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Fourier Transform Carbon-13 NMR Spectra of Ampyrone and Aminopyrine

SHIVA P. SINGH, SYLVIA A. FARNUM, VIRGIL I. STENBERG, and SURENDRA S. PARMAR ˣ

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Abstract □ The natural abundance ^{13}C-NMR spectra of ampyrone and aminopyrine were obtained using the pulse Fourier transform technique. The chemical shifts were assigned with the help of the chemical shift theory, multiplicity generated in single-frequency off-resonance decoupled spectra, relaxation time, and comparison with structurally related compounds.

Keyphrases □ Ampyrone—Fourier transform carbon-13 NMR spectra □ Aminopyrine—Fourier transform carbon-13 NMR spectra □ NMR spectroscopy—ampyrone and aminopyrine

The assignments of ^{13}C-NMR chemical shifts of synthetic and natural therapeutic agents (1–6) initiated the carbon-13 analysis of 4-amino-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one (I, ampyrone) and 4-dimethylamino-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one (II, aminopyrine), both of which possess antipyretic and analgesic properties. The natural abundance ^{13}C-NMR spectra, both proton noise decoupled and single frequency off-resonance decoupled (SFORD), of ampyrone and aminopyrine were recorded using the Fourier transform technique. The proton noise-decoupled spectra gave the chemical shift of various carbon resonances of I and II while the SFORD spectra differentiated the methyl, methine, and quaternary carbons.

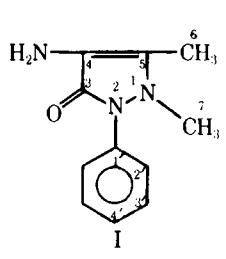
The assignments of carbon-13 signals are based on the chemical shift theory, multiplicity generated in SFORD spectra, percent intensity of signals, and carbon chemical shifts of the model compounds. These studies could possibly contribute toward the understanding of the biotransformation of I and II.

EXPERIMENTAL

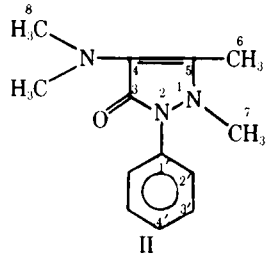
The ^{13}C-NMR spectra of ampyrone, aminopyrine, and 1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one were obtained on a spectrometer[1] operating at 15.00 kHz. The samples were run in a 10-mm tube with deuterochloroform (30% w/v) as an internal lock and solvent and tetramethylsilane as a reference. The spectrometer settings during the experiment were: spectral width, 4 kHz; pulse width, 18 msec (90°); repetition rates, 5, 15, and 45 sec; and data points, 4 K.

The T_1 measurements of these two compounds were carried out in undegassed solution and were automatically calculated[2] by least-squares analysis (10) of the plot of ln $(I_\infty - I_T)$ *versus* T.

[1] Jeol FX 60 spectrometer.
[2] By FX-60 computer.



I



II

Ampyrone, aminopyrine, and antipyrine were obtained from commercial sources[3].

DISCUSSION

Ampyrone (I)—The carbon-13 chemical shifts of I are recorded in Table I, and its carbon resonances are illustrated in Fig. 1. The proton noise-decoupled spectrum of I gave seven signals in the lower field region and two signals in the higher field region. The quartets centered at δ 36.7 and 9.0 ppm could be easily assigned to C-7 and C-6, respectively, on the basis of chemical shift theory (7).

Feeney *et al.* (8) obtained the ^{13}C-NMR spectrum of 1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one (III, antipyrine) in dimethyl sulfoxide and reported the chemical shift of the ring carbon resonances relative to the upfield of carbon disulfide. To check the chemical shift of the carbons of two methyl groups present at positions 1 and 5 of the pyrazole ring in III, the proton noise-decoupled and SFORD spectra of III were recorded in deuterochloroform. The chemical shifts of the carbon signals of III obtained are represented on the structure of III while the figures in parenthesis indicate the chemical shifts reported earlier (8).

Table I—Carbon-13 Chemical Shifts of Ampyrone

Assignment[a]	Multiplicity[b]	Chemical Shift[c]	Relaxation Time[d], T_1, sec
C-3	s	160.7	27.4
C-5	s	136.3	18.9
C-1′	s	134.2	17.8
C-3′	d	127.8	1.08
C-4′	d	124.4	0.77
C-2′	d	121.4	1.11
C-4	s	118.0	13.8
C-7	q	36.7	1.55
C-6	q	9.0	2.90

[a] Numbering of carbons are shown in the structure. [b] Signal multiplicity obtained from SFORD; s = singlet, d = doublet, and q = quartet. [c] Chemical shifts are expressed in parts per million relative to tetramethylsilane. [d] The relaxation time was obtained in undegassed solution.

[3] Sigma Chemical Co., St. Louis, Mo.

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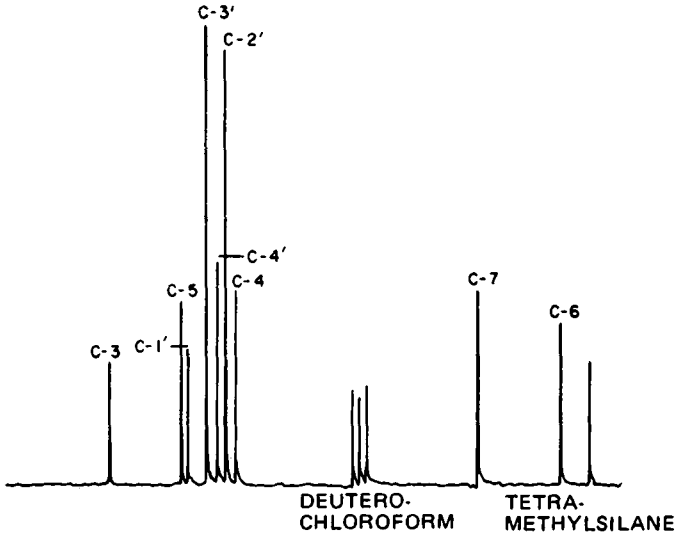

Figure 1—*Proton noise-decoupled spectrum of ampyrone.*

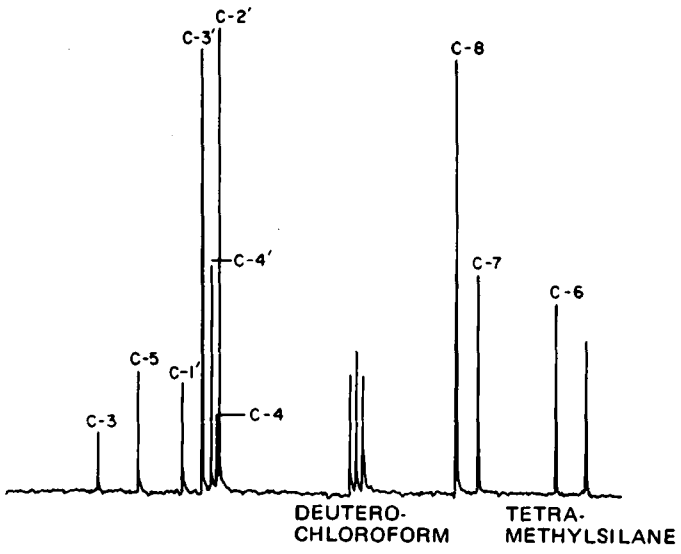

Figure 3—*Proton noise-decoupled spectrum of aminopyrine.*

The two quartets centered at δ 33.8 and 11.2 ppm were assigned to the carbon of methyl groups present at positions 1 and 5 of the pyrazoline ring, respectively, on the basis of chemical shift theory and comparison with the carbon signal of the methyl group of IV. These assignments further support the assignments of C-7 and C-6 of I. The chemical shifts of the ring carbons of III in the present study are in agreement with the chemical shifts of III (8) under the experimental limit due to the solvent effect (7). However, the assignments of C-2′ (122.4 ppm) and C-3′ (127.4 ppm) differ from the assignments of C-2′ (130.8 ppm) and C-3′ (124.8 ppm) reported earlier for III (8). The electronic effect of the nitrogen atom attached to the benzene nucleus produces an upfield shift to its *ortho*- and *para*-carbons, and the former appears at a higher field than the latter (7). On this basis and by comparison with the chemical shift of the corresponding carbons of V (9) and VI (4), the signals at δ 127.4 (reported earlier at 124.8 ppm) and 122.4 (reported earlier at 130.8 ppm) were assigned to C-3′ and C-2′, respectively.

The SFORD spectrum of I showed four singlets, which could be assigned to C-3, C-4, C-5, and C-1′. These quaternary carbons were also distinguished, as compared to methine carbons, by running the proton noise-decoupled spectrum of I at three different pulsing sequences of 5, 15, and 45 sec (Fig. 2). The longer relaxation time for quaternary carbons as compared to other carbons indicated that the increase in time between pulsing sequences provides these carbons more time to relax, which consequently results in their larger peaks (Fig. 2). Furthermore, the chemical shift of the quaternary carbons, C-3, C-4, C-5, and C-1′, were separated from methine carbons based on their longer relaxation times (Table I). Since the carbon signal of the carbonyl group in various amides was in the δ 160–180-ppm region (7), the singlet at δ 160.7 ppm was assigned to C-3.

An electronegative group attached to vinylic carbon causes a pronounced paramagnetic shift to the directly bonded carbon and a dimagnetic shift to the next carbon of the vinyl group. The dimagnetic shift decreases with the steric bulk of the electronegative group (7). On this basis and by comparison with the chemical shifts of III and VI, the singlets at δ 136.3, 134.2, and 118.0 ppm were assigned to C-5, C-1′, and C-4, respectively.

The chemical shift of C-4′ could be differentiated from the chemical shift of C-2′ and C-3′ by its shorter relaxation time (T_1). Since C-4′ is *para* to the phenyl ring, it should have a shorter T_1 value compared to C-2′ and C-3′ due to the motion along the C-1′–C-4′ axis where C-2′ and C-3′ can rotate, resulting in longer T_1 values due to less favored dipole–dipole interactions. As is evident from Table I, C-4′ has a shorter T_1 value than C-2′ and C-3′. The doublets centered at δ 127.8, 124.4, and 121.4 ppm were assigned to C-3′, C-4′, and C-2′, respectively, by comparing the percent integration of the signals in the proton noise-decoupled spectrum of I, relaxation time (T_1), and chemical shift theory (7). These assignments were supported by the chemical shifts observed for III, V (9), and VI (4).

Aminopyrine (II)—The proton noise-decoupled spectrum of II is shown in Fig. 3, and the chemical shifts of the carbon resonances with their relaxation times are shown in Table II. There were seven signals in the downfield and three signals in the upfield region. The three quartets

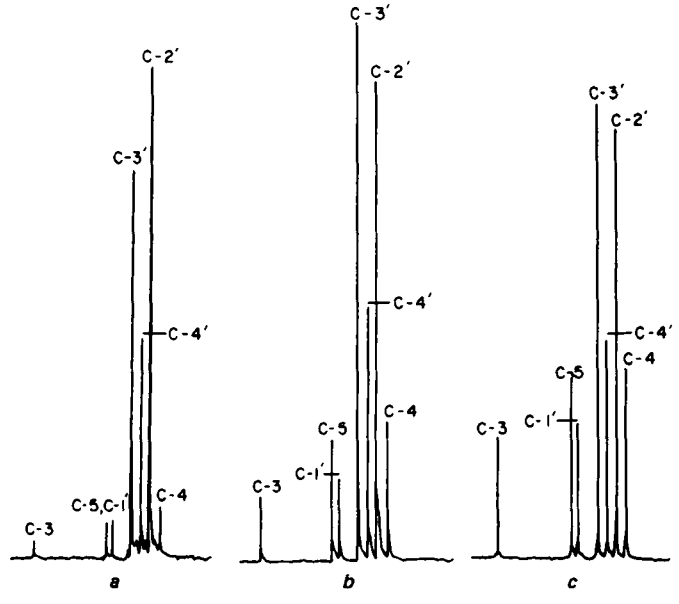

Figure 2—*Pulse repetition. Key:* a, *5 sec;* b, *15 sec; and* c, *45 sec.*

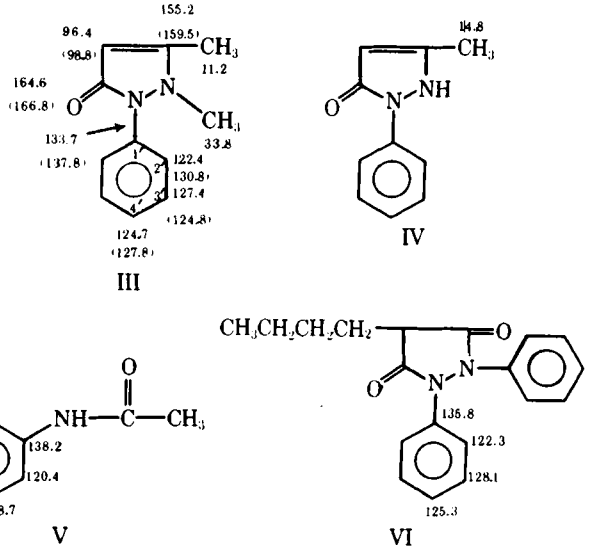

Table II—Carbon-13 Chemical Shifts of Aminopyrine

Assignment[a]	Multiplicity[b]	Chemical Shift[c]	Relaxation Time[d], T_1, sec
C-3	s	163.6	48.9
C-5	s	150.2	30.7
C-1′	s	135.4	32.7
C-3′	d	128.9	2.54
C-4′	d	125.7	1.28
C-4	s	123.9	41.4
C-2′	d	123.0	2.32
C-8	q	43.8	2.37
C-7	q	36.6	3.23
C-6	q	10.2	4.40

[a,b,c,d] See corresponding footnotes in Table I.

centered at δ 43.8, 36.6, and 10.2 ppm were assigned to C-8, C-7, and C-6, respectively, on the basis of chemical shift theory (7), percent intensity of the signals, and comparison with the chemical shifts of I and III. The four singlets at δ 163.6, 150.2, 135.4, and 123.9 ppm observed in the SFORD spectrum of II were assigned to C-3, C-5, C-1′, and C-4, respectively, on the basis of chemical shift theory (7), relaxation time, and comparison of the assignments of the corresponding carbons of I and III.

The chemical shifts of C-4 and C-5 in II were at a lower field as compared to the chemical shift of the coresponding carbons in I. This shift was due to the dimethyl amino group present at position 4 in II, which is more electronegative and bulky than the amino group present at position 4 in I. Earlier studies indicated that the electronegative group produces a downfield shift to the attached carbon of the vinyl group and an upfield shift to the next carbon of the vinyl group. The upfield shift decreases with an increase in the bulkiness of the electronegative group (7). The three doublets centered at δ 128.9, 125.7, and 123.0 ppm were attributed to C-3′, C-4′, and C-2′, respectively, on the basis of chemical shift theory, relaxation time, and comparison with the chemical shift of structurally related compounds I, III, V, and VI.

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Evaluation of Adsorption from Dispersion Charge Profile

A. ATILLA HINCAL * and BHOGI B. SHETH ‡x

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*Present address: Faculty of Pharmacy, University of Hacettepe, Ankara, Turkey. ‡Present address: Vick Divisions Research and Development, Mt. Vernon, NY 10553.

Abstract □ The evaluation of adsorption behavior from the charge profile of an adsorbent dispersion determined as a function of the adsorbate concentration was investigated by the streaming current measurement, using methylene blue and erythrosine as adsorbates and activated charcoal, microcrystalline cellulose, and polyvinylpolypyrrolidone as adsorbents. Adsorption capacity was evaluated using streaming current *versus* solute concentration plots of dye solutions and of corresponding dye solutions equilibrated with the adsorbent. It was also determined by adsorption isotherm measurement and application of the Langmuir equation. Good agreement was obtained between the adsorption capacity values from streaming current data and adsorption isotherm measurements for microcrystalline cellulose, suggesting that adsorption here was a surface phenomenon without water-soluble extractives affecting particle charge. Similar agreement was not obtained for charcoal adsorption, and this result was attributed to the unusual adsorption behavior of charcoal. Since polyvinylpolypyrrolidone gave a dispersion with high particle charge, the streaming current method could not be used with this system. The charge profile could be useful in characterizing powders for unusual adsorption behavior and possible water-soluble extractives as well as for surface area estimation in the absence of these factors.

Keyphrases □ Adsorption—evaluated from charge profile, streaming current measurement □ Charge profile—used to evaluate adsorption of dispersion, streaming current measurement □ Powders—application of charge profile for characterizing unusual adsorption behavior

New methods for screening powders for adsorption behavior are of significant pharmaceutical interest. Reports deal with the adsorption of drugs by excipients (1–3), the use of adsorbents in the treatment of accidental poisoning (4, 5), the estimation of surface area by solute adsorption (6, 7), and the control of particle charge by polyelectrolytes (8, 9).

The initial inflection point of a charge profile may be considered to represent monolayer adsorption capacity (10). Therefore, it is potentially feasible to estimate the monolayer adsorption capacity from charge profiles. This approach was utilized in systems involving chemical adsorption in an industrial application requiring surface area control of a fine particle dispersion. However, it should also

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