over 2 hr. at 0°. The reaction mixture was then allowed to stand at room temperature for 2 hr. The reaction mixture was hydrolyzed using a small quantity of water and alkali and the product was taken up in ether. An aliquot was titrated, indicating a yield of 83%. The solvent was distilled off through a column, and the solution was subjected to gas chromatographic examination (10% primine on Fluoropak). There was 8.6 mmoles of n-hexylamine, a yield of 86%.

Selective Reductions. VIII. The Stereochemistry of Reduction of Cyclic and Bicyclic Ketones by the Alkoxy-Substituted Lithium Aluminum Hydrides[1]

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The introduction of alkoxy substituents into lithium aluminum hydride provides a simple, convenient means of modifying the steric requirements and reducing properties of this powerful reducing agent. In order to ascertain the effect of these modifications on the stereochemistry of reduction of monocyclic and bicyclic ketones, a systematic survey was undertaken of the reduction under standard conditions (tetrahydrofuran solution at 0°) of a set of selected monocyclic and bicyclic ketones by lithium aluminum hydride and certain of its alkoxy derivatives. The results reveal that lithium trimethoxyaluminohydride is more stereoselective than either lithium aluminum hydride or lithium tri-t-butoxyaluminohydride. In the case of bicyclic ketones, the trimethoxy reagent provides the less stable of the two possible alcohols in high isomeric purity. The results confirm the earlier conclusion that the direction of reduction is controlled by the stability of the product in flexible, relatively unhindered ketones and by the steric factor in rigid, sterically congested ketones.

The stereochemistry of the reduction of ketones by hydride reagents is an interesting problem which has attracted considerable attention.[3-9] In the case of rigid bicyclic ketones, the transfer of hydride from the reagent to the carbonyl group occurs predominantly from the less hindered direction, producing preferentially the more hindered or less stable of the two possible alcohols.[5] On the other hand, in the less rigid monocyclic systems, such as 2-methylcyclopentanone[4] and 2-methylcyclohexanone,[3] the transfer of hydride proceeds preferentially to give the more stable of the two possible alcohols.

We had earlier established that the addition of 3 moles of t-butyl alcohol to 1 mole of lithium aluminum hydride forms lithium tri-t-butoxyaluminohydride,[10] a reagent with greatly modified reducing characteristics.[10,11] Similarly, the use of methanol produces lithium trimethoxyaluminohydride,[10,12] a more active reducing agent.[13] Finally, the use of ethanol produces a less homogeneous material,[12] but one which was nevertheless found utility for the selective reduction of nitriles[14] and dimethylamides[15] to aldehydes. It appeared desirable to explore the possible utility of these reagents for the stereoselective reduction of cyclic and bicyclic ketones. Accordingly, we selected a group of model ketones, 2-methylcyclopentanone, 2-methylcyclohexanone, and 2-t-butylcyclohexanone for the monocyclics and norcamphor, camphor, and isopinocamphone for the bicyclics, and subjected them to reduction by lithium aluminum hydride and its alkoxy derivatives under standard conditions—tetrahydrofuran solution at 0°.[16] The discovery that lithium trimethoxyaluminohydride is especially effective for the stereoselective reduction of bicyclic ketones led us to extend our study of this reagent to a number of additional bicyclic structures.

Results

In the procedure as it was finally developed, a 0.4 M solution of lithium aluminum hydride or of the modified reagent (prepared *in situ* by adding the calculated quantity of alcohol) was cooled to 0°. A measured

(1) Based upon a thesis submitted by H. R. Deck in Aug. 1963, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Graduate Research Assistant on Research Grant DA-ARO(D)-31-124-G106 supported by the U. S. Army Research Office (Durham).

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(9) J. C. Richer, *ibid.*, 30, 324 (1965).

(10) H. C. Brown and R. F. McFarlin, *J. Am. Chem Soc.*, 78, 252 (1956); 80, 5372 (1958).

(11) H. C. Brown and P. M. Weissman, *Israel J. Chem.*, 1, 430 (1963).

(12) H. C. Brown and C. J. Shoaf, *J. Am. Chem. Soc.*, 86, 1079 (1964).

(13) H. C. Brown and P. M. Weissman, *ibid.*, 87, 5614 (1965).

(14) H. C. Brown and C. P. Garg, *ibid.*, 86, 1085 (1964).

(15) H. C. Brown and A. Tsukamoto, *ibid.*, 86, 1089 (1964).

(16) A number of applpications of the alkoxy-substituted lithium aluminum hydrides for the reduction of cyclic ketones have been described.[6,7,9] Fortunately, the overlap with the data available is not significant.

Table I. Reductions of Cyclic Ketones with Lithium Aluminum Hydride and Its Alkoxy Derivatives in Tetrahydrofuran at 0°

Ketone	Mmoles	Reagent	Mmoles	Hydride used, mmoles	Alcohol found, mmoles	Product, % trans
2-Methylcyclopentanone	20	LiAlH₄	20	22.3	21.8	76[d]
	80		20	77.5	76.1[a]	79
	15	LiAlH(OMe)₃	20	15.0	13.4	56
	15	LiAl(OEt)₃	20	15.1	16.6	77
	15	LiAl(O-t-Bu)₃	20	14.1	14.3	72
2-Methylcyclohexanone	20	LiAlH₄	20	19.5	19.5	76[e]
	40		20	40.9	38.0	75
	60		20	60.7	55.2	75
	80		20	71.9	66.5[b]	74
	15	LiAlH(OMe)₃	20	14.8	14.7	31
	15	LiAlH(OEt)₃	20	14.7	14.2	73
	20	LiAlH(O-t-Bu)₃	20	19.8	18.6	70[f]
2-t-Butylcyclohexanone	10	LiAlH₄	10	7.8	10.9	42
	10	LiAlH(OMe)₃	13.3	8.9	10.2	36
	10	LiAlH(O-t-Bu)₃	13.3	6.2	6.3[c]	46

[a] 5.5 mmoles of ketone. [b] 10.1 mmoles of ketone. [c] 4.0 mmoles of ketone. [d] Umland and Jefraim[4] report 75% trans for reduction in ether, temperature not specified. [e] Dauben, Fonken, and Noyce[3] report 82% trans for reduction in ether, temeprature not specified. [f] Richer[9] reports 63% trans for reduction in tetrahydrofuran at room temperature.

quantity of the ketone was injected. After 1 hr., ethylene glycol (1 mole per mole of hydride) was added to destroy residual hydride and to precipitate inorganic components of the reaction mixture. The supernatant solution was then analyzed by gas chromatography for total yield and isomeric ratio.

To test the procedure cyclohexanone was reduced; excellent material balances were realized for both hydride utilized and alcohol obtained. To check the possibility that equilibration might occur following reduction, a standard mixture of cis- and trans-2-methylcyclohexanol was added to 0.4 M solutions of lithium aluminum hydride, lithium trimethoxyalumino-hydride, and lithium tri-t-butoxyaluminohydride to give reaction mixtures identical in concentrations with those realized in the reduction experiments. After 1 hr. at 0°, ethylene glycol was added to destroy the excess hydride and to precipitate the inorganic components. Both the yield and the isomeric ratios corresponded quantitatively to the standard mixture added. Consequently, equilibration is not a factor under these conditions.

Cyclic Ketones. Under the standard conditions the reaction of 20 mmoles of 2-methylcyclopentanone with 20 mmoles of lithium aluminum hydride gives 76.4% trans- and 25.6% cis-2-methylcyclopentanol. Use of 80 mmoles of ketone to 20 mmoles of the reagent (80 mmoles of "hydride") gives almost the same distribution, 79.1% trans. Lithium trimethoxyalumino-hydride forms 55.5% trans, but the ethoxy and t-butoxy derivatives give results quite close to those realized for the parent compound.

The experimental data are summarized in Table I.

In the case of 2-methylcyclohexanone, no change in the isomer distribution (75% trans) was observed as the ketone:LiAlH₄ ratio was changed from 1:1, 2:1, 3:1, to 4:1. This is in agreement with previous observations that neither the ratio nor the mode of addition appears to influence significantly the isomer distribution in this reaction.[7] On the other hand, the use of lithium trimethoxyaluminohydride actually results in the preferential formation of the cis isomer (31% trans, 69% cis). This was quite promising and we considered exploring the possibility that the use of

this reagent at low temperatures (−80°) would produce the cis isomer as a state of reasonable purity. However, we were dissuaded from this endeavor by the discovery that 2-methylcyclopentanone and 2-methyl-cyclohexanone can be converted into the corresponding cis alcohols in purities of 92 to 94% by the use of di-isopinocampheylborane.[17]

Here again it was observed that the use of the ethoxy and t-butoxy reagents gave results that were very close to the isomer distribution realized with lithium aluminum hydride itself (Table I).

Finally, it was observed that the reduction of 2-t-butylcyclohexanone by lithium aluminum hydride proceeds to give the less stable isomer preferentially, 42% trans. The methoxy derivative gave even less of the trans (36%), and the t-butoxy reagent, in a slow, incomplete reaction, again produced a distribution that agreed closely with that produced by the parent hydride.

Bicyclic Ketones. The study of the bicyclic ketones proved more rewarding. With norcamphor, lithium aluminum hydride gave 11% exo-norbornol (89% endo-), and this distribution was inverted by the gem-dimethyl substituents of camphor,[5] yielding 91% isoborneol (exo) and 9% borneol (endo). However, the lithium trimethoxyaluminohydride gave much higher stereoselectivity: 2% exo-norborneol and 99% isoborneol. Similarly, in the case of isopinocam-phone, the 89% endo attack by lithium aluminum hydride, to give 89% of neoisopinocampheol, was increased, to 98% endo attack by the use of lithium trimethoxyaluminohydride.

Again, the use of the ethoxy or t-butoxy derivatives gave less favorable results, more comparable to the distributions realized with lithium aluminum hydride itself.

The experimental results are summarized in Table II.

Other Bicyclic and Tricyclic Ketones. It is well known that reduction of bicyclic ketones, such as norcamphor and camphor, by lithium aluminum hydride proceeds with preferential attack of the hydride

(17) H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.*, **83**, 3166 (1961).

Table II. Reductions of Bicyclic Ketones with Lithium Aluminum Hydride and Its Alkoxy Derivatives in Tetrahydrofuran at 0°

| Ketone	Mmoles	Reagent	Mmoles	Hydride used, mmoles	Alcohol found, mmoles	Product, % endo
Norcamphor	20	LiAlH₄	20	21.9	19.2	89
	15	LiAlH(OMe)₃	20	17.9	15.1	98
	15	LiAlH(OEt)₃	20	16.4	15.3	85
	15	LiAlH(O-t-Bu)₃	20	13.5	14.5	93
Camphor	20	LiAlH₄	20	26.4	18.2	8
	15	LiAlH(OMe)₃	20	19.0	11.8[a]	1
	15	LiAlH(O-t-Bu)₃	20	14.3	14.7	7[d]
Isopinocamphone	20	LiAlH₄	20	20.4	21.3	11
	15	LiAlH(OMe)₃	20	13.7	14.2[b]	2
	15	LiAlH(O-t-Bu)₃	12.8		7.3[c]	16

[a] 4.8 mmoles of ketone. [b] 0.4 mmole of ketone. [c] 7.0 mmoles of ketone. [d] Richer[9] reports 5% *endo* for reduction in tetrahydrofuran at room temperature.

reagent from the less hindered side.[6] This provides a convenient synthetic route to the less stable of the two possible alcohols, such as *endo*-norborneol from norcamphor and isoborneol from camphor. However, it is commonly observed that the reaction product is commonly contaminated with minor quantities of the more stable isomer, approximately 10% in each of the two examples under discussion. These bicyclic derivatives often form mixed crystals and it becomes a tedious task to remove the minor component. Consequently, the observation that the use of lithium trimethoxyaluminohydride decreases the minor component to 1–2% in the three model compounds examined (norcamphor (I), camphor (II), and isopinocamphone (III)) appeared highly promising.

|	I	II	III
LiAlH₄, %	11	8	11
LiAlH(OMe)₃, %	2	1	2
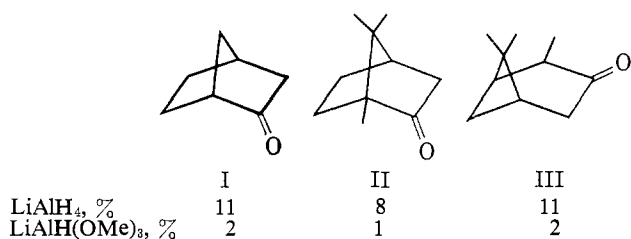
The reagent was therefore applied to the reduction of several additional cases to test the generality of the results.

Fenchone (IV) yielded *endo*-fenchyl alcohol in a purity of at least 97%.

IV   97%   3%
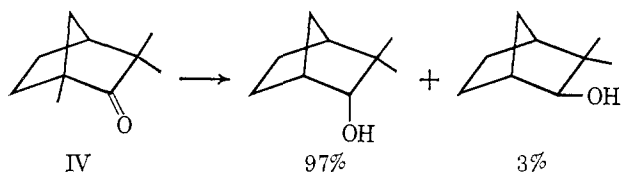
Tricyclo[2.2.2.0³,⁵]octan-2-one (V) yields material of 91% isomeric purity with lithium aluminum hydride and 98% with lithium trimethoxyaluminohydride.[18]

	91	9
LiAlH₄, %	91	9
LiAlH(OMe)₃, %	98	2
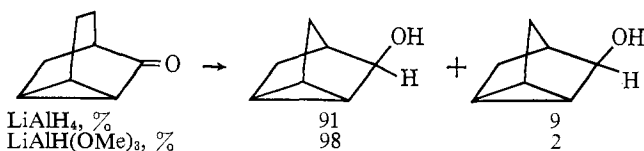
(18) We are indebted to Professor Norman A. LaBel of Wayne State University for samples of the ketone and the two isomeric alcohols.

Finally, we observed that the hydroboration of Δ³-carene (VI) yields an alcohol which is readily oxidized to a ketone.[19] Reduction of this ketone with lithium aluminum hydride gives 59% of the original alcohol and 41% of an epimeric compound. On the other hand, lithium trimethoxyaluminohydride is much more stereospecific; it yields only 12% of the original alcohol, 88% of the epimer.

It should be pointed out that this new reagent can be coupled with hydroboration–oxidation of many bicyclic olefins to give the two epimeric alcohols in high purity. For example, the hydroboration–oxidation of norbornene yields *exo*-norborneol in isomeric purity of >99%.[20] Oxidation to the ketone, followed by reduction with lithium trimethoxyaluminohydride, yields the epimer, *endo*-norborneol, in isomeric purity of 98%. Similarly, α-pinene can be converted to pure isopinocampheol *via* hydroboration.[20] Oxidation and reduction by the reagent under discussion yields neoisopinocampheol in 98% isomeric purity.

Discussion

It was originally pointed out by Dauben and co-workers that there does not appear to be any significant steric influence in the reduction of simple monocyclic ketones by lithium aluminum hydride.[3] In the absence of any significant steric influence of the substituent, the reaction course is determined primarily by the relative stability of the two isomeric products. Such reductions were termed "product development control."[21]

The results obtained for the reduction of 2-methyl-cyclopentanone and 2-methylcyclohexanone by lithium aluminum hydride are in good agreement with the data reported earlier.[3,4] In both cases, the predominant product formed was the thermodynamically more stable *trans* alcohol.

The increase in the steric requirements of the alkyl substituent in 2-alkylcyclohexanone from methyl to *t*-butyl results in a change in this pattern. The predominant isomer is now *cis*-2-*t*-butylcyclohexanol. Evidently the steric requirements of the substituent are

(19) The precise configuration of these alcohols and ketones is currently under investigation in our laboratory.

(20) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 83, 2544 (1961).

(21) Richer[9] has recently suggested that there may be a small steric factor influencing the direction of reduction of these cyclic ketones. He proposes that the 2,6-axial hydrogen atoms of 4-*t*-butylcyclohexanone interfere with the approach of the reagent from that axial direction, so that the reduction occurs preferentially from the alternative axial direction to give the alcohol with equatorial hydroxyl.

sufficiently large as to overcome the usual preference for the reduction to proceed to give the more stable of the two possible alcohols. Dauben and co-workers termed such reductions "steric approach control."[3]

While we are in complete agreement with their analysis, we feel that the terms proposed are unfortunate. They give the impression that for the first group the isomer distribution is determined primarily by the relative thermodynamic stability of the two isomers, whereas for the second group the distribution arises from another cause, the different steric environment involved in the two possible reaction paths. These terms therefore give the impression that the reaction course of the first group is described by the activated complex theory, whereas the second group is controlled by the collision theory. However, it is clear that in both groups the relative importance of the two paths leading to the two isomers must be controlled by the relative stabilities of the two possible transition states in each group. In the first group, steric strains are small, and the relative stabilities of the two possible products play a dominant role in directing the course of the reaction. In the second group, steric strains are dominant and control the direction taken by the reduction, overcoming the effect of the stabilities of the products.

Perhaps it would be desirable to modify the two terms proposed by Dauben and co-workers to "product stability control" and "steric strain control" to avoid the possible ambiguous implications of the original terms.

The observation that the increase in the steric requirements of the alkyl substituent had caused a change from predominant product stability control in 2-methylcyclohexanone to steric strain control in 2-*t*-butylcyclohexanone suggested the possibility that the use of the alkoxy-modified reagents should have a similar effect. Indeed, the use of lithium trimethoxy-aluminohydride resulted in an increase from 23% to 44% *cis* in the reduction of 2-methylcyclopentanone. Moreover, the effect was even larger with 2-methyl-cyclohexanone, the distribution increasing from 25% to 69% *cis*.

Wheeler and Mateos had previously reported that the use of lithium tri-*t*-butoxyaluminohydride had enhanced the steric factor and achieved the stereoselective reduction of a number of steroidal ketones.[6] Moreover, it had been observed in our laboratories that the use of dialkylboranes of large steric requirements achieved the conversion of 2-methylcyclo-pentanone and -cyclohexanone to the *cis* alcohols in purities of 92 to 94%.[17] Consequently, it was a considerable surprise and disappointment that lithium tri-*t*-butoxyaluminohydride gave results that were inferior to the methoxy derivative and no significant improvement over the results realized with lithium aluminum hydride itself. This suggests that the reduction of hindered ketones by lithium tri-*t*-butoxy-aluminohydride may not involve a simple hydride transfer from the reagent to the ketone. We shall return to this point later in this paper.

In contrast to the monocyclic ketones, the reduction of bicyclic ketones clearly proceeds to give the less stable of the two possible isomers. That is, the reduction is controlled primarily by the effect on the relative stabilities of the two transition states of conflicting steric requirements of the ketone and reagent, rather than by the relative stabilities of the incipient products. That is, the reduction of these bicyclic ketones appears to exhibit "steric approach control" (or "steric strain control").

It is probable that a major factor in the difference in the behavior of the mono- and bicyclic ketones is the result of the flexibility of the former and the rigidity of the latter. Because of its flexibility, the monocyclic ketone can adapt itself so as to minimize the steric interactions of the 2-alkyl substituent with the reagent. Consequently, these steric interactions become quite small and no longer exert a controlling influence on the reaction course, unless the steric requirements of the substituent or of the reagent are increased considerably. On the other hand, the rigid bicyclic system offers no possibility for such minimization of the steric interactions. Consequently, any differences in the steric interactions in the two possible transition states will exert their full effect on the course of the reaction, overpowering the influence of the relative stabilities of the two isomers.

The reduction of many bicyclic ketones with lithium aluminum hydride proceeds to give the major (less stable) isomer in yields of the order of 90%, with the minor isomer present in yields of 10%. The decrease in the amount of the minor isomer to approximately 2% in the case of bicyclic ketones such as norcamphor, camphor, isopinocamphone, and fenchone represents a major change in the relative magnitudes of the rates leading to the two isomeric alcohols. This agrees with the above argument that the rigid bicyclic system serves to magnify the importance of the steric effect as compared to that observed in flexible monocyclic derivatives.

Here again the results with lithium tri-*t*-butoxy-aluminohydride appear anomalous. Instead of exhibiting an even greater steric influence, this reagent yields results more comparable to those realized with lithium aluminum hydride. We appear to be forced to conclude that reductions of hindered ketones by lithium tri-*t*-butoxyaluminohydride must involve a mechanism different from that utilized by lithium tri-methoxyaluminohydride.

It was previously observed that the stereochemistry of reduction of 3,3,5-trimethylcyclohexanone with lithium aluminum hydride in diethyl ether or tetrahydrofuran is independent of the ratio of the reactants or the order of their addition, giving in all cases 55 ± 3% of the axial (*trans*) alcohol.[7] Similar results were realized in the present study (Table I). To account for his observations Eliel suggested that the initially formed alkoxyaluminohydrides must disproportionate to give the tetralkoxy derivative, so that the reduction proceeds predominantly through the parent compound.[22]

Support for this position is provided by the observations of Shoaf.[12] He noted that the addition of 3 moles of isopropyl alcohol or of acetone to 1 mole of lithium aluminum hydride in tetrahydrofuran or diglyme gave a precipitate and a solution which gave analyses for lithium, aluminum, and hydrogen corresponding closely to LiAlH₄.

(22) For a detailed discussion of the problem and interpretation, see ref. 7.

On the other hand, the behavior exhibited by methyl and *t*-butyl alcohols was quite different. In these cases, no precipitate was observed, although the corresponding tetralkoxyaluminohydrides are insoluble. Consequently, the products must exist in solution as the soluble lithium trimethoxyaluminohydride and lithium tri-*t*-butoxyaluminohydride. Confirmation for this conclusion in the case of the former reagent is provided by the present results. It would be very difficult to account for the marked alteration in the stereochemical results achieved by lithium trimethoxyaluminohydride if this reagent were undergoing disproportionation and reacting in the form of lithium aluminum hydride.

However, then we are faced with the problem of lithium tri-*t*-butoxyaluminohydride. In spite of its evident much larger steric requirements, the stereochemical results with this reagent resemble those realized with lithium aluminum hydride much more closely than they do those realized with the methoxy derivative (Tables I and II).

Solutions of lithium tri-*t*-butoxyaluminohydride appear quite stable. Over long periods of time standard solutions of this reagent have exhibited no change in hydride content and no precipitation of lithium tetra-*t*-butoxyaluminohydride.[11] Moreover, such solutions do not react with *t*-butyl alcohol or with ethyl benzoate, although lithium aluminum hydride reacts instantly with these materials. Clearly, then, these solutions do not contain a significant amount of lithium aluminum hydride, and it is not possible to attribute the stereochemical results to lithium aluminum hydride present in the solution of the reagent.

One possible way out of this apparent impasse is the suggestion that either the ketone itself, or its initial reduction product, catalyzes the disproportionation of the reagent, so that the reduction does proceed predominantly through lithium aluminum hydride even though it is not present in the original solution. Another possibility is that the reagent exists as an equilibrium distribution of the parent compound and its dissociation products, lithium *t*-butoxide and di-*t*-butoxyaluminohydride. Hindered ketones, whose re-

$$\text{LiAlH(O-}t\text{-Bu)}_3 \rightleftharpoons \text{LiO-}t\text{-Bu} + (t\text{-BuO)}_2\text{AlH}$$
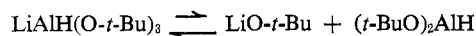
action with the parent compounds might be very slow, might then be diverted to an alternative reaction path, reduction by di-*t*-butoxyaluminohydride.

We hope to explore these possible explanations for the unusual behavior of lithium tri-*t*-butoxyaluminohydride in these stereoselective reductions.

Irrespective of the final explanation for the behavior of lithium tri-*t*-butoxyaluminohydride it is evident from this study that lithium trimethoxyaluminohydride is the most stereoselective of the reagents examined and should prove highly useful to achieve stereoselective reductions, especially in bicyclic structures and polycyclic steroids, where the greater rigidity of the system should serve to enhance the steric factor.

Experimental Section

Materials. Tetrahydrofuran was treated with small quantities of lithium aluminum hydride until hydrogen evolution ceased. The tetrahydrofuran was then distilled off of the residual hydride at atmospheric pressure, protecting the distillate from moisture.

Standard solutions of lithium aluminum hydride in tetrahydrofuran were prepared in the following manner. In a 1-l. flask was placed 750 ml. of freshly distilled tetrahydrofuran and sufficient lithium aluminum hydride to provide a solution about 0.5 *M*. The slurry was stirred overnight with a magnetic stirrer under a dry nitrogen atmosphere. The clear solution was then transferred by slight nitrogen pressure through a filter stick into a storage flask fitted with a closure which permitted removal of samples with a hypodermic syringe as nitrogen was introduced to maintain the pressure at slightly above atmospheric. The solution was standardized by removing an aliquot with a syringe, injecting it into a glycerol–water mixture, and measuring the hydrogen evolved.

2-Methylcyclopentanone (b.p. 137° (748 mm.), n^{20}D 1.4352), 2-methylcyclohexanone (b.p. 163° (749 mm.), n^{20}D 1.4485), norcamphor (m.p. 93–94°), and camphor (m.p. 176.5–177.5°) were commercial materials, purified by distillation or sublimation. Isopinocamphone (b.p. 42° (0.5 mm.), n^{20}D 1.4740, αD −9.8°) and 2-*t*-butylcyclohexanone (b.p. 42–43° (1 mm.), n^{20}D 1.4582, m.p. semicarbazone, 180–181°) were prepared by the hydroboration–oxidation[23] of α-pinene and 1-*t*-butylcyclohexane, followed by oxidation of the alcohols in ether solution by chromic acid.[24]

Reduction Procedure. The reaction conditions and procedure, utilized for the examination of the stereochemical characteristics of the different reagents, were maintained constant. A 100-ml. flask, fitted with an inlet port for syringes, a magnetic stirrer, a thermometer, and a reflux condenser connected to a gas-measuring system, was flamed out in a slow stream of nitrogen to remove residual moisture. The flask was then cooled to 0° and the desired quantity of the standard solution of lithium aluminum hydride in tetrahydrofuran was added to the flask. The hydrogen evolved was noted. The ketone dissolved in a small quantity of tetrahydrofuran was added and the hydrogen evolved again was noted. The reaction was permitted to stand at 0° for 1 hr. At that point 1 mmole of ethylene glycol per millimole of hydride was added slowly by means of a syringe and the hydrogen evolved was measured. After the precipitate settled,[25] the clear solution was analyzed by gas chromatography, utilizing external standards to establish the quantity and identity of the components.

In cases where the reducing agents were the alkoxy derivatives, the apparatus was prepared as described above and the lithium aluminum hydride solution was injected and cooled to 0°. Then 3 moles of alcohol per mole of lithium aluminum hydride was introduced slowly. There was an immediate evolution of hydrogen. The amount was noted and the solution was allowed to come to thermal equilibrium with the ice bath. Then the ketone was injected, the reaction was allowed to proceed for 1 hr., and the work-up then followed an identical procedure with that described above. The experimental results are summarized in Tables I and II.

(23) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).
(24) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2952 (1961).
(25) It was established that this procedure gives a quantitative precipitation of the inorganic components of the solution, without loss of the alcohol products.

Preparation of dl-endo-Fenchyl Alcohol. The reduction of fenchone was carried out on a preparative scale to test the utility of the procedure for such preparations. In a 1-l. flask was placed 750 ml. of distilled tetrahydrofuran, and 0.4 mole of lithium aluminum hydride was added. The mixture was stirred overnight with a magnetic stirrer. The solids were allowed to settle and an aliquot of the clear solution was analyzed for dissolved hydride by the usual procedure. A sufficient quantity of the clear solution was placed in a 1-l., three-neck flask, fitted with condenser, stirrer, and addition funnel, to provide 0.3 mole of the reagent. The solution was cooled to 0° and 0.9 mole of methanol was slowly added (exothermic reaction) as the hydrogen evolved was vented. Then 35 g. (0.25 mole) of dl-fenchone was added from the dropping funnel at such a rate that the temperature

could be maintained at approximately 0°. After addition was complete, the solution was stirred at 0° for 1 hr. Residual hydride was then destroyed by the slow addition of water. The reaction mixture was then transferred to a separatory funnel, ether was added, and then the mixture was treated with a saturated solution of sodium potassium tartrate. The organic phase was separated, the aqueous layer was extracted with ether, and the combined ether extract was dried over anhydrous magnesium sulfate. The solvents were removed on a rotary evaporator. Distillation provided 30.7 g., 80% yield, of dl-endo-fenchyl alcohol, b.p. 43–45° (1 mm.), 97% isomerically pure by gas chromatographic examination, m.p. p-nitrobenzoate 93–94.5° (lit.[26] m.p. 94–95°).

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Intramolecular Catalysis of Ketone Enolization in o-Acylbenzoic Acids[1]

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The kinetics of enolization of o-isobutyrylbenzoic acid has been measured in aqueous solution from pH 0 to 11 at 25°. Enolization rates were calculated from spectrophotometrically determined rates of iodination. Four kinetic terms contributed to the enolization: (1) the reaction of hydronium ion and the undissociated carboxylic acid; (2) the reaction of hydroxide ion and the carboxylate ion; (3) the reaction of the undissociated carboxylic acid; and (4) the reaction of the carboxylate anion. Of these four reactions, the last is the most important, being the predominant reaction from pH 2.5 to 10. In this region, the rate of the enolization reaction is dependent on the ionization of a group of $pK_a = 4.4$ and is unaffected by external buffers. The facile catalysis of enolization in the carboxylate anion can be mechanistically interpreted in terms of intramolecular general basic catalysis by the o-carboxylate ion, or alternatively in terms of intramolecular general acidic catalysis by the o-carboxylic acid group in a reaction with hydroxide ion. The former interpretation is preferred on kinetic and steric grounds. Intramolecular catalysis by o-carboxylate ion corresponds in efficiency to a concentration of the corresponding intermolecular catalyst of the order of 50 M. This intramolecular catalysis of enolization may serve as a model for the intracomplex catalysis of enolization of dihydroxyacetone phosphate by the enzyme aldolase.

Introduction

The initiating step of many organic reactions, synthetic and biochemical, is the transfer of a hydrogen

atom from a carbonyl compound to a base, leading to the formation of an enolate ion or enol. Catalysis of enolization has been one of the most thoroughly studied of all organic catalytic processes.[3,4] Recent work has attempted to extend our understanding to enzyme-catalyzed reactions which depend on enolization.[5–7] If an enzymatic group of an enzyme–substrate complex catalyzes the enolization of the substrate, the process may be described as an intracomplex catalysis. A suitable model for the elucidation of possible mechanisms of intracomplex catalysis has been the use of intramolecular catalysis.[8] Therefore, it seemed desirable to examine the intramolecular catalysis of enolization.

In classic work on the mechanism of enolization, Ingold, Wilson, and Hsu[9] compared the rates of racemization and bromination of 2-(o-carboxybenzyl)-indanone, in which intramolecular catalysis of enolization by the carboxyl group could occur, but they did not discuss this possibility. The enolization of a number of aliphatic ketones containing potential intramolecular catalytic groups has been investigated. Both the bromination of levulinic acid[10] and the

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