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ON THE STRUCTURE OF THE INDOLE GRIGNARD REAGENT

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THE structure of the Grignard reagent derived from indole has been the object of speculation for many years.[1,2] Depending on the reaction conditions, alkylation, acylation, and carbonation of indolylmagnesium halides yields 1-,3-,1,3-, and occasionally even 2-substituted products.[2] These results have led to formulations of the indole Grignard reagent as an N-MgX,[3] C-MgX,[4] or essentially ionic species.[5] Evidence in favor of the latter possibility has now been obtained from a study of the N. M. R. spectra of these reagents.[6]

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[1] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances." Prentice-Hall, New York, 1954, p. 75-86.

[2] W. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," Interscience, New York, 1954, p. 50.

[3] C. D. Nenitzescu, Bull. Soc. Chim. Romania, 11, 130 (1930); Chem. Abstr., 24, 2458 (1930).

[4] R. C. Elderfield, "Heterocyclic Compounds," Vol. 3, John Wiley and Sons, New York, 1952, p. 42.

[5] G. M. Badger, "The Chemistry of Heterocyclic Compounds," Academic Press, New York, 1961, p. 64.

[6] All N.M.R. spectra were taken as 10-20% solutions in tetrahydrofuran (THF) at room temperature on a Varian Associates Model DP-60 high resolution spectrometer operating at 56.4 megacycles per second. Chemical shifts were determined by the audio-frequency side-band technique and referred to methylene chloride as an external standard.

The N.M.R. spectrum of indolylmagnesium bromide (see Figure) shows only three peaks, at -45, -69, and -103 cps (relative areas 1:2:3). The high field peak was assigned to the β-proton because of its relative area, its disappearance in 3-, but not 2-methylindolylmagnesium bromide, and its shift to higher fields in 2-methylindolylmagnesium bromide as compared to indolylmagnesium bromide.[7] The resonance of the α-proton must occur in the low field peak along with two protons of the benzene ring since the relative area of this peak decreases from three to two in going from indolylmagnesium bromide to 2-methylindolylmagnesium bromide.[9] The remaining two protons of the benzene ring are responsible for the peak of intermediate shielding. No peaks which might be assigned to an N-H were detected in any of the spectra of the Grignard reagents, although such peaks were observed in indole (-255cps) and 3-methylindole (-221cps).

A priori the indolylmagnesium halides might be considered to be represented by one of the species I-IV or a mixture thereof. The simplicity of the N.M.R. spectra, with respect

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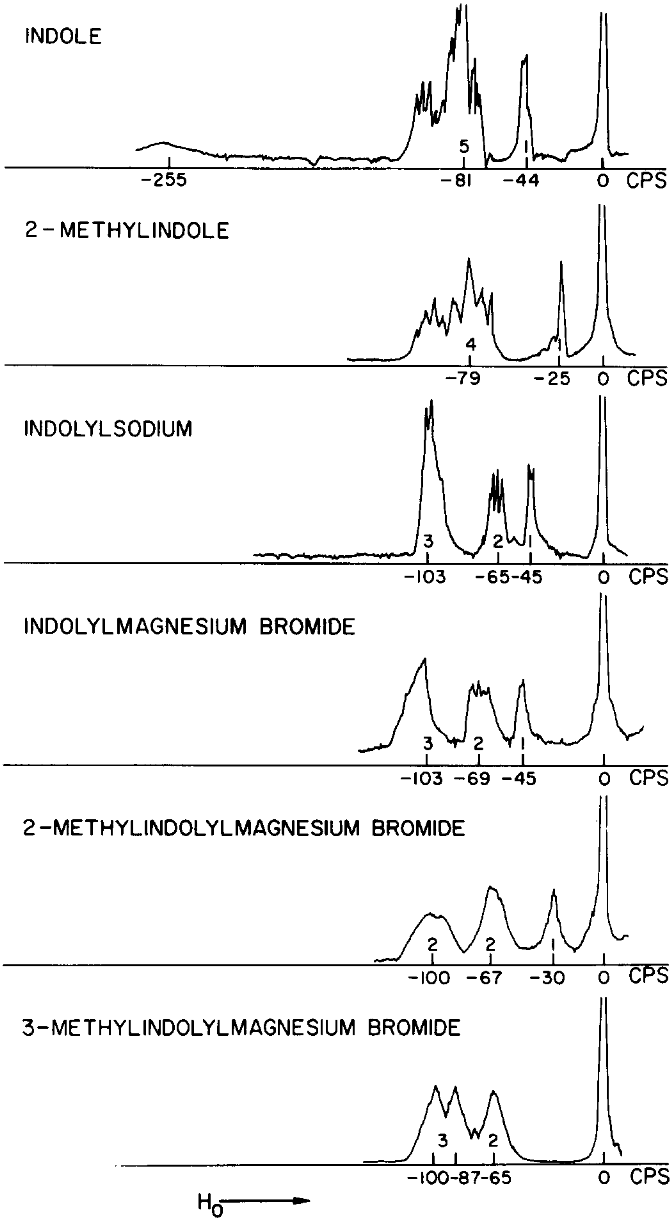
[7] A similar diamagnetic shift of the β-proton has been noted in the N.M.R. spectra of indole and 2-methylindole in carbon tetrachloride[8] and THF (see Figure).

[8] L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Amer. Chem. Soc.*, *82*, 2184 (1960).

[9] The surprisingly low chemical shift of the α-proton (in carbon tetrachloride and deuterochloroform the α-proton resonances of indoles occur between those of the β- and benzenoid protons[8]) is due, at least in part, to a solvent effect and not to formation of the Grignard reagent. This is shown by the fact that in the N.M.R. spectra of the indoles in THF the α-proton resonances also occur among those of the benzenoid protons (the relative area of this complex multiplet is five in indole and four in 2-methylindole). The nature of this solvent effect is presently under study and will be discussed at a later date.


INDOLE
5
1
-255
-81
-44
0 CPS
2-METHYLINDOLE
4
-79
-25
0 CPS
INDOLYLSODIUM
3
2
1
-103
-65-45
0 CPS
INDOLYLMAGNESIUM BROMIDE
3
2
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-103 -69 -45
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2-METHYLINDOLYLMAGNESIUM BROMIDE
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3-METHYLINDOLYLMAGNESIUM BROMIDE
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0 CPS
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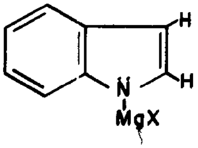
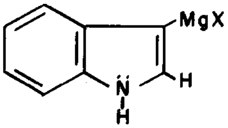
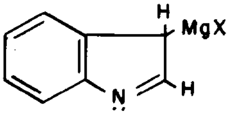
to both the number of peaks and their relative areas, indicates that either one species is predominant or that any mixture of species is in rapid equilibrium. The failure to detect an N-H in the N.M.R. or infrared spectra effectively eliminates the presence of significant quantities of II.



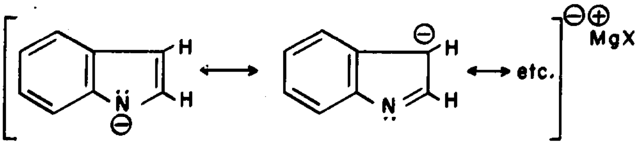
I



II



III



IV

Furthermore, the fact that the β-proton resonances are not shifted to higher field on converting indole and 2-methylindole to their respective Grignard reagents[10] is evidence for the absence of appreciable amounts of III, since both the magnesium atom[11, 12, 13] and the change in the hybridization of the β-carbon atom from sp^2 to sp^3 [14] would be expected to cause a considerable diamagnetic shift of this proton.

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[10] The assignment of the peak at -44cps in the N.M.R. spectrum of indole to the β-proton was made on the same basis as for indolylmagnesium bromide.

[11] Pople, Schneider and Bernstein, "*High-resolution Nuclear Magnetic Resonance*," McGraw-Hill, New York, 1959, p. 294.

[12] M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Rüchardt, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 2647 (1960).

[13] D. F. Evans and J. P. Maher, *J. Chem. Soc.*, 5125 (1962).

[14] Reference 11, p. 238.

Finally, structure I, containing a covalent N-Mg bond, can probably be excluded because of the striking similarity of the N.M.R. spectra of indolylmagnesium bromide and indolylsodium, which presumably contains a largely ionic N-Na bond.[15] The possibility that the N.M.R. spectrum of indolylsodium (IV with Na for MgX) would be similar to that of I seems unlikely since both the change in electron density due to the formal charge and the increased magnetic anisotropy of the nitrogen arising from the free electron pair would be expected to have a pronounced effect on the magnetic environment of the protons.[16] It is therefore concluded that in THF solution the indole Grignard reagent is predominantly the largely ionic resonance hybrid IV.[17]

The Grignard reagents were prepared in THF at room temperature from the appropriate indole and a 10% excess of ethylmagnesium bromide. The theoretical amount of ethane was liberated in all cases. Indolylsodium was prepared by refluxing indole with an excess of sodium hydride in THF for one-half hour. These solutions were transferred by syringe, with suitable precautions against air and water, to a dry N.M.R. tube which was immediately sealed with molten wax.[18]

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[15] L. Pauling, "The Nature of the Chemical Bond", Cornell University Press, Ithaca, New York, 1960, p. 93.

[16] These types of effects have recently been discussed in connection with the N.M.R. spectra of pyridine and pyridinium ion. T. Schaefer and W. G. Schneider, *Can. J. Chem.* **41**, 974 (1963).

[17] Preliminary results indicate that the same conclusion holds for the pyrrole Grignard reagent.

[18] The assistance of Mr. Robert Iwamasa in obtaining the N.M.R. spectra is gratefully acknowledged. This research was sponsored in part by grants from the Research Committee of the University of California, Riverside.