pression, eq 6, may be written as $v = (k_2/K_1)h_0[\mathrm{Cr^{VI}}][\mathrm{RPNO}]$, which agrees with the rate law reported for the oxidation of diphenylmethane in acetic acid.[3] This indicates that the kinetic behavior is essentially the same in both the aqueous sulfuric and the acetic acid system. However, since the value of K_1 presumably depends on the nature of the anions present,[5] the equilibrium constants are not expected to be identical for the two solvent systems.

Registry No.—$\mathrm{Cr^{VI}}$, 18540-29-9; PNO, 2398-81-4; NPNO, 1078-05-3.

The Effect of Solvent and Cation on the Reaction of Organometallic Derivatives of Indole with Methyl Iodide[1]

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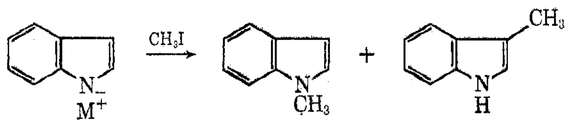
The alkali metal salts of indole behave as typical ambident anions in their reactions with methyl iodide. Indolylmagnesium halides reveal their ambident character only in HMPT which breaks up the tight N–Mg association *via* a 2:1 complex. This observation can be used to reveal structural effects on the reactions of indole Grignard reagents as illustrated by the variation of the C- to N-methylation ratio with the halogen atom of the Grignard reagent.

The rate and position of reaction of ambident anions is markedly affected by a variety of structural and experimental variables.[3,4] Among heterocyclic compounds this phenomenon is most obvious in the chemistry of alkali metal and Grignard derivatives of pyrrole[5] and indole[6] which may react with electrophiles at either carbon or nitrogen. As part of the study of the structure of these derivatives by nmr,[7-9] detailed information on their reactivity as ambident anions was desired. Since such data was already available in the pyrrole series,[5] an examination of the related indole derivatives was undertaken.[1]

The reaction selected for investigation, the methylation of indole salts (eq 1), was known for both the sodium[10] and Grignard[11] derivatives, which yield primarily the N- and C-methylated products 2 and 3, respectively. A methyl halide was chosen rather than an allyl or benzyl halide, since the latter reagents increase the tendency toward reaction at the less electronegative atom of an ambident system[4,12] thereby leading, particularly with the Grignard derivatives, to essentially exclusive C-alkylation.[13,14] By using methyl iodide, however, some reaction on nitrogen was anticipated with the Grignard reagent,[11] thus permitting an examination of C- *vs.* N-alkylation as a function of structural and media effects for both the Grignard and alkali metal derivatives of indole. The results of this study, as summarized in Tables I–III,



(1)

1 2 3

TABLE I

EFFECT OF CATION AND SOLVENT ON THE REACTION OF INDOLE SALTS WITH METHYL IODIDE (EQ 1)

Cation	Per cent of methylation on carbon[a] THF	Et$_2$O	Toluene
K	2		13
Na	12	35	60
Li	44	85	91
MgBr	100		100

[a] ±4% calculated as $[\mathbf{3}/(\mathbf{2} + \mathbf{3})] \times 100$; in several experiments traces (<4%) of 1,3-dimethylindole were also found and counted as C-methylation product **3**.

TABLE II

EFFECT OF SOLVENT COMPOSITION ON REACTION OF INDOLYLMAGNESIUM BROMIDE WITH METHYL IODIDE

Equiv of HMPT/InMgBr	Vol % HMPT in THF	Per cent of methylation on carbon[a]
0	0	100
1	12.5	100
2	25	97
2.5	22	62
2.8	22	36
3.1	24	30
3.4	22	9
3.9	30	5
4.4	33	0
6.4	50	0
10.3	100	0

[a] See footnote to Table I.

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TABLE III

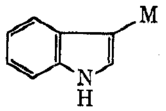
HALIDE EFFECT IN THE REACTION OF INDOLYLMAGNESIUM HALIDES WITH METHYL IODIDE IN THF–HMPT[a]

Halide	Per cent methylation on carbon[b]
Cl	11
Br	37
I	79

[a] 2.8 equiv of HMPT per InMgX. [b] See footnote to Table I.

complement and extend those of Lerner[13] and Cardillo[14] obtained primarily with allyl halides.

For the alkali metals increasing ionic radius or electropositivity leads to less carbon and more nitrogen methylation in the three solvents studied (Table I). This observation is consistent with generalizations from other ambident ion systems,[3-5] including the reactions of indole metal derivatives with allyl halides in THF[13,14] and dioxane,[13] and has been rationalized by assuming that the smaller, less positive cations are more tightly associated with the electronegative end of the ambident ion system, thereby hindering attack at that position. Support for this explanation in the case of indole salts comes from a study of their nmr spectra,[7,9,15] which clearly show these to be nitrogen (**1**) and not carbon (**4**, **5**) derivatives. The magnesium of the indole Grignard reagent must be the most tightly associated of all, since no N-alkylated product is found. The results also indicate that indolyllithium is more associated than the sodium and potassium derivatives. This does not contradict the nmr studies,[9] which indicate that the former is a solvent-separated ion pair in THF while the latter are contact ion pairs, since solvent-separated lithium ion pairs may still be strongly associated in THF.[16]



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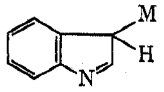

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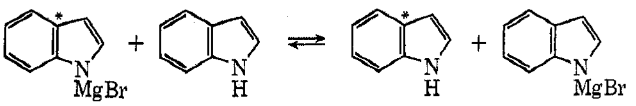
The increasing percentage of C- *vs.* N-methylation of a particular salt as the polarity and cation-solvating ability of the solvent decreases (Table I) again finds analogy in other ambident ion systems,[3-5] including the reactions of indolylpotassium with allyl bromide in THF, dioxane, toluene, and heptane[13] as well as indolylsodium in THF and dimethylformamide.[17] Presumably the more polar solvents are better able to break up the association of the cation with the nitrogen atom, thereby permitting reaction at that site. Once again the magnesium atom of the indole Grignard reagent apparently is held so tightly that N-alkylation is not obtained in either the above reaction solvents or in diethyl ether[13,14] and dibutyl ether.[14] In hexamethylphosphortriamide (HMPT), however, a solvent with a remarkable ability to dissociate organometallic compounds,[18,19] indolylmagnesium bromide gives exclusive N-methylation (Table II). Similar observations have been made[20] for the reaction of the indole and pyrrole Grignard reagents with allyl bromide and in the former case for isoamyl bromide as well.[14] The exchange reaction between the indole Grignard reagent and indole (eq 2) has also been shown to be markedly accelerated in the presence of HMPT.[9] None of these results indicate whether HMPT simply modifies the bulk solvent properties of the media[14] or forms a complex with the Grignard reagent.



(2)

The existence of 2:1 complexes of HMPT and Grignard reagents has been proposed,[21-23] as has one between indolylmagnesium iodide and D_2O.[24] However, Cardillo found that with 2 equiv of HPMT per Grignard reagent (solvent composition unspecified) both isoamyl and allyl bromide still gave predominantly C-alkylation.[14]

The nature of the interaction between HMPT and indolylmagnesium bromide is revealed from a study of the methylation reaction in mixed THF–HMPT solvent systems (Table II). The ratio of C- to N-methylation is clearly related to the equivalents of HMPT per Grignard reagent present and not the bulk composition of the solvent. Below 2 and above 4 equiv of HMPT the position of alkylation is independent of solvent composition, occurring predominantly on carbon in the former situation and on nitrogen in the latter. The region of transition is relatively narrow and suggests the existence of a 2:1 complex of indolylmagnesium bromide and HMPT in which the magnesium is still tightly associated with the nitrogen atom. Additional HMPT dissociates this complex until at 4 equiv no effective hindrance to attack by methyl iodide at the nitrogen atom remains.

In the intermediate solvent composition range (2–4 equiv of HMPT) the C- to N-alkylation ratio should display maximum sensitivity to structural variations in the reactants, thus permitting an examination of these factors. This hypothesis was verified from a study (Table III) which reveals a strong halide effect in the reaction of indolylmagnesium halides with methyl iodide. Significant halide effects have been observed previously[25] but are by no means common. The present results indicate that the magnesium and nitrogen are most tightly associated in the iodide and least in the chloride. This trend could be explained by the increased electronegativity of the latter halogen imparting more ionic character (polarity) to the N–MgX bond, thereby leading to more extensive dissociation

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by the solvent. Alternatively, the nature of the halogen may also effect the Schlenk equilibrium, intermolecular aggregation, or solvent complexation in such a manner as to alter the degree of N–Mg association. A further possibility, suggested by a referee, is that the indolylmagnesium halides and methyl iodide undergo halogen exchange to give indolylmagnesium iodide and methyl halides, which might display a leaving group effect in the observed direction.[12,26] Additional studies are obviously required to determine the cause of this halogen effect as well as other structural effects which may be revealed in mixed HMPT–ether solvent systems.

Experimental Section

Nmr spectra were measured on a Varian A-60 or A-60A spectrometer and the infrared spectra on a Perkin-Elmer 137 instrument. Gas chromatographic analyses were carried out on an Aerograph Autoprep A-700 using a 5 ft × 0.25 in. column of 20% Carbowax 20M on firebrick at 220°.

Chemicals.—THF and ether were distilled from lithium aluminum hydride immediately before use. Toluene was distilled from sodium and HMPT was dried over BaO powder, decanted, and distilled under a nitrogen atmosphere at 84° (2 mm). The magnesium (99.99%) was purchased from A. D. Mackay, Inc., New York, N. Y. Indole (mp 52–53°), 2-methylindole (mp 59–61°), and 3-methylindole (mp 94–96°) were purchased from the Aldrich Chemical Co. and were used without further purification. 1-Methylindole was prepared by the method of Potts and Saxton[27] and purified by elution from a neutral alumina column with petroleum ether (bp 60–90°). 1,3-Dimethylindole was prepared from 3-methylindolyllithium and methyl iodide in HMPT as described below.

General Procedure for the Preparation and Methylation of Indolylmetal Derivatives. A. In THF.—Observing the usual precautions[9] against H_2O and CO_2, a solution of indole in THF was added to a 10% excess of potassium metal, NaH, LiH, or EtMgBr in THF and the mixture was heated to reflux until reaction was complete. A solution of methyl iodide (10% excess) in THF was slowly added and the reaction was allowed to proceed at room temperature until complete as determined from preliminary experiments (from 30 min for the potassium compound to 48 hr for the Grignard reagent).

B. In Ether.—The same procedure as above was followed except that the ether was used in place of THF and MeLi in place of LiH.

C. In Toluene.—With the exception of indolylpotassium, which was synthesized directly in toluene from metallic potassium and indole, the indole derivatives were first prepared in THF as above, dry toluene was added, and the THF was removed by distillation. Methyl iodide in toluene was added to the heterogeneous mixtures and the reaction was allowed to proceed for 6–8 days.

D. In HMPT.—Indolylmagnesium bromide and 3-methylindolyllithium were prepared in ether as described in B, HMPT was added, and the ether was removed by distillation up to 90° at 30 mm. Methyl iodide in HMPT was added and the reaction was carried out for 15 hr at room temperature.

E. In THF–HMPT Mixtures.—*n*-Butylmagnesium chloride, ethylmagnesium bromide, or methylmagnesium iodide were prepared in THF and a solution of indole in THF–HMPT was added so that the desired final solvent composition was obtained. A solution of methyl iodide in THF–HMPT of the same composition was added and the reaction was allowed to proceed at room temperature for 3–45 hr (the more HMPT the faster the reaction). To a first approximation the C- to N-methylation ratio was found to be independant of reaction time, as is also the case with indolylsodium.[17]

F. Work-Up and Analysis.—The reaction mixtures were treated with water (alkali metals) or 5% NH_4Cl (Grignards) and then extracted with ether. After the mixtures were dried and ether was evaporated, the products were collected by preparative glc and identified by a comparison of their nmr and infrared spectra with those of authentic samples. Quantitative analyses were carried out by glc and nmr spectroscopy of the crude reaction mixtures utilizing in the latter case the relative areas of the aromatic (τ 2.3–3.7), 1-methyl (τ 6.3–6.4), and 3-methyl (τ 7.7) resonances. The 1-methyl resonances of 1-methylindole and 1,3-dimethylindole could be cleanly detected in one another's presence. No evidence for the presence of any 2-methylindole was obtained in any of these reactions.

Registry No.—Indole (K salt), 31163-74-3; indole (Na salt), 16982-67-5; indole (Li salt), 18344-49-5; indolylmagnesium bromide, 20356-50-7; methyl iodide, 74-88-4; indolylmagnesium chloride, 35099-77-5; indolylmagnesium iodide, 13884-15-6.

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