Stereochemistry of the Addition of Methylcadmium and Methylzinc Reagents to 4-*t*-Butylcyclohexanone

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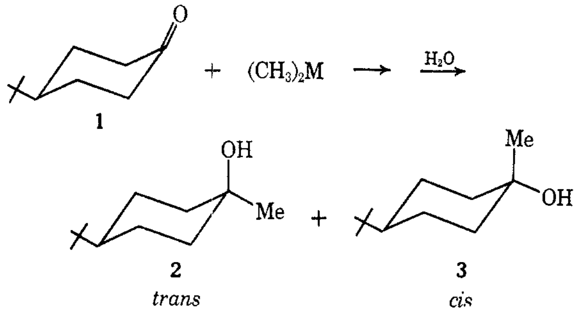
Reactivity and stereochemistry were used as criteria for comparison of the methyl reagents of Mg, Cd, and Zn toward 4-*t*-butylcyclohexanone. Characteristic differences in the behavior of all three were observed as a function of concentration and halide ion present. The greater amount of axial attack by Cd and Znre agents, compared with Mg reagents, is rationalized as arising from tighter, four-center transition states for the first two. The results fit a steric-approach control consistent with models proposed by Marshall and Felkin.

Although organocadmium and -zinc compounds are well known as reagents for the synthesis of ketones, very little has been established about their structures in solution. The mechanism of their reaction with acid chlorides, anhydrides, and other carbonyl groups is not understood. The observation by Kollonitsch[2] in 1960, that *in situ* organocadmium reagents react rapidly and efficiently with simple carbonyl compounds, served to dispel the notion[3] that these reagents are significantly less reactive toward aldehydes and ketones than their Grignard counterparts. In turn, this has required a reassessment of the scope and mechanism of the reactions of cadmium and zinc reagents with the whole array of functional groups, which are attacked by Grignard and lithium reagents: aldehydes, ketones, esters, amides, nitriles, nitro groups, etc.

One approach to an understanding of the reactions of cadmium and zinc reagents with various functional groups is to compare their behavior with that of the Grignard reagent. In view of the careful studies of the stereochemistry of the addition of methyl Grignard reagents to 4-*t*-butylcyclohexanone (**1**) reported in 1962[4] and 1965,[5] we have undertaken a detailed investigation of the same reaction where the additive reagent is a methylcadmium or methylzinc compound. As shown in eq 1, the reaction is expected to lead to a mixture of *trans*- and *cis*-[6]methyl-4-*t*-butylcyclohexanols (**2** and **3**), in which the alcohol function is, respectively, axial and equatorial.



(1)

M = Li, Mg, Cd, Zn

From previous work,[4,5] it has been convincingly demonstrated that magnesium reagents attack 4-*t*-butylcyclohexanone from the less hindered side with preferential formation of the thermodynamic product, the *trans* alcohol. Additon of hydride from a variety of metal hydride reagents, on the other hand, occurs predominantly *via* axial approach. These observations have led to two divergent views on the controlling factors in addition: "steric-approach" *vs.* "product-development" control.[7] Marshall and Carroll[8] proposed a model for the transition state, by which one could estimate semiquantitatively the magnitude of the steric effect on the basis of the transition state bond lengths. From this model, it has been rationalized that 1,3 (diaxial) interactions are less important than 1,2 (equatorial axial) interactions in the formation of a C–H bond, while, with the longer C–C bond being formed during Grignard addition, the importance of the interactions is reversed. A corollary of this hypothesis is the prediction that, within certain rather narrow limits of bond distances, the amount of axial attack will increase as the transition-state bond distance decreases.

Cherest and Felkin[9] have pointed out the importance of considering torsional effects as well. Recent results on hydride reduction[10] can best be explained with the Mashall and Felkin models.

Results

Results are compiled in Tables I–III. Experiments were carried out in such a way that the number of transferable methyl groups was held constant. Thus, for 1 mol of ketone, there were introduced 2 mol of $(CH_3)_2Cd$ or $(CH_2)_2Zn$; 4 mol of CH_3MgX, CH_3CdX, or CH_3ZnX.[11] In a few instances olefin formation, caused by the presence of zinc or cadmium salts, was observed, but the amount was well below the level required to affect the ratio of alcohols (See Experimental Section).

Several general observations can be noted from inspection of the tables.

1.—On the basis of the values of unchanged ketone in comparable experiments, the following reactivity series can be written: CH_3Li, $CH_3MgX > (CH_3)_2Cd > (CH_3)_2Zn > CH_3CdX$, CH_3ZnX.

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(1) (a) National Defense Education Act Fellow, 1966–1969. (b) National Science Foundation Trainee, 1966–1969.

(2) J. Kollonitsch, *J. Chem. Soc., A*, 453 (1966).

(3) H. Gilman and J. F. Nelson, *Rec. Trav. Chem.*, **55**, 518 (1936).

(4) W. J. Houlihan, *J. Org. Chem.*, **27**, 3860 (1962).

(5) H. O. House and W. L. Prespess, *ibid.*, **30**, 301 (1965).

(6) The *trans* and *cis* notation is in reference to methyl and *t*-butyl groups.

(7) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

(8) J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30**, 2748 (1965).

(9) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968); M. Cherest and H. Felkin, *ibid.*, 2205 (1968).

(10) E. L. Eliel and Y. Senda, Abstracts of 156th National Meeting of the American Chemical Society, Atlantic City, N. J., 1968, ORGN-138; J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968).

(11) Under these conditions the reaction can be considered to involve R_2M or RMX but not RMOR′. In separate experiments it was demonstrated that methylcyclohexyloxycadmium (and -zinc), $CH_3MOC_6H_{11}$, was considerably less reactive than $(CH_3)_2M$ toward cyclohexanone.

TABLE I

REACTION OF *in situ* ORGANOMETALLIC REAGENTS IN ETHER WITH 4-*t*-BUTYLCYCLOHEXANONE

Entry	Reagent	Concn, *M*	Unchanged ketone, $\%^a$	*trans* alcohol, $\%^b$	*trans/cis*
1	CH_3MgI	0.8	1	53.8^c	1.2
2	CH_3MgI	0.1	1	61.7	1.6
3	CH_3MgBr	0.8	1	61.8^c	1.6
4	CH_3MgBr	0.1	1	68.4	2.2
5	CH_3Li	0.8	1	63.7^c	1.8
6	$(CH_3)_2Cd(I,I)^d$	0.4	7.5	51.6^e	1.1
7	$(CH_3)_2Cd(Br,Br)$	0.4	50	51.5^e	1.1
8	$(CH_3)_2Cd(I,Br)$	0.4	5	53.5	1.2
9	$(CH_3)_2Cd(Br,I)$	0.4	5	53.1^e	1.1
10	$(CH_3)_2Cd(Br,Cl)$	0.4	55	50.2	1.0
11	$(CH_3)_2Cd(I,Cl)$	0.4	5	42.4^e	0.74
12	$(CH_3)_2Cd(I,Cl)$	0.9	5	40.7	0.69
13	$(CH_3)_2Cd(CH_3Li,CdI_2)$	0.4	99		
14	$(CH_3)_2Cd(CH_3Li,CdBr_2)$	0.4	99		
15	$CH_3CdX(I,Cl)$	0.8	90	37.7^e	0.61
16	$(CH_3)_2Zn(I,I)$	0.3	20	46.5	0.87
17	$(CH_3)_2Zn(Br,Br)^f$	0.3	85	44.4^e	0.80
18	$(CH_3)_2Zn(I,Br)$	0.3	20	46.8^e	0.88
19	$(CH_3)_2Zn(Br,Cl)$	0.3	97	44	0.8
20	$(CH_3)_2Zn(I,Cl)$	0.3	60	38.3	0.62
21	$(CH_3)_2Zn(I,Cl)$	0.1	65	38.7	0.63
22	$(CH_3)_2Zn(CH_3Li,ZnI_2)$	0.3	99		
23	$CH_3ZnI(I,I)$	0.3	90	49.0^e	0.96
24	$CH_3ZnX(I,Cl)$	0.3	99		

[a] $\% = \text{area}_{\text{ketone}}/(\text{area}_{\text{ketone}} + \text{area}_{trans + cis \text{ alcohols}}) \times 100$. [b] Normalized %: % *trans* + % *cis* = 100; yield of alcohols = 100 − % ketone. [c] For comparable results at similar concentrations see ref 4. [d] Halogens in parentheses indicate, respectively, the methyl halide from which RMgX was prepared and the metal halide used for the exchange (eq 2). [e] Result of at least two separate runs with a maximum deviation of ±1%. [f] Reaction time was 8 hr, and 3 molar equiv of zinc reagent was used.

2.—Reactivity of the reconstituted reagent is lower than that of the comparable *in situ* reagent and found to be dependent on the amount of halide present.

3.—Reagents were more reactive to addition when MgI_2 rather than $MgBr_2$ was present.

4.—Reactivity of cadmium and zinc reagents prepared from methyllithium was nil.

5.—Monomeric CH_3MgX (0.1 *M*) gives more *trans* alcohol, resulting from equatorial attack, than the corresponding associated species (0.8 *M*). At the same concentration, CH_3MgBr shows a greater preference for equatorial attack than does CH_3MgI. By contrast, there is no appreciable change in reactivity or stereochemistry when the concentration of $(CH_3)_2Cd(I,Cl)$ is increased from 0.4 *M* to 0.9 *M*, or when the concentration of $(CH_3)_2Zn(I,Cl)$ is decreased from 0.3 *M* to 0.1 *M*.

6.—Preference for axial attack follows the series: $(CH_3)_2Zn > (CH_3)_2Cd > CH_3MgX$.

7.—Contrary to the Grignard reagents, in all cadmium and zinc reagents except $R_2M(I,Cl)$, the stereochemistry of addition was independent of the halogens or of their source. For $R_2M(I,Cl)$, the amount of axial attack was significantly increased (*trans/cis* decreased).

8.—The stereochemistry of addition was essentially the same for comparable *in situ* and reconstituted reagents.

9.—Variation of the amount of magnesium salt in the reagent had little effect on the stereochemistry until it was reduced to 1 molar equiv relative to ketone (compared with 4 molar equiv in the *in situ* reagent). The effect was most pronounced in the prior coordination experiments and with magnesium iodide, where the relative amount of axial attack increased (*trans/cis* decreased). See Tables II and III.

Discussion

Three mechanistic pathways for the addition of dimethylcadmium and dimethylzinc to 4-*t*-butylcyclohexanone will be considered: addition of the Grignard reagent, present in small concentration in the reaction mixture (eq. 2); addition of the cadmium or zinc reagent by way of some six-center transition state; and addition of the cadmium or zinc reagent by way of some four-center transition state.

An important consideration in any mechanism is the degree of association of the reagents. On the basis of earlier work,[12a,b] we assume that the Grignard reagents in 0.1 *M* concentration and the cadmium and zinc[12c] reagents in 0.3–0.4 *M* concentrations are monomeric, while the 0.8 *M* solutions of Grignard reagent are polymeric. Magnesium halides present in the cadmium and zinc reagents (0.6–0.8 *M*) are undoubtedly polymeric.

Our reagents were prepared from the Grignard reagent according to the stoichiometry represented in eq 2. Although it can be argued that RMgX might be

$$2RMgX + MX_2 \longrightarrow R_2M + 2MgX_2 \qquad (2)$$

present by reversal of eq 2, this is contrary to the general observation[13] that a metal–metal exchange between organometallic and metal salt proceeds in the direction of formation of the less reactive organometallic.

Qualitative tests support the conclusion that Grignard reagent is present in very low concentration if at all. The familiar Gilman color test[14] for RMgX was negative in every experiment. The characteristic color of a charge-transfer complex between either 2,2′-biquinoline or 1,10-phenanthroline and Grignard reagent[15] was not observed with our reagents. Although the increased reactivity of cadmium and zinc reagents in the presence of magnesium halide would be compatible with attack by the Grignard reagent, our stereochemical results do not support this mechanism. Inspection of the tables reveals that both cadmium and zinc reagents lead to more *cis* alcohol (less thermodynamically stable),[16] resulting from axial attack, than do the Grignard reagents at low concentration. Indeed, the zinc reagents, in all but one case, gave *cis* alcohol as the major product. The leveling effect of % *trans* alcohol with increasing $MgBr_2$ concentration shown in Tables II and III would not be expected if the added salt were shifting eq 2 to the left.

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(12) (a) E. C. Ashby, *Quart. Rev.*, **21**, 259 (1967); (b) M. Abraham and P. Rolfe, *J. Organometal. Chem.*, **7**, 35 (1967); (c) K. S. Rao, B. P. Stoicheff, and R. Turner, *Can. J. Phys.*, **38**, 1516 (1960).

(13) R. G. Jones and H. Gilman, *Chem. Rev.*, **54**, 835 (1954).

(14) H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **47**, 2002 (1925).

(15) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(16) (a) J. J. Uebel and H. W. Goodwin, *J. Org. Chem.*, **33**, 3317 (1968); (b) N. L. Allinger and C. D. Liang, *ibid.*, **33**, 3319 (1968).

TABLE II

REACTION OF RECONSTITUTED DIMETHYLZINC AND -CADMIUM REAGENTS WITH 4-*t*-BUTYLCYCLOHEXANONE (1 MOLAR EQUIV) IN ETHER[a]

Molar equiv		Unchanged ketone, %	*trans* alcohol, %	*trans*/*cis*
Reagent (concn, *M*)	Salt			
$2(CH_3)_2Cd$ (0.4)	$8MgBr_2$	66	52.4[b]	1.1
$2(CH_3)_2Cd$ (0.4)	$4MgBr_2$	68	52.6[b]	1.1
$2(CH_3)_2Cd$ (0.4)	$2MgBr_2$	67	51.5[b]	1.1
$2(CH_3)_2Cd$ (0.4)	$1MgBr_2$	80	50.1[b]	1.0
$2(CH_3)_2Cd$ (0.4)	$2MgI_2$	60	50.4	1.0
$2(CH_3)_2Cd$ (0.4)	$1MgI_2$	75	44.2[b]	0.79
$2(CH_3)_2Cd$ (0.1)	$2MgI_2$	75	53.5	1.2
$2(CH_3)_2Cd$ (0.4)	$2MgI_2 + 2MgF_2$	76	49.8	0.99
$2(CH_3)_2Zn$ (0.3)	$4MgI_2$	67	45.2	0.83
$2(CH_3)_2Zn$ (0.3)	$2MgI_2$	80	46.6	0.87
$2(CH_3)_2Zn$ (0.3)	$1MgI_2$	88	44.1[b]	0.79

[a] Columns 3, 4, and 5 defined as in Table I. [b] Results of at least two separate runs with a maximum deviation of ±1%.

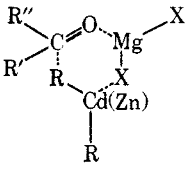
TABLE III

REACTION OF "PURIFIED" DIMETHYLZINC AND -CADMIUM REAGENTS IN ETHER WITH 4-*t*-BUTYLCYCLOHEXANONE(1 MOLAR EQUIV)·MgX_2[a]

Molar equiv		Unchanged ketone, %	*trans* alcohol, %	*trans*/*cis*
Reagent (concn, *M*)	Salt			
$2(CH_3)_2Cd$ (0.4)	$8MgBr_2$	47	51.7	1.1
$2(CH_3)_2Cd$ (0.4)	$4MgBr_2$	66	52.1	1.1
$2(CH_3)_2Cd$ (0.4)	$2MgBr_2$	66	49.1	0.97
$2(CH_3)_2Cd$ (0.4)	$1MgBr_2$	87	46.8[b]	0.88
$3.6(CH_3)_2Cd$ (0.4)	$2MgBr_2$	62	50.0	1.0
$2(CH_3)_2Cd$ (0.4)	$2MgI_2$	50	52.8	1.1
$2(CH_3)_2Cd$ (0.4)	$1MgI_2$	71	37.5[b]	0.60
$2(CH_3)_2Zn$ (0.3)	$4MgI_2$	60	47.3	0.90
$2(CH_3)_2Zn$ (0.3)	$2MgI_2$	66	46.7	0.88
$2(CH_3)_2Zn$ (0.3)	$1MgI_2$	90	36.1[b]	0.57

[a] Columns 3, 4, and 5 defined as in Table I. [b] Results of at least two separate runs with a maximum deviation of ±1%.

R_2M as the attacking agent might be involved in a six-center or four-center transition state, similar to those already proposed for ketone reactions with $RMgX$[12a] and Me_2Mg,[17] respectively. In the analogous transition states **4** and **5** for Cd and Zn reagents, solvent molecules are omitted for simplicity.



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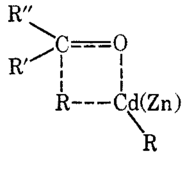

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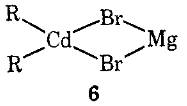
Although a distinction between transition states **4** and **5** is a subtle one, we feel that all our results considered together are better accommodated by **5**. Reasons for this conclusion are presented in the following discussion.

In accord with Felkin's suggestion,[9] it is reasonable to consider reactantlike rather than productlike transition states. This is supported in our work by the fact that a decrease in reactivity of reagent because of a variation of halide present generally is not accompanied by any change in stereochemistry.[18] In fact, the *less* reactive zinc reagent typically leads to *more* of the less stable *cis* alcohol.

We can conclude that steric interference to axial attack is diminished in both Cd and Zn reactions, compared with Mg reactions. Since the alkyl group has remained the same (methyl throughout), this lowering of steric interference can be explained as arising from a tighter transition state for Cd and Zn.[8] If one compares two six-center transition states for Mg (X = Br) and Cd (X = I), the former should be tighter on the basis of relative metal and halogen covalent bond distances. It would follow that the reaction with Mg should lead to more axial attack, which is exactly the reverse of what is observed. On the other hand, if the Cd (and presumably Zn) reactions were proceeding through four-center transition states, these should be tighter and lead to more axial attack, as is the case. The greater preference for axial attack by Zn over Cd is consistent with expected metal–oxygen bond distances, the shorter Zn–O bond giving rise to a tighter transition state **5**, when M = Zn.

The stereochemistry of addition of $RMgX$ is sensitive to changes in concentration of reagent, as is evident from Table I. If the addition of cadmium and zinc reagents were to involve a similar transition state **4** containing MgX_2, one might expect a similar effect. In fact, the stereochemistry of addition of both cadmium and zinc *in situ* reagents is independent of concentration changes, in ranges where the association of MgX_2 is changing drastically.[12a] No change in stereochemistry is observed in the prior coordination experiments (Table III) until the amount of MgI_2 is reduced to 1 molar equiv per equivalent of ketone. The change is toward more axial attack, the opposite of the trend in dilution of the Grignard reagent.

The activating effect on R_2M by addition of MgX_2 may be ascribed to activation of the ketone and/or the organometallic compound through coordination with magnesium salt. Infrared evidence[19] has been obtained for the existence of **6** in ether. The superior reactivity



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of those reagents containing magnesium iodide rather than bromide is in accord with the electronegativity, *i.e.*, the electron-donator ability of the halide. Lack of

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(17) H. O. House and J. E. Oliver, *J. Org. Chem.*, **33**, 929 (1968).

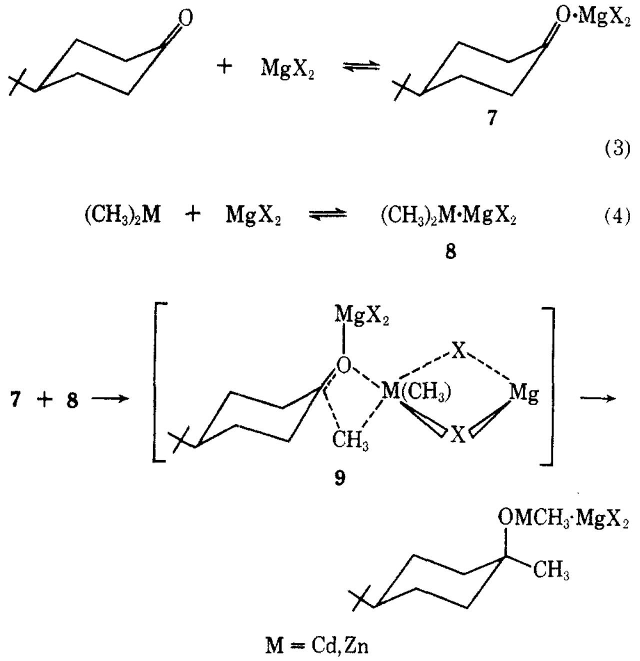
(18) See, for example, entries 6 and 7, 16 and 17 in Table I.

(19) H. Condan, E. Henry-Basch, J. Michel, B. Marx, and P. Freon, *Compt. Rend.*, **262**, 861 (1966).

reactivity of RMX and of R_2M derived from lithium reagents may reflect the lowered tendency of RMX or of monodentate ligands (LiX) to form electron-donor complexes[20] similar to **6**.

The sequence of steps shown in Scheme I is consistent with results being reported here. Thus, both ketone and R_2M are substantially associated with MgX_2 (eq 3 and 4). The four-center transition state **9**, written for equatorial attack, still contains strongly associated MgX_2. The coordination of the central metal atom in **9** may vary for Zn and Cd, for it is well known that Cd exhibits a greater tendency than Zn toward formation of octahedral complexes.[21] On the other hand, there is ample precedent for the octahedral configuration of organozincs;[22] and a pentacoordinate magnesium species from additive reactions with dimethylmagnesium has recently been proposed.[17]

Scheme I



The difference in stereochemistry observed with 0.8 *M* and 0.1 *M* Grignard reagents (Table I) suggests a tighter six-center transition state for the associated reagents (more axial attack). It is noteworthy that our stereochemical results with 0.1 *M* CH_3MgBr in ether are close to those obtained for 1 *M* THF solutions, which are also monomeric.[12a] Dependency of the stereochemistry of RMgX addition on the halogen present can be explained by consideration of the association. If we assume that methylmagnesium bromide is less highly associated than methylmagnesium iodide, as is the case for the corresponding ethyl reagents,[12a,b] we should predict more axial attack with methylmagnesium iodide. This is indeed the case.

Experimental Section

Instrumentation.—Infrared spectra were recorded with a Perkin-Elmer Model 337 grating spectrophotometer; nmr spectra, obtained with a Varian A-60 spectrometer, were recorded in parts per million downfield from tetramethylsilane used as an internal standard. Gas–liquid partition chromatographic (glpc) analysis and separations were accomplished with a Varian Model 90-P gas chromatograph on either SAIB (20%, 10′) or FFAP (10%, 10′) deposited on 60/80 mesh Chromosorb W at a column temperature of 190°.

Analyses were carried out on crude, isolated product and no correction made for mass balance. Values for the relative amounts of product alcohols were reproducible within ±1% and those of unchanged ketone within ±5% (Cd and Zn) in separate reaction runs. Areas under the peaks were determined as the product of the height and half-height peak width. The response ratios of the two alcohols are known to be the same.[16a]

Materials.—Methylmagnesium iodide was prepared in a dry nitrogen atmosphere from singly sublimed magnesium (Dow Chemical Co.). Methylmagnesium bromide was obtained from Arapahoe Chemical Co. Methyllithium, from Foote Mineral Co., had been prepared from methyl chloride and contained less than 1% LiCl. The solutions were refrigerated in serum-capped bottles, and their concentrations checked weekly by titration with 1,10-phenanthroline or 2,2′-biquinoline.[15] 4-*t*-Butylcyclohexanone was purchased from Aldrich Chemical Co. Anhydrous cadmium chloride (Fisher certified), bromide, and iodide (Alfa Inorganics) were used after oven drying for 48 hr at 110°. Zinc chloride (Fisher, N.F.) and bromide (Matheson Coleman and Bell) were fused and stored in a desiccator over phosphorus pentoxide.

Preparation of Anhydrous Zinc Iodide.—A 1-l., three-necked flask was fitted with a mechanical stirrer and a pressure-equalizing addition funnel. The flask contained a suspension of 37.7 g (0.58 mol) of powdered zinc in 500 ml of anhydrous ether. A piece of glass wool placed in the funnel served to support 126.9 g (0.50 mol) of iodine. A reflux condenser was connected above the addition funnel, and served to condense the ether vapors generated from heating the contents of the flask. The condensed solvent then passed over the iodine on its return to the reaction vessel, thus bringing the iodine in contact with the zinc. Because the reaction is exothermic, it was necessary to adjust the external heat periodically so as to maintain a gentle reflux. The addition of iodine was complete in 8 hr, but vigorous stirring was continued overnight to insure maximum reaction. The entire process was carried out under an atmosphere of dry nitrogen.

The final solution was centrifuged under nitrogen to remove the excess zinc and the final volume of the solution measured. Calculation of the concentration of zinc iodide (generally 1 *M*) was based on the volume of solution and the weight of zinc metal recovered. The colorless solution was stored over molecular sieves (3 A) in a serum-capped bottle and used as required.

Preparation of Anhydrous Zinc Bromide.—A procedure similar to that above was employed except that liquid bromine was added slowly to the ether suspension of zinc. The best results were obtained when the quantities of reagents were such that the final concentration of zinc bromide did not exceed 1 *M*. Unlike the zinc iodide, the final solution was initially yellow-orange but became dark on storage. The nmr spectrum indicated ether as the only organic component. Glpc analysis on FFAP, after precipitation of zinc bromide dioxanate, indicated 98% ether (minimum) with a maximum of 2% a component whose retention time was identical with that of ethanol. No higher boiling materials could be detected. The dioxanate was precipitated by addition of dioxane; the solid was collected, recrystallized from chloroform, and dried over P_2O_5.

Anal. Calcd for $C_4H_8Br_2O_2Zn$: C, 15.33; H, 2.57; Br, 51.01. Found: C, 15.12; H, 2.59; Br, 50.84.

Ethereal solutions of anhydrous zinc bromide and chloride were also prepared by dissolving the fused salts in anhydrous ether. In order to avoid a two-phase system with the chloride, it was necessary to prepare a concentrated solution (4-5 *M*). At this concentration a one-phase liquid was obtained. These solutions were also stored over molecular sieves in serum-capped bottles.

Preparation of Anhydrous Magnesium Iodide.—The procedure employed was identical to that described above for the preparation of zinc iodide. The final solution, however, consisted of two phases[23] which, if allowed to cool, yielded a third, solid phase

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(20) K-H. Thiele and P. Zdunneck, *Organometal. Chem. Rev.*, **1**, 331 (1966).

(21) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1962, p 479.

(22) W. H. Eisenhuth and J. R. VanWazen, *J. Amer. Chem. Soc.*, **90**, 5397 (1968).

(23) W. F. Linke and A. Seidell, "Solubilities of Inorganic and Metal Organic Compounds," Vol. II, American Chemical Society, Washington, D. C., 1965, p 503.

($MgI_2 \cdot 2C_4H_{10}O$). Generally the liquid became colored after a few hours, apparently because of the liberation of iodine.

The colorless two-phase system was filtered before cooling through a glass wool plug under a current of dry nitrogen. Removal of solvent was effected at room temperature and aspirator pressure, in the presence of both calcium chloride and phosphorus pentoxide to insure anhydrous conditions. The residual solid magnesium iodide diethereate was placed in a drybox and transferred to a tightly sealed container under dry nitrogen. This material could be stored for several days before appreciable iodine color developed.

Preparation of Anhydrous Magnesium Bromide.—Magnesium bromide was prepared as previously reported.[24]

Reaction of Methylmagnesium Bromide and Iodide with 4-*t*-Butylcyclohexanone.—The following procedure will serve to illustrate the reaction of the various Grignard and lithium reagents with 4-*t*-butylcyclohexanone. An ethereal solution of 27.4 ml of 1.90 *M* methylmagnesium iodide (0.053 mol) was added by means of a 20-ml syringe to 39 ml[25] of diethyl ether with stirring under an atmosphere of dry nitrogen. The reagent was then cooled with an ice–salt bath and stirred until the internal temperatue reached 0–5°. A solution of 2.0 g (0.013 mol) of 4-*t*-butylcyclohexanone in 15 ml of ether was added at such a rate that the temperatue did not exceed 5°. After the addition was complete the solution was stirred for 30 min more at ice–salt bath temperature. The bath was then removed and the reaction stirred at ambient temperature for an additional 2.5 hr.

The solution was cooled by an ice–salt bath and slowly hydrolyzed with 30 ml of saturated sodium bicarbonate solution such that the internal temperature did not exceed 5°. The ether layer was separated and the aqueous layer extracted twice with ether. The combined ether layers were dried over magnesium sulfate and concentrated at room temperature on a rotary evaporator, to give 2.0 g of crude product. Analysis was carried out by glpc on FFAP, as previously described. The order of elution on FFAP and SAIB was the same.

Reaction of 4-*t*-Butylcyclohexanone with *in situ* Dimethylzinc and Dimethylcadmium.—The following procedure will serve to illustrate the reaction of the *in situ* reagents with 4-*t*-butylcyclohexanone. An ethereal solution of 27.4 ml of 1.90 *M* (0.052 mol) methylmagnesium iodide was added to 24.0 ml of anhydrous ether. Then 20.0 ml of 1.3 *M* zinc bromide (0.026 mol) was added slowly with stirring and cooling. The resultant zinc reagent (two-phase liquid) gave a negative Gilman test.[14] A constant pressure of nitrogen was maintained throughout.

The reagent was cooled and 2.0 g (0.013 mol) of 4-*t*-butylcyclohexanone in 10 ml of ether was added at 0–5°. At the start of the reaction, the solution was 0.3 *M* in dimethylzinc. The ice–salt bath was removed and the reaction mixture stirred for 3 hr at room temperature.[26]

Hydrolysis was accomplished at 0–5° with 25 ml of saturated sodium bicarbonate. The ether layer was separated, dried over magnesium sulfate, and concentrated on a rotary evaporator at room temperature. The residual crude product amounted to 2.3 g.

Glpc analysis on FFAP sometimes showed varying amounts of dehydration product, especially in instances where large amounts of ketone remained. In such cases the crude product was taken up in benzene and any solid zinc salts which precipitated were removed.[27] For all values reported in Table I, the per cent olefin did not exceed 5% (see below). Redissolving the salts in ether gave a solution whose glpc analysis showed no trace of alcohols or olefin.

Preparation and Analysis of "Purified" Dimethylzinc and Dimethylcadmium.—The preparation of dimethylcadmium was taken from the work of Krause[28] except extensive fractionation of ether from the cadmium reagent was not performed. The preparation of dimethylzinc was accomplished according to the procedure of Krug and Tang.[29] A weighed amount of the solvent-free product was then dissolved in a known volume of ether and its concentration checked as described below.

Analysis of the dimethylzinc and dimethylcadmium was accomplished by treating a 5-ml aliquot of the reagents with 50 ml of 0.58 *N* sulfuric acid and back titrating with 0.40 *N* sodium hydroxide. The end point was determined by use of a pH meter and by use of Mallinckrodt "Indicator" (pH range 6–7). Both methods yielded comparable results. No basic cadmium or zinc salts precipitated until after the end point was reached, and values obtained were reproducible. The ether solutions were stored in a refrigerator in serum-capped amber bottles. To check on the possibility of $Cd(OH)_2$ formation in these titrations and its effect on the titration values, control experiments were run. Four times the amount of cadmium present in the above titration was added in the form of $CdCl_2$ to the same amount of standard sulfuric acid solution used in the titrations. This solution was then titrated with standard base under the conditions described above. It was found that the presence of cadmium salt had no effect on the titration values.

Reaction of "Reconstituted" Dimethylzinc and Dimethylcadmium with 4-*t*-Butylcyclohexanone.—The following procedure will serve to illustrate the reaction of "reconstituted" reagents with 4-*t*-butylcyclohexanone. An ethereal solution of 8.9 ml of 1.53 *M* dimethylcadmium (0.013 mol) was added to a stirred solution of 10.2 ml of 2.64 *M* magnesium bromide (0.027 mol) and 14 ml of anhydrous ether. Upon complete addition the mixture was stirred for 15 min at room temperature and then 15 min at 0°. One gram of 4-*t*-butylcyclohexanone in 5–10 ml of ether was added at such a rate that the temperature did not exceed 5°. The concentration at the start of each reaction was 0.4 *M* in dimethylcadmium. The mixture was stirred for 30 min at 0° and finally at room temperature for 2.5 hr. The reaction mixture was then cooled, hydrolyzed, and worked up as described above.

Reconstitution with magnesium iodide was accomplished by addition of the solid diethereate to an ethereal solution of dimethylcadmium or -zinc. The resultant mixture was stirred at room temperature until all the salt had dissolved (~20 min).

Reaction of 4-*t*-Butylcyclohexanone · MgX_2 with "Purified" Dimethylzinc and -cadmium.—The following procedure will serve to illustrate the reaction of salt-free dimethylzinc and -cadmium with prior coordinated 4-*t*-butylcyclohexanone. A solution of 1.0 g of ketone (0.007 mol) in 20 ml of anhydrous ether and 10.2 ml of 2.6 *M* magnesium bromide (0.026 mol) was stirred for 15 min at room temperature. The mixture was cooled to 0° and 8.9 ml of 1.53 *M* dimethylcadmium added as rapidly as possible below 5°. Addition time normally was 15–30 sec. The reaction mixture was stirred at 0° for 30 min and then at room temperature for 2.5 hr. Hydrolysis and work-up were the same as previously described. As in the earlier reactions, the concentration of dimethylcadmium was 0.4 *M*.

In the cases where iodide salts were used, the solid $MgI_2 \cdot 2Et_2O$ was dissolved in the appropriate ethereal solution of 4-*t*-butylcyclohexanone, immediately prior to addition of the organometallic reagent.

1-Methyl-4-*t*-Butylcyclohexene.—Glpc analysis of the crude reaction mixtures indicated that in some instances a considerable amount of zinc and cadmium salts was carried through the work-up procedure, as evidenced by the presence of variable amounts of 1-methyl-4-*t*-butylcyclohexene in addition to the desired alcohols. The per cent olefin increased drastically unless the injector port of the chromatograph was cleaned regularly. Infrared and nmr spectra gave no evidence of olefin in the samples prior to injection. Some of the excess salts could be removed by dissolving the sample in cyclohexane or benzene and filtering the mixture.[27]

1-Methyl-4-*t*-butylcyclohexene was collected by preparative glpc. The ether solutions of zinc salts were injected into the chromatograph and the injector port coated with salt. Subsequent injection of the mixture of alcohols obtained from reaction of methylmagnesium iodide with ketone produced mainly 1-methyl-4-*t*-butylcyclohexene. Its nmr spectrum determined in CCl_4 was essentially the same as that recently reported by Allinger.[16b] Its infrared spectrum was also consistent[30] with the assigned structure.

By varying the amount of salt on the injector port, the course of the dehydration could be followed. No change in the *trans/cis*

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[24] H. O. House, D. Traficante, and R. Evans, *J. Org. Chem.*, **28**, 351 (1963).

[25] The volume of ether varied depending on the concentration (0.8 or 0.1 *M*) of Grignard reagent desired.

[26] In the case of dimethylcadmium, the ice–salt bath was not removed until 30 min had elapsed after addition, and the solution was stirred at ambient temperature for 2.5 hr.

[27] We have since found that extraction of the crude reaction mixture with ammonium hydroxide removes the undesirable salts. See E. E. Blaise, *Bull. Soc. Chim. Fr.*, [4] **9**, 1 (1911).

[28] E. Krause, *Ber.*, **50**, 1813 (1917).

[29] R. C. Krug and P. J. C. Tang, *J. Amer. Chem. Soc.*, **76**, 2262 (1954).

[30] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1964, p 34.

ratio was detected until the amount of olefin exceeded 10%. Above 10% small differences were noted and the values indicated that the *cis* alcohol (equatorial OH) was being dehydrated at a faster rate than the *trans* alcohol.

Control Experiment.—The isolated product obtained from the reaction of methylmagnesium bromide (0.1 *M*) with 4-*t*-butylcyclohexanone (Table I) was dissolved in 10 ml of ether and added to dimethylcadmium or dimethylzinc reagents under the conditions previously described for the reaction of *in situ* reagents with ketone. After hydrolysis and work-up, percentages obtained by glpc were unchanged within experimental error.

Registry No.—Methylcadmium, 506-82-1; methylzinc, 544-97-8; **1**, 98-53-3; methylmagnesium iodide, 917-64-6; methylmagnesium bromide, 75-16-1; methyllithium, 917-54-4.

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New Friedel–Crafts Chemistry. XIX. Cyclialkylations of Some Phenylalkanols[1]

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Tertiary 3- and 4-phenylalkanols underwent cyclialkylation readily at room temperature with sulfuric acid to yield the corresponding indans and tetralins. Primary and (ordinary) secondary 3-phenylalkanols did not undergo cyclialkylation even at high temperature with phosphoric acid; 1,3-diphenyl-1-propanol cyclized readily. 3-Methyl-3-phenyl-1-butanol was dehydrated (mainly) by phosphoric acid at 230°, but some cyclialkylation occurred. The requirement of a stable secondary or tertiary carbonium-ion intermediate is implied by these results; in the case of the last example, a 1,3-phenyl shift provides the required intermediate.

Some time ago Bogert and coworkers[2,3] investigated the cyclialkylations of some phenylalkanols and related alkenes. They identified their cyclization products by means of qualitative elemental analyses, comparison of physical constants, and characterization, of oxidation products. Since such identification methods are qualitative at best and probably liable to failure in detecting minor components, we decided to reinvestigate some of the reported results, applying modern instrumental methods of separation and identification. Some of the experiments are repetitions of cyclialkylations reported previously,[2,3] but others are new ones designed to provide more insight into the mechanisms of these reactions.

Results and Discussion

The conditions and results of our cyclization experiments are summarized in the accompanying Table I. 3-Phenyl-1-propanol (**1**) and 4-phenyl-1-butanol (**2**) were reported by Bogert and Davidson[2] to yield polymer and pure tetralin, respectively, upon treatment with phosphoric acid at high temperature. We obtained a product from the former that was shown to contain a trace of indan and a little *n*-propylbenzene, but the major constituents were the three isomeric phenylpropenes resulting from normal dehydration. Confirmatory evidence for the structure of the latter isomers was obtained by catalytic reduction which converted them to *n*-propylbenzene. The product from **2** was found to consist of tetralin (80%) and three lower boiling unidentified products (20%).

4-Phenyl-2-butanol (**3**) was reported by Bogert and Davidson[2] to yield polymer on treatment with sulfuric acid. When we treated this alcohol with phosphoric acid, we found the product to be a mixture of three isomeric phenylbutenes. This was confirmed by comparison with the alkene mixture obtained by the dehydration of 4-phenyl-2-butanol with 30% sulfuric acid at reflux temperature, as well as by catalytic reduction to *n*-butylbenzene.

Upon treatment with sulfuric acid at room temperature, the two tertiary alcohols, 2-methyl-4-phenyl-2-butanol (**4**) and 2-methyl-5-phenyl-2-pentanol (**5**), gave 1,1-dimethylindan and 1,1-dimethyltetralin, respectively. The secondary alcohol, 5-phenyl-3-pentanol (**6**), gave 1-methyltetralin. These were the products reported by Roblin, Davidson, and Bogert.[3] It should be noted that a hydrogen shift, converting one secondary carbonium ion to another, allows the formation of the tetralin in preference to the indan[4] in the last case.

It is clear from our present and previous work,[4] as well as from the work of Bogert and coworkers,[2,3] that ordinary primary and secondary phenylalkanols (or phenylalkyl chlorides) do not undergo ring closure to an indan derivative. However, 1,3-diphenyl-1-propanol (**7**) gave up to 34% cylization product, 1-phenylindan, as well as the main product, a higher boiling one which we believe to be the result of intermolecular condensation reactions.[5] The ability of this secondary phenylalkanol to undergo cyclialkylation confirms the idea that a stable carbonium ion intermediate, in this case stabilized by a phenyl group, is required.

The reaction of 2-methyl-4-phenyl-1-butanol (**8**) with phosphoric acid presents a case of special interest, since it provides more insight into the cyclidehydration mechanism. The product of direct cyclization at the primary carbon atom, 2-methyltetralin, was obtained in smaller yield than the products involving rearrangement and cyclization at secondary and tertiary carbon atoms. These results may be rationalized in terms of the mechanism proposed for the formation of the same

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[1] Generous support of this research, including a postdoctoral fellowship for A. A. Khalaf, by the Robert A. Welch Foundation is gratefully acknowledged.

[2] M. T. Bogert and D. Davidson, *J. Amer. Chem. Soc.*, **56**, 185 (1934).

[3] R. O. Roblin, Jr., D. Davidson, and M. T. Bogert, *ibid.*, **57**, 151 (1935).

[4] A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **31**, 89 (1966).

[5] A. A. Khalaf and R. M. Roberts, *ibid.*, **31**, 926 (1966), and references there given.