Long Range Heteronuclear Chemical Shift Correlation with One Bond Modulation Decoupling: Phenanthro[1,2-b]thiophene

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Dedicated to Professor Norman H. Cromwell

Long range heteronuclear chemical shift correlation has become an extremely useful technique for complex spectral assignment and structure elucidation. The sensitivity is higher than that afforded by ^{13}C-^{13}C double quantum INADEQUATE experiment. The long range heteronuclear correlation provides the means of establishing connectivities across heteroatoms. Early attempts to use long range heteronuclear chemical shift correlation by simply optimizing the delays for long range couplings met with varied success. Long range coupling responses to protonated carbon resonances can be modulated by the one bond coupling of the protonated carbon. These modulations can lead to precipitous valleys in the response curve and a corresponding loss of connectivity information. A newly reported pulse sequence employing a BIRD pulse midway through the Δ_2 refocusing delay "decouples" one bond modulation effects substantially increasing the likelihood of observing the desired connectivities. The application of this technique is reported for phenanthro[1,2-b]thiophene. Unequivocal assignment of the title compound is reported using heteronuclear chemical shift correlation and long range correlation with modulation decoupling. The assignment took a total of <15 hours of spectrometer time.

Introduction.

Two-dimensional (2D) nmr spectroscopy has had a major impact on structure elucidation and spectral assignment studies. It is now possible to successfully assign the highly congested nmr spectra of complex polynuclear aromatics in an unequivocal fashion. Many, if not all, of these assignment problems would be intractable by more conventional techniques.

Partial assignment of the proton and carbon nmr spectra of phenanthro[1,2-b]thiophene (1) were reported in our first paper describing the application of two-dimensional nmr techniques to polynuclear aromatic compounds [1]. All of the protonated carbon resonances were successfully assigned. Several of the nonprotonated carbon resonances were left unassigned because of the difficulty of obtaining the necessary connectivity information to assign these resonances *via* a ^{13}C-^{13}C double quantum INADEQUATE experiment. At higher fields we have been able to successfully complete total assignments using ^{13}C-^{13}C double quantum INADEQUATE spectral data [2-5]. However, these studies still require very substantial amounts of time for two reasons: first, the sample pool to which the experiment is restricted is very small, consisting statistically of only 1 molecule in 10,000; second, the experiment must be recycled as a function of ^{13}C T_1, ideally about 1.5 x the T_1

relaxation time of the most slowly relaxing carbon if high quality data are to be obtained. In the case of helical polynuclear aromatic systems where the carbons located along the interior of the helix may have relaxation times ranging into the tens or even hundreds of seconds, this is obviously a condition which must be compromised. While using an interpulse delay shorter than necessary is sometimes an acceptable compromise, it can obviously lead to breaks in the connectivity network and/or an incomplete assignment.

Long range heteronuclear chemical shift correlation provides a highly viable alternative to the ^{13}C-^{13}C double quantum INADEQUATE experiment. Sensitivity is much higher since all ^{13}C resonances may be sampled; the experiment may be recycled as a function of the proton T_1 relaxation time rather than the ^{13}C relaxation time. Since the former are generally much shorter than the latter, the experiment may be cycled much more rapidly thus providing adequate signal-to-noise ratios more quickly. The long range heteronuclear chemical shift correlation experiment also has a further advantage in that it can provide connectivity information across heteroatoms when there are protons in appropriate locations.

Several studies have been performed on polynuclear aromatics to confirm the utility of long range hetero-
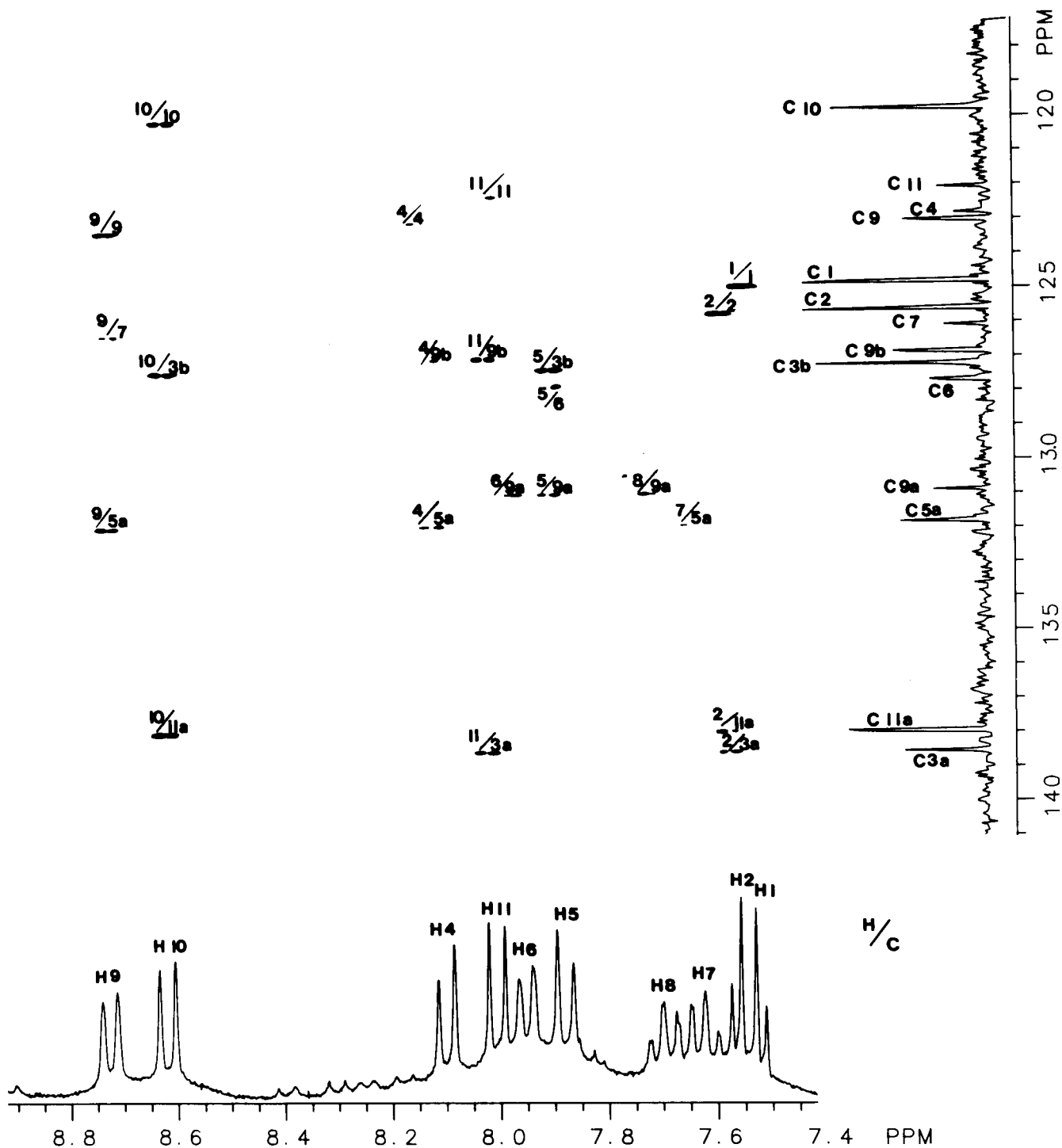
Figure 1. Long range heteronuclear chemical shift correlation spectrum of phenanthro[1,2-*b*]thiophene (**1**) recorded in deuteriochloroform at observation frequencies of 300.042/75.455 MHz for ¹H and ¹³C, respectively.

nuclear chemical shift correlation based assignments [4,6]. Efforts have been extended to molecules as complex as phenanthro[3,4:3',4']phenanthro[2,1-b]thiophene [7]. Hence it can be safely stated long range heteronuclear correlation is a viable experimental technique for the assignment of polynuclear aromatic compounds. However, long range heteronuclear correlation experiments should not be naively trusted to give unquestionably accurate data, especially when a compound of unknown structure is to be identified. Long range heteronuclear chemical shift correlation suffers from a potentially devastating complication when the simplest variants of the experiment are employed. As suggested by Bauer, Freeman and Wimperis [8], the intensity of long range correlations to protonated carbon resonances may be modulated by the one bond coupling. More recently, we have demonstrated [9] that one bond modulation can introduce rather precipitous valleys in the response curve with differences in optimization of as little as 0.2 Hz taking a given response from readily visible to an intensity comparable to the noise threshold of the contour plot. As a remedy to this problem, Freeman and coworkers [8] have suggested the incorporation of a bilinear rotational decoupling (BIRD) pulse [10] midway through the refocusing delay which follows magnetization transfer. Recent work from these laboratories [11-13], by Reynolds and coworkers [14] and by Krishnamurthy and colleagues [15] has confirmed the beneficial decoupling of the one bond modulation effects which are afforded by the inclusion of the BIRD pulse. Thus, there are now several pulse sequences available for long range heteronuclear chemical shift correlation which incorporate a BIRD pulse midway through the refocusing delay to eliminate the adverse effects of one bond modulation [11,12,15,16].

In light of the developments just described, we would now like to report the reinvestigation of phenanthro[1,2-b]-thiophene (1) using the long range heteronuclear chemical shift correlation pulse sequence shown in Figure 2. The pulse sequence provided one bond modulation decoupling
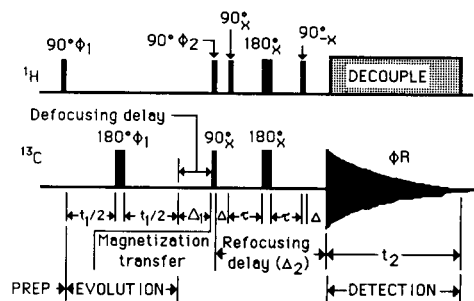

Figure 2. Modified Freeman-Morris heteronuclear chemical shift correlation pulse sequence designed to provide decoupling one-bond modulation of long range response intensity as described by Zektzer, John and Martin [12].

[12] and resulted in a completion of the total assignment, including those quaternary carbon resonances which were previously unassignable on the basis of an early 50 MHz ^{13}C-^{13}C double quantum INADEQUATE experiment.

Results and Discussion.

The long range heteronuclear chemical shift correlation spectrum of 1 was acquired using the pulse sequence shown in Figure 2 which incorporates a BIRD pulse [10] midway through the final refocusing delay, Δ_2. The one bond modulations of long range response intensity [11-15] were decoupled. Multiple correlations were observed for each of the quaternary carbon resonances in the structure which are summarized in Figure 3. Quite clearly, there is sufficient redundancy to allow unequivocal quaternary carbon resonance assignments in most cases. Furthermore, assignments may be made with considerably greater sensitivity than with the ^{13}C-^{13}C INADEQUATE experiment.
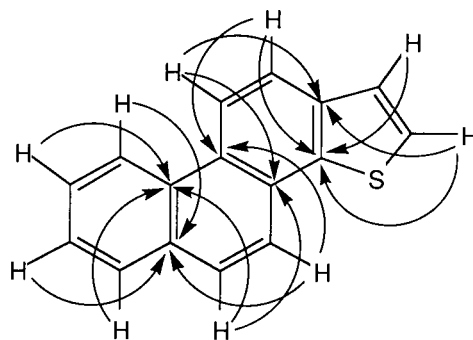

Figure 3. Long range heteronuclear correlations to quaternary carbons of phenanthro[1,2-b]thiophene (1). Correlations involving protonated carbons are not shown.

One further point of interest should also be noted, however. Specifically, the spectrum shown in Figure 1 was recorded with the duration of the defocusing (Δ_1) and refocusing (Δ_2) delays optimized for 10 Hz. Reynolds and coworkers [17] and later Wernly and Lauterwein [18] have suggested 10 Hz as being near optimal for many applications. Indeed, a substantial number of studies in the literature have employed a 10 Hz optimization. Under these conditions, multiple three bond heteronuclear correlations to quaternary carbons are usually observed where the dihedral angle is essentially 180°, e.g. H9 to C5a. This trend is quite reasonable since these couplings would be expected to be in the range of 8-10 Hz [19]. In contrast, in those cases where the dihedral angle would be approximately 0°, e.g. correlation of H9 with C9b and H4 with C3a, there are no responses observed in the spectrum shown in Figure 1 which is also reasonable since these coupling pathways would be expected to have heteronuclear couplings in the range of about 5 Hz [19]. Hence,

care must be taken in the interpretation of long range heteronuclear correlation data, particularly when there are several quaternary carbons adjacent to one another.

In the present example, there is no direct means of establishing the proximity of H9 and H10 by correlating them to a common quaternary carbon. Practically, it might be advisable to perform two experiments, one optimized at about 10 Hz and a second optimized in the range of 5 Hz.

In conclusion, longe range heteronuclear chemical shift correlation has become an extremely valuable technique for complex assignment and structure elucidation problems. Long range correlation is particularly useful when it is necessary to unequivocally assign quaternary carbon resonances or to establish connectivities across heteroatoms because of the multiple redundant nature of the correlation information obtained (see Figure 3). Despite the value of the technique, care must still be taken to preclude the loss of long range connectivity information due to one bond modulation of long range response intensity [11-14]. It is recommended that one of the modified pulse sequences which are capable of suppressing such modulations should be employed. An illustration of the

differences in results obtained when the conventional experiment is used, as opposed to the modified experiment used in this study, is presented in the work of Johnston and coworkers [20]. It should also be noted that direct responses will be only partially suppressed through the inclusion of the BIRD pulse midway through the Δ_2 refocusing delay [12]. We have observed that as the congruence between the actual one bond coupling and that optimized for in the BIRD pulse decreases, the number of direct responses increases. A recent study by Salazar, Zektzer and Martin [21] has shown that direct responses may be almost uniformly suppressed by low pass J-filtration.

In the present case, the use of the long range heteronuclear chemical shift correlation experiment has quickly led to the unequivocal assignment of all the quaternary carbon resonances of **1** (see Table 1). Several of the assignments previously reported [1] made on the basis of a ^{13}C-^{13}C INADEQUATE spectrum which had marginal signal to noise level have been revised.

Table 1

Chemical Shift Assignments for Phenanthro[1,2-b]thiophene (1)
Recorded in Deuteriochloroform at 17°
Using the Long Range Heteronuclear Chemical Shift
Correlation Pulse Sequence Shown in Figure 2

1
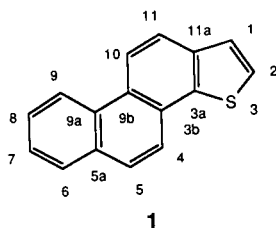
Carbon	Chemical Shift (δ)	Protons to Which Correlations Were Observed in the Long Range Correlation Experiment	
		Direct (ppm)	Long Range
1	124.80	H1 (7.52)	none
2	125.58	H2 (7.57)	none
3a	138.54	-----	H1, H2, H11
3b	127.19	-----	H5, H10
4	122.79	H4 (8.11)	none
5	127.70	H5 (7.87)	none
5a	131.80	-----	H4, H7, H9
6	128.74	not obs (7.95)	H5
7	126.78	not obs (7.62)	H9
8	126.07	not obs (7.70)	none
9	123.00	H9 (8.73)	none
9a	130.88	-----	H5, H6, H8
9b	126.83	-----	H4, H11
10	119.72	H10 (8.62)	none
11	122.05	H11 (8.02)	none
11a	137.95	-----	H2, H10

EXPERIMENTAL

REFERENCES AND NOTES

[1] G. E. Martin, S. L. Smith, W. J. Layton, M. R. Willcott, III, M. Iwao, M. L. Lee and R. N. Castle, *J. Heterocyclic Chem.*, **20**, 1367 (1983).

[2] M. J. Musmar, M. R. Willcott, III, G. E. Martin, R. T. Gampe, Jr., M. Iwao, M. L. Lee, R. E. Hurd, L. F. Johnson, and R. N. Castle, *J. Heterocyclic Chem.*, **20**, 1661 (1983).

[3] M. J. Musmar, G. E. Martin, R. T. Gampe, Jr., M. L. Lee, R. E. Hurd, M. L. Tedjamulia, H. Kudo and R. N. Castle, *J. Heterocyclic Chem.*, **22**, 219 (1985).

[4] J. G. Stuart, M. J. Quast, G. E. Martin, V. M. Lynch, S. H. Simonsen, M. L. Lee, R. N. Castle, J. L. Dallas, B. K. John and L. F. Johnson, *J. Heterocyclic Chem.*, **23**, 1215 (1986).

[5] M. J. Musmar, A. S. Zektzer, G. E. Martin, R. T. Gampe, Jr., M. L. Lee, M. L. Tedjamulia, R. N. Castle and R. E. Hurd, *Magn. Reson. Chem.*, **24**, 1039 (1986).

[6] M. J. Quast, E. L. Ezell, G. E. Martin, M. L. Lee, M. L. Tedjamulia, J. G. Stuart and R. N. Castle, *J. Heterocyclic Chem.*, **23** 1453 (1985).

[7] A. S. Zektzer, J. G. Stuart, G. E. Martin and R. N. Castle, *J. Heterocyclic Chem.*, **23**, 1587 (1986).

[8] C. Bauer, R. Freeman and S. Wimperis, *J. Magn. Reson.*, **58**, 526 (1984).

[9] M. J. Quast, A. S. Zektzer, G. E. Martin and R. N. Castle, *J. Magn. Reson.*, **71**, 554 (1987).

[10] J. R. Garbow, D. P. Weitekamp and A. Pines, *Chem. Phys. Letters*, **93**, 504 (1982).

[11] A. S. Zektzer, B. K. John, R. N. Castle and G. E. Martin, *J. Magn. Reson.*, **72**, 556 (1987).

[12] A. S. Zektzer, B. K. John and G. E. Martin, *Magn. Reson. Chem.*, **25** 752 (1987).

[13] M. Salazar, A. S. Zektzer and G. E. Martin, *Magn. Reson. Chem.*, **26**, 24 (1988).

[14] M. Perpick-Dumont, R. G. Enriquez, S. McLean, F. V. Puzzuoli and W. F. Reynolds, *J. Magn. Reson.*, **75**, 416 (1987).

[15] V. V. Krishnamurthy and J. E. Casida, *Magn. Reson. Chem.*, **25**, 837 (1987).

[16] W. F. Reynolds, D. W. Hughes, M. Perpick-Dumont and R. G. Enriquez, *J. Magn. Reson.*, **63**, 413 (1985).

[17] W. F. Reynolds, R. G. Enriquez, L. I. Escobar and X. Lozoya, *Can. J. Chem.*, **62**, 2421 (1984).

[18] J. Wernly and J. Lauterwein, *J. Chem. Soc., Chem. Commun.*, 1221 (1985).

[19] J. Wasylishen and J. Schaefer, *Can J. Chem.*, **50**, 2710 (1972).

[20] M. D. Johnston, Jr., M. Salazar, G. E. Martin and R. N. Castle, *J. Heterocyclic Chem.*, submitted.

[21] M. Salazar, A. S. Zektzer and G. E. Martin, *Magn. Reson. Chem.*, **26**, 28 (1988).

[22] R. Freeman and G. A. Morris, *J. Chem. Soc., Chem. Commun.*, 684 (1978).

[23] A. Bax and R. Freeman, *J. Magn. Reson.*, **42**, 501 (1981).