(see previous experiment) followed by washing to neutrality and drying over sodium sulfate yielded, after solvent removal, 0.656 g of crude product, [α]D +25.3° (c 2.6, pentane), which was contaminated by a small amount of silanol. Chromatography on a 18 × 0.5 in. silica gel column with elution by pentane–benzene (70:30) gave 0.400 g (63% yield) of (+)-R₃Si*-neo-C₅H₁₁, [α]D +28.5° (c 1.6, pentane), identified by its infrared spectrum.

Reaction of (+)-R₃Si*SCH₃ with Benzyllithium. A solution of 0.426 g (1.45 mmoles) of (+)-R₃Si*SCH₃, [α]D +10.5°, in 7 ml of dry ethyl ether, was added over 1 min to a rapidly stirred solution of 6 mmoles of benzyllithium[8] in 30 ml of ethyl ether. The addition caused the red color of the lithium reagent solution to diminish somewhat, and the solution was allowed to stand at ambient temperature for 10 hr. Acidic work-up (see previous experiment) followed by drying over sodium sulfate and removal of solvent gave 1.07 g of colorless product mixture. This mixture was taken up in pentane and chromatographed on a 18 × 0.5 in. silica gel column. Elution was effected by 125 ml of pentane–benzene (60:40 by volume), yielding 0.376 g (77% yield) of (−)-R₃Si*CH₂Ph, [α]D −2.4° (c 2.7, cyclohexane).[8] The infrared spectrum of the viscous product was identical with that of authentic R₃Si*CH₂Ph.[8] Correcting for optical impurity of the starting material, the reaction proceeded with a stereospecificity of 70% inversion.

Protonation of the Indole Grignard Reagent and Other Organometallic Derivatives of Indole[1]

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Abstract: Alkali metal derivatives of indole protonate predominantly on nitrogen. The Grignard reagent on the other hand gave carbon protonation when intermediate amounts of D₂O were added. Addition of very large or very small amounts of D₂O yielded either N-protonation or no reaction followed by N-protonation in the work-up. The effects of concentration, solvent, and heterogeneity on the amount of carbon protonation of the indole Grignard reagent are described. The results are discussed in terms of the structure of the organometallic derivatives of indole and the mechanism of their protonation.

Ten years after the discovery of alkylmagnesium halides by Grignard, Oddo found that indole and ethylmagnesium iodide reacted in diethyl ether with the evolution of ethane to produce the indole Grignard reagent (indolylmagnesium iodide).[3] This Grignard reagent undergoes many of the reactions characteristic of simple alkylmagnesium halides, such as carbonation, alkylation, and acylation.[4,5] The products formed are substituted predominantly at the 3 position of the indole ring, although small amounts of 1-substituted and 1,3-disubstituted products have been reported. This selectivity in substitution reactions has led to the widespread use of the indole Grignard reagent in the synthesis of naturally occurring and pharmacologically important substances.[6]

Since its discovery, the structure of the indole Grignard reagent has been the subject of considerable controversy mainly as a result of its substitution behavior. The indole Grignard reagent is alkylated and carbonated predominantly at the 3 position,[7] while alkali metal derivatives of indole yield mostly 1-substituted products. This has led to the formulation of the Grignard reagent variously as an N–MgX or a C–MgX species. Recently two studies of the alkylation of organometallic derivatives of indole have been reported.[8,9] The Grignard reagent reacts with methyl iodide in THF or toluene to give exclusively skatole, while the alkali metal derivatives (Li, Na, K) give varying amounts of skatole and 1-methylindole. The data suggest that increased dissociation of the organometallic derivatives of indole leads to 1-alkylated products, while associated salts yield 3-alkyl products. Thus factors which increase the ability of these organometallic indole derivatives to dissociate, such as an increase in solvent polarity, increasing homogeneity of the reaction mixture, and increasing electropositive character of the metal ion, tend to produce more N-alkylation.[9] This hypothesis is in agreement with results obtained in the alkylation of alkali metal salts of pyrrole[10,11] and other ambident anions.

Recent nmr investigations of the organometallic derivatives of indole have cast much light upon their structures.[9,12,13] The C–MgX formulation (2) for the

(1) Presented in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.
(2) National Science Foundation Undergraduate Research Participant, 1964.
(3) B. Oddo, *Gazz. Chim. Ital.*, **41**, 211 (1911); B. Oddo and L. Sessa, *ibid.*, **41**, 234 (1911).
(4) W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954; T. S. Stevens in "Chemistry of Carbon Compounds," Vol. IVA, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1957, pp 71–100.
(5) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp 80–84.
(6) For recent examples of the usefulness of the indole Grignard reagent in synthesis see J. C. Powers, *J. Org. Chem.*, **30**, 2534 (1965); H. Bader and W. Oroshnik, *J. Am. Chem. Soc.*, **81**, 163 (1959); R. M. Acheson and A. R. Hands, *J. Chem. Soc.*, 744 (1961).

(7) S. Kasparek and R. A. Heacock, *Can. J. Chem.*, **44**, 2805 (1966), have observed that the reaction of ethyl chloroformate with the indole Grignard reagent gives approximately a 1:1 ratio of 1-carbethoxyindole and 3-carbethoxyindole. The ratio varied with reaction conditions but with the 3 isomer predominating most of the time. Carbonation of the Grignard reagent gives a similar ratio of products (R. A. Heacock, personal communication).
(8) N. Lerner, *Dissertation Abstr.*, **24**, 4982 (1964).
(9) J. F. Sebastian, Ph.D. Thesis, University of California, Riverside, Calif., June 1965.
(10) C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **84**, 43 (1962).
(11) C. E. Griffin and R. Obrycki, *J. Org. Chem.*, **29**, 3090 (1964).

indole Grignard reagent was clearly excluded by these nmr investigations. In fact the alkali metal derivatives of indole and the Grignard reagent 1 had nearly identical nmr spectra and were clearly N–metal derivatives of indole. It was also concluded on the basis of these nmr data that indole salts are "largely ionic nitrogen–metal species, but with a higher degree of ionic character in the nitrogen–alkali metal bond than in the nitrogen–magnesium bond." [9]
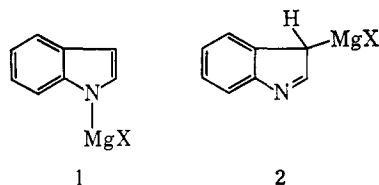
In this paper we wish to report an investigation of the protonation of various organometallic derivatives of indole which we feel contributes to an understanding of the structure of these compounds, their reactivity, and the mechanism of their protonation.

Experimental Section

3-Deuterioindole. Deuterated indole was prepared by the method of Hinman and Bauman,[14] which consisted of heating at reflux a mixture of indole and 0.001 M sulfuric acid in D_2O (10 moles of D_2O/mole of indole). The deuterated indole was purified by rapidly passing it through a column of alumina in benzene followed by crystallization. Chromatography of the deuterated indole probably resulted in some loss of deuterium bound to carbon, but was necessary in order to remove impurities formed upon treatment of indole with acid. The deuterium content was determined by nmr. Isotopic purities of 90, 87, and 95% were obtained in different runs.

Preparation and Protonation of the Sodium Salt of Indole. The sodium salt of indole was prepared by adding 0.017 mole of indole in *ca.* 50 ml of benzene to a mixture of sodium hydride (0.46 mole) and DMSO (6 ml) in *ca.* 44 ml of benzene. The DMSO was necessary in order to achieve a reasonable rate of reaction. The reaction mixture was stirred until the theoretical amount of hydrogen had been evolved (1–6 hr). The concentration of the sodium salt of indole was then approximately 0.17 M.

Protonation was accomplished by the addition of 0.28 mole (16 equiv) of D_2O. The protonation mixture, a clear two-phase system, was stirred for 5 min and then worked up in the same manner as is described for the Grignard reactions. The results are recorded in Table II (experiments 1 and 2). An analogous experiment (experiment 3) was performed by substituting 3-deuterioindole and H_2O for indole and D_2O.

Preparation and Protonation of the Lithium Salt of Indole. The lithium salt of indole was prepared by adding 2.0 g (0.017 mole) of indole dissolved in *ca.* 90 ml of ether to 11.9 ml of 1.6 N *n*-butyllithium (0.019 mole) in hexane and allowing the mixture to stir for 10 min. The concentration of the lithium salt of indole was approximately 0.17 M.

Protonation was carried out by adding varying amounts of D_2O (1, 2, 4, 6, 8, and 10 equiv) followed by rapid stirring for 5 ± 0.5 min. The appearance of the protonation mixture varied. When large amounts of D_2O were added, two clear phases were obtained. The addition of small amounts of D_2O resulted in the formation of a gummy precipitate. The protonation mixtures were poured into 1 M ammonium chloride solution, and the indole was isolated and analyzed in the same manner as described for the Grignard reactions. The results are recorded in Table II (experiments 4–9).

Preparation of the Indole Grignard Reagent in Diethyl Ether. A solution of ethylmagnesium iodide was prepared from 0.019 g-atom of magnesium and ethyl iodide in ether. Addition of 2 g (0.017

mole) of indole to the clear dark ether solution caused gas evolution and formation of the indole Grignard reagent. Most of our experiments were performed with the 0.17 M Grignard reagent in ether. Under these conditions, the indole Grignard reagent was soluble, and a clear ether solution was obtained. Occasionally, addition of indole to a solution of ethylmagnesium iodide resulted in the formation of a white flocculent precipitate. This usually dissolved after 30 sec of stirring. Experiments were either discarded or repeated when the precipitate did not dissolve. In several cases where it was checked, the presence or absence of this flocculent precipitate did not seem to affect the protonation results. No heterogeneity was ever observed at concentrations less than *ca.* 0.1 M. At concentrations of greater than 0.2 M. addition of indole to a solution of ethylmagnesium iodide resulted in the formation of a milky white suspension. Upon standing, a viscous layer began to appear on the sides of the flask and rapidly formed a puddle on the bottom of the flask. At least 90% of the indole was in the oily layer at 0.28 M. The results plotted in Figure 4 were obtained with a heterogeneous Grignard reagent in ether (0.31 M).

The neat Grignard reagent (Figure 2) was prepared by removing the ether from 100 ml of 0.17 M indolylmagnesium iodide using a rotary evaporator under reduced pressure.

The results described in Table II were carried out under slightly different conditions than the rest of our experiments. In this case, the indole Grignard reagent was prepared by adding 0.017 mole of indole to 0.041 mole of ethylmagnesium iodide in 100 ml of ether. Thus the reaction mixture contained an excess of ethylmagnesium iodide.

Protonation of the Indole Grignard Reagent in Diethyl Ether. Protonation of the indole Grignard reagent was accomplished by the rapid addition of D_2O by means of a syringe to a rapidly stirred solution of the Grignard reagent (0.017 mole) in 100 ml of diethyl ether. A white curdy precipitate formed instantly. Occasionally the precipitate would be yellowish, but it usually turned milky white within a few seconds after D_2O addition. When more than *ca.* 10 equiv of D_2O had been added, this precipitate would usually dissolve within 15–30 sec and a clear, two-phase system would be obtained. Addition of 1–3 equiv of D_2O yielded the curdy white precipitate and a clear ether solution. When water was added to this clear ether solution, an exothermic reaction took place and more precipitate would form. This second precipitate was not soluble in ether, but would dissolve in additional water, leaving both phases clear. When 4–10 equiv of D_2O was added, the curdy precipitate often was very sticky and would coat the side of the flask. The distinction between getting a milky solution followed by formation of curdy precipitate or getting a sticky precipitate on the sides of the flask was not sharp. Occasionally matched sets of reactions (*i.e.*, prepared at the same time side by side, same amount of added D_2O, etc.) exhibited different behavior. This was found to make no substantial difference in deuterium incorporation.

The protonation mixture was worked up after 5 ± 0.5 min by pouring into 0.1 M ammonium chloride solution and extracting the indole immediately with ether. No difference in deuteration was observed when the reaction mixture was poured into water or onto ice in the work-up procedure. The indole was then isolated and crystallized before deuterium analysis. Care must be taken during the work-up procedure to prevent loss of deuterium bound to carbon. It was found, for example, that chromatography of a sample of deuterated indole on Woelm neutral alumina resulted in the loss of 79% of the deuterium at the 3 position.

Some results which we obtained are plotted in Figure 1. The values reported in Table II were obtained by adding 0.017 mole of indole or 3-deuterioindole to 0.041 mole of ethylmagnesium iodide in 100 ml of ether followed by protonation with 0.28 mole of D_2O or H_2O (experiments 10–16). Experiments 17–18 were protonated by pouring the Grignard reaction mixtures into a large volume of water or 0.1 M ammonium chloride solution.

Protonation of the neat indole Grignard reagent with D_2O (Figure 2) resulted in an exothermic reaction and formation of a semicrystalline white solid. If enough D_2O were present, this would dissolve and a clear solution would be obtained.

The percentage theoretical deuterium incorporation at the 3 position of the indole ring was calculated assuming complete exchange. For example, with 1 added equiv of D_2O, there are 2D for every exchangeable H in the indole Grignard. If complete scrambling took place then the indole isolated should contain 66.7% D at the 3 position. The calculated curve is plotted in Figure 2.

(12) M. Reinecke, H. W. Johnson, and J. F. Sebastian, *Tetrahedron Letters*, 1183 (1963).

(13) M. G. Reinecke, H. W. Johnson, and J. F. Sebastian, *Chem. Ind.* (London), 151 (1964).

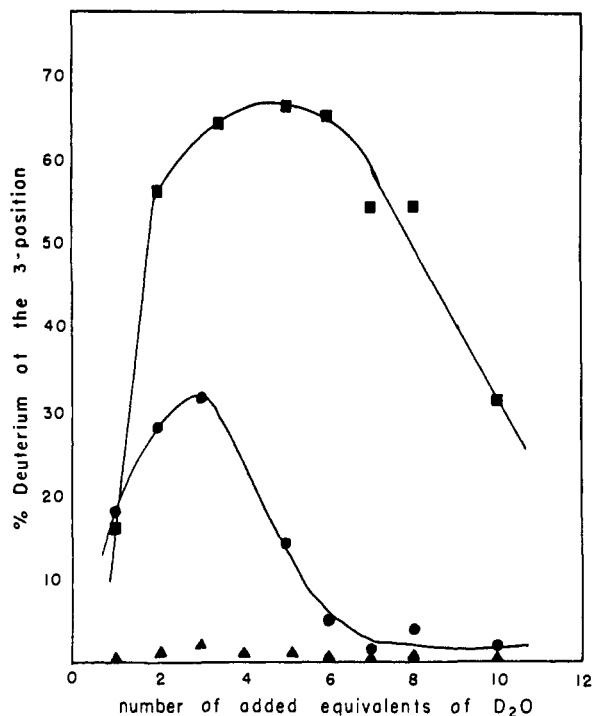(14) R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, 29, 2437 (1964).

Figure 1. A plot of the number of equivalents of D_2O added to the indole Grignard reagent *vs.* the amount of deuterium obtained at the 3 position of the indole thus formed: ■, indole Grignard reagent in diethyl ether (0.17 *M*); ▲, blank reactions; ●, addition of D_2O dissolved in ether to 0.17 *M* indole Grignard reagent.

Experiment 22 in Table II was an unsuccessful attempt to imitate the Grignard results using the sodium salt of indole and anhydrous magnesium chloride.

Analysis of Indole for Deuterium. The indole which was isolated from the protonation experiments was analyzed for exchange at the 3 position of the indole ring by nmr. The relative intensities of the signals due to the 2- and 3-protons on the indole ring[15] were obtained by electronic integration. The percentage hydrogen at the 3 position was then calculated from these values using the signal due to the 2-hydrogen as a standard (equal to one proton). This method of analysis gives an accuracy of ±4% except at low deuterium values. Samples of pure indole would often integrate as though they were 5–10% deuterated. Thus we feel that the deuterium content of samples under 10% is meaningless and probably represents little or no deuteration. This was born out by combustion analysis of several samples of partially deuterated indole in which the nmr would invariably give results 3–4% higher than the actual value with samples containing less than 10% deuterium.

The nmr method of analysis makes the assumption that no exchange of hydrogen for deuterium had occurred at the 2 position of indole. This was in accord with the results of Hinman and Whipple[16] who found that protonation of indoles at the 2 position was much slower than protonation at the 3 position. This assumption was checked by obtaining deuterium analysis by combustion and by mass spectroscopy on several samples of indole and comparing their results with those obtained by nmr (see Table I). The combustion deuterium analyses were run by Dr. Joseph Nemeth, Urbana, Ill.

Since there is reasonable agreement between the deuterium analysis obtained by these independent methods (the nmr results were usually higher), protonation must have occurred only on nitrogen or at the 3 position of the indole ring and not at the 2 position. Deuterium bound to the nitrogen atom of indole is exchanged with extreme rapidity. The nmr signal due to the proton on nitrogen disappears completely within several minutes of adding a drop of D_2O to an nmr sample of indole. Thus any deuterium on nitrogen would be lost during our work-up procedure and no attempt was made to analyze for deuterium in this position.

(15) L. A. Cohen, J. W. Daly, J. W. Kny, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960).
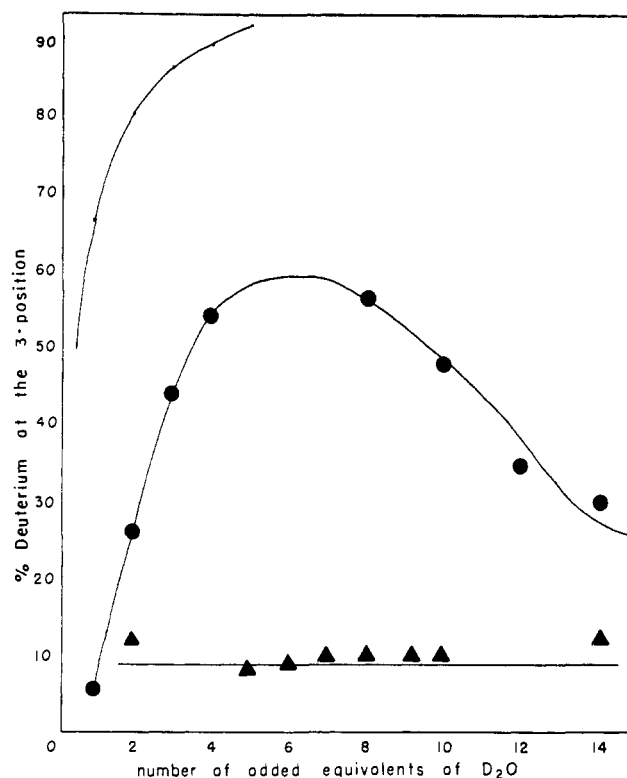(16) R. L. Hinman and E. B. Whipple, *ibid.*, **84**, 2534 (1962).

Figure 2. A plot of the number of equivalents of D_2O added to the indole Grignard reagent *vs.* the amount of deuterium obtained at the 3 position in the indole thus formed: ●, neat indole Grignard reagent; ▲, indole Grignard reagent in THF (0.17 *M*); ———, calculated deuterium incorporation at the 3 position assuming complete exchange.

Blank Reactions. These experiments were designed to measure the amount of base-catalyzed exchange at the 3 position of the indole ring taking place in the reaction mixture subsequent to protonation and before work-up. A solution of ethylmagnesium iodide (0.019 *M*) was prepared in 100 ml of ether. A known amount of D_2O was then introduced by means of a syringe. Gas evolution was 80–85% complete within 60–90 sec after the addition of 1

Table I

Sample no.	% D at the 3 position by nmr	Deuterium anal, %	Total D by mass spectry, %
1	22 ± 4	18.41	16 ± 3
2	7 ± 4	2.90	...
3	4 ± 4	1.47	...
4	47 ± 4	...	49 ± 3

equiv of D_2O. The rest of the gas was evolved with the addition of a further 1 or 2 equiv of D_2O. Upon adding more than 2 equiv of D_2O to a ethylmagnesium iodide solution, gas evolution proceeded very rapidly at first, but nevertheless required 1–2 min to be complete. This would certainly seem to indicate that part of the initially added D_2O is tied up and able to react only slowly with the Grignard reagent. Indole (0.017 *M*) was added, the reaction mixture was stirred for 5 min, and the indole was isolated and analyzed as previously discussed. If the indole was added too rapidly to a protonated Grignard solution, higher banks were observed. Possibly the indole completed favorably with the D_2O (for the remaining Grignard) because of its solubility in ether and formed indole Grignard reagent which then protonated. The results are plotted in Figure 1. The blank reactions listed in Table II (experiments 20–21) were carried out in a similar fashion with 0.041 *M* of ethylmagnesium iodide, 0.28 *M* of D_2O, and 0.017 *M* of indole in 100 ml of ether.

Blank Reactions. Magnesium Bromide and Sodium Hydroxide. These blank reactions were designed to imitate the basic conditions existing in a protonated Grignard solution to test for the possibility of base-catalyzed exchange subsequent to protonation and before work-up. A solution of 0.017 M anhydrous magnesium bromide and 0.017 M sodium hydroxide in various amounts of D_2O was stirred with a solution of 0.017 M indole in 100 ml of ether for 5 min. The indole was then isolated and analyzed as described for the indole Grignard reagent.

Substantial exchange was not observed. The results are not plotted since they essentially duplicated the blank reactions plotted in Figure 1. The blank experiment (no. 19) described in Table II was carried in an analogous fashion using 3-deuterioindole, magnesium chloride, and sodium hydroxide in water and ether.

Preparation and Protonation of the Zinc Salt of Indole. The zinc salt of indole was prepared by adding anhydrous zinc chloride (0.017 mole) to a solution of the indole Grignard reagent (0.017 mole) in ca. 100 ml of ether.[17] The clear solution, obtained after the initial exothermic reaction, was stirred at room temperature for 0.5 hr. Addition of D_2O to this solution caused the formation of a white precipitate. After stirring for 5 min, water was added, and a clear solution was obtained. The indole was extracted with ether, isolated, and analyzed as described for the Grignard reagent. The results are listed in Table II (experiments 23–26).

Indole failed to react with ethylzinc iodide prepared from ethyl iodide and a zinc–copper couple,[18] even though the ethylzinc iodide was reactive enough to be destroyed by water. Alkylation of the zinc salt of indole with iodomethane in refluxing ether gave a mixture of skatole (60%) and indole (40%). No N-methylindole was detected by thin layer chromatography.

Protonation of the Indole Grignard Reagent with D_2O Dissolved in Diethyl Ether. A solution of D_2O in ether was prepared by stirring overnight excess D_2O with diethyl ether which had been dried over molecular sieves. The ether solution was then decanted and a solution with 1.38 g of D_2O in 100 ml of solution was obtained. Protonation of the indole Grignard reagent (100 ml of 0.17 M) was accomplished by the rapid addition of the D_2O in ether solution by means of a separatory funnel. The addition of 1–3 equiv of D_2O in ether resulted in the instantaneous formation of a milky solution. Addition of more than 3 equiv led to a milky solution and the precipitation of a white solid after 0.5 min. This white curdy solid would usually dissolve after 45 sec of stirring when more than 10 equiv of D_2O in ether (380 ml solution) had been added. The protonation mixtures were stirred for 5 min and then worked up in the same manner as was described for the other Grignard reactions. None of the reaction mixtures gave any visible reaction upon pouring into water. It should be noted that addition of D_2O in ether results in an increase in the volume of ether in the protonation mixture (more than twofold at 3 equiv) and thus a decrease in concentration. The results are plotted in Figure 1.

Preparation and Protonation of the Indole Grignard Reagent in Tetrahydrofuran. A solution of ethylmagnesium bromide was prepared from 0.452 g (0.019 g-atom) of magnesium in 100 ml of THF. Addition of 2 g (0.017 mole) of indole to the clear ethylmagnesium bromide solution produced the indole Grignard reagent with evolution of gas (~400 ml). The Grignard reagent was completely homogeneous in THF.

Protonation of this Grignard solution was accomplished by the addition of D_2O with efficient stirring. A white precipitate formed. The reaction was worked up after 5 ± 0.5 min by pouring into a separatory funnel containing ether and water and extracting the indole immediately. The indole was analyzed in the same manner as was described for the Grignard reactions in ether, and the results are plotted in Figure 2.

Indole Grignard Reagent Protonation–Separation of Precipitate and Solution. The indole Grignard reagent was prepared in ether and protonated as described above. The mixture was stirred for 5 min and then the precipitate was separated from the ether solution by filtration. The precipitate (including any gummy material coating the sides of the flask) and the ether solution were worked up separately by quenching with 0.1 N ammonium chloride solution, extraction, and analysis of the indole as previously described. The percentage of indole in each phase was determined by weighing the indole obtained after work-up of the solid and of the solution.
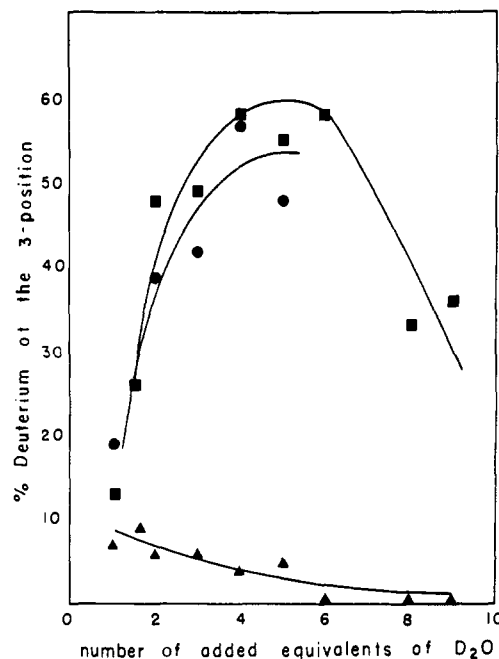
(17) N. Sheverdina, I. Paleeva, N. Zaitseva, and K. Kockeshkov, *Dokl. Akad. Nauk SSSR*, **155**, 623 (1964).
(18) E. Le Goff, *J. Org. Chem.*, **29**, 2048 (1964).

Figure 3. Protonation of the indole Grignard reagent (0.17 M in ether) with D_2O and separation of the precipitate from the solution: ▲, the percentage of the total isolated indole found in the precipitate; ■, amount of deuterium found at the 3 position of the indole isolated from the ether solution; ●, amount of deuterium found at the 3 position of the indole isolated from the precipitate.

The results obtained upon protonation of 0.017 mole of indole Grignard in 100 ml of ether with D_2O are plotted in Figure 3. Very little indole was found in the precipitate. Addition of 8 or more equiv of D_2O yielded no precipitate, and no separation was performed. Addition of 6 equiv yielded less indole in the precipitate than was required for nmr analysis.

The results obtained upon protonation of 0.017 mole of indole Grignard in ca. 55 ml of ether (0.31 M) with D_2O are plotted in Figure 4. The Grignard reagent is heterogeneous under these conditions with most of the indole present in a viscous layer at the bottom of the flask. Addition of a small amount of D_2O resulted in the formation of a white semicrystalline precipitate. This probably occluded indole which might otherwise have been found in the ether solution. This white precipitate dissolved when 14 equiv of D_2O had been added and a two-phase system resulted.

Results

Protonation of the organometallic derivatives of indole was accomplished by the rapid addition of deuterium oxide to a solution of the indole salt or of water to the organometallic derivative of 3-deuterioindole. Some results are listed in Table II.

There are several striking aspects to the results shown in Table II. First, the Grignard reagent of indole was the only organometallic derivative which gave substantial protonation on carbon (experiments 10–16). The sodium (experiments 1–3) and lithium salts (experiments 4–9) showed very little exchange at the 3 position, indicating that they were undergoing mostly nitrogen protonation. The zinc salt (experiments 23–26) gave a small percentage of carbon protonation, but it too reacted mostly on nitrogen. A most surprising feature of our results was the strange behavior of the indole Grignard reagent. It gave up to 75% exchange with a moderate excess of water, while swamping with water led to virtually complete N-protonation (experiments 17–18). Finally, addition of D_2O to the indole Grignard reagent (experiments 10–13)
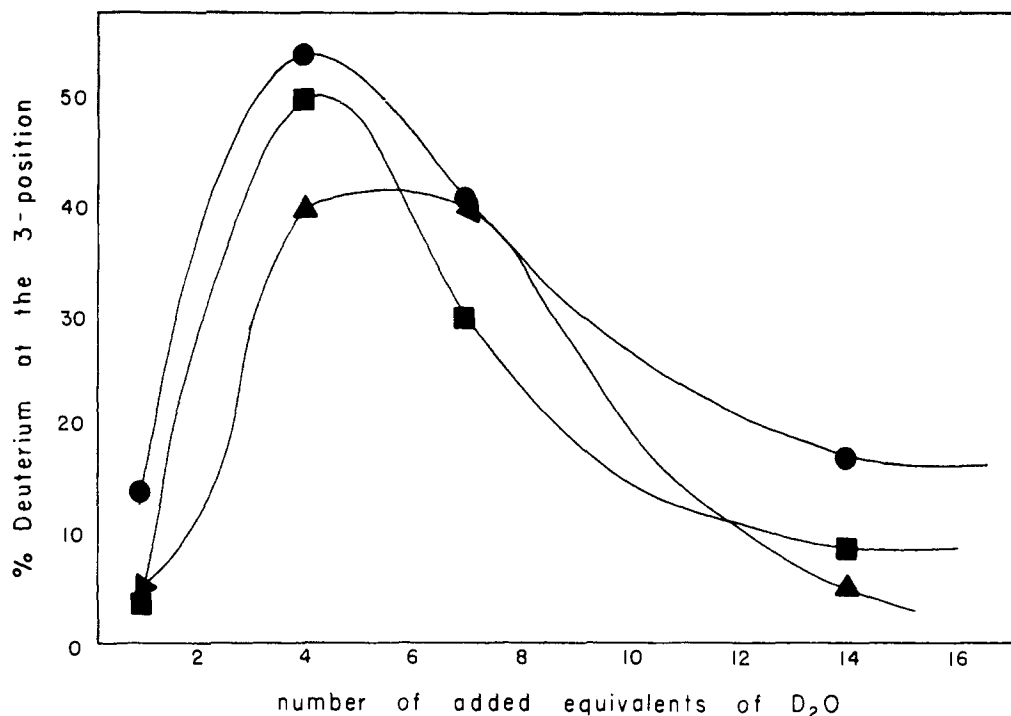
Figure 4. Protonation of the heterogeneous indole Grignard reagent in ether (0.31 M) with D_2O and separation of the precipitate from the solution: ▲, the percentage of the total isolated indole found in the precipitate; ■, amount of deuterium found at the 3 position of the indole isolated from the ether solution; ●, amount of deuterium found at the 3 position of the indole isolated from the precipitate.

and protonation of Grignard reagent of 3-deuterioindole (experiments 14–16) gave similar amounts of exchange, not the same ratio of deuterated to undeuterated product as was expected.

Concentration and Solvent Effects. The extent of protonation of the indole Grignard reagent on carbon depends to a remarkable extent on the number of equivalents of added D_2O. The first indication of this effect was the observation that addition of the Grignard reagent of 3-deuterioindole to a large excess of water or ammonium chloride solution (experiments 17–18) led to N-protonation and practically no exchange at the 3 position. On the other hand, addition of lesser amounts of water gave substantial carbon protonation (experiments 14–16). We then acquired the data plotted in Figures 1 and 2. These were obtained by adding varying amounts of D_2O to the indole Grignard reagent, quenching after 5 min with a large excess of water, and analyzing the indole thus produced for deuterium at the 3 position of the indole ring.

Our results clearly show that addition of both very large and very small amounts of D_2O to the indole Grignard reagent led to mostly N-protonation and gave little substitution at the 3 position of the indole ring, while intermediate amounts of D_2O gave the highest percentage of carbon protonation. This is true for the indole Grignard reagent neat (Figure 2) or dissolved in ether (Figure 1). Protonation of the indole Grignard reagent in THF (Figure 1) or as a very dilute solution in ether (0.034 M) resulted in no carbon protonation and thus no incorporation of deuterium into the 3 position of the indole ring. Addition of D_2O dissolved in ether to the Grignard reagent gave much less carbon protonation (Figure 1). This is probably a simple concentration effect. Since D_2O is only slightly soluble in ether, protonation in this manner results in a dilution

of the reaction mixture. Thus a point is reached where the amount of carbon protonation falls off as the concentration of Grignard reagent in the reaction mixture decreases. The results then resemble those obtained upon protonation of a dilute ether solution (0.034 M) of the indole Grignard reagent. It is unlikely that the results obtained with D_2O dissolved in ether are a heterogeneity effect since the reaction mixtures appeared to be as heterogeneous as those protonated with D_2O.

Base-Catalyzed Exchange. Indole undergoes ready base-catalyzed exchange at the 3 position.[19] Thus the possibility that our protonation results could be explained by exchange subsequent to protonation had to be considered. Blank experiments were carried out to measure any exchange taking place at the 3 position of the indole ring after protonation but before work-up of our reaction mixture (see experiments 19–21 in Table II and results plotted in Figure 1). These experiments clearly show that less than 10% exchange is taking place once protonation has been accomplished, and *the indole is in solution.* None takes place during our work-up procedure. The deuterium incorporated into the indole never approaches that theoretically possible assuming complete exchange (calculated curve plotted in Figure 2).

Heterogeneity Effects. Protonation of the indole Grignard reagent under most conditions yields a heterogeneous mixture of solution and precipitate. Because of the nature of this reaction mixture, the per cent deuterium incorporation upon protonation probably depends not only on the total amount of D_2O added but on the speed of addition, drop size, and the efficiency of stirring. Every effort was made to keep

(19) B. C. Challis and F. A. Long, *J. Am. Chem. Soc.*, **85**, 2524 (1963).

Table II

Expt	Indole	Metal salt[a]	Solvent	Added (equiv)	% exchange at the 3 position
1–2	3-H	Sodium	Benzene–DMSO	D_2O (16)	6
3	3-D	Sodium	Benzene–DMSO	H_2O (16)	3
4–9	3-H	Lithium	Ether–hexane	D_2O (1,2,4,6,8,10)	3–8
10–13	3-H	Grignard	Diethyl ether	D_2O (7)	75
14–16	3-D	Grignard	Diethyl ether	H_2O (7)	68
17	3-D	Grignard	Diethyl ether	0.1 M NH_4Cl soln (>50)	3
18	3-D	Grignard	Diethyl ether	H_2O (>50)	1
19	3-D	None	Diethyl ether	$MgCl_2$, NaOH, H_2O	9
20–21	3-H	Blank	Diethyl ether	D_2O (7)	10
22	3-H	Sodium	Benzene–DMSO	$MgCl_2$ then D_2O (2)	0
23	3-H	Zinc	Diethyl ether	D_2O (1)	23
24	3-H	Zinc	Diethyl ether	D_2O (2)	23
25	3-H	Zinc	Diethyl ether	D_2O (4)	20
26	3-H	Zinc	Diethyl ether	D_2O (8)	5

[a] The concentrations of all the organometallic derivatives was ca. 0.17 M.

these variables constant in order to obtain meaningful comparisons. We did however investigate the effect of occlusion of the indole into the precipitate on the per cent deuterium incorporation. This was done by carrying out protonation experiments as before, followed by separation of the precipitate from the solution before work-up. The indole in each was then individually analyzed for deuterium (see Figure 3).

These results show that very little indole is trapped in the precipitate upon protonation of an ether solution of the indole Grignard, and, more significantly, deuterium content of trapped indole does not vary substantially from that of the indole found in solution. Thus a hypothesis that the occluded indole might be undergoing more exchange due to a more basic environment is untenable.

Much more indole is found in the solid phase upon protonation of a heterogeneous mixture of the indole Grignard reagent in ether (Figure 4). This was especially true when intermediate amounts of D_2O were added. The indole found in the solid phase contained approximately 10% more deuterium than that found in solution indicating either that more exchange was taking place in the solid phase under these conditions or that the indole Grignard was subjected to different conditions of protonation in solution than in the solid phase.

Unreacted Grignard Reagent after Protonation. Addition of 3 or less equiv of D_2O to the indole Grignard reagent yields a mixture which contains unreacted Grignard reagent or a Grignard-like substance. Two observations support this (see the Experimental Section for a more complete discussion of the appearance of Grignard reactions upon protonation). First, filtration of Grignard reaction mixtures after protonation with 1–3 equiv of D_2O yielded clear ether solutions. An exothermic reaction took place when water was added to these solutions and more precipitate would form. Second, methylation of indole Grignard reagent solutions which had been protonated with 1–3 equiv of water gave up to 10% yields of skatole. No skatole was detected in the reactions quenched with 4 equiv of water.

The fact that unreacted Grignard remains after protonation under these conditions indicates some of the D_2O is tied up and unavailable to the Grignard reagent. It seems unlikely that it would remain free in solution

and not react since addition of water does result in a reaction with the clear ether solution. It also seems unlikely that the soluble Grignard reagent would be occluded on the precipitate and removed from reaction. A more reasonable explanation is that the D_2O is removed from the reaction mixture by coordination with magnesium, either as part of a as yet unreacted Grignard molecule or by being tied up around the magnesium salts formed upon destruction of the Grignard reagent. An attempt to investigate the nature of freshly protonated indole Grignard reaction mixtures by means of nmr was unsuccessful due to the formation of precipitate on the sides of the nmr tube.

Discussion

Mechanism of Protonation of the Indole Grignard Reagent. Protonation of the Grignard reagent of indole at the 3 position must involve some type of indolenine intermediate, probably complexed with magnesium.[20] Addition of D_2O to the Grignard reagent of indole (4) and protonation of 3-deuterioindole Grignard reagent (3) would yield the same intermediate indolenine complex 5. This is still quite far removed from indole and further transformations are necessary before complete destruction of the Grignard reagent is accomplished. Complete demolition of 5 involves severing the bond with magnesium and tautomerization of the indolenine to an indolic system. The indolenine (5) would be expected to tautomerize to a mixture of indole (7) and 3-deuterioindole (9) which would be rich in the 3-deuterio compound due to an expected isotope effect in the tautomeric shift. Thus, approach to this complex (5) from either 3-deuterioindole Grignard reagent (3) or from the indole Grignard reagent (4) and its eventual destruction would be anticipated to yield the same mixture of indole (7) and 3-deuterioindole (9). This was not substantiated by our experimental results. Protonation of 3 gives indole with 32% deuterium at the 3 position (experiments 14–16) while addition of D_2O to 4 gives indole with 75% deuterium at the 3 position (experiments 10–13).

These results can be rationalized by assuming that the indolenine complex has a substantial lifetime and

(20) R. L. Hinman and J. Lang, *J. Am. Chem. Soc.*, 86, 3796 (1964), and Hinman and Whipple[16] present evidence for this type of mechanism in the protonation of indoles.

undergoes exchange before its eventual destruction. This exchange could occur by re-formation of the Grignard reagent from complex 5 followed by reprotonation. It would then be expected that reversion of complex 5 to the Grignard reagent would lead to both 3 and 4. Protonation of this mixture would then yield a mixture of the complexes 5 and 6, and their subsequent destruction would yield indole containing predominantly hydrogen at the 3 position. Likewise, if 4 were partially destroyed by D_2O to yield indole (7 and 9) and if it were partially converted by the above exchange mechanism to 8 which in turn were converted to indole, the over-all result would be predominance of 3-deuterioindole (9) in the product. Direct base-catalyzed exchange of the indole, once formed, was excluded by several blank experiments (experiments 19–21).

3   4

5

6   8

7   9
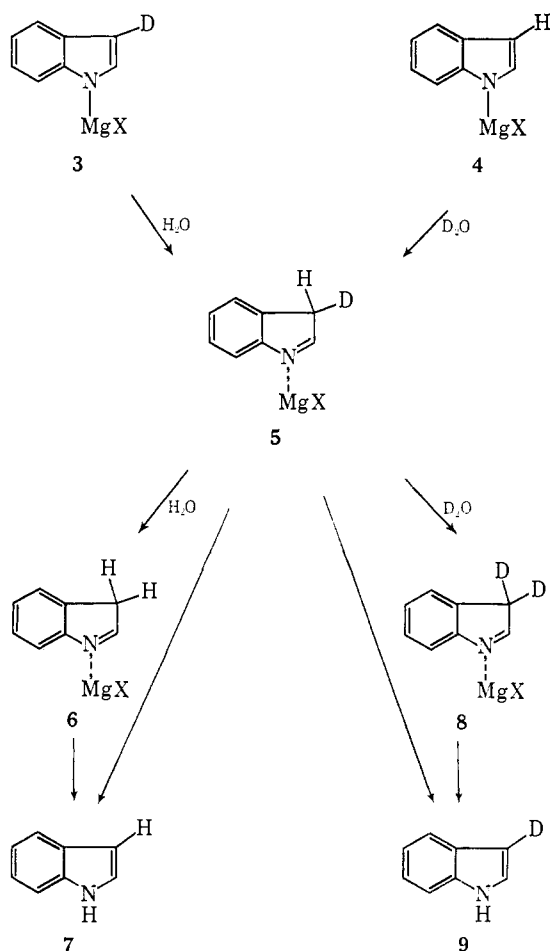
Indole Grignard–D_2O Complex. The concentration of added D_2O has a profound effect on the amount of 3-protonation of the indole Grignard reagent (Figures 1 and 2). These results can best be explained by assuming that a complex (11) between the Grignard reagent (10) and D_2O is formed initially in the protonation experiments.[21,22] This complex would be formed by the displacement of ether molecules in the coordination sphere of each magnesium atom by D_2O molecules.[23,24]

(21) R. Hamelin, Bull. Soc. Chim. France, 698 (1961), has postulated a similar mechanism for the hydrolysis of ethylmagnesium bromide with $MgBr_2(H_2O)_2$ or wet ether.

(22) E. C. Ashby, R. B. Duke, and H. M. Meuman, J. Am. Chem. Soc., 89, 1965 (1967), have presented evidence for the formation of a Grignard–ketone complex in the reaction of ketones with Grignard reagents.

(23) S. Nakamura and S. Meiboom, ibid., 89, 1765 (1967), have studied the solvation shell of magnesium ion in methanol by nmr. They

Protonation would then take place in a subsequent step.

The addition of large amounts of D_2O to the indole Grignard reagent would yield a complex in which D_2O has completely replaced ether in the coordination sphere of magnesium. This would be expected to result in increased dissociation of the N–Mg bond for two reasons. First, the increased polarity of the reaction medium due to the presence of large excesses of D_2O would favor increased dissociation, and second, replacement of ether by D_2O about the magnesium atom to form a complex (11) would weaken the N–Mg bond as the vacant orbitals of the magnesium atom are satiated by the nonbonding electrons of the more basic D_2O molecules.[25] Thus, addition of large amounts of D_2O to the Grignard reagent would yield an ionic species 12, which would protonate predominately at the position of highest electron density, the nitrogen atom. The alkali metal derivatives of indole, which are certainly more ionic than the Grignard reagent, likewise gave largely N-protonation.

Addition of intermediate amounts of D_2O would give a complex 11 in which D_2O has partially replaced the ether molecules coordinated to magnesium. This undergoes protonation on carbon possibly because solvation about the magnesium atom prevents reaction at nitrogen. These are the conditions (Table II) in which exchange is occurring through an indolenine–indole Grignard protonation–re-formation mechanism.

When small amounts of D_2O are added, only part of the indole Grignard reagent is destroyed. This is borne out by two observations. First, there is further reaction when additional D_2O is added, and second, the partially destroyed Grignard solution is alkylated by methyl iodide. The partial destruction of the Grignard reagent is the result of several factors. Part of the D_2O is probably complexed with the indole Grignard reagent and is undergoing slow intramolecular protonation. The remainder is either complexed with or trapped in the magnesium salts formed upon protonation.[26] Since work-up of all Grignard reactions was performed under conditions (large excesses of H_2O) where only N-protonation occurs, little deuterium incorporation into the 3 position was thus observed.

Two questions arise in connection with the above hypothesis. First, is it reasonable to assume that coordination of D_2O with magnesium would proceed protonation and second, could the results be explained

have shown that water will preferentially replace methanol in the solvation shell of the magnesium ions.

(24) E. C. Ashby, ibid., 87, 2509 (1965). Reaction of triethylamine with ethereal ethylmagnesium bromide results in formation of the solid complex $C_2H_5MgBr \cdot N(C_2H_5)_3$. This must be produced by displacement of the ether molecules coordinated to magnesium (by triethylamine).

(25) Tetrahydrofuran coordinates more strongly with the magnesium atom of alkylmagnesium halides than the less basic diethyl ether. The Grignard reagent is thus monomeric in THF since the magnesium atom is less electropositive than in ether and is unable to form a stable halogen bridge compound.[24] This same reasoning would apply to dissociation of the N–Mg bond. Coordination of several D_2O molecules around the magnesium atom of the indole Grignard reagent would result in increased dissociation due to the resulting decrease in the electropositive character of the magnesium atoms.

(26) We would expect this to account for only a small portion of the D_2O for two reasons. First, the indole Grignard reagent should not be a less effective scavenger for the D_2O, at least initially, than the magnesium salts formed when part of the Grignard reagent is destroyed. Second, hydrated magnesium salts are effective at protonating Grignard solutions. The dihydrate of magnesium bromide is soluble in ether [R. Hamelin, Bull. Soc. Chim. France, 684 (1961)] and is effective in protonating ethylmagnesium bromide.[21]
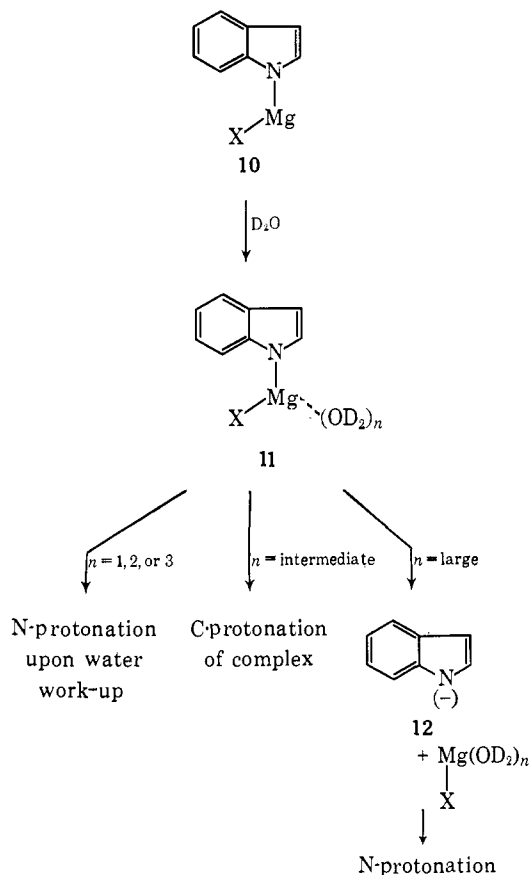
on the basis of solubility and heterogeneity effects? There appears to be no simple explanation of observed maximum in the amount of 3-protonation (Figures 1–4), using solubility and heterogeneity effects alone. If we were observing a blend of homogeneous protonation (at high concentrations) and removal of available D_2O by occlusion (at low concentrations) then we should have obtained smooth curves with no maxima. Certainly our results show that the amount of 3 substitution is qualitatively unaffected by changes in the homogeneity of the starting Grignard reagent or by changes in the heterogeneity of the resulting protonation mixture (Figures 1–4).

Our assertion that coordination of D_2O with the magnesium atom of the indole Grignard reagent precedes protonation is certainly more difficult to document. Ligand exchange reactions about magnesium ions are extremely fast in aqueous solution[27] and only slightly less so in nonaqueous solution.[23] By analogy, one would expect the exchange rate of ligands around the magnesium atom of the indole Grignard reagent to also be fast. The displacement of ether by D_2O molecules to form the Grignard–D_2O complex is in effect a ligand exchange reaction and should proceed at a faster rate than exchange of identical ligands because of the substantial pK difference between water and ether. On the other hand, many proton-transfer reactions in aqueous solution are diffusion controlled.[28] In dipolar aprotic solvents, however, the rates of such reactions are comparable with or slower than ligand exchange reactions about magnesium ions, and in ether they are even slower.[29] The indole Grignard reagent is not a very

(27) M. Eigen, Z. Elektrochem., 64, 115 (1960).
(28) M. Eigen, Angew. Chem. Intern. Ed. Engl., 3, 1 (1964).
(29) J. T. Brauman, D. F. McMillen, and Y. Kanazawa, J. Am. Chem.

peppy Grignard reagent and does not undergo many normal Grignard reactions. There are several reasons for also expecting its protonation to have a slow rate. First, protonation requires considerable bond rehybridization which has been shown to slow considerably hydrogen-transfer reactions.[29,30] Molecular association or ion pairing at the concentrations we employed should have the same effect.[29] Finally, because of the nonionic nature of the indole Grignard reagent and the nonhydroxylic nature of the solvent, we would not expect the electrostatic attractive forces and the hydrogen-bonded solvent structure which operate in fast proton-transfer reactions to be effective.[28] On the basis of available evidence we feel that it is reasonable to assume that coordination of D_2O proceeds protonation. Thus, although the evidence is circumstantial, there is a strong case for the formation of a D_2O–Grignard complex in the protonation of the indole Grignard reagent.

Structure of the Indole Grignard Reagent. It has been demonstrated recently that RMgX is the initial species formed in the reaction of RX with magnesium in diethyl ether,[24] although the over-all composition involves equilibria with dimeric species.[31] Grignard compounds are monomeric in THF.[31] No evidence has appeared concerning the molecularity of the indole Grignard reagent and for the present discussion we have assumed that it is probably monomeric. The fact that the protonation behavior of the indole Grignard reagent varies in dilute solution (0.034 M) and in concentrated solution (0.17 M) may indicate that the molecularity differs.

The nmr investigations of Reinecke, Johnson, and Sebastian have clearly demonstrated the existence of an N–Mg bond in the indole Grignard reagent.[9,12,13] On the basis of the similarity of the nmr spectra of the indole Grignard reagent and alkali metal salts of indoles these authors have concluded that the indole Grignard reagent is predominantly a largely ionic resonance hybrid in THF.[32] Since the indole Grignard reagent does not exchange with indole in the nmr, while the alkali metal salts do,[9] it must possess considerably more covalent character in the N–metal bond. Our results seem to agree with this conclusion. The indole Grignard reagent in THF and the alkali metal salts of indole exhibited similar reactivity: they both undergo N-protonation. The Grignard reagent, however, exhibits entirely different behavior in ether and undergoes C-protonation. Ether has no good way of solvating a

Soc., 89, 1730 (1967); C. D. Ritchie and R. E. Uschold, ibid., 89, 1730 (1967); J. I. Brauman and N. J. Nelson, ibid., 88, 2334 (1966); C. D. Ritchie and R. Uschold, ibid., 86, 4489 (1964).
(30) M. Eigen and J. S. Johnson, Ann. Rev. Phys. Chem., 11, 307 (1960).
(31) E. C. Ashby and W. E. Becker, J. Am. Chem. Soc., 85, 118 (1963); E. C. Ashby and M. B. Smith, ibid., 86, 4363 (1964); R. E. Dessy, S. Green, and R. M. Salinger, Tetrahedron Letters, 1369 (1964).
(32) The conclusion that the N–Mg bond in the Grignard reagent is "largely ionic" simply on the basis of the similarity of the nmr spectra with that of the N–Na derivative seems risky without the availability of adequate models. The nmr spectra of vinyl metal compounds and other organometallic compounds are surprisingly similar even though the metal atom is varied through a wide range of electropositivities. See, for example, C. S. Johnson, M. Weiner, J. S. Waugh, and D. Seyferth, J. Am. Chem. Soc., 83, 1306 (1961); D. Seyferth and L. G. Vaughan, J. Organometal. Chem. (Amsterdam) 1, 138 (1963); D. W. Moore and J. A. Haape, J. Phys. Chem., 65, 224 (1961), for vinyl compounds; J. E. Nordlander and J. D. Roberts, J. Am. Chem. Soc., 81, 1769 (1959), and reference therein for allyl compounds; T. Schaefer and W. G. Schneider, Can. J. Chem., 41, 966 (1963), and J. A. Dixon, P. A. Gwinper, and D. C. Lini, J. Am. Chem. Soc., 87, 1379 (1965), for fluorenyl and indenyl carbanions.

carbanion, and it would appear that the N–Mg bond in the Grignard reagent in ether must have substantial covalent character.[33] THF, being a stronger base than ether, would coordinate more strongly with magnesium and increase the ionic character of the N–Mg bond.[34,35] Similarly, coordination of several molecules of water

about each magnesium would likewise increase the ionic character of this N–Mg bond until a point is reached where its behavior is identical with that of the alkali metal derivatives of indoles and N-protonation occurs. Our results seem to exclude a highly ionic Grignard reagent in ether, since its behavior would then follow that of alkali metal derivatives of indole. Therefore, we conclude that the N–Mg bond of the Grignard reagent has considerable covalent nature in ether.[36]

(33) An N–Mg bond has 55% ionic character and an N–Na bond 67% ionic character calculated on the basis of electronegativity differences: L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, Chapter 3.

(34) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

(35) L. I. Zakharkin, O. Y. Okhlobystin, and K. A. Bilevitch, *Tetrahedron*, **21**, 881 (1965), report that the more solvating (complexing) the medium, the higher the nucleophilic activity of organomagnesium compounds.

(36) A referee has pointed out that our results are easily interpreted in terms of ion-pair association. The problem of greater covalent character *vs.* more ion pairing in organometallic derivatives of this type seems to be very subtle and differences are not readily discernible to us. Thus the terms could be used interchangeably for the purposes of the above discussion.
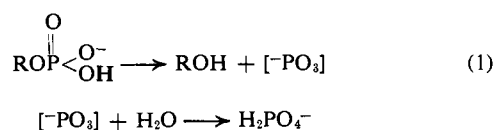
The Hydrolysis of S-Aryl Phosphorothioates

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Abstract: The rates of hydrolysis of the p-H, p-Cl, and p-NO$_2$ S-phenyl phosphorothioates have been measured in water at 35° as a function of pH. The typical maximum in rate for the monoanionic species was found for the p-H and p-Cl derivatives, although the dianion rate of hydrolysis was of much greater magnitude for p-Cl than for p-H. No rate maximum for the monoanionic species was found for S-(4-nitrophenyl) phosphorothioate, the dianion rate being 16.2 times more rapid than the monoanion rate. Deuterium oxide has little effect on the rates of the dianion reactions, but for monoanion hydrolysis k_{H_2O}/k_{D_2O} is 1.78 for p-NO$_2$ and 1.4 for p-H. These values may indicate that the mechanism for monoanion hydrolysis involves a proton-transfer step that is partially rate determining. The monoanion rates are nearly insensitive to electronic effects, decreasing slightly as the leaving group becomes better. The values of ΔS^* are -1.9 eu for hydrolysis of S-(4-nitrophenyl) phosphorothioate monoanion and $+7.9$ for hydrolysis of the dianion, consistent with decomposition to metaphosphate ion for both species. Acid catalysis is not observed with any of the compounds, the rates being nearly invariant at concentrations of HCl from 1.0 to 6.12 M. Electron withdrawal in the leaving group facilitates to only a small extent hydrolysis of the neutral species ($k_{NO_2}/k_H = 1.7$). The neutral species of the p-NO$_2$ derivative hydrolyzes much more slowly in D$_2$O than in H$_2$O ($k_{H_2O}/k_{D_2O} = 1.83$) and has a ΔS^* of -13.2 eu. Thus the mechanism of neutral species hydrolysis probably involves nucleophilic attack by water in concert with a proton-transfer step. The amount of methyl phosphate formed from solvolysis reactions in aqueous methanol solutions is two to three times greater for both monoanion and dianion reactions of the p-NO$_2$ derivative than would be expected from a nonselective phosphorylation of the solvent components, but the p-Cl and p-H compounds give ratios of inorganic phosphate to methyl phosphate similar to the solvent ratios of H$_2$O/CH$_3$OH.

The hydrolysis reactions of various types of phosphate esters have been actively studied.[2] The pH–rate profiles for hydrolysis of monoalkyl phosphates generally show a maximum around pH 4.[2] To account mechanistically for this relatively rapid monoester monoanion reaction has been one of the intriguing problems of phosphate ester chemistry. It has been postulated that this reaction involves the formation of metaphosphate as a reactive intermediate[2,3] (eq 1). The hydrolysis of the dianionic species

$$\text{RO}\overset{\overset{O}{\|}}{P}\!\!<\!\!\overset{O^-}{\underset{OH}{}} \longrightarrow \text{ROH} + [^-\text{PO}_3] \qquad (1)$$

$$[^-\text{PO}_3] + \text{H}_2\text{O} \longrightarrow \text{H}_2\text{PO}_4^-$$

of acetyl phosphate[4] and 2,4-dinitrophenyl phosphate[3,5] very likely also involves metaphosphate formation. Kirby and Varvoglis[3b] have recently suggested that hydrolysis of phosphate monoester monoanions proceeds with preequilibrium zwitterion formation in which the leaving group is protonated, but when the pK_a of the leaving group is low the protonation step may become partially rate determining.

The same general pH dependence has been found for hydrolysis of thiolphosphates as for the oxygen esters of orthophosphoric acid,[6–10] with P–S cleavage oc-

(1) This study represents part of the work to be submitted by S. Milstien in partial fulfillment of the requirements for the Ph.D. degree, University of Southern California, Los Angeles, Calif.

(2) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 11, W. A. Benjamin, Inc., New York, N. Y., 1966.

(3) (a) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964); (b) A. J. Kirby and A. G. Varvoglis, *J. Am. Chem. Soc.*, **89**, 415 (1967).

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(9) S. Akerfeldt, *ibid.*, **14**, 1980 (1960).