The Assignment of the ^{1}H-NMR and ^{13}C-NMR Spectra of 5*H*-Dibenz[*b*,*f*]azepine and 10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepine

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The total assignments of the ^{1}H-nmr and ^{13}C-nmr spectra of 5*H*-dibenz[*b*,*f*]azepine [1] and 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (**2**) have been made based on comparison with the corresponding 4,6-dideuterated derivatives **3**, and **4**. These compounds were prepared *via* repeated lithiations and subsequent deuterations of **1** and **2**.

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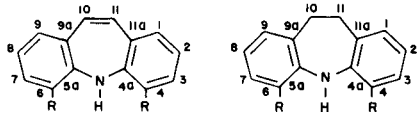
5*H*-Dibenz[*b*,*f*]azepine (**1**) and 10,11-dihdyro-5*H*-dibenz-[*b*,*f*]azepine (**2**) are parent systems of several clinically useful psychotropic drugs [1]. Especially derivatives bearing dimethylaminopropyl- (for example, imipramine) and carbamoyl- (for example, carbamazepine) substituents at the 5-position are of importance. Barriers to inversion of the central azepine ring of *N*-alkyl-5*H*-dibenz[*b*,*f*]azepines have been studied [2] and the assignment of the ^{1}H-nmr spectrum [3] and, very recently, the ^{13}C spectrum [4] of **1** have been reported using carbon disulfide as the solvent (since **1** was considered to be unstable in deuteriochloroform). Despite the fact that the conformational equilibria in 5-substituted-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepines have been studied extensively [5,6] by variable temperature ^{1}H and ^{13}C-nmr spectroscopy, no chemical shift assignments for the aromatic portion have been made in the ^{1}H-nmr spectrum. Provisional assignments for ^{13}C-nmr chemical shift of **2** and related compounds based on relative intensities of quarternary and methine carbons and considerations of steric and functional group parameters have also been made [5]. We want now to report an unequivocal assignment of the ^{1}H and ^{13}C-nmr spectra of **1** and **2** in deuteriochloroform, based on comparison with the corresponding 4,6-dideuteriodervatives **3** and **4**. At

Table

^{1}H-NMR and ^{13}C-NMR Chemical Shifts for **1-4**



1 R = H
3 R = D

2 R = H
4 R = D

^{1}H-NMR Data

	H-1 (9)	H-2 (8)	H-3 (7)	H-4 (6)	H-11 (10)	NH
1 (Deuteriochloroform)	6.85	6.81	7.02	6.47	6.32	4.92
2 (Deuteriochloroform)	7.03	6.76	7.06	6.70	3.06	5.94
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{1,3}$		
1 (Deuteriochloroform)	7.3	6.6	7.7	2.3		
2 (Deuteriochloroform)	7.4	7.4	8.1	1.6		

^{13}C-NMR Data

	C-1 (9)	C-2 (8)	C-3 (7)	C-4 (6)	C-10 (11)	C-9a (11a)	C-4a (5a)
1 (Deuteriochloroform)	130.51	123.00	129.45	119.30	132.12	129.75	148.39
3 (Deuteriochloroform)	130.50	122.98	129.34	118.98 [a]	132.11	129.73	148.35
Difference	-0.01	-0.02	-0.11	-0.32	-0.01	-0.2	-0.04
1 (d_6-DMSO)	130.44	121.90	129.48	119.10	132.06	129.10	149.48
3 (d_6-DMSO)	130.43	121.85	129.37	118.8 [b]	132.06	129.09	149.43
Difference	0.01	-0.05	-0.11	-0.3	0.00	0.01	-0.05
2 (Deuteriochloroform)	130.65	119.44	126.78	117.92	34.94	128.63	142.45
4 (Deuteriochloroform)	130.65	119.44	126.69	117.55 [c]	34.94	128.62	142.37
Difference	0.00	0.00	-0.09	-0.37	0.00	-0.01	-0.08

[a] Triplet, $J_{^{13}C^2H}$ = 18.9 HZ. [b] Poorly resolved triplet. [c] Triplet, $J_{^{13}C^2H}$ × 21.0 HZ.

the same time we report a correction in assignments of two of the resonances in the reported ^{13}C-nmr spectrum [4] of **1** in d_6-DMSO.

Metalation of **1** and **2**, followed by trapping with different electrophiles, have provided access to the corresponding 4-substituted derivatives [7,8]. We have treated the 4,5-dilithio derivatives of **1** and **2** with deuterium oxide, which gave an almost quantitative yields of the 4,5-dideuterated compounds. Repeated lithiations and deuterations gave eventually **3** and **4**. Examination of the product after the second deuteration of **1** revealed that 87% of **3** had been obtained indicating the existence of a large isotope effect.

Considering the ^{1}H-nmr spectrum of **1**, the most shielded proton was assigned to H-4 since the corresponding signals were absent in the spectrum of **3**. The low field five line pattern at 7.02 ppm in **1** appears as a double doublet in **3** and this resonance has consequently been assigned to H-3. The overlapping double doublet and triplet at 6.85 and 6.81 ppm were therefore assigned to H-1 and H-2, respectively. The vinylic protons appeared as a sharp singlet at 6.32 ppm and the nitrogen proton at 4.92 ppm as a broad signal.

All carbons except for C-1 and C-6 were assigned by comparison of the ^{13}C-nmr spectra of **1** and **3** (in deuteriochloroform); wherein the data were collected under identical conditions (table). The most shielded signal in **1** appears as a triplet in **3** and is assigned to C-4. The signal at 129.45 ppm is derived from C-3, since this signal is shifted 0.11 ppm upfield in the spectrum of **3**; typical for carbons attached to a deuterium substituted carbon [9]. Analogously the downfield quaternary carbon was assigned to C-4a, since the corresponding resonance appears 0.04 ppm upfield in the ^{13}C-nmr spectrum of **3**. The signal at 123.00 ppm was assigned to C-2, since the corresponding signals in the deuterated compound **3** appeared to be considerably broadened. This broadening is due to the unresolved $^3J_{CD}$ coupling to deuterium, being larger than $^2J_{CD}$ and $^4J_{CD}$ [10,11]. In order to differentiate C-1 and C-11, a single frequency decoupling at 6.32 ppm was performed, to give the final assignment of this system. Similar results were obtained for the ^{13}C spectra of **1** and **3** in d_6-DMSO. Thus, C-4 appeared as a poorly resolved triplet at around 118.8 ppm in **3**. The signal at 129.48 ppm in **1** is assigned to C-3 (and not to C-1 as previously reported [4]) since this signal is shifted 0.11 ppm upfield in the deuterated derivative **3** [9]. The only other resonance to undergo a shift is the quaternary carbon signal at 149.48 ppm which experienced an *up*-field shift of 0.05 ppm in **3**. The signal at 130.44 ppm in **1** must, therefore, be assigned to C-1 and not to C-3.

The ^{1}H-nmr spectrum of **2** shows two 2-hydrogen multiplets centered at 6.73 and 7.05 ppm. In the spectra of the dideuterated compound **4** the upfield resonances were simplified into a triplet, which was assigned to H-2. The low field multiplet appeared as two double doublets in the spectra of **4** which consequently made it possible to assign the remaining two protons; H-3 being slightly more deshielded than H-1.

The assignment of the ^{13}C-nmr spectrum of **2** was made by direct comparison with the spectrum of **4**. The most shielded signal in the spectrum of **2** appears as an upfield shifted triplet in the spectrum of **4** and is assigned to C-4. The signal at 126.78 ppm and the quaternary downfield signal at 142.45 are both shifted upfield in the spectrum of **4** and are derived from C-3 and C-4a, respectively. The signal at 119.44 ppm was considerably broadened in the spectrum of **4** and was assigned to C-2 (*vide supra*), and the remaining signals at 130.65 ppm and 128.63 ppm were consequently assigned to C-1 and C-11a, respectively. Single frequency decoupling at 6.73 ppm and at 7.05 ppm, as well as chemical shifts arguments support this assignment.

In conclusion, the total assignment of the ^{1}H-nmr and ^{13}C-nmr spectra of **1** and **2** have been unequivocally made almost entirely by comparison of their spectra with that of the easily accessible dideuterated compounds **3** and **4**. The assignments do not require the invocation of chemical shift or coupling constant arguments.

EXPERIMENTAL

The ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a Bruker WH-250 NMR spectrometer at a frequency of 250.13 MHz (data point resolution 0.37 Hz) and 62.9 MHz (data point resolution 1.8 Hz) respectively. A 5 mm ^{1}H probe and a 10 mm broadband probe (32-105 MHz) were used. The samples were run as 0.5*M* solutions and tetramethylsilane was used as internal standard. Mass spectra were recorded on a MAT 311A double focusing mass spectrometer at 70 eV.

4,6-Dideuterio-5*H*-dibenz[*b*,*f*]azepine (**3**) and 4,6-dideuterio-10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepine (**4**).

To a solution of 0.10 mole of dibenz[*b*,*f*]azepine (**1**) (19.3 g) or 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (**2**) (19.5 g) in 500 ml of dry ether, 0.25 mole (151.5 ml) of 1.65 *N* *n*-butyllithium in hexane was added at room temperature under nitrogen. After stirring for 20 hours, 0.50 ml (9.0 g) of deuterium oxide was added and the reaction mixture was then poured into water. The organic phase was separated and the aqueous phase was extracted several times with ether. The combined organic phases were washed with water and dried. After filtration of the drying agent, the organic phase was evaporated to a total volume of 500 ml and then transferred to a reaction flask for further addition of *n*-butyl lithium. After the lithiation procedure and work up had been repeated five times, the solvent was evaporated and the residue chromatographed (silica, ether) to give 18.1 g (93%) of 4,6-dideuterio-5*H*-dibenz[*b*,*f*]azepine (**3**), mp 195-197° or [5*H*-dibenz[*b*,*f*]azepine (**1**) lit [12] 196.5-198°] or 17.9 g (91%) of 4,6-dideuterio-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (**4**), mp 105-107° (10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (**2**), lit [13] 110°), ms (high resolution) m/e calcd. for $C_{14}H_9D_2N$(3) 195.1017; found 195.1020, and calcd. for $C_{14}H_{11}D_2N$(4) 197.1173; found 197.1164, respectively. No traces of either undeuterated or monodeuterated compound could be detected in the ^{1}H-nmr or ^{13}C-nmr spectra. A sample taken out after the second metalation and deuteration of **1** showed an 89% yield of **3** according to ^{1}H-nmr and ms analyses.

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