^{13}C NMR Studies on Dibenz[*b*,*f*]azepines

Frank F. Molock and David W. Boykin*

Department of Chemistry and Laboratory for Microbial and Biochemical Sciences,
Georgia State University, Atlanta, GA 30303

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The assignment of the ^{13}C nmr resonances of six dibenz[*b*,*f*]azepines (**1-6**) in dimethylsulfoxide-d_6 was made using chemical shift arguments, coupling to a fluorine substituent, selective proton decoupling, and fully coupled spectra. Exchange of the heterocyclic N-H with deuterium simplified and clarified the coupled spectrum of **1**.

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There is considerable interest in the ^{13}C nmr spectral characteristics of heterocyclic molecules which display useful biological properties (1-4). In previous investigations, we have reported the assignments of ^{13}C nmr spectra for various nitrogen-containing heterocyclic systems including isoxazoles (5), quinolines (6), acridines (6), phenanthridiniums (7), and pyridoquinolines (8). A variety of 5*H*-dibenz[*b*,*f*]azepines constitutes an important class of antidepressant drugs (9). The study of the ^{13}C nmr spectra of these compounds is important for future chemical and biological studies. We are reporting the ^{13}C nmr spectral properties of six 5*H*-dibenz[*b*,*f*]azepines including the parent molecule of several clinically useful drugs.

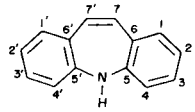
The six 5*H*-dibenz[*b*,*f*]azepines studied include 5*H*-dibenz[*b*,*f*]azepine (**1**), 3,7-dichloro-5*H*-dibenz[*b*,*f*]azepine (**2**), 2-fluoro-5*H*-dibenz[*b*,*f*]azepine (**3**), 2,8-dibromo-5*H*-dibenz[*b*,*f*]azepine (**4**), 2-chloro-5*H*-dibenz[*b*,*f*]azepine (**5**), and 2-methoxy-7-chloro-5*H*-dibenz[*b*,*f*]azepine (**6**). The dibenzazepines **1**, **3**, **5**, and **6** have been reported previously (10). The new compounds **2** and **4** were prepared following a previously reported approach (10) which begins with the conversion of 9-chloroacridines into 9-methylacridines by nucleophilic displacement of the 9-chloro group with the anion of diethylmalonate. The resulting acridinyl diethylmalonate gave 9-methylacridines on saponification and decarboxylation. The 9-methylacridines were oxidized to form the corresponding acridine-9-carboxaldehydes which were reduced to produce 9-hydroxymethyl-9,10-dehydroacridines. The dihydroacridines were subjected to acid treatment which resulted in dehydration with accompanying ring expansion to produce the 5*H*-dibenz[*b*,*f*]azepines.

The proton decoupled ^{13}C nmr spectrum of 5*H*-dibenz[*b*,*f*]azepine (**1**) exhibits seven signals appearing between 120 and 150 ppm (Figure I and Table I). The signals for five protonated carbons can be readily distinguished from those of the two quaternary carbons by intensity differences. The two low intensity signals at 149.5 and 129.0 ppm are assigned to C-5 and C-6, respectively. These assignments are based upon chemical shift considerations and the splitting patterns observed in its fully coupled spectrum. In the coupled spectrum of **1** the signal at 149.5 ppm shows multiplicity with enhanced coupling constants compared to that of the signal at 129.0 ppm as might be expected as a result of the proximity of the nitrogen atom.

Assignment of the five signals corresponding to the proton bearing carbons is more involved. The signal at 132.1

Table I

Assignment of C-13 NMR Chemical Shifts for Dibenz[*b*,*f*]azepine (a)



Compound Number	Carbon Number													
	1	1'	2	2'	3	3'	4	4'	5	5'	6	6'	7	7'
1	129.5		121.9		130.4		119.1		149.5		129.0		132.1	
2	131.3*		122.0		134.2		118.6		149.9		127.9		132.1*	
3 (b)	115.4	129.5	158.1	122.1	116.1	129.9	120.3	119.3	145.7	149.8	131.1	129.0	130.1	133.6
4	131.8		113.6		132.6		120.9		148.4		131.0		132.1	
5	129.8	129.4	128.6	120.1	130.6	130.5	120.4	119.1	148.4	149.0	130.9	128.8	133.4	130.6
6 (a)	114.7	131.5*	155.1	121.0	115.7	133.9	120.1	118.2	141.4	151.6	130.1	127.8	131.7*	131.9*

(a) Primed numbers are used for the unsubstituted ring in the dissymmetrical compounds. For compound **6** the chloro bearing carbon is 3' and the methoxy bearing carbon is 2. The methyl carbon of **6** appears at 55.2 ppm. (b) $^1J_2$(CF) = 237, $^2J_1$(CF) = 22, $^2J_3$(CF) = 23, $^3J_4$(CF) = 8, $^3J_6$(CF) = 10, $^4J_5$(CF) = 3, $^4J_7$(CF) = 5; coupling constants are given in hertz, superscripts correspond to number of bonds of coupling and subscripts correspond to carbon numbers.

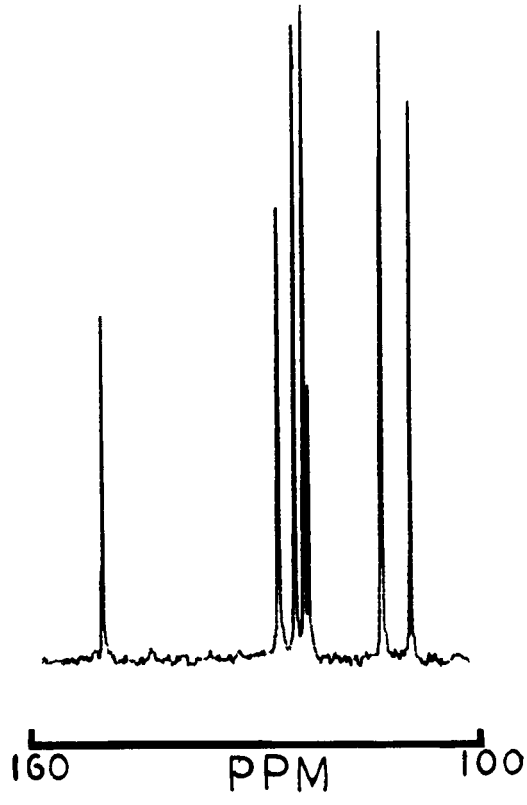


Figure 1. Dibenz[*b,f*]azepine: Proton decoupled ^{13}C nmr spectrum of the aromatic region.

ppm is assigned to C-7 as a result of selective irradiation at the proton frequencey (6.69 ppm) corresponding to H-7 based upon the reported ^1H assignment of 5*H*-dibenz-[*b,f*]azepine (11). Further selective proton decoupling experiments were not feasible with our instrumentation (60 MHz). In the coupled spectrum the signal at 132.1 showed the expected coupling ($^1J_{C_7H_7}$ = 156 Hz, $^3J_{C_7H_1}$ = 3 Hz). Chemical shift considerations based upon the amino function effects allow the separation of the remaining four carbon signals into pairs; C-1 and C-3 at 129.5 and 130.4 ppm and C-2 and C-4 at 121.9 and 119.1 ppm. Chemical shift arguments, assuming additivity of the amino and vinyl functions, support the assignments as given. However, such an assignment is tenuous at best since the signals in both pairs differ from each other by less than 2 ppm. Examination of the fully coupled spectrum of **1** allows the assignment of the signal at 129.5 ppm to C-1 since its multiplicity is greater as a result of 3-bond coupling to both H-7 and H-3 ($^1J_{C_1H_1}$ = 163 Hz, $^3J_{C_1H_3}$ = 7 Hz, $^3J_{C_1H_7}$ = 3 Hz). The signal at 130.4 appears as a pair of doublets since it experiences only one 3-bond coupling interaction with H-1 ($^1J_{C_3H_3}$ = 158 Hz, $^3J_{C_3H_1}$ = 8 Hz). The signal at 119.1 ppm exhibits three bond coupling from both the N-H and from H-2 ($^1J_{C_4H_4}$ = 167 Hz, $^3J_{C_4H_2}$ = 5 Hz), whereas the signal at 121.9 ppm undergoes 3-bond coupling only with H-4 ($^1J_{C_2H_2}$ = 162 Hz, $^3J_{C_2H_4}$ = 7 Hz). Thus the assignment of C-2 and C-4 can be made from the fully coupled spectrum. This assignment of signals corresponding to C-2 and C-4 is supported by comparison of the fully coupled spectrum of **1** with that of **1** in which the nitrogen proton has been exchanged for deuterium. Exchange of the N-H for N-D results in simplification of the signal at 119.1 ppm. The assignment of the signal at 119.1 ppm to C-4 is further supported by a larger $^1J_{CH}$ value than the other proton bearing carbons which is consistent with its proximity to the nitrogen atom (12).

In a related manner the assignment of the carbon resonances for 3,7-dichloro-5*H*-dibenz[*b,f*]azepine (**2**) was carried out. The seven signals for **2** are readily divided into a set of three low intensity ones corresponding to the non-protonated carbons and a set of four intense ones arising from the proton bearing carbon atoms. The furthermost downfield low intensity signal at 149.9 ppm is assigned to C-5 based upon chemical shift considerations and its simpler appearance in the coupled spectra resulting from only three bond coupling with H-1. The signal at 127.9 ppm is assigned to C-6 based upon the three bond coupling interactions with H-2 and H-4. The assignment of the signal at 134.2 ppm to C-3 is based upon its complex coupling pattern involving three bond coupling with H-1 and two bond coupling with H-2 and H-4.

The assignment of the four signals corresponding to the proton bearing carbons is made separating them into pairs, C-2 and C-4 at 122.0 and 118.6 ppm based upon the assignment of **1** and substituent induced chemical shift effects (scs). The interpretation of the coupled spectrum of **2** supports the assignment of C-2 to the signal at 122.0 ppm since it appears as a sharp doublet of doublets ($^1J_{C_2H_2}$ = 169 Hz, $^3J_{C_2H_4}$ = 6 Hz). The signal at 118.5 ppm in the coupled spectrum is a broadened doublet ($^1J_{C_4H_4}$ = 164 Hz) which is not resolved further presumably as a result of N-H coupling as noted for **1**. The assignment of the signals coresponding to C-1 and C-7 could be reversed since they are less than 1 ppm apart. Nevertheless, consideration of substituent effects would predict little change in the chemical shift of C-7 on introduction of a chlorine atom and scs considerations predict a downfield shift for C-1. The observed results are in accord with these expectations. In the coupled spectrum the signals for C-1 and C-7 appear as broadened doublets arising from one bond and three bond coupling with their respective protons. Since the proton spectrum of **2** has not been reported and it was not assignable by inspection, selective decoupling was not possible for identification of the carbon signal due to C-7.

Fluorine-carbon coupling has been used to advantage as an assignment aid in heterocyclic systems such as the isox-

azoles (5). Consequently, the assignment of the carbon spectrum of 2-fluoro-5*H*-dibenz[*b*,*f*]azepine (**3**) was undertaken to augment the assignments for the dibenz[*b*,*f*]azepine system by employing a different assignment approach. The introduction of only one fluorine atom results in dissymmetry in the parent ring system and produces fourteen lines in its carbon spectrum. Examination of the proton decoupled spectrum of **3** reveals five low intensity signals and nine intense ones. The assignment of the low intensity signals at 158.1, 145.7 and 131.1 ppm to C-2, C-5 and C-6, respectively, is based upon the magnitude of the corresponding J_{CF} values $^{1}J_{C_2F}$ = 237 Hz, $^{4}J_{C_5F}$ = 3 Hz and $^{3}J_{C_6F}$ = 10 Hz (Table 1). Assignment of the signals at 149.8 and 129.0 ppm to C-5′ and C-6′ is in accord with substituent chemical shift arguments and is consistent with the assignments made for the analogous carbons in **1**.

The assignments of signals for the proton bearing carbon pairs C-1 - C-1′ and C-3 - C-3′ found in Table 1 are based exclusively upon scs considerations derived from the previous assignment of **1**. The differentiation within pairs C-1 - C-1′ and C-3 - C-3′ is readily made using carbon-fluorine coupling noted for the unprimed carbons. The C-4 -C-4′ pair is easily distinguished in the coupled spectrum from the other proton bearing carbons due to their broadened signal arising from coupling to the N-H. Differentiation between these two carbons is also based upon carbon-fluorine coupling. Finally, the olefinic carbons C-7 - C-7′ are identified based upon chemical shift consistency with the parent **1** and they are distinguished from one another by carbon-fluorine coupling.

The chemical shift assignments for the remaining three compounds studied, **4**, **5**, and **6**, are based primarily upon scs considerations. The approach used **1** as the model compound and standard aromatic scs values (13) for the substituents were used. Interpretation of the coupled spectra, where resolution allowed, provided independent evaluation of the assignments based upon scs considerations for a number of the carbons.

EXPERIMENTAL

The ^{13}C nmr spectra were obtained from a JEOL FX-600 Fourier transform spectrometer operating at 15.04 MHz. Data were accumulated on a Texas Instrument 980B computer using 8192 data points over a 4 KHz spectra width to yield a data point resolution of 0.06 ppm. Noise-decoupled spectra were obtained by irradiation with a pulse width corresponding to 45° and a 5-s pulse repetition time. For the proton coupled spectra, a gated pulse sequence was used to obtain NOE intensification of the signals, with a 5 s pulse repetition to reduce the saturation of the non-protonated carbons. The selective proton decoupling experiments were facilitated using the JEOL dual ^{13}C-^{1}H probe which allowed observation of the proton spectrum at 59.79 MHz. The desired irradiation frequency was selected and subsequent recording of the ^{13}C selectively decoupled spectrum was made without removal of the sample from the magnetic field. The routine operating temperature was 40°, which was maintained using a JEOL variable temperature controller.

The ^{13}C nmr samples were prepared as 0.2*M* solutions in commercial grade dimethyl-d_6-sulfoxide and run in 10 mm tubes. The signals were referenced to tetramethylsilane by giving the most intense dimethyl-d_6-sulfoxide line the value of 39.6 ppm.

Melting points were taken on a Thomas-Hoover Uni-Melt apparatus in open capillary tubes and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Satisfactory ir spectra were recorded for all compounds using a Perkin-Elmer Model 337 spectrophotometer.

General Method for Synthesis of 5*H*-dibenz[*b*,*f*]azepines.

The procedure for the synthetic sequence used to prepare the new 5*H*-dibenz[*b*,*f*]azpeines **2** and **4** has been described earlier (10) and will not be repeated here. The physical properties of the intermediates, as well as, **2** and **4** are listed below.

3,6-Dichloro-9-methylacridine.

This compound was recrystallized from chloroform to give a mp of 216-217° [lit (14) 214°], yield 50%.

3,6-Dichloroacridine-9-carboxaldehyde.

This compound was obtained in a 70% yield after recrystallization from carbon tetrachloride, mp 222-224°. Recrystallization from several solvents failed to achieve analytical purity and the aldehyde was converted to its oxime which on recrystallization from ethanol gave a mp of 257-258° dec and gave satisfactory analytical results.

Anal. Calcd. for $C_{14}H_6Cl_2N_2O$: C, 57.77; H, 2.77; N, 9.62. Found: C, 57.95; H, 2.88; N, 9.67.

3,6-Dichloro-9-hydroxymethyl-9,10-dihydroacridine.

This compound was obtained by lithium aluminum hydride reduction of the corresponding aldehyde in an 80% yield after recrystallization from benzene. It had a mp of 152-153°.

Anal. Calcd. for $C_{14}H_{11}Cl_2N_2O$: C, 60.02; H, 3.95; N, 5.00. Found: C, 59.90; H, 4.08; N, 4.84.

3,7-Dichloro-5*H*-dibenz[*b*,*f*]azepine (**2**).

This compound was obtained in a 55% yield and on recrystallization from cyclohexane gave a mp of 258-260°.

Anal. Calcd. for $C_{14}H_9Cl_2N$: C, 64.15; H, 3.46; N, 5.34. Found: C, 64.24; H, 3.51; N, 5.41.

2,7-Dibromo-9-methylacridine.

This compound was obtained in a 20% yield and after recrystallization from acetonitrile gave a mp of 213-215°.

Anal. Calcd. for $C_{14}H_9Br_2N$: C, 47.90; H, 2.58. Found: C, 47.75; H, 2.61.

2,7-Dibromoacridine-9-carboxaldehyde.

This compound was obtained in a 30% yield and gave a mp of 237-238° after recrystallization from chloroform.

Anal. Calcd. for $C_{14}H_7Br_2NO_2$: C, 46.06; H, 1.93; N, 3.84. Found: C, 46.28; H, 2.01; N, 4.02.

2,8-Dibromo-5*H*-dibenz[*b*,*f*]azepine (**4**).

This compound was prepared directly from the unpurified (165-169° mp) and uncharacterized 3,7-dibromo-9-hydroxymethyl-9,10-dihydroacridine. Compound **4** was obtained in a 50% yield and after recrystallization from cyclohexane gave a mp of 173-174°.

Anal. Calcd. for $C_{14}H_9Br_2N$: C, 47.90; H, 2.58; N, 3.99. Found: C, 47.70; H, 2.48; N, 3.98.

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