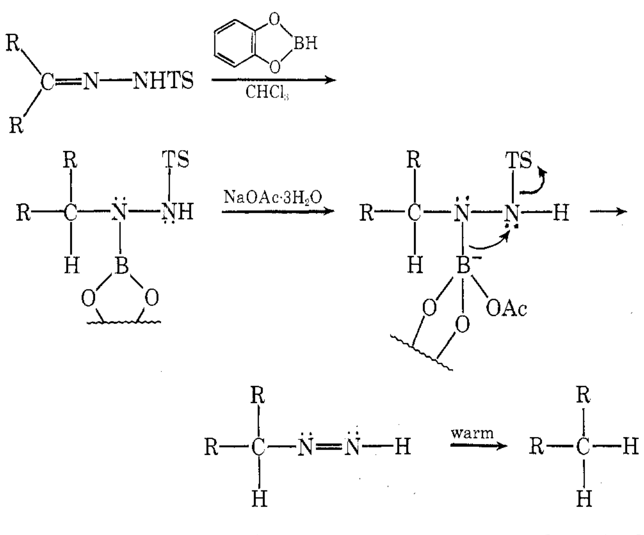
### Scheme II



should permit the reduction of functionally substituted carbonyl compounds.[5,6]

A reasonable mechanism for the reduction is outlined in Scheme II and is based on analogy to known reactions. Thus, it has long been recognized that organoboranes which contain an electronegative substituent $\beta$ to the boron atom are prone to elimination, especially in the presence of nucleophiles.[7,8] Furthermore, diazenes are unstable and decompose to yield alkanes in the presence of proton sources.[9,10]

The reaction appears to be a general one, producing good yields of the reduction products. It depends only on the availability and stability of the tosylhydrazone derivative. Owing to the mildness of the reaction, we feel that it should be applicable to a variety of substituted ketones.[5]

Our results are summarized in Table I.

**Table I**
**Conversion of Ketones to the Corresponding Methylene Derivatives[a]**

| Ketone[a] | Registry no. | Product[b] | Registry no. | Yield, %[c] |
|---|---|---|---|---|
| 2-Octanone | 111-13-7 | Octane | 111-65-9 | 91 (81)[d] |
| Isophorone | 78-59-1 | 3,5,5-Trimethylcyclohexene[e] | 933-12-0 | 41 |
| Cyclohexanone | 108-94-1 | Cyclohexane | 110-82-7 | 92 |
| 2-Methylcyclohexanone | 583-60-8 | Methylcyclohexane | 108-87-2 | 64 |
| Norbornanone | 497-38-1 | Norbornane | 279-23-2 | 63 |

[a] The ketones were first converted to the corresponding tosylhydrazones. [b] Products exhibited physical and spectral parameters in agreement with those of authentic samples. [c] GLC analysis. [d] Isolated yield. [e] Reduction occurs with migration of the double bond.

## Experimental Section[11]

**Materials.** The tosylhydrazones (Table II) were prepared according to the method described by Hutchins et al.[3a]

**General Procedure for Reductions.** The reduction of 2-octanone is representative. The tosylhydrazone of 2-octanone (52.7 mmol, 15.64 g) was dissolved in 105 ml of chloroform at −10°.[12] Catecholborane (58 mmol, 6.31 ml) was added and the hydroboration was allowed to proceed for 20 min. Sodium acetate trihydrate[13] (155 mmol, 21.1 g) was then added and the reaction mixture was brought to a gentle reflux for 1 hr.[14] GLC analysis indicated a 90.8% yield of octane with no evidence for alkene formation. The product was distilled from the reaction mixture, bp 124–127°. The yield of octane was 4.78 g (81%).

**Table II**
**Melting Points of the Tosylhydrazones Utilized**

| Ketone | Registry no. | Mp, °C |
|---|---|---|
| 2-Octanone | 54798-76-4 | 96.5–98 |
| Isophorone | 21195-62-0 | 142–144 |
| Cyclohexanone | 4545-18-0 | 155–158 |
| 2-Methylcyclohexanone | 52826-41-2 | 112–114 |
| Norbornanone | 38397-34-1 | 194–196 |

**Acknowledgment.** We wish to thank the Research Corporation for support of this study.

## References and Notes

(1) See, for example, (a) W. Reusch, "Reduction", R. L. Augustine, Ed., Marcel Dekker, New York, N.Y., 1968, pp 171–211; (b) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 4.

(2) For example the strongly basic conditions required in the Wolff-Kishner reductions preclude the incorporation of functionality such as amide, ester, cyano, halogen, etc. A similar situation holds for the Clemmensen reduction.

(3) See, for example, (a) R. O. Hutchins, C. Milewski, and B. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973); (b) L. Caglioti, *Tetrahedron*, **22**, 487 (1966).

(4) Another useful route involves the reduction of the ketone to the corresponding alcohol, transformation of the alcohol to a suitable leaving group, and displacement of that group with hydride reagents: C. W. Jefford, D. Kirkpatrick, and F. Daley, *J. Am. Chem. Soc.*, **94**, 8905 (1972).

(5) Control experiments indicated that catecholborane did not react with *n*-octyl bromide and acetonitrile after 2 hr under the conditions reported. Even more surprising, 1-octene was not hydroborated after 4 hr by catecholborane at 0° in $CHCl_3$.

(6) Boron hydrides react extremely rapidly with carbonyl groups and their derivatives. See H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972, pp 227–251.

(7) D. J. Pasto and R. Snyder, *J. Org. Chem.*, **31**, 2777 (1966).

(8) H. C. Brown and R. M. Gallivan, *J. Am. Chem. Soc.*, **90**, 2906 (1968).

(9) C. E. McKenna and T. G. Traylor, *J. Am. Chem. Soc.*, **93**, 2313 (1971).

(10) It should be noted that the reduction of isophorone occurs with migration of the double bond. This phenomenon has been cited as evidence against a mechanism involving carbanion formation. See, for example, ref 3a.

(11) Melting points and boiling points are uncorrected. NMR spectra were obtained using a Varian Associates A-60 instrument.

(12) Methylene chloride gives similar results.

(13) Sodium acetate induces the decomposition of the intermediate **2**. The product is obtained in lower yields if no acetate is added.

(14) The product may also be obtained in an identical yield by stirring the mixture at room temperature for 24 hr.

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# Reaction of *o*-Chlorotoluene with Alkali Amides. A Study of the Metal Effect in Benzyne Reactions

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Since the pioneering work by Wittig[1] and Roberts[2] on the chemistry of arynes, extensive research has been done in this area. A monograph which summarizes much of this work has appeared.[3] Roberts[4] and coworkers have observed that *the reaction of o-chlorotoluene with potassium amide yields o- and m-toluidine in approximately equal amounts*. This result is surprising, since one would expect the inductive effect of the methyl group to operate in such a way as to make the amount of the ortho isomer which is formed much greater than that of the meta isomer. For example, treatment of *p*-chlorotoluene with potassium amide in liquid ammonia yields *m*- and *p*-toluidine in a 3:2 ratio, meta to para, respectively. Roberts suggested that the low yield of the ortho isomer may be due to the operation of a steric factor. It is conceivable that the methyl group offers some steric hindrance to the attacking species, be it ammonia or amide ion. Additionally, Roberts et al.[4] have observed that *the reaction of o-chlorotoluene with sodium amide in liquid ammonia yields o- and m-toluidine in a ratio of 2:1.* If one is to argue that steric hindrance of the methyl group makes it difficult for the carbon atom which is ortho to be attacked by amide ion or ammonia, it is hard to offer a reasonable explanation for the difference in the isomer distribution which is obtained by the action of sodium and potassium amide with *o*-chlorotoluene in liquid ammonia.

The change in isomer distribution may be linked to the amide's counterion. With this in mind, three experiments were conducted, viz., the reaction of *o*-chlorotoluene with lithium, sodium, and potassium amide. The results are listed in Table I.

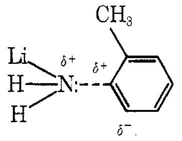
**Table I**
**Reactions of *o*-Chlorotoluene with Alkali Amides, $MNH_2$**

| M | % *o*-toluidine | % *m*-toluidine | Ratio, *o*-:*m*- |
|---|---|---|---|
| Li | 73 | 27 | ~3:1 |
| Na | 67 | 33 | 2:1 |
| K | 54 | 46 | ~1:1 |

In this study the isomer distributions were determined by vapor phase chromatography. Reference to Table I shows that as the metal is varied from lithium to sodium to potassium, the percentage of *o*-toluidine decreases in this order. A possible explanation for this trend follows. It is probable that the metal cation–amide anion bond has some degree of covalency. The extent of covalent bonding should increase as the metal cation is varied from potassium to sodium to lithium since the ionic radii of the metal cations are as follows: $Li^+$, 0.6 Å; $Na^+$, 0.95 Å; and $K^+$, 1.22 Å.[5] Thus lithium ion, having a greater concentration of charge, would have an inherently greater polarizing effect upon the amide ion than would sodium or potassium. This would lead to greater covalent bonding in lithium amide than in sodium or potassium amide.

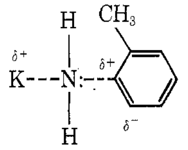
The differences in the basicities of the alkali amides is also a basis for the contention that there are differences in covalent bonding in alkali amides. Leake[6] found that the reaction of sodium and potassium amide with chlorobenzene gives fair yields of aniline whereas the same reaction with lithium amide gives no aniline and results in a high recovery of chlorobenzene. Since Roberts and coworkers[4] have been able to show that the rate-determining step of the benzyne reaction is the abstraction of a benzenoid hydrogen atom by a strong base, it is possible that Leake's results may be due to differences of basicity of the alkali amides. It is likely that the degree of covalency in the alkali amide series is related to their basicity. The more the electron pair of the basic nitrogen is called on for bond formation, the less it will be available for acid–base reactions. Thus lithium amide would be the least basic, since it probably has the highest degree of covalency.

If the assumption is made that the alkali amides have different degrees of covalency in liquid ammonia, then the results become intelligible on the basis of steric repulsion in the transition state. The transition state is pictured as involving the bond formation between the 2-toluyne and the lone pair of electrons on the nitrogen atom of the alkali amide. The geometry of the metal amide is dependent upon the degree of covalency of the metal–nitrogen bond. The more covalent the metal–nitrogen bond is, the more $sp^3$ character it will have. Conversely, the less covalent character the metal–nitrogen bond has, the more sp character it will have. The proposed transition state of the addition of lithium amide to the toluyne is represented by **1**. It is seen that there is very little steric repulsion between the methyl group of 2-toluyne and the hydrogen atoms of the amide ion because the geometry of the amide ion is probably much closer to a tetrahedron ($sp^3$ hybridization) than to a linear molecule (sp hybridization) owing to the increased covalency of the lithium amide species. Thus, the ortho isomer can be formed without much difficulty, since there is little interaction between the methyl group and the hydrogen atoms of the amide ion.



**1**

However, since potassium amide is not as covalent a compound as lithium amide, it probably has a larger degree of sp character and thus there will be steric repulsion between the methyl group and the amide ion hydrogen atoms. The proposed transition state for the addition of potassium amide to 2-toluyne is shown in **2**.



**2**

Thus, it appears likely that the metal associated with the alkali amide makes an important contribution to the observed results. The ability of the metal to coordinate with the amide ion in varying degrees probably controls the geometry of the transition state. It should also be pointed out that the nucleophilicity (because of basicity and solvation effects) increases in the order $LiNH_2 < NaNH_2 < KNH_2$. Furthermore, it is known[7] that the species of greatest nucleophilicity ($KNH_2$ is this case) results in the least selectivity, which in the present experiments would oppose the steric effect and would agree with the results reported in Table I.

## Experimental Section

**Vapor Phase Chromatography.** The isomer distribution analyses were performed with a Kromo-Tog K-2 vapor phase chromatograph. Good resolution of the *o*- and *m*-toluidine mixture (retention times: *o*-toluidine, 26.5 min; *m*-toluidine, 30.5 min) was obtained by use of a column containing 10% UCON HB-2000 on Fluropak-80 using helium as the carrier gas at a flow rate of 80 ml/min, a detector voltage of 170 mA, and a temperature of 130°.

**Reaction of *o*-Chlorotoluene with Sodium Amide in Liquid Ammonia.** Liquid ammonia (500 ml) and a few crystals of ferric nitrate were added to a 1-l., three-neck, round-bottom flask equipped with a slip-seal stirrer, Dry Ice condenser, and a glass plug. Sodium (4.6 g, 0.2 mol) was added over a 10-min period. After the discharge of the blue color 12.7 g (0.1 mol) of *o*-chlorotoluene was added dropwise over a 15-min period. The reaction was allowed to continue for 15 min. Then 13.5 g (0.25 mol) of ammonium chloride was added. The Dry Ice condenser was replaced by a West condenser, 150 ml of ether was added, and the ammonia was removed by heating on a water bath. The reaction mixture was poured onto an ice–hydrochloric acid slurry and was extracted with three 100-ml portions of ether. The residual aqueous phase was made basic with sodium carbonate and extracted with three 100-ml portions of ether. The combined ether extracts were dried over sodium sulfate. After evaporation of the solvent, a liquid residue (6.4 g, 60%) containing a mixture of *o*- and *m*-toluidine was obtained. The mixture consisted of 67% *o*-toluidine and 33% *m*-toluidine as determined by vapor phase chromatographic analysis. In addition 4.0 g (31.5%) of *o*-chlorotoluene, bp 157–159° (760 mm), was recovered.

**Reaction of *o*-Chlorotoluene with Lithium Amide in Liquid Ammonia.** Using the same procedure as that which was employed with sodium amide and *o*-chlorotoluene, the reaction of lithium amide (0.2 mol) and *o*-chlorotoluene (12.7 g, 0.1 mol) gave upon the removal of the solvent 0.5 g (2%) of a mixture containing 73% *o*-toluidine and 27% *m*-toluidine. In addition, 11.5 g (90.5) of *o*-chlorotoluene, bp 157–159° (760 mm), was recovered.

**Reaction of Potassium Amide and *o*-Chlorotoluene in Liquid Ammonia.** The reaction of potassium amide (0.20 mol) and *o*-chlorotoluene (12.7 g, 0.10 mol) gave upon removal of the solvent 6.7 g (63%) of a mixture containing 54% *o*-toluidine and 46% *m*-toluidine. Also, 3.9 g (30.7%) of *o*-chlorotoluene, bp 156.5–159° (760 mm), was recovered.

**Registry No.**—Lithium amide, 7782-89-0; sodium amide, 7782-92-5; potassium amide, 17242-52-3; *o*-toluidine, 95-53-4; *m*-toluidene, 108-44-1; *o*-chlorotoluene, 95-49-8.

## References and Notes

(1) G. Wittig, *Naturwissenschaften,* **30,** 696 (1942).
(2) J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith, and C. W. Vaughan, *J. Am. Chem. Soc.,* **75,** 3290 (1953).
(3) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes", Academic Press, New York, N.Y., 1967.
(4) J. D. Roberts, C. W. Vaughn, L. A. Carlsmith, and D. A. Semenow, *J. Am. Chem. Soc.,* in press.
(5) T. Moeller, "Inorganic Chemistry", Wiley, New York, N.Y., 1958, p 575.
(6) W. W. Leake, Ph.D. Thesis, University of Pittsburgh, 1958, p 11.
(7) See ref 3, p 149.

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# The Imidazole–Formaldehyde Reaction. Formation of 1-Imidazolemethanol

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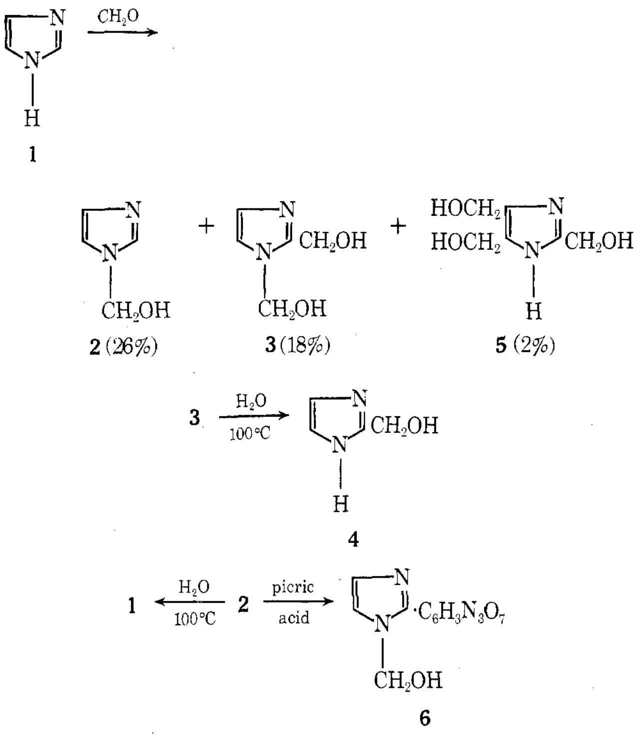
Spectral,[1,2] NMR,[3] and potentiometric[4] studies have shown the formation in solution of 1-imidazolemethanol (1) from the reaction of imidazole and formaldehyde, although 1 was not isolated. These studies show that only one nitrogen is involved in methylol formation in basic media.[3,4] In an acid medium,[3,4] both ring nitrogens may be hydroxymethylated. Jones[5] has shown that 1-benzylimidazole forms the 2-hydroxymethyl derivative in nearly quantitative yield in a sealed tube reaction between formaldehyde and 1-benzylimidazole.

From a sealed tube reaction between imidazole and formaldehyde at 120–130°, a liquid fraction was isolated by chromatography of the crude product. This material gave a picrate derivative (6) corresponding to that of a methylolated imidazole. NMR data on the methylolated imidazole indicates the presence of the –$NCH_2O$– protons by a singlet at δ 5.39 (in $D_2O$), in agreement with the values reported by Dunlop, Marini, Fales, Sokoloski, and Martin[3] (δ 5.40 in $D_2O$). Boiling this material in water yields imidazole. These data indicate that the liquid is 1-imidazolemethanol (2).

### Scheme I



From this same reaction there was obtained a white, crystalline solid (mp 126–127°) which appears to be 1,2-bis(hydroxymethyl)imidazole (3). NMR data on this material also show the presence of an $NCH_2O$– methylene group (NMR peak at δ 5.47 in $D_2O$) as well as a methylene group (NMR peak at δ 4.75 in $D_2O$) at the 2 position.

A small amount of a second white, crystalline material (mp 158–159°) was also isolated. Elemental analysis and NMR data indicate that the material is 2,4,5-tris(hydroxymethyl)imidazole (5).

Table I summarizes the NMR data on the products of this reaction.[7] Scheme I summarizes the principal reactions.

## Experimental Section

Ir spectra were obtained using a Beckman Model 10 grating ir spectrophotometer with potassium bromide cells. Solids were pressed into 1% KBr pellets. NMR spectra, graciously run by Dr.

Table I
Proton Chemical Shifts for Imidazole Derivatives[a–c]

| | Proton bands, ppm | | | |
|---|---|---|---|---|
| Compd | $C_2$ | $C_4$, $C_5$ | –$NCH_2O$– | –$CCH_2O$ |
| 2-Imidazolemethanol[c] | | 7.06 (s) | | 4.64 (s) |
| 1,2-Bis(hydroxymethyl)-imidazole[c] | | 7.05 (bs) | 5.47 (s) | 4.75 (s) |
| 1-Imidazolemethanol[c] | 7.70 (bs) | 7.07 (bs) | 5.39 (s) | |
| 2,4,5-Tris(hydroxymethyl)-imidazole[c,d] | | | | 4.57 (bs),[c]<br>4.50, 4.30[d] |

[a] Legend to symbols: s, singlet; bs, broad singlet. [b] All chemical shifts are reported in parts per million (δ). [c] $D_2O$ solvent. [d] $CH_3OD$ solvent.