTED THIENO[2,3-*b*]- AND THIENO[3,2-*b*]PYRIDINES AND THEIR USE IN STRUCTURAL ASSIGNMENTS

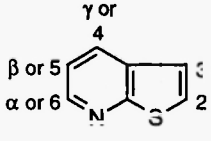
LeRoy H. Klemm* and John N. Louris
Department of Chemistry, University of Oregon, Eugene, Oregon 97403-1253, USA

Abstract: One-bond ^{13}C-^{1}H coupling constants ($^{1}J_{CH}$) are reported for all of the CH units in the parent thieno[2,3-*b*]- and thieno[3,2-*b*]pyridines, their *N*-oxides, and 44 of their monosubstituted derivatives in $CDCl_3$ as solvent. In every derivative the location of the substituent on the thienopyridine ring can be assigned precisely from a combination of the ^{1}H NMR spectral pattern plus a complete array of $^{1}J_{CH}$ values. Electronic effects on $^{1}J_{CH}$ of substituents in these systems are consistent with observations made in other aromatic compounds. From the $^{1}J_{CH}$ values for the parent thienopyridines one can assign percentages of *s*-hybridization to the various C-H bonds.

Introduction

Tori and Nakagawa (1) summarized early reported data on one-bond ^{13}C-^{1}H coupling constants ($^{1}J_{CH}$) for numerous heteroaromatic compounds including pyridine, quinoline, isoquinoline, and thiophene parent molecules, some substitution products of these systems, and (for comparison) benzene and some of its derivatives. $^{1}J_{CH}$ data have also been measured for the benzo[*b*]thiophene (2) and thieno[3,2-*b*]thiophene systems (3). We now report extension of these measurements to the parent bicyclic compounds thieno[2,3-*b*]pyridine **1** and thieno[3,2-*b*]pyridine **28**, their *N*-oxides **27** and **40**, plus 44 monosubstituted derivatives (**2**-**26**, **29**-**39**, and **41**-**48**) of these systems (see Tables 1 and 2).

It has been noted that the size of the coupling constant is a measure of the hybridization of the C-H bond; in particular, increasing values of $^{1}J_{CH}$ imply increasing *s*-character to the bond (4-8) and shortening of the bond length (5). Additionally, electron-withdrawing substituents (such as nitro, halo, and cyano) increase $^{1}J_{CH}$; while electron-donating substituents (such as methyl and methoxy) decrease $^{1}J_{CH}$, particularly for nearby CH units (1, 5, 9-12). *N*-Oxidation of pyridine serves to increase $^{1}J_{CH}$ values (1,13).



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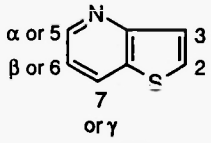

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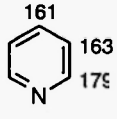

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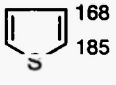

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Experimental and Procedure

N-Oxides **27** and **40**, available from previous studies (14, 15), were distilled *in vacuo* to remove water of hydration. Other compounds were synthesized and purified as noted in a previous publication (16). The positional location of the substituent in each compound was either completely or tentatively assigned, as based on chemical considerations and/or ^{1}H NMR spectral data prior to this study. The ^{13}C NMR spectra were obtained in $CDCl_3$, as indicated before (16). The

^{13}C signals were correlated with the ^{1}H signals, and the structural assignment of each CH unit was corroborated by observance of the multiplicity in its long-range splitting. $^{1}J_{CH}$ values were measured to an accuracy of ±1 Hz.

Table 1: One-bond ^{13}C-^{1}H Coupling Constants (in Hz) for Substituted Thieno[2,3-*b*]pyridines in $CDCl_3$

Comp.	Substituent	Position on Ring System					Other C
		2	3	4[a]	5[b]	6[c]	
1	none	184	170	163	164	180	
2	2-C(=O)H		171	165	165	181	181
3	2-C(=O)CH_3		171	160	165	181	128[d]
4	3-NO_2	192		169	165	182	
5	3-NH_2	181		161	164	180	
6	3-NHC(=O)CH_3	190		162	165	181	128[d]
7	3-Cl	189		166	165	181	
8	3-Br	190		166	165	181	
9	3-I	191		165	165	181	
10	4-CH_3	186	170		161	179	128
11	4-Cl	187	175		168	183	
12	4-NH_2	186	168		160	176	
13	5-Cl	186	170	168		188	
14	5-NO_2	187	173	171		193	
15	5-NH_2	184	170	160		177	
16	5-CN	187	173	169		188	
17	5-C(=O)CH_3	184	171	165		182	128[d]
18	5-C(=O)OCH_3	184	173	167		186	148[d]
19	5-CH_2CH_3	184	170	160		177	127[e]
20	6-Cl	185	171	165	171		
21	6-CN	186	173	167	169		
22	6-C(=O)CH_3	186	172	165	168		129[d]
23	6-C(=O)NH_2	186	172	165	169		
24	6-C(=S)NH_2	186	173	165	167		
25	6-C(=NH)NH_2	185	172	165	166		
26	6-C(=NH)OCH_3	185	173	164	166		146[d]
27	7-oxide	187	175	169	166	186	

a) γ-position on pyridine ring. b) β-position. c) α-position. d) For methyl group. e) For both methylene and methyl groups (overlapping quartet and triplet signals).

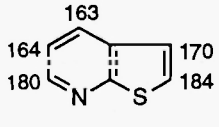
Table 2: One-bond ^{13}C-^{1}H Coupling Constants (in Hz) for Substituted Thieno[3,2-*b*]pyridines in $CDCl_3$

Comp.	Substituent	Position on Ring System					Other C
		2	3	5[a]	6[b]	7[c]	
28	none	186	172	178	164	165	
29	2-Cl		176	179	165	166	
30	2-Br		177	179	165	166	
31	2-I		177	179	165	166	
32	2-C(=O)H		172	180	165	167	182
33	2-CH_2OH		170	179	165	165	145
34	2-C(=O)CH_3		171	180	165	167	129[d]
35	2-CN		178	181	166	168	
36	3-Cl	190		181	166	167	
37	3-Br	191		180	165	166	
33	3-I	193		182	167	167	
39	3-NO_2	192		182	166	168	
40	4-oxide	189	179	187	167	171	
41	5-Cl	186	173		172	167	
42	5-CN	187	175		170	169	
43	5-C(=O)NH_2	186	173		169	168	
44	5-C(=S)NH_2	186	174		169	167	
45	6-C(=O)CH_3	186	174	180		167	128[d]
46	7-Cl	187	174	181	169		
47	7-NH_2	187	171	175	161		
48	7-NO_2	185	175	185	172		

a) α-position on pyridine ring. b) β-position. c) γ-position. d) For methyl group.

Discussion of Results

The following figures compare the $^{1}J_{CH}$ values (in Hz) for positions in the heterocyclic rings of our parent thienopyridines with those reported for quinoline **49** (1, 17) and benzo[*b*]thiophene **50** (2). Data for pyridine **51** (13) and thiophene **52** (12) are given above. It is readily apparent that the coupling constant varies with the position of the CH unit



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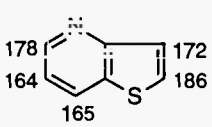

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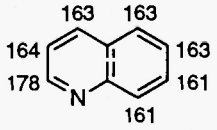

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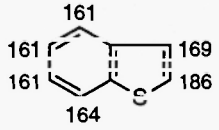

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in its heterocyclic ring in the order 2 > α > 3 > β = γ, where the numbers refer to the thiophene ring (with the sulfur atom in position 1) and the Greek letters refer to positions in the pyridine ring with regard to the heteroatomic nitrogen atom. The numerical values in these six parent compounds are 185±1, 179±1, 170±2, 163±1, and 163±2 Hz, respectively. From the simple relationship of $^{1}J_{CH}$ = 5 x (% *s*-character) (18) one calculates corresponding values of 37-33% *s*-hybridization in the various C-H bonds, as compared to 32% calculated for benzene ($^{1}J_{CH}$ = 159 Hz) (1) or 33.3% expected for a theoretical sp^2 bonding. Electronic effects of substituents on the thienopyridine rings in our compounds broaden the range of $^{1}J_{CH}$ values to 186±5, 179±4, 173±6, 166±6, and 166±6. Thus, one concludes that in all of the compounds in Tables 1 and 2, every C-H bond has one-third or more *s*-character.

Specific *proximity effects* on $^{1}J_{CH}$ are notable in derivatives of molecule **1** where the 3-nitro group (see **4**) raises the coupling constants at C-2 and C-4 by 6 Hz, while the 3-amino group (see **5**) lowers these by 2-3 Hz. Neither substituent alters $^{1}J_{CH}$ values at C-5 and C-6 as much. Nearly analogous effects are observed for the nitro-amino pairs at C-5 in **1** (see **14** and **15**) and C-7 in **28** (see **47** and **48**). The proximity effect is apparent for the eight isomeric chloro-thienopyridines **7**, **11**, **13**, **20**, **29**, **36**, **41**, and **46**, where the largest values of $\Delta^{1}J_{CH}$ occur for the adjacent position(s). The same relationships are observed for the more limited arrays of cyano (**16**, **21**, **35**, **42**), bromo (**8**, **30**, **37**), and iodo (**9**, **31**, **38**) derivatives. *N*-Oxidation of **1** and **28** (see **27** and **40**) increases $^{1}J_{CH}$ appreciably at all positions, consistent with withdrawal of electronic charge from both rings.

Twenty-one derivatives listed in Tables 1 and 2 were obtained by direct substitution into the parent thienopyridines or their *N*-oxides. In each of these cases observation of the ^{1}H NMR spectrum plus the array of $^{1}J_{CH}$ values for the product permits a definitive assignment of position to the substituent in the system. First, one notes that parent compounds **1** and **28** present a characteristic doublet of doublets ($J_{2,3}$ = 6 Hz) for the protons in the thiophene portion (19). Retention of this spectral feature in the derivative implies that the substituent is located in the pyridine ring, while replacement of this feature by a singlet heralds substitution into the thiophene ring at either C-2 or C-3. The magnitude of the ^{13}C-^{1}H one-bond coupling constant then clearly establishes the location of any substituent on the thiophene ring. In this manner structures **4**, **7-9**, **29-31**, and **36-39**, where the substituent is either a nitro or a halo group, were easily established (20-22). For these electron-attracting groups the remaining $^{1}J_{CH}$ was 189-193 Hz for the unsubstituted 2-position and 176-177 Hz for the unsubstituted 3-position. Aldehydes **2** and **32** and alcohol **33** were assigned positions in like manner, though they exhibited little change in $^{1}J_{CH}$ value from that of the parent (22, 23). Though $^{1}J_{CH}$ for the aldehyde function has essentially the same value as that for the α-CH, the ^{1}H and ^{13}C NMR spectra clearly serve to prevent confusion in structural assignments. Chemical transformations of **4** produced **5** and **6**, while **31** was converted into **35** (20, 22). The structures of acetyl derivatives **3** and **34** were known from their methods of synthesis (19).

Seven compounds in the tables resulted from direct substitution into the pyridine ring. For these, observed changes in the proton-proton coupling scheme (average constants: $J_{\alpha,\beta}$ = 4.6, $J_{\beta,\gamma}$ = 8.4, and $J_{\alpha,\gamma}$ = 1.6 Hz) suffice to assign ring positions (19). However, the $^{1}J_{CH}$ values then serve to corroborate these assignments, whereby α-substituents are clearly differentiated from those in β- or γ-positions. Chlorination of **27**, accompanied by de-*N*-oxygenation, gave both the **4**- and 6-chloro derivatives (**11** and **20**), distinguished by the number (2 and 1, respectively) of large $^{1}J_{CH}$ values in the range of 185±2 Hz (24). Analogously, *N*-oxide **40** produced the 5- and 7-chloro isomeric derivatives of **28** (see **41** and **46**) (15). Reissert-Henze reaction on these *N*-oxides produced α-cyano derivatives **21** and **42**, converted chemically into **22-26** and **43-44** (25). Nitration of **40** led indirectly to **47** and **48** (15). Structures of other compounds with a substituent in the pyridine ring were based on syntheses (19, 26, 27).

Conclusions

The location of a substituent on either thieno[2,3-*b*]pyridine or thieno[3,2-*b*]pyridine can be determined precisely from a combination of its ^{1}H NMR spectrum plus its array of ^{13}C-^{1}H one-bond coupling constants (i.e., $^{1}J_{CH}$). In these molecules the magnitude of $^{1}J_{CH}$ varies with its position in the heterocyclic ring, as well as with the electronic nature and proximity of a substituent group. These nuclear magnetic properties have been used in assigning positions of substitution in five-membered monocyclic heterocycles (1, 28, 29) and should be useful in extensions to various other bicyclic heterocyclic systems.

References and Notes

(1) K. Tori and T. Nakagawa, J. Phys. Chem. 68, 3163 (1964)

(2) S. S. Al-Showiman, I. M. Al-Najjar and H. B. Amin, Org. Magn. Reson. 20, 105 (1982)

(3) S. Gronowitz, I. Johnson and A. Bugge, Acta Chem. Scand. B30. 417 (1976)

(4) J. N. Shoolery, J. Chem. Phys. 31, 1427 (1959)

(5) N. Muller and D. E. Pritchard, J. Chem. Phys. 31, 768, 1471 (1959)

(6) N. Muller, J. Chem. Phys. 36, 359 (1962)

(7) H. A. Bent, Chem. Rev. 61, 275 (1961)

(8) G. E. Maciel, J. W. McIver, N. S. Ostlund and J. A. Pople, J. Am. Chem. Soc. 92, 1 (1970)

(9) K. Takahashi, T. Sone and K. Fujieda, J. Phys. Chem. 74, 2765 (1970)

(10) M. Hansen and H. J. Jakobsen, J. Magn. Reson. 10, 74 (1973)

(11) Y. Takeuchi and N. Dennis, J. Am. Chem. Soc. 96, 3657 (1974)

(12) S. Gronowitz, I. Johnson and A.-B. Hörnfeldt, Chem. Scr. 7, 76 (1975). See also T. J. Batterham, NMR Spectra of Simple Heterocycles, John Wiley, New York, 1973, pp 442

(13) F. A. L. Anet and I. Yavari, J. Org. Chem. 41, 3589 (1976). See also J. D. Memory and N. K. Wilson, NMR of Aromatic Compounds, John Wiley, New York, 1982, pp 153

(14) L. H. Klemm, J. J. Lu, D. S. Greene and W. Boisvert, J. Heterocycl. Chem. 24, 1467 (1987)

(15) L. H. Klemm, J. N. Louris, W. Boisvert, C. Higgins and D. R. Muchiri, J. Heterocycl. Chem. 22, 1249 (1985)

(16) L. H. Klemm and J. N. Louris, Heterocycl. Commun. 1, 375 (1995)

(17) A. M. Kook, S. L. Smith and E. V. Brown, Org. Magn. Reson. 22, 730 (1984)

(18) J. A. Pople and D. P. Santry, Mol. Phys. 8, 1 (1964)

(19) L. H. Klemm, C. E. Klopfenstein, R. Zell, D. R. McCoy and R. A. Klemm, J. Org. Chem. 34, 347 (1969)

(20) L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopfenstein and D. R. McCoy, J. Heterocycl. Chem. 7, 373 (1970)

(21) L. H. Klemm, R. E. Merrill, F. H. W. Lee and C. E. Klopfenstein, J. Heterocycl. Chem. 11, 205 (1974)

(22) L. H. Klemm and J. N. Louris, J. Heterocycl. Chem. 21, 785 (1984)

(23) L. H. Klemm and R. E. Merrill, J. Heterocycl. Chem. 11, 355 (1974)

(24) L. H. Klemm and R. Hartling, J. Heterocycl. Chem. 13, 1197 (1976)

(25) L. H. Klemm and D. R. Muchiri, J. Heterocycl. Chem. 20, 213, 1717 (1983)

(26) L. H. Klemm and R. Zell, J. Heterocycl. Chem. 5, 773 (1968)

(27) L. H. Klemm, I. T. Barnish and R. Zell, J. Heterocycl. Chem. 7, 81 (1970)

(28) F. Fringuelli, S. Gronowitz, A.-B. Hörnfeldt, I. Johnson and A. Taticchi, Acta Chem. Scand. B28, 175 (1974)

(29) C. W. Bird, G. W. H. Cheeseman and A.-B. Hörnfeldt, Selenophene, Tellurophenes and Their Benzo Derivatives, in A. R. Katritzky and C. W. Rees (Eds.), Comprehensive Heterocyclic Chemistry, Vol 4, Part 3, Pergamon, New York, 1984, pp 940

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