But weakly aids formation of ion **4**;
Release of chlorine then from ion **3**,
Preferred over **4** in its free energy,
Creeps close to that of iodine less firmly bound.
para-Bromoiodobenzene demonstrates
An inversion of mobility
As the proton-seeking reagent is changed
From amide ion (in Table I or II)
To anilide (in Table IV). Release
Of iodine is preferred with anilide.
The same effect has three times been observed
With oligohalobenzenes, although
Interpretation is obscured somewhat
By disproportionations which occur
In several cases.[7,11] Isomerizations
Are improbable with the present substrate.
In the anilide–aniline milieu,
ortho-halophenyl anions revert
To parent molecules more frequently
Than they do with the amide base. Therefore,
Release of halide ion is determined
Relatively more by the lability
Of the carbon–halogen bonds concerned
Than by rates of abstraction of protons.
The haloanilines do not react
Extensively with excess amide ion,
As shown in Table III. In harmony
Appears the fact that yields of halide ion
With surplus amide ion slightly exceed
One ion from each dihalobenzene molecule
(Table I). However, *ortho*-iodo
Substrates afford much more halide ion
Than can be attributed to subsequent
Attack on the haloanilines that form.
An unexpected pathway of reaction,
Unclear in its details, is thus revealed.
This complication, our thanks to him,
Is under study by Jhong Kook Kim.

Experimental Section

Materials.—All dihalobenzenes were used as supplied by Eastman Kodak Co., except *m*-bromoiodobenzene which was distilled [bp 72.5–73.5° (1 Torr)] to remove a colored impurity. *p*-Bromo- and *p*-chloroanilines (from Eastman Kodak) and *m*-chloro-, *m*-iodo-, and *p*-iodoanilines (from Aldrich Chemical Co.) were used without further purification. 2-Bromo-4-iodotoluene, bp 96.5–97.0° (1 Torr), was synthesized by standard methods from a sample of 3-bromo-4-methylacetanilide which had been prepared by Dr. T. Okamoto.

Reaction Procedure.—Reactions were carried out substantially as described by Bunnett and Moyer.[11] In all cases, 500 ml of liquid ammonia was used, the dihalobenzene or halobenzene was added in solution in diethyl ether, and the addition funnel was rinsed with ether, the total volume of ether used being 70 ml. Reaction mixtures were usually dark red-brown in color. After the times listed in the tables, an excess of crushed ammonium nitrate was added, the ammonia was allowed to evaporate, and the residue was transferred to a separatory funnel with alternate washings of water and ether. The (alkaline) water layer was separated, and the ether layer was washed with water. The combined aqueous layers were adjusted to pH 3–4 by addition of dilute nitric acid, warmed briefly to expel dissolved ether, and diluted to the mark in a volumetric flask. Aliquots were titrated potentiometrically with silver nitrate, a radiometer titrator–titrigraph being used.

For reactions with dihalobenzenes in excess (Table II), the apparatus and procedure of Bunnett and Hrutfiord[12] were used without modification.

Registry No.—2-Bromo-4-iodotoluene, 26670-89-3; potassium amide, 17242-52-3.

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(11) J. F. Bunnett and C. E. Moyer, Jr., *J. Amer. Chem. Soc.*, in press.

(12) J. F. Bunnett and B. F. Hrutfiord, *ibid.*, **83**, 1691 (1961).

The Reactions of *in situ* *n*-Propylmagnesium, -cadmium, and -zinc Reagents with 4-*tert*-Butylcyclohexanone. Addition *vs.* Reduction and the Stereochemistry of Each

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The stereochemistry of both addition and reduction products of 4-*tert*-butylcyclohexanone with *n*-propylmagnesium, -cadmium, and -zinc reagents has been determined. Reactivity among Cd and Zn reagents varies over a wide range with a change in metal and halide ion, factors which also affect addition–reduction and the stereochemistry of both reactions. Cd reagents exhibit the greatest preference for addition over reduction. The Zn reagent leads to the nonthermodynamic reduction product (axial alcohol) in two instances.

In view of the striking tendency of methylcadmium and methylzinc reagents to add to 4-*tert*-butylcyclohexanone (**1**) from the axial side,[2] we undertook an investigation of the addition of *n*-propyl organometallics to the same ketone. The reaction of *n*-PrM (M = Mg, Cd, Zn) with **1** offered the opportunity to determine both the relative importance of addition and reduction with the various reagents as well as the stereochemistry of both processes (Scheme I).

After our experiments had been completed, preliminary results by Abenhaim[3] were published, including some experiments on the addition and reduction, with the stereochemistry of addition (only) reported for these same propyl reagents with 4-*tert*-butylcyclohexanone. Although no experimental details were described, the organometallic reagents employed by Abenhaim were presumably those containing bromide ion exclusively. His results are somewhat misleading inasmuch as he reported neither the yield of alcohol products nor the stereochemistry of reduction.

We should like to report our detailed study of the

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

(2) P. R. Jones, E. J. Goller, and W. J. Kauffman, *J. Org. Chem.*, **34**, 3566 (1968).

(3) M. Abenhaim, *C. R. Acad. Sci., Ser. C*, **267**, 1426 (1968).

TABLE I

REACTION OF *n*-PROPYL ORGANOMETALLIC REAGENTS WITH 4-*tert*-BUTYLCYCLOHEXANONE[a]

Reagent[b] (*M*)	% unchanged ketone[c]	% addition[d]	Ratio, addn/redn	% **2**[e]	% **5**[f]
PrMgBr (0.8)	1	66	1.9 (2.3)[h]	68	95
PrMgBr (0.1)	1	57	1.3	69[g]	95
PrMgI (0.8)	4	66	1.9	67	87
Pr_2Cd (I, I, 0.4)	11	86	6.1	52[g]	72
Pr_2Cd (I, Cl, 0.4)	19	91	10	61	70
Pr_2Cd (I, Br, 0.4)	22	91	10	55	72[j]
Pr_2Cd (Br, Br, 0.4)	63	89	8.1 (4.66)[h]	75 (80)[h]	74
Pr_2Zn (I, I, 0.3)	77	65	1.9	54	74[i]
Pr_2Zn (I, Br, 0.3)	77	54	1.2	57	48[i,j]
Pr_2Zn (Br, Br, 0.3)	87	28	0.39 (0.89)[h]	69 (75)[h]	19[i]

[a] Values are averages of at least two experiments with deviation of ±2% unless otherwise stated. For each experiment the value was the average of at least three glpc injections, for which deviation was ±2%. Corrections have been made for differences in response ratios (see Experimental Section). [b] Mg and Zn reactions were run with 4 molar equiv/equiv of ketone; Cd reactions were run with 2 molar equiv. Halogens in parenthesis indicate, respectively, the propyl halide and metal halide used. [c] Reproducible within ±5% in separate reaction runs. % = [area (ketone)/area (ketone) + Σ area (alcohols)] × 100. [d] Normalized yields: % addition + % reduction = 100%. [e] Normalized yields: % **2** + % **3** = 100%. [f] Normalized yields: % **4** + % **5** = 100%. [g] Single reaction run. [h] Reference 3. [i] Deviation of ±3% in separate reaction runs. [j] In the Zn reaction, **4** underwent 5% equilibration to **5** after 3 hr; no equilibration was noted with Cd.

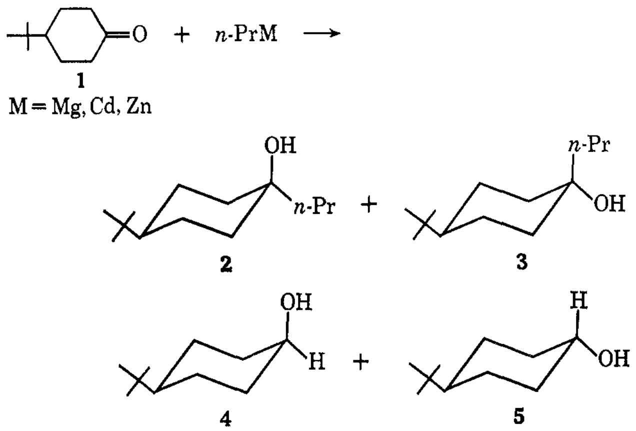
reactions of a variety of *n*-propyl reagents of Mg, Cd, and Zn, containing various halides, from the point of view of addition *vs.* reduction as well as the stereochemistry of *both* the addition and reduction process.

Some striking contrasts among Mg, Cd, and Zn reagents and between the methyl[2] and *n*-propyl reagents are evident from Table I. The nature of the metal and halide ions present exerts marked effects on reactivity, addition *vs.* reduction, and stereochemistry. A rough measure of reactivity, based on the amount of unchanged ketone under standard reaction conditions, indicates the superior reactivity of Mg and the very low reactivity of Zn reagents, in particular, the propylzinc (Br, Br) reagent employed by Abenhaim.[3] The propyl reagents of Cd and Zn are less reactive than the methyl[2] compounds, as well.

With regard to competition between addition and reduction, the cadmium reagents show the least tendency to effect reduction, the zinc reagents the greatest. Only in the latter case does the nature of the halide ion have any significant effect on addition–reduction although one would predict that the behavior of Grignard and cadmium reagents would be sensitive to halide, too, on the basis of currently accepted mechanisms for the additions[4] and reductions[5] with RMgX.

With all of the propyl reagents there is more equatorial addition than from the corresponding methyl compounds. This reflects the greater steric interference to axial attack with the larger propyl group, in accord with the transition state model recently proposed by Cherest and Felkin.[6] It should be noted that the cadmium and zinc reagents containing only bromide ion act as the "bulkiest," affording the least amount of axial attack. In the four-center transition state postulated for addition of cadmium and zinc reagents,[2] a tightening of the transition state (by a change from I to Br, for example) may well increase steric interactions between the β- and γ-propyl carbons and the 3,5-diaxial hydrogens, and thus the formation of **3** by axial attack would be impaired.

SCHEME I



The stereochemistry of reduction shows a striking contrast. Whereas both Mg and Cd reagents give preferentially axial reduction (the former being more stereoselective), the Zn reagents in two cases gave the nonthermodynamic isomer **4** as the major product. Because **4** was shown to undergo some equilibration to **5** (see Table I, footnote *j*), the stereoselectivity of the propylzinc reductions is in fact higher than that indicated in Table I. This serves as still further evidence[7] against product-development control in reactions of cyclohexanones. The fact that only zinc reagents show a change in stereochemistry of reductions with halide is surprising because reductions with all those reagents presumably involve six-center transition states. It would have been expected that the stereochemistry of all reductions would be insensitive to halide, as is the case for asymmetric reduction of methyl *tert*-butyl ketone with Grignard reagents from (+)-1-halo-2-methylbutane.[5b]

These many variations in behavior may represent a delicate balance between steric and electronic effects, which depend, among other things, on the dimensions of four- and six-center transition states, size and electronegativity of halide, and the differences in length and strength of carbon–metal bonds.

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Experimental Section

The experimental conditions, modeled closely after those with methyl reagents,[2] are typified by the following representative procedures.

Reaction of *n*-Propylmagnesium Bromide and Iodide with 4-*tert*-Butylcyclohexanone (1).—To a reaction flask containing 7 ml of anhydrous ether was added an ethereal solution of 11.2 ml of 2.32 *M* *n*-propylmagnesium bromide (26 mmol). The contents were cooled to 0° by means of an ice bath prior to the addition of a solution of 1.0 g (6.5 mmol) of **1** in 15 ml of ether. The temperature remained below 5° during addition. After a total of 15 min at ice-bath temperature, the bath was removed and stirring continued at ambient temperature for 2.75 hr. The Grignard concentration was initially 0.8 *M*, and the reaction was carried out under an atmosphere of dry nitrogen. Hydrolysis of the mixture was carried out at 0–10° with 25 ml of saturated sodium bicarbonate. The ether layer was separated, the aqueous layer was extracted once with 20 ml of ether, and the organic layers were combined and dried over magnesium sulfate. The ether was removed at room temperature on a rotary evaporator to yield 1.1–1.2 g of crude product.

Reaction of Di-*n*-propylcadmium with 1.—An ethereal solution of 11.5 ml of 2.32 *M* *n*-propylmagnesium bromide (26.6 mmol) was added to a stirred mixture of 4.87 g of CdI$_2$ (13.3 mmol) and 22 ml of anhydrous ether, which was cooled in an ice bath. This addition was carried out such that no ebullition occurred. The ice bath was removed, and the Gilman test was negative after 15 min.

After the di-*n*-propylcadmium reagent had been cooled in an ice bath to an internal temperature of 0–5°, 1 g of **1** (6.5 mmol) dissolved in ether or benzene was added such that the internal temperature did not exceed 5° (addition time approximately 5 min). The mixture was stirred an additional 15 min at ice-bath temperature and then for 105 min (165 min for Zn reagents) at ambient temperature. The solution was cooled in an ice bath to an internal temperature of 0° and hydrolyzed with 30 ml of saturated NaHCO$_3$ solution such that the internal temperature did not exceed 10°. The bath was then removed and the mixture stirred for an additional 5 min. Residual cadmium or zinc salts could be removed by preferential solution of the organic material in benzene, and washing of the solution with ammonia.[8] Unless this purification step was carried out, dehydration products (retention times 2.1 and 6.0 min) appeared in the chromatogram. After work-up and removal of salts, the crude product weighed 1.0–1.2 g.

***cis*- and *trans*-4-*tert*-Butylcyclohexanols (4 and 5).**—Reduction products **4** and **5** were synthesized from **1** by reduction with trimethylamine borane-BF$_3$[9] and separated on a neutral alumina column by elution with 10% ether-pentane (98 and 90% purity, respectively, by glpc).

***trans*- and *cis*-1-*n*-Propyl-4-*tert*-butylcyclohexanols (2 and 3).**—Identification of the addition products **2** and **3** was based on the previous report[3] that the major isomer from propyl Grignard addition is that of equatorial attack (**2**). Confirmation of this was achieved by isolation of the two epimers from a neutral alumina column by elution with 10% ether–pentane, the axial alcohol **2** being eluted first with mp 73.0–74.5°. *Anal.* Calcd for C$_{13}$H$_{26}$O: C, 78.72; H, 13.21. Found: C, 79.06; H, 13.45.

3 gave mp 87.0–87.5°. Found: C, 78.80; H, 13.39. The infrared spectra (CS$_2$) of **2** and **3** bear close analogies in the fingerprint regions with axial and equatorial isomeric pairs previously described by Cross and Whitham:[10] **2** [942, 987, 1188 cm^{-1} (all strong)]; **3** [985, 1022, 1139 cm^{-1} (all strong)]. Further support for the structural assignment comes from Cd or Zn salt-catalyzed dehydration experiments with **2** and **3** during glpc analysis. The epimer with equatorial -OH underwent dehydration preferentially, as shown by the relative decrease in area of the peak assigned to **3**. The analgous behavior has already been reported for the methyl analogs of **2** and **3**.[2]

Equilibration Experiments with 4 and 5.—The following is typical of control experiments to determine whether any equilibration of **4** and **5** occurred during the reactions with Cd or Zn reagents.

A mixture of 0.6 g of 4-*tert*-butylcyclohexanone and 0.4 g of 4-*tert*-butylcyclohexanol (98% **4**) was dissolved in 10 ml of anhydrous ether and added to *in situ* di-*n*-propylcadmium (I, Br) under the same reaction conditions as previously described for this reagent with 4-*tert*-butylcyclohexanone. Aliquots were taken at 3, 8, 12, and 23 hr and hydrolyzed as previously described. Normalized per cent of **4** was found by glpc to be 90% (3 hr) and 88% (23 hr). The calculated value based on ratios shown in Table I is 90%. Similar experiments were carried out with **5** and Cd or Zn reagents. Only in the case of the control experiment of di-*n*-propylzinc (I, Br) with **4** was any equilibration noted [Normalized % of **4**. Calcd: 93 (3 hr); 88 (24 hr). Found: 89 (3 hr); 73 (24 hr).].

Analysis of Reaction Products.—Glpc analyses (STAP, 10% deposited on Chromosorb W, 140°, helium flow rate of 100 ml/min) were performed on crude, isolated products (see above) with no correction for mass balance. The nmr spectrum of a mixture from *n*-propyl Grignard reagent contained no peaks attributable to any materials other than **1**, **2**, **3**, **4**, and **5**. The retention times for **1**, **2**, **3**, **4**, and **5**, respectively, were 12.9, 24.1, 26.3, 15.0, and 17.9 min. In no case could higher boiling components be detected by glpc. Response ratios, as determined from weighed mixtures of two-component pairs, is as follows: **1**:**2**, 0.82 ± 0.01; **1**:**3**, 0.90 ± 0.02; **1**:**4**, 1.02 ± 0.03; **1**:**5**, 1.01 ± 0.05.

Registry No.—*n*-Propylmagnesium bromide, 927-77-5; *n*-propylmagnesium iodide, 10557-57-0; di-*n*-propylcadmium, 5905-48-6; di-*n*-propylzinc, 628-91-1; **1**, 98-53-3.

Acknowledgment.—We thank the Central University Research Fund (University of New Hampshire) for partial support.

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