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^{15}N NMR SHIFTS FOR IMIDAZOLE AND 1-METHYL IMIDAZOLE IN CH_2Cl_2 RELATIVE TO AQUEOUS SOLUTION[1]

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Abstract

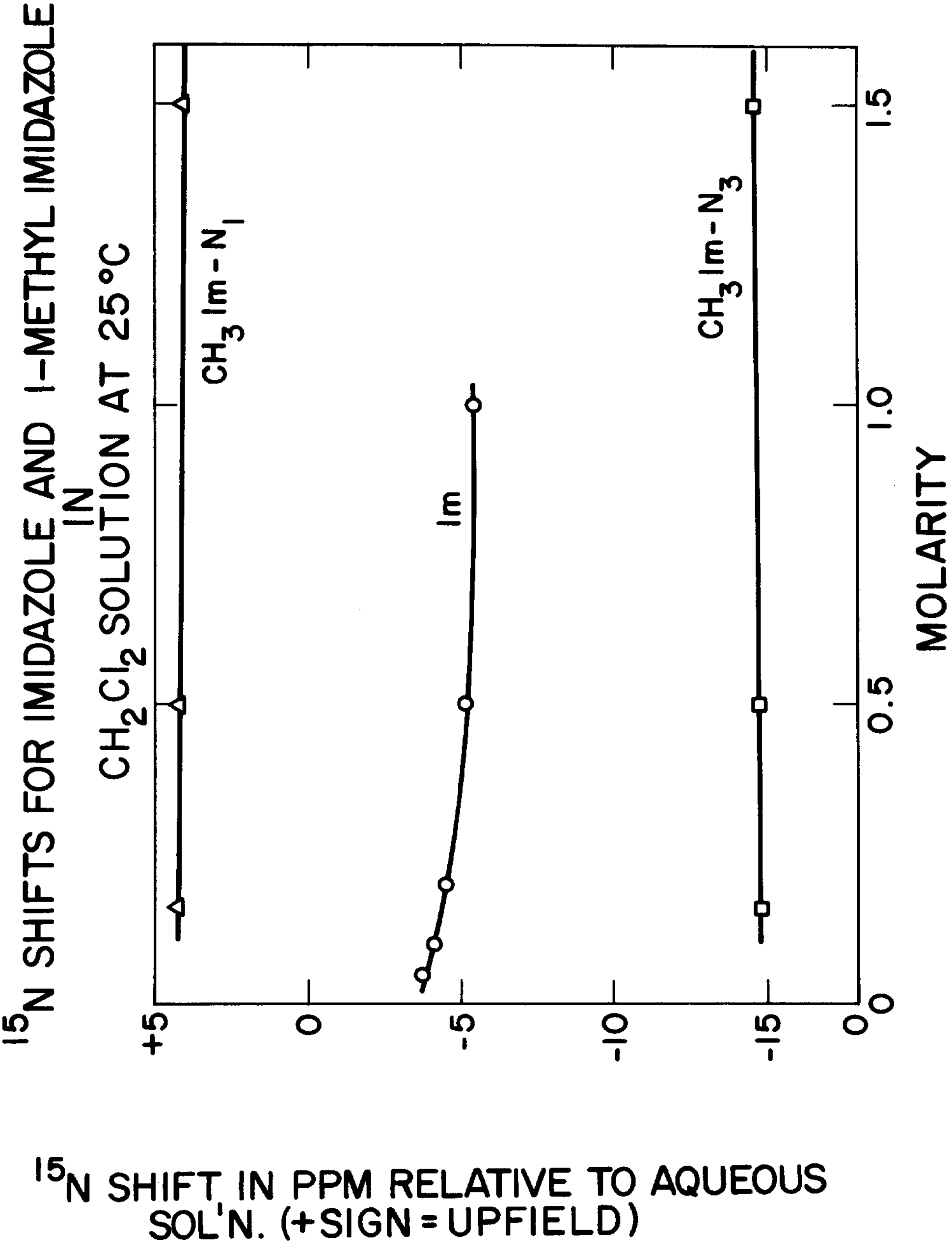
The ^{15}N NMR frequencies for imidazole nitrogens undergo significant shifts when imidazole or 1-methyl imidazole is taken from aqueous to CH_2Cl_2 solution. This shift is probably primarily due to strong hydrogen-bonding between $^{15}N_3$ of imidazole and H_2O protons in aqueous solution.

It has been known for some time[2,3,4] that hydrogen-bonding interactions involving nitrogen lone-pair electrons can produce measurable ^{15}N NMR shifts. In the present study, we have measured ^{15}N shifts for imidazole and 1-methyl imidazole in CH_2Cl_2 relative to H_2O as solvent. There are two main points of interest in such a study: 1) The transfer of imidazole from an aqueous to a CH_2Cl_2 solution takes $^{15}N_3$ from a strongly hydrogen-bonded environment ($^{15}N_3$... H-O) to one in which the $^{15}N_3$ lone-pair electrons interact comparatively weakly, if at all, with CH_2Cl_2 protons. The magnitude and direction of the $^{15}N_3$ shift produced by such a change would be interesting to know since it might serve to distinguish between imidazole rings in aqueous and non-aqueous environments. 2) Proton NMR studies have indicated that imidazole undergoes extensive self-association via hydrogen-bonding (N_3 of a given imidazole with H_1 of a neighboring imidazole) in CH_2Cl_2.[5] It would be interesting to know if such self-association leads to a measurable concentration dependence for the $^{15}N_3$ shift of imidazole in CH_2Cl_2. For 1-methyl imidazole, where self-association via hydrogen-bonding is unlikely, no concentration dependence would be expected.

^{15}N shift measurements were made in cylindrical 12 mm o.d. tubes on a Varian XL-100 spectrometer operating in F.T. mode at 10.16 MHz. External D_2O in a concentric 5 mm capillary provided the deuterium lock signal and all measurements were made at 25 ± 1°C. Susceptibility corrections are negligible since the volume susceptibilities of H_2O and CH_2Cl are nearly identical.[6] CH_2Cl_2 used was Eastman Kodak Co., white label, refluxed with P_2O_5 and distilled under Ar before use.

The principal results of this study are shown in Fig. 1. For imidazole in H_2O (pH > 10) we observed a single, sharp resonance due to rapid averaging of $^{15}N_1$ and $^{15}N_3$ via proton exchange. Line sharpness and resonant frequency were independent of concentration over the range studied. For 1-methyl imidazole in H_2O at high pH we observed separate resonances for $^{15}N_1$ and $^{15}N_3$ ($^{15}N_3$ is 80.8 ppm downfield of $^{15}N_1$) with linewidths and resonant frequencies independent of concentration. For imidazole in CH_2Cl_2 we observed a single ^{15}N resonance which progressively broadens and moves upfield with decreasing imidazole concentration. This result is consistent with rapid proton exchange between monomeric and polymeric species. Even at the lowest concentration (0.05 M) this exchange is still rapid enough to preclude observation of directly-bonded $^{15}N_1$-H coupling. For 1-methyl imidazole we observed two sharp resonances over the entire concentration range used in this study.

The important results of this work are: 1) The $^{15}N_3$ nitrogen undergoes a downfield shift of nearly 15 ppm when 1-methyl imidazole is transferred from aqueous to CH_2Cl_2 solution. An upfield shift of ∿4 ppm is simultaneously experienced by $^{15}N_1$. The larger effect at $^{15}N_3$ is probably due to the change in hydrogen-bonding environment at $^{15}N_3$ as indicated earlier. Since the $^{15}N_3$ resonance of 1-methyl imidazolium ion in aqueous solution is known to undergo a large downfield shift (72.9 ppm) on deprotonation,[7] it is reasonable to expect breakage of the $^{15}N_3$...H-O hydrogen-bond to lead to further shift of smaller magnitude in the same direction. In any case, this result indicates that ^{15}N NMR shift data for imidazole-ring nitrogen may be useful in protein conformation studies to distinguish between histidine residues in aqueous vs. non-aqueous environments. 2) The concentration dependence of the average ^{15}N shift for imidazole, not shown by either $^{15}N_1$ or $^{15}N_3$ of 1-methyl imidazole, is probably the result of self-association via hydrogen-bonding. Since the proton-acceptor nitrogen (N_3) almost surely experiences an upfield shift on self-association of imidazole, the proton-donor (N_1) must simultaneously undergo a somewhat larger downfield shift. It should be recognized that this shift at $^{15}N_1$ is the sum of at least two contributions: a) a small downfield shift due to the lone-pair interaction at $^{15}N_3$ (same effect as seen at $^{15}N_1$ in 1-methyl imidazole when $^{15}N_3$ is protonated or forms a strong hydrogen-bond) and b) a shift contribution at $^{15}N_1$ due to H_1 entering into a hydrogen-bond with an electron-pair donor (in this case $^{15}N_3$ of a neighboring imidazole). Since the average ^{15}N resonance moves downfield with increasing degree of self-association (higher concentration), we conclude that contribution b) must be downfield and that the sum of a) and b) must be larger than the anticipated upfield shift at $^{15}N_3$. The fact that for 1 M solutions, the average ^{15}N resonance in imidazole is almost exactly at the average of the $^{15}N_1$ and $^{15}N_3$ resonance positions in 1-methyl imidazole is probably fortuitous. 3) The upfield shift of $^{15}N_1$ on transferring 1-methyl imidazole from H_2O to CH_2Cl_2 is in the same direction as the $^{15}N_1$ shift produced on deprotonation of 1-methyl imidazole in H_2O,[7] but is only about half as large. This suggests that the effect at $^{15}N_1$ is the result of the perturbation at $^{15}N_3$ being propagated through the $^{15}N_3$–C_2–^{15}N bond system.


^{15}N SHIFTS FOR IMIDAZOLE AND 1-METHYL IMIDAZOLE IN CH_2Cl_2 SOLUTION AT 25 °C
CH_3 Im - N_1
Im
CH_3 Im - N_3
+5
0
-5
-10
-15
0
0
0.5
1.0
1.5
MOLARITY
^{15}N SHIFT IN PPM RELATIVE TO AQUEOUS SOL'N. (+SIGN = UPFIELD)

References

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