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NMR STUDIES OF INDOLE

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Abstract - Definitive assignment of the ^{13}C-nmr spectra of indole in DMSO-d_6 and $CDCl_3$ were obtained by two-dimensional HETCOR spectra combined with homonuclear ^{1}H double resonance measurements. The deuterium/hydrogen isotope effects on carbon-13 chemical shifts, measured after interchange of the labile proton of indole, are discussed.

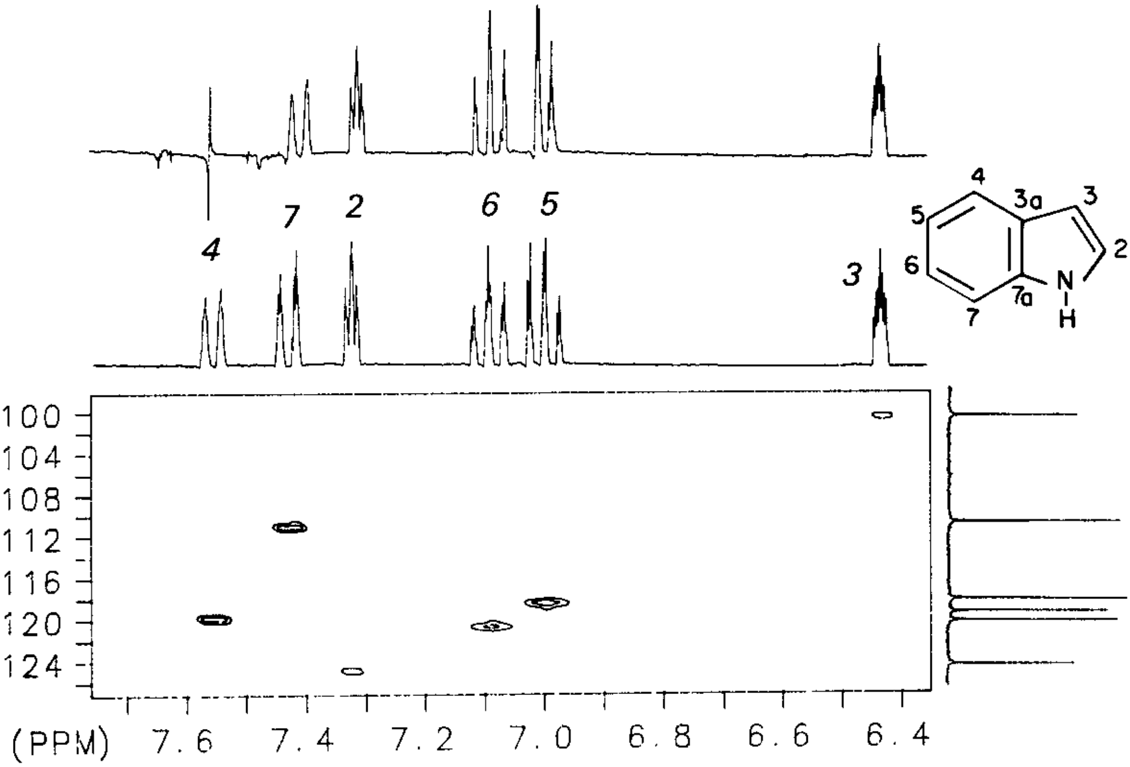
A recent review about the ^{13}C-nmr spectra of almost 300 indole derivatives[1] unsubstituted at the benzene ring highlighted the need for careful experimentation that allows secure interpretations, since in many cases contradictory assignments for C-4, C-5 and C-6 are reported. Some 67% of the literature data were measured from $CDCl_3$ solutions, some 15% in DMSO-d_6, some 8% in mixture of these two solvents and only the remaining 10% in a variety of other solvents. Furthermore, many assignments were derived using the contradictory chemical shifts of parent indole either in chloroform[2-7] or in dimethylsulfoxide[8-11] solutions as the model compound, and therefore for this compound further evaluation, specially at high magnetic fields, seems desirable.

Since the ^{1}H-nmr chemical shifts of indole are solvent and concentration dependent[12], safe assignments of both the ^{1}H and ^{13}C-nmr spectra in $CDCl_3$ and in DMSO-d_6 can be obtained from two-dimensional heteronuclear chemical shifts (HETCOR) contour plots combined with homonuclear double resonance experiments as shown in Figure 1. Since the signal owing to C-7 is well defined[1] for most compounds as to appear in the 111-115 ppm region, direct assignment of H-7 follows from the two-dimensional experiments.

This allows to assign H-4, which upon homonuclear irradiation provides direct interpretation of the remaining benzene ring protons, and then the HETCOR allows the assignment of the carbon signals. The determination of HETCOR contour plots at different indole concentrations, revealed that although in $CDCl_3$ solutions some ^1H signals change in their chemical shift apparition order, their order do not changes in the ^{13}C domain. For DMSO-d_6 solutions no such changes occur at all, a situation which is understandable due to strong solvation.

Figure 1

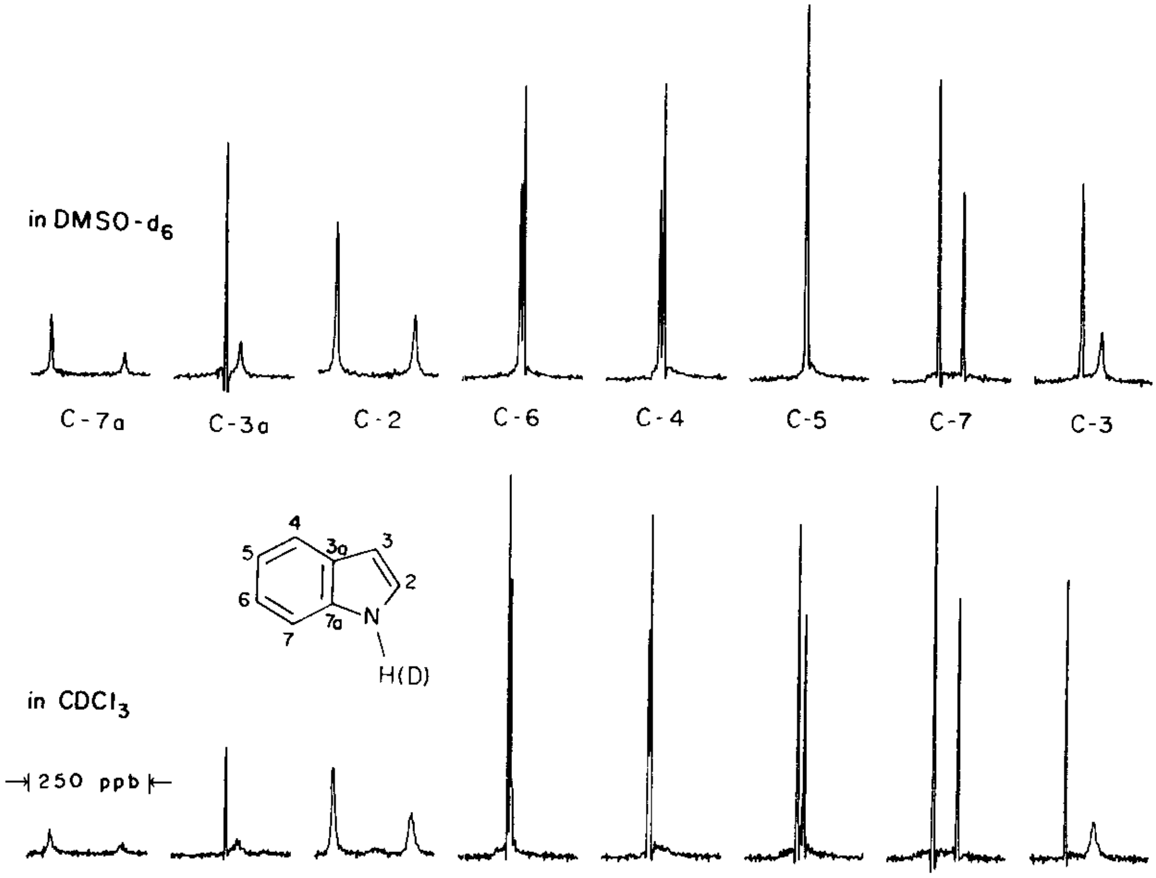
Contour plot of ^{13}C-^1H shift correlated 2D nmr spectrum of indole in $CDCl_3$ solution.



On the other hand, due to the aromatic character of the pyrrole ring of indole, the electron pair of the nitrogen atom is not easily available for protonation. Therefore it could be anticipated that hydrogen/deuterium exchange of the labile proton of indole should be slow on the "nmr time scale" even in solvents like the popular $CDCl_3$, thus allowing to measure Deuterium/Hydrogen NMR Isotope Effects on ^{13}C Chemical Shifts (DHIECS)[13].
Table 1 lists the ^1H and ^{13}C chemical shifts of indole at various concentrations in $CDCl_3$, while the corresponding data measured from DMSO-d_6 solutions are given in Table 2. The Tables also show the DHIECS values in parts per billion (ppb = 10^{-9}) and the widths for the ^{13}C signals at half-high ($C(W_{\frac{1}{2}})$) for the proton (H) and the deuterium (D) containing species, in Hz.

Figure 2

75.4 MHz ^1H-decoupled ^{13}C-nmr spectra of mixtures of deuterated and isotope-free indole



The DHIECS results are also depicted in Figure 2 and they suggest that the method seems to be useful for detailed evaluations, since each carbon atom of indole behaves in a particular way. The experiments in each solvent were performed at two ratios of normal to deuterated indole, to determine the sign (positive is upfield) of the shifts. As expected, the largest DHIECS values for indole are observed over two bonds and are essentially solvent independent, the effect being larger for C-2 than for C-7a. These two signals are broadened by the electric quadruple moment of the nitrogen atom more severely in $CDCl_3$ than in DMSO-d_6 and further broadened by the deuterium atom, as evidenced from the $C(W_{\frac{1}{2}})$ values given in Tables 1 and 2.

The effects over three bonds are larger for both CH signals (C-3 and C-7) than for quaternary C-3a, but while the bahavior of C-7 is solvent independent, both C-3 and C-3a effects are solvent dependent. The C-3 signal is shifted more in $CDCl_3$ than in DMSO-d_6 while the reverse situation holds for C-3a. Broadening of carbon signals by the nitrogen and the deuterium is evident only for the atoms of the pyrrole ring. The broadening effect of the deuterium, due to coupling over three bonds is also more effective in $CDCl_3$ than in DMSO-d_6 and in both solvents C-3a is less affected than C-3. A geometrical dependence over four bonds is evident since in $CDCl_3$ solutions C-6 shows a positive DHIECS value, while C-4 shows a negative value. In addition the DHIECS value for C-5, induced over five bonds, is much larger in $CDCl_3$ than those observed over four bonds.

Table 1. Nmr Data of Indole in $CDCl_3$

[c]M	2.56	1.99	1.42	0.83	2.56	1.99	1.42	0.83	Δδ	$C(W_{\frac{1}{2}})$	Hz
Atom	δ_H(ppm)				δ_C(ppm)				(ppb)	H	D
2	6.690	6.774	6.863	7.005	124.32	124.29	124.25	124.19	165.5	0.67	1.07
3	6.402	6.438	6.467	6.514	102.01	102.10	102.18	102.38	58.3	0.25	0.96
3a	-	-	-	-	127.59	127.62	127.64	127.75	23.6	0.26	0.79
4	7.585	7.603	7.619	7.642	120.56	120.59	120.61	120.67	-4.8	0.29	0.29
5	7.071	7.085	7.099	7.115	119.67	119.69	119.70	119.76	13.9	0.28	0.28
6	7.121	7.141	7.150	7.180	121.75	121.78	121.82	121.89	5.2	0.24	0.24
7	6.987	7.049	7.147	7.242	111.12	111.10	111.08	111.05	51.0	0.29	0.29
7a	-	-	-	-	135.51	135.55	135.56	135.67	148.6	0.67	1.07
NH	7.154	7.300	7.458	7.735	-	-	-	-	-	-	-

Table 2. Nmr Data of Indole in DMSO-d_6

[c]M	2.56	1.99	1.42	0.83	2.56	1.99	1.42	0.83	$\Delta\delta C$	$C(W_{\frac{1}{2}})$ Hz	
Atom	δ_H (ppm)				δ_C (ppm)				(ppm)	H	D
2	7.300	7.318	7.325	7.324	125.04	125.06	125.06	125.06	163.6	0.46	0.68
3	6.454	6.446	6.440	6.427	101.07	101.01	100.95	100.90	41.9	0.33	0.71
3a	-	-	-	-	127.70	127.65	127.59	127.57	31.4	0.23	0.59
4	7.576	7.570	7.560	7.546	120.06	120.01	119.96	119.92	-8.0	0.30	0.30
5	7.019	7.012	7.003	6.878	118.82	118.77	118.72	118.67	nm	0.40	
6	7.110	7.105	7.095	7.080	120.92	120.87	120.82	120.78	-7.4	0.30	0.30
7	7.460	7.450	7.433	7.413	111.41	111.37	111.33	111.31	51.6	0.27	0.28
7a	-	-	-	-	135.93	135.89	135.83	135.81	156.2	0.41	0.49
NH	11.072	11.085	11.085	11.076	-	-	-	-	-	-	-

nm: not measured

Excepting hydrocarbons, for which some quantitative relations were derived recently[14], the theoretical interpretation of DHIECS in polyatomic molecules is still incomplete. Indole represents a case wherein conformational processes are absent and steric effects are negligible due to the flat molecular architecture. Thus the suggested vibrational origin[15] of DHIECS appears to hold. This is particularly evident over several bonds, by comparing measurements in $CDCl_3$ with those in DMSO-d_6, where it can be anticipated that intermolecular indole-solvent hydrogen-bonding can effectively modify the vibrational behavior of the N-H and N-D bonds. Thus, in DMSO-d_6, the DHIECS of C-5 vanishes to a small value beyond the magnet resolution, which has been evaluated in the range of 0.19 Hz (~2.5 ppb at 75 MHz), while the values (C-4 and C-6) over four bonds are both negative in contrast to a positive value for C-6 measured in $CDCl_3$.

Our results suggest that careful measurements of DHIECS can be extended far beyond the distinction of the C-5 and C-7a signals in 5-nitroindole and of C-3 and C-6 in 7-methoxyindole reported from measurements performed at 20 MHz in DMSO-d_6 when high field superconducting spectrometers are used[10].

EXPERIMENTAL

Measurements were performed in 5 mm O.D. sample tubes on a Varian Associates

XL-300GS spectrometer operated with the software version 6.1D provided by the manufacturer at ambient probe temperature (22°C) excepting the DHIECS which were done at 27 ± 0.1°C. Chemical shifts are given in ppm from internal TMS, with digital resolutions of 0.245 and 0.333 Hz/point for ^1H and ^{13}C spectra, respectively. For the DHIECS measurements the samples were degased by bubbling argon, the ^1H interactions were eliminated by the low energy Waltz-16 decoupling pulse technique[16] and the recycling time was set to 5 sec, thus allowing the acquisition of 24,496 and 28,288 data points for the $CDCl_3$ and DMSO-d_6 solutions, respectively. The FID data were zero-filled to 128 K-data points and resolution enhanced prior to Fourier transform, providing digital resolutions of 0.0404 Hz/point (0.54 ppb/point) and of 0.0434 Hz/point (0.58 ppb/point) for the $CDCl_3$ and DMSO-d_6 solutions, respectively, in the transformed spectra. To replace the exchangeable proton by deuterium, samples were dissolved in $CDCl_3$ and shaken with D_2O, the water was removed and the organic layer was dried over Na_2SO_4. After measurements, the $CDCl_3$ solutions were evaporated under reduced pressure and the residue was dissolved in $(CD_3)_2SO$. Deuteration was better than 92%. Mixtures of the deuteriated and non-deuteriated isotopomers having the desired H/D ratio were prepared by addition of the protonated compound.

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