

GEORGIA INSTITUTE OF TECHNOLOGY

OFFICE OF RESEARCH ADMINISTRATION

Date: 7 November 1969

RESEARCH PROJECT INITIATION

Project Title: Organometallic Compounds: Composition in Solution, Mechanisms and Stereochemistry of Reaction

Project No.: B-1572 (G-33-614)

Project Director: Dr. Eugene C. Ashby

Sponsor: National Science Foundation

Agreement Period: From 1 November 1969 until 31 October 1970

Type Agreement: Grant No. GP-14795

Amount: \$40,000 NSF Funds (B-1572)
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\$55,991 Total Budget

Grant Administrator

Dr. Donald A. Speer, Director
Chemical Dynamics Program
National Science Foundation
Washington, D.C. 20550

Reports Required

Annual - 3 Oct70
Reprints - As they occur
Final - Upon completion of project

NOTE: Continuation of B-1515

Assigned to: School of Chemistry

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GEORGIA INSTITUTE OF TECHNOLOGY
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RESEARCH PROJECT TERMINATION

Date: 15 September 1972

Project Title "Organometallic Compounds: Composition in Solution, Mechanisms,
and Stereochemistry of Reaction"

Project No: G-33-614

Principal Investigator: Dr. E. C. Ashby

Sponsor: National Science Foundation

Effective Termination Date: April 30, 1972

Clearance of Accounting Charges: All charges have cleared

Grant/Contract Closeout Actions Remaining:

Assigned to: School of Chemistry

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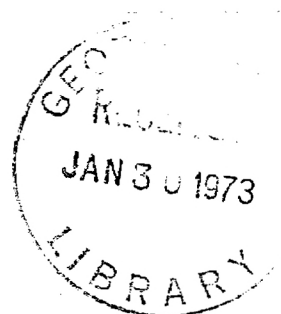
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G-33-617



Name of Institution: Georgia Institute of Technology

Name of Principal Investigator: E. C. Ashby

Grant Number: GP-14795

Starting Date: November 1, 1969

Completion Date: October 31, 1971

Grant Title: "Organometallic Compounds.
Composition in Solution, Mechanisms
and Stereochemistry of Reaction".

Brief Description of Research and Results

During the past two years of this grant period nmr, molecular association, and infrared studies concerning the composition of Grignard reagents and organocadmium reagents in ether solvents have been completed and the results published. The results are reported in detail in publications 1, 13 and 18 listed in the section entitled, "Publication of Work Supported by NSF Since Last Report Period". We are quite satisfied with the outcome of this work and plan no further studies. In May of 1971 we were invited to present a plenary lecture on the "Composition of Grignard Reagents" at the national meeting of the French Chemical Society in Lyon, France. After this lecture we were awarded the "Lavoisier Medal" for our contributions in the area of Grignard Reagent structure elucidation. All of our research in this area has been supported by NSF, a fact which we gratefully acknowledged in Lyon and also acknowledge at this time.

Our main efforts more recently are concerned with mechanisms and stereochemistry of organometallic alkylation reactions. We have finally arrived at a successful solution to the major problems concerned with Grignard reagent addition to ketones and nitriles. We have determined the reaction order of the Grignard reagent directly and thus the controversy concerning this aspect of the problem should be settled. Although earlier we proposed the reaction to be second order in Grignard reagent and since have received considerable support for this position, we have unequivocally found that the reaction is first order in Grignard reagent. The data justifying our earlier conclusion is good data because

it can and has been repeated. The conclusions drawn based on this data are clearly valid. The problem was that Grignard reagents prepared with triply sublimed magnesium have ppm impurities that affect the reaction rate enough to give misleading data. When we obtained some very high purity single crystal magnesium, we were able to prepare Grignard reagents of sufficient purity such that the kinetic data obtained were not influenced by any of the impurities. Since no one has previously observed the order of the Grignard reagent directly, it would seem that the present data now resolves that problem. We have found that both R_2Mg and $RMgX$ react in alkylation reactions. The reaction is first order in R_2Mg and $RMgX$ species with R_2Mg species reacting about 10 times faster than $RMgX$ species, however, there are about 20 $RMgX$ molecules for every molecule of R_2Mg . The rate of reaction of $RMgX$ species was determined by adding sufficient MgX_2 to the Grignard reagent so as to shift the Schlenk equilibrium completely in the direction of $RMgX$. Rates of R_2Mg were determined by simply studying the kinetics of the R_2Mg compound with ketone or nitrile. Although there is still about 6 months - 1 year work left in this study, it is clear that we should complete this study by the end of the next report period.

We have completed kinetic studies concerning the reaction of $(CH_3)_3Al$ with benzophenone in benzene and ether. The purpose of this study was to obtain thermodynamic parameters (ΔS^\ddagger , ΔG^\ddagger , ΔH^\ddagger) for this reaction in an attempt to equate the values of the thermodynamic functions to the nature of the transition state. For example, ΔS^\ddagger should be significantly different for a 4-center transition state as compared

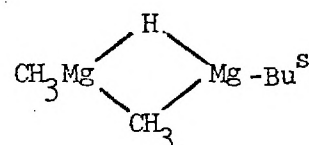
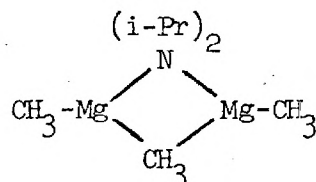
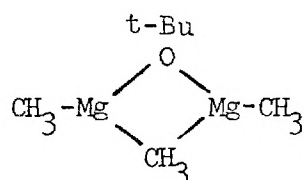
to a 6-center transition state. We have felt that the determination of ΔS^\ddagger for organometallic reactions (alkylation, reduction, etc.) may enable one to determine the nature of the transition state. We have been successful through this study in obtaining some very important information about the transition state in organometallic alkylation reactions. For example, it appears that although a complex is formed initially between RM and ketone in the alkylation reaction, the complex dissociates prior to reaction to form the reactive intermediate in a solvent cage. The data appears to be convincing. So far all 4-center transition states in benzene or Et_2O involving R_3Al alkylation reactions have a ΔS^\ddagger value of about -10 eu whereas 6-center transition states have a ΔS^\ddagger value about -20 eu. Data of this type need to be interpreted with caution in terms of deciding whether a 4-center or 6-center transition state is involved, however, it is clear that such information does reveal a solvent cage intermediate.

The importance of reaction mechanisms and pictures of transition states is not only in the understanding of these fundamental reactions, but more importantly what can be done with this understanding in terms of manipulating the reaction in a more specific way. It is our hope that a better understanding of organometallic alkylation reactions will allow greater developments in the utility of these reagents with respect to stereoselectivity. Simultaneous with our mechanistic studies we have been carrying out fundamental stereochemical evaluation studies in an attempt to evaluate both old and new organometallic alkylating agents. We have been applying the new mechanistic concepts to the stereochemical

studies and have made a very unique finding. When 4-t-butylcyclohexanone is allowed to react with Me_3Al in 1:1 ratio in benzene, equatorial attack by the methyl group takes place to the extent of about 75%. On the other hand, when the Me_3Al :ketone ratio is 2:1, attack is approximately 90% axial. Thus the stereochemistry was completely changed by a variation of the stoichiometry; a result which we predicted earlier. This result is not surprising since we had previously shown that the reaction of Me_3Al and benzophenone proceeds through a 4-center transition state when the reactants are in 1:1 ratio and a 6-center transition state when the reactants are in 2:1 ratio. In an attempt to understand this reaction completely we have carried out the above reactions in benzene, hexane, diphenyl ether, diethyl ether, tetrahydrofuran and triethylamine. We have studied the stereochemistry of alkylation reactions using other ketones in addition to 4-t-butylcyclohexanone such as 2-methylcyclohexanone, 3,3,5-trimethylcyclohexanone, camphor and norcamphor. In addition, we have also studied the alkylation of the above ketones with RMgX compounds where X = halogen and alkoxy groups. The RMgOR' compounds studied are $\text{CH}_3\text{MgOR}'$ where $\text{R}' = \text{n-Pr, i-Pr, t-Bu, Ph}$. The work so far is incomplete, however, it is clear that this broad, fundamental approach to stereoselective alkylation has already been fruitful and hopefully will eventually lead to a clear concept of the important factors involved in determining the stereochemistry of an alkylation reaction.

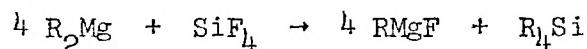
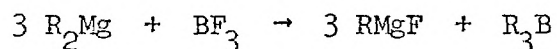
During the grant period, we have described in the literature the first example of a stable mixed bridge organometallic compound in solution. The observation of this stable mixed alkoxy-alkyl compound also provided a

more detailed understanding of the mechanism of benzophenone alkylation by Me_3Al . We have now found that stable mixed bridge organomagnesium systems also exist. An example of a stable alkoxy-alkyl, dialkylamino-alkyl and hydrogen-alkyl bridge system is shown below.



We are attempting to correlate mixed bridge systems to some of the complications encountered in describing the latter stages of the reaction of Grignard compounds with ketones and nitriles.

During the grant period we have also studied methods of preparation of alkyl and arylmagnesium fluorides by the reaction of R_2Mg compounds with metal halides. Very satisfactory methods of preparation were found using BF_3 and SiF_4 as the source of fluorine.



Publication of Work Supported by NSF During the Grant Period

1. F. Walker and E. C. Ashby, "Composition of Grignard Compounds. VI. In Diethylether and Tetrahydrofuran," J. Am. Chem. Soc., 91, 3845-3850. (1969).
2. E. C. Ashby, Redistribution of Group II Organometallic Compounds," Ann. N. Y. Acad. Sci., 159, 131-142 (1969).
3. E. C. Ashby, J. Laemmle and G. Parris, "Stable Mixed Alkoxy-Alkyl Bridge Organoaluminum Systems," J. Organometal. Chem. 19, 24 (1969).
4. E. C. Ashby, "Organomagnesium Chemistry," Organometal. Chem. Rev., 5, 225 (1969).
5. E. C. Ashby, "Organoberyllium Chemistry," Organometal. Chem. Rev., 5, 218 (1969).
6. E. C. Ashby, "Organocalcium Chemistry," Organometal. Chem. Rev., 5, 268 (1969).
7. E. C. Ashby, G. Parris and Frank Walker, "Direct Nuclear Magnetic Resonance Observation of Me_2Mg and MeMgBr in a Diethyl Ether Solution of Methylmagnesium Bromide," Chem. Comm., 1464 (1969).
8. E. C. Ashby, S. Yu and R. Beach, "The Preparation of Alkylmagnesium Fluorides," J. Am. Chem. Soc., 92, 433 (1970).
9. E. C. Ashby and R. C. Arnott, "The Preparation of Stable Complexes of Magnesium Aryls and Alkyls," J. Organometal. Chem. 21, 29-31 (1970).
10. E. C. Ashby and Simon H. Yu, "Organometallic Reaction Mechanisms. IV. The Mechanism of Ketone Reducation by Aluminum Alkyls," J. Org. Chem., 35, 1034 (1970).
11. E. C. Ashby, F. Walker and H. M. Neumann, "Concerning the Reaction of Methylmagnesium Bromide with Benzophenone," Chem. Comm. 330 (1970).
12. E. C. Ashby, "Grignard Reagents," Encyclopaedia Britannica, 926-929 (1970).
13. G. E. Parris and E. C. Ashby, "The Composition of Grignard Compounds. VII. The Composition of Methyl- and Tertiary-Butylmagnesium Halides and Their Dialkylmagnesium Analogs in Diethyl Ether and Tetrahydrofuran as Inferred from NMR Spectroscopy," J. Am. Chem. Soc., 93, 1206 (1971).

14. E. C. Ashby and J. A. Nackashi, "A New and Convenient Method for the Preparation of Alkyl and Aryl Fluoro Grignard Compounds. The Reactions of Magnesium Alkyls and Metal Fluorides," J. Organometal. Chem., 24, C17 (1970).
15. E. C. Ashby, "Annual Survey of Organometallic Chemistry. Magnesium," Organometal. Chem. Rev., 6, 73 (1970).
16. E. C. Ashby, "Annual Survey of Organometallic Chemistry. Beryllium," Organometal. Chem. Rev., 6, 67 (1970).
17. E. C. Ashby, "Annual Survey of Organometallic Chemistry. Calcium," Organometal. Chem. Rev., 6, 211 (1970).
18. J. R. Sanders and E. C. Ashby, "The Composition of Organocadmium Compounds in Diethyl Ether Solvent. II. The Organocadmium Reagent," J. Organometal. Chem. 25, 277 (1970).
19. E. C. Ashby and Simon H. Yu, "Stereoselective Alkylation Reactions. I. Organomagnesium and Organoaluminum Addition to 4-t-Butylcyclohexanone. Unusual Stereoselectivity Involving Trimethylaluminum Alkylation in Benzene," Chem. Comm., 351 (1971).

Publications in Press

1. E. C. Ashby and Simon H. Yu, "Composition of Grignard Compounds. VIII. Alkylmagnesium Fluorides," J. Organometal. Chem., (in press).
2. E. C. Ashby and Simon H. Yu, "Alkylmagnesium Fluorides. II. Preparation and Properties," J. Org. Chem., (in press).
3. J. Iaemmle, E. C. Ashby and H. M. Neumann, "Organometallic Reaction Mechanisms. V. The Mechanism of Dialkylmagnesium Addition to Ketones," J. Am. Chem. Soc., (in press).
4. E. C. Ashby, J. Iaemmle and H. M. Neumann, "Direct Evidence for the Reaction Species and Their Reaction Orders in the Addition Reaction of Methylmagnesium Bromide Grignard to 2-Methylbenzophenone," J. Am. Chem. Soc., (in press).

Theses

Joseph Laemmle, "Mechanisms of Organometallic Alkylation Reactions," Ph.D. Thesis, Georgia Tech, 1971.

Simon Yu, "Synthesis and Reaction Mechanisms in Organoaluminum and Organo-magnesium Chemistry," Ph.D. Thesis, Georgia Tech, 1971.

Inventions or Discoveries

"Synthesis of Fluoro Grignard Reagents", Patent applied for by E. C. Ashby. Royalty free patent rights provided to the United States Government.

Scientific Collaborators Connected with Grant

Mr. Simon Yu (Ph.D. Student)

Mr. Joseph Laemmle "

Mr. John Nackashi "

Mr. John Oliver "

Dr. Henry Neumann (Professor of Chemistry)

E. C. Ashby

September 28, 1972