and 5 g. of sodium acetate. The brownish solid which precipitated was recrystallized from methylene chloride and ethanol to yield 5.1 g. (85%) of reddish-violet prisms, m.p. 190° dec.

Anal. Calcd. for $C_{16}H_{16}N_2S_2Cu$: S, 17.62; mol. wt., 364. Found: S, 17.68; mol. wt., 348, 354.

The copper chelate of 1-(*p*-tolylamino)-7-thioxo-1,3,5-cycloheptatriene was prepared by combination of a solution containing 2 g. of this material in 25 ml. of methylene chloride with 75 ml. of an aqueous solution containing 1.5 g. of copper acetate, 2 g. of sodium acetate and 25 ml. of ethyl alcohol. The methylene chloride was removed by distillation and the resulting violet precipitate was recrystallized from methylene chloride and ethyl alcohol to yield 2.5 g. (96%) of the chelate.

Anal. Calcd. for $C_{28}H_{24}N_2S_2Cu$: S, 12.42; mol. wt., 516. Found: S, 12.50; mol. wt., 665, 685.

The mercury chelate of 1-(*p*-tolylamino)-7-thioxo-1,3,5-cycloheptatriene was prepared by combining a solution of 2.27 g. of the aminothioxo compound in 20 ml. of ethyl alcohol with a solution of 2.7 g. of mercuric chloride in 20 ml. of ethyl alcohol. Addition of 2 g. of triethylamine precipitated a red crystalline solid which was recrystallized from methylene chloride and ethyl alcohol to yield 2.8 g. (85%) of the chelate, m.p. 166–167°.

Anal. Calcd. for $C_{28}H_{24}N_2S_2Hg$: S, 9.82; mol. wt., 653. Found: S, 9.98; mol. wt., 740, 750.

Amination of 1-(*p*-Tolylamino)-7-thioxo-1,3,5-cycloheptatriene.—A solution of 4.54 g. of the thioxo compound, 10.7 g. of *p*-toluidine (5 molar equivalents) and 100 ml. of 1-butanol was refluxed for 3 days under a slow stream of nitrogen. During this time, hydrogen sulfide could be detected in the effluent nitrogen stream. The solution was cooled and the precipitated solid was recrystallized four times from ethanol. The yield of 1-(*p*-tolylamino)-7-(*p*-tolylimino)-1,3,5-cycloheptatriene was 2.05 g. (33%). The melting point of this product with an authentic sample of the aminoimine was not depressed.

Acknowledgments.—The authors gratefully acknowledge the determination and interpretation of infrared and ultraviolet absorption spectra by Miss Naomi E. Schlichter and Miss Ellen Wallace, and of the n.m.r. spectra by Dr. D. B. Chesnut and Dr. W. D. Phillips. In addition, we wish to acknowledge the many helpful discussions of the infrared spectra with Professor R. C. Lord of Massachusetts Institute of Technology.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIF.]

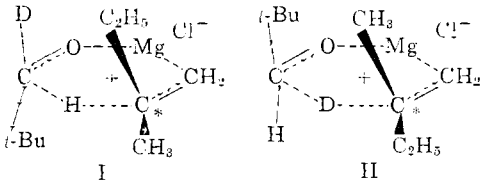
Asymmetric Reductions. X. Formation of Optically Active Neopentyl Alcohol-1-*d* by Asymmetric Grignard Reduction[1]

BY VICTOR E. ALTHOUSE, ERNA KAUFMANN, PAULA LOEFFLER, KANICHI UEDA AND HARRY S. MOSHER

RECEIVED DECEMBER 15, 1960

Trimethylacetaldehyde-1-*d* has been reduced by the Grignard reagent from (+)-1-chloro-2-methylbutane to give neopentyl alcohol-1-*d* which has the same configuration and 12% of the optical activity of the product from the reduction of this same aldehyde by actively fermenting yeast. Furthermore the reduction of non-deuterated trimethylacetaldehyde with the Grignard reagent from (−)-1-chloro-2-methylbutane-2-*d*, the deuterated enantiomorph of the above reagent, has given neopentyl alcohol-1-*d* with the same configuration and approximately 36% of the optical purity of the enzymically produced material. The absolute configuration of these products, the deuterium isotope effect and the relationship of this model chemical system to the enzymic system are considered.

Certain aspects of the asymmetric reduction of carbonyl compounds by optically active reducing agents[2] closely resemble those of enzymic reductions by the isolated alcohol dehydrogenase–diphosphopyridine nucleotide (ADH-DPNH) system[3] and by microbiological systems.[4] In the reduction of alkyl *t*-butyl ketones by the Grignard reagent from (+)-1-chloro-2-methylbutane[2] the extent of asymmetric reduction has been shown to depend upon the relative size of the alkyl and *t*-butyl groups. As the size of the alkyl group in this series of *t*-butyl ketones increases, the asymmetric bias of the reaction decreases, with the largest percentage asymmetric synthesis, 13%, being observed when the alkyl group was methyl. In this case (reduction of methyl *t*-butyl ketone) the transition state of lower energy leading to the preponderant isomer is symbolized by I where the deuterium atom is replaced by a methyl group.



The relationship between relative size of the groups on the ketone and the percentage asymmetric synthesis was not as simple in the alkyl phenyl ketones[5] nor the alkyl cyclohexyl ketones,[6] but there was excellent correlation in the purely aliphatic series represented by I where D was replaced by methyl through isobutyl.

For various reasons, including a desire to increase the asymmetric bias by increasing the difference in the steric effect of the R group and *t*-butyl group in the carbonyl compound, trimethylacetaldehyde-1-*d* (transition state I) was prepared and reduced by this same optically active Grignard reagent. Fur-

(1) We acknowledge with thanks the support of this investigation by a grant from the National Science Foundation and by research grant No. 5248 from the National Institutes of Health of the U. S. Public Health Service.

(2) See W. M. Foley, F. J. Welch, E. M. La Combe and H. S. Mosher, *J. Am. Chem. Soc.*, **81**, 2779 (1959), and references therein.

(3) (a) H. R. Levy, E. A. Loewus and B. Vennesland, *ibid.*, **79**, 2949 (1957); (b) J. Van Eys and N. O. Kaplan, *ibid.*, **79**, 2782 (1957); (c) E. S. G. Barron and S. Levine, *Arch. Biochem. Biophys.*, **41**, 175 (1952); (d) A. Grierer, *Biochim. Biophys. Acta*, **17**, 111 (1955).

(4) (a) C. Neuberg and F. F. Nord, *Ber.*, **52**, 2237 (1919); (b) C. Neuberg, "Advances in Carbohydrate Chemistry," Academic Press, Inc., New York, N. Y., Vol. 4, 1949, pp. 75–117; (c) P. Levene and A. Walti, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 545; (d) D. Müller, *Biochem. Z.*, 268 (1934).

(5) R. MacLeod, F. J. Welch and H. S. Mosher, *J. Am. Chem. Soc.*, **82**, 876 (1960).

(6) E. P. Burrows, F. J. Welch and H. S. Mosher, *ibid.*, **82**, 880 (1960).

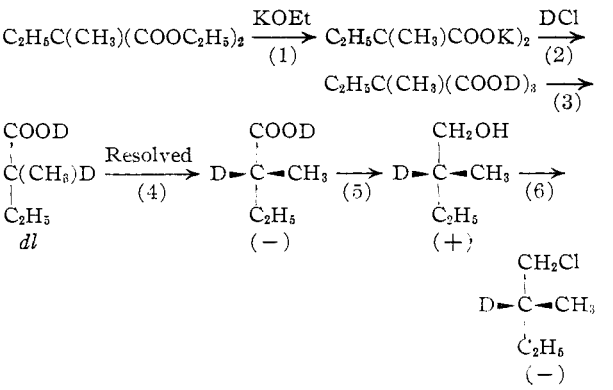
thermore, we have studied the reverse case where a deuterium atom is transferred from the isotopically substituted enantiomorphic Grignard reagent prepared from (−)-1-chloro-2-methylbutane-2-*d* to the non-deuterated trimethylacetaldehyde as indicated in II.

Since trimethylacetaldehyde-1-*d* has been reduced enzymically by actively fermenting yeast to give optically active neopentyl alcohol-1-*d*,[7] it now becomes possible to compare the steric and configurational requirements for the related enzymic and chemical hydrogen (and deuterium) transfer reactions.

Results

Trimethylacetaldehyde-1-*d*[7] was treated with an excess of the optically active Grignard reagent from (+)-1-chloro-2-methylbutane. The products were separated by fractionation and the neopentyl alcohol-1-*d* converted to the crystalline acid phthalate[8] which after two and three crystallizations had a constant melting point and rotation $[\alpha]^{27}D$ −0.115 ± 0.010°. Since this had 86% of the theoretical deuterium content, the calculated rotation for the completely deuterated product derived from optically pure chloride would be $[\alpha]^{27}D$ −0.138 ± 0.01°, which is 12% of the maximum rotation obtained for this same alcohol made by enzymatic reduction of trimethylacetaldehyde-1-*d*. The infrared spectra for both the free alcohol and its acid phthal ate were identical with those of the products obtained by fermentation. These results were duplicated in a completely independent experiment. Furthermore, the control reaction with non-deuterated trimethylacetaldehyde led to completely inactive products demonstrating again the freedom from optically active impurities.

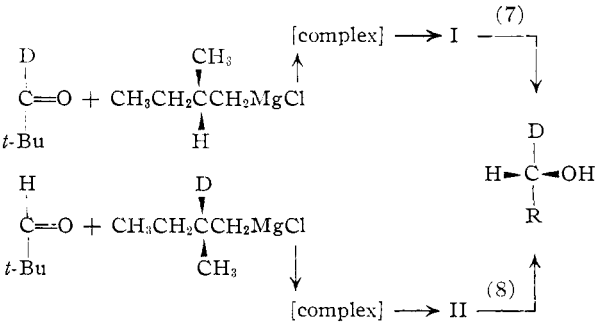
Deuterium transfer in the Grignard reduction reaction has been demonstrated previously.[9] The demonstration of an *asymmetric* deuterium transfer required the preparation of optically active 1-chloro-2-methylbutane-2-*d*. This was accomplished by the decarboxylation of methylethylmalonic acid-d_2 (step 3) and subsequent laborious resolution *via* the brucine salt[10] (step 4) to give the (−)-α-methylbutyric acid. Reduction of the acid with lithium aluminum hydride (step 5) gave the (+)-2-methyl-1-butanol-2-*d*. The (−)-acid which was used has the absolute configuration shown and gave on reduction the alcohol with the configuration opposite to the naturally occurring primary active amyl alcohol and with deuterium replacing hydrogen at the asymmetric center.



The reduction of trimethylacetaldehyde using the Grignard reagent from (−)-1-chloro-2-methylbutane-2-*d* gave neopentyl alcohol-1-*d* which was converted to the acid phthalate, $[\alpha]^{27}D$ −0.18 ± 0.01°. If the (−)-neopentyl alcohol-1-*d* acid phthalate had been 100% deuterated (instead of 56%) and the Grignard reagent had been prepared from optically pure (instead of 77% optically pure) (+)-2-methyl-1-butanol-1-*d*, the rotation would have been $[\alpha]^{27}D$ −0.42 ± 0.03°. Although the available supply of deuterated optically active Grignard reagent limited us to one successful experiment, we consider this value to be reliable.

Discussion

The postulated mechanism for the asymmetric Grignard reduction reaction demands that the preponderant enantiomorph of the neopentyl alcohol-1-*d* arising from the transfer of hydrogen from the (+)-Grignard reagent to the deuterated aldehyde (eq. 7 and transition state I) be the same as that arising from the transfer of deuterium from the (−)-β-deuterated Grignard reagent on the non-deuterated aldehyde (eq. 8 and transition state II).



This was confirmed since in both cases the neopentyl alcohol-1-*d* gave a levorotatory acid phthalate. Based upon the accepted mechanism for this reaction the absolute S-configuration[11] as represented must be assigned to this neopentyl alcohol-1-*d*. The S-configuration is that also assigned by Streitwieser[12] to the (+)-butanol-1-*d* (which also gives a levorotatory acid phthalate) obtained in the related asymmetric reduction of *n*-butyraldehyde-1-*d* by

(7) V. E. Althouse, K. Ueda and H. S. Mosher, *J. Am. Chem. Soc.*, 5938 **82**, (1960).

(8) The neopentyl alcohol-1-*d* was not purified further at this initial stage since previously it had been shown[7] that this product, although optically active, did not rotate the plane of polarized sodium light appreciably. The acid phthalate, however, was a suitable derivative for purposes of purification and evaluation of the extent of optical activity. The same rigorous criteria of purity were exercised here as previously[7] to ensure that the observed rotation was not due to some impurity. In contrast to the many possible contaminants in the reduction by the actively fermenting yeast, the only likely optically active impurities in this chemical reduction were (−) primary active amyl alcohol, from air oxidation of the Grignard reagent, and the normal addition product. The latter is high boiling and the acid phthalate of primary active amyl alcohol is an oil and thus its removal *via* this crystalline derivative was assured.

(9) G. E. Dunn and J. Warkentin, *Can. J. Chem.*, **34**, 75 (1956).

(10) (a) O. Shutz and W. Marckwald, *Ber.*, **29**, 52 (1896); (b) W. Marckwald, *ibid.*, **32**, 1089 (1899).

(11) Notation of R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956).

(12) A. Streitwieser, Jr., J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 340 (1959).

isobornyloxymagnesium bromide. It is the opposite configuration assigned by Levy, Loewus and Vennesland[3] to the (−)-ethanol-1-*d* obtained by reduction of acetaldehyde-1-*d* with the enzyme system ADH–DPHN. As pointed out earlier,[7] this latter assignment probably is incorrect and thus (−)-ethanol-1-*d*, (+)-butanol-1-*d* and the neopentyl alcohol-1-*d* which gives a (−)-acid phthalate all have the same absolute configuration, namely, S.[12]

A tentative estimate of the asymmetric bias in the reduction of trimethylacetaldehyde-1-*d* by the undeuterated optically active Grignard reagent can be made on the assumption that the neopentyl alcohol-1-*d* obtained by fermentation[7] was optically pure.[13] We had anticipated that the extent of asymmetric reduction, 12%, would be much higher when we studied this case involving the extreme difference in steric bulk between the deuterium atom and *t*-butyl group. The asymmetric bias when methyl *t*-butyl ketone (where methyl is pitted against *t*-butyl) was reduced by this same reagent[2] was 13%. Thus the concept of the preferred transition state being that one where groups arrange themselves to minimize their interactions in the transition state with large *versus* small and small *versus* large on opposite sides of the transition ring (as represented in I and II) may be satisfactory for predicting the *configuration* of the preponderant enantiomorph, but obviously it is inadequate in this oversimplified form for estimating the *extent of asymmetric reduction*. Thus it appears probable that the inherent flexibility of the bonds in the transition state permits minimizing the steric interactions by the bending of the *t*-butyl group away from the interfering methyl group. This is equivalent to saying that, due to a lack of buttressing effect of the *t*-butyl group by the deuterium atom, the *t*-butyl group is able to assume a more equatorial and thus less interacting position in the transition ring. This requires a certain nonplanarity of this transition ring which is quite possible although must be limited because of the conversion of one double bond to a single bond, and one single bond to a double bond during the progress of this reaction.

The observation that there was a 12 ± 1% asymmetric reduction when hydrogen was transferred (eq. 7, R = D) and 36 ± 4% asymmetric reduction when deuterium was transferred (eq. 8) was quite unexpected. We had anticipated that the two values might not be identical but that they would differ by a factor of three was indeed surprising. It is unlikely that the formation of a Grignard–trimethylacetaldehyde complex could be influenced appreciably by the substitution of hydrogen for deuterium on the carbonyl carbon of the aldehyde and completely improbable that this would have any measurable effect when deuterium was substituted on the β-carbon atom of the Grignard reagent. Furthermore, the formation of the complex prior to the hydrogen transfer step cannot be controlling from a stereochemical point of view since it already has been demonstrated by Dunn and Warkentin[9] that a kinetic isotope effect of approximately two exists in the Grignard reduction reaction of benzophenone by β-deuterio-isobutylmagnesium bromide; this constitutes proof that hydrogen transfer is involved in the rate-determining step. Furthermore, it seems impossible that the non-bonded interactions in transition states I and II could be measurably different, especially since it has now been shown by Mislow, O'Brien and Schaefer,[14] in a very sensitive Meerwein–Ponndorf asymmetric reduction of a 2,2′-bridged-6,6′-dimethyl-1,1′-biphenyl ketone by (+)-2-propanol-1-d_3, that the differences in non-bonded interactions between CH_3 and CD_3 are too small to be detected.

It is quite likely that the stereospecificity of the Grignard reductions would be very sensitive to the average C—H—C bond distance in the transition state of the hydrogen transfer step. As deduced from ground state measurements on CH_4 *versus* CD_4,[15] however, the average differences between the two carbon atoms in C—H—C (I) and C—D—C (II) would be extremely small, perhaps in the order of 0.008 Å. Again this does not seem adequate to explain the threefold difference observed. Thus it seems that the most likely cause of the observed difference in asymmetric bias in deuterium *versus* hydrogen transfer is connected with the slower rate of the former. It may in some way be connected with the much greater probability of tunnelling in the case of hydrogen transfer. If the differences in asymmetric bias are a direct result of a rate difference in the two processes, then comparable variations in asymmetric bias should be observed by conducting the hydrogen transfer at different temperatures. This has not been done for this particular example but it has already been observed that lowering the temperature from 35 to −75° in the reduction of methyl *t*-butyl ketone by the Grignard reagent from (+)-1-chloro-2-methylbutane only raised the asymmetric reduction from 13 to 16%. We feel that it is necessary to study further the effect of temperature on the specific case in point and that additional examples of this phenomenon must be explored to establish the generality of this observation before any substantial conclusions can be reached.

It is of great interest that the stereospecific enzymic reduction of acetaldehyde-1-*d* may be formally represented by eq. 7 merely by replacing the optically active Grignard reducing agent by the biochemical reducing agent DPNH (reduced diphosphopyridine nucleotide) in the presence of an alcohol dehydrogenase enzyme. Although the magnitudes of the asymmetric reductions are quite dif-

(13) (a) If subsequent work reveals that the enzymically produced neopentyl alcohol-1-*d* whose acid phthalate has $[\alpha]^{25}D$ −1.14 ± 0.04° is only partially active, the estimates of asymmetric bias must be revised downward. This would in no way change any of the conclusions of the present work. We are hoping to establish the configuration and optical purity of this alcohol by independent means. (b) These figures are calculated from the observed rotations and deuterium analysis for the product with one deuterium atom per molecule on the assumption that there is a linear relationship between rotation and concentration of the deuterated alcohol and in the solution of the nondeuterated alcohol.

(14) K. Mislow, R. E. O'Brien and H. Schaefer, *J. Am. Chem. Soc.*, **82**, 5512 (1960).

(15) V. W. Laurie and D. Herschbach, *Bull. Am. Phys. Soc.*, [11] **5**, 500 (1960); L. S. Bartell, K. Kuchitsu and R. J. de Neui, *J. Chem. Phys.*, **33**, 1254 (1960). Although the absolute values for the average bond distances for C–H and C–D do not check by the two methods reported, the differences are in good agreement by both methods.

ferent, we feel that the similarities are more than superficial and that a further study of this model system will prove valuable in understanding the enzymic process. It seems likely that just as magnesium and aluminum play key roles in the Grignard and Meerwein–Ponndorf reductions, the zinc atom present in alcohol dehydrogenase may play a key part in the enzymic hydrogen transfer process as has been suggested by Wallenfels.[16]

Experimental

(−)-Neopentyl Alcohol-1-*d* Acid Phthalate.—Trimethylacetaldehyde-1-*d*[17] (10.5 g., 0.12 mole), dissolved in 50 ml. of anhydrous ether, was added under a nitrogen atmosphere over a 1.3-hour period to a stirred solution of 140 ml. of 0.95 *N* Grignard reagent prepared in the usual way[2] from (+)-1-chloro-2-methylbutane, $\alpha^{25}D$ +1.42°, and magnesium. After refluxing for 10 minutes and standing 12 hours, the reaction mixture was decomposed with 25 ml. of water and worked up by combining the ether layer and ether extracts, drying over anhydrous sodium sulfate, and fractionating through a 30-plate semi-micro column packed with $^3/_{32}$" Pyrex helices to give 5.2 g. (50%) of neopentyl alcohol-1-*d*.[3] The center cut was converted to the acid phthalate (85% yield) and gave, after 2 and 3 recrystallizations, the following melting points and rotations, the latter being taken in a 4-dcm. center-filled tube: 68.2–70.0°, $\alpha^{27}D$ −0.19 ± 0.01° (*l* 4, *c* 41; acetone); 68.0–69.0°, $\alpha^{27}D$ −0.20 ± 0.01 (*l* 4, *c* 44; acetone); $[\alpha]^{27}D$ −0.115 ± 0.01°. The infrared spectrum of this compound was identical with that of the acid phthalate from the phytochemically produced alcohol.[7] Analysis for deuterium[18] showed 0.86 atom per molecule.

Neopentyl Alcohol-1-*d*.—The purified optically active acid phthalate (10.0 g., 0.04 mole) was hydrolyzed and the neopentyl alcohol-1-*d* isolated by ether extraction from the steam distillate. Distillation through a Vigreux column gave a near quantitative yield, m.p. 46–50°, $[\alpha]^{27}D$ −0.01 ± 0.01° (*l* 4, *c* 24; acetone). Previous experiments[7] have shown that this optically active alcohol which does not rotate the plane of polarized sodium light appreciably was reconverted to the acid phthalate of unchanged rotation.

Potassium Methylethylmalonate.—To a solution of 256.0 g. (4.6 moles) of potassium hydroxide in 2 l. of absolute ethanol was added 230 g. (1.14 moles) of ethyl methylethylmalonate.[19] The mixture was allowed to reflux for 5 hours on a steam-bath, cooled and the potassium salt separated, washed with a dry ether–ethanol mixture (1:1) and dried under vacuum over phosphorus pentoxide; yield 227 g. (90%).

α-Methylbutanoic-2-*d*-Acid.—An ether solution of deuterium chloride was prepared as follows in a manner similar to that of Ives and Nettleton.[20] Phosphorus pentachloride, 182 g., which previously had been heated under reduced pressure to remove traces of phosphorus oxychloride and hydrogen chloride, and 250 ml. of dry benzene were placed in a three-necked round-bottom flask. Deuterium oxide (6.6 g., 0.33 mole) was added dropwise and the generated deuterium chloride swept by a stream of dry nitrogen through a condenser and into an absorption flask containing 300 ml. of dry ether, cooled to −30° in a Dry Ice–acetone-bath. When the deuterium oxide addition was complete (4 hours), the nitrogen pressure was increased and the reaction mixture heated to a reflux in order to remove any residual deuterium chloride.

The cold deuterium chloride–ether solution was forced with nitrogen pressure into a flask immersed in a Dry Ice–acetone-bath which was charged with 38.0 g. (0.17 mole) of potassium methylethylmalonate in 200 ml. of dry ether. The reaction mixture was then stirred for 1 hour at room temperature and the ethereal solution decanted under dry nitrogen. The residual potassium chloride was washed with dry ether and the ethereal extracts combined with the main portion.

The crude methylethylmalonic acid-2-*d* which was left on removal of the ether was heated to 160–170° until the evolution of carbon dioxide ceased (4 hours). Distillation of the reaction mixture gave 14.2 g. (78.9%) of product, b.p. 168–174°. A total of 75.9 g. of α-methylbutanoic-2-*d* was obtained by this method. This was converted to α-methylbutanoic-2-*d* acid by treatment with saturated sodium bicarbonate solution, acidification with hydrochloric acid and extraction with ether. The product was isolated in 90% yield on removal of the ether; b.p. 173–176°.

Resolution of *dl*-α-Methylbutanoic-2-*d* Acid.[21]—The brucine salt of *dl*-α-methylbutanoic-2-*d* acid was subjected to a twenty-stage systematic fractional crystallization from water according to the method of Marckwald.[10] Repeated crystallizations resulted in some hydrolysis with accumulation of brucine and apparent loss of the acid by volatilization. The highest optical purity obtained was $\alpha^{25}D$ −14.6° and the yield of this material was small. The (+)-acid which accumulated in the mother liquors from the crystallizations was treated with silver nitrate. The *dl*-silver salt which was more insoluble was removed and the (+)-acid from the more soluble silver salt obtained by regeneration. It was necessary to repeat this treatment 3 times to bring the $\alpha^{25}D$ +7° acid to the $\alpha^{26}D$ +14.45° material which was used in some exploratory experiments. This was quite unsatisfactory but we were unable to improve on the procedure of Marckwald.[21]

(+)-2-Methyl-1-butanol-1-*d*.—Lithium aluminum hydride (2.7 g., 0.071 mole) in 50 ml. of anhydrous ether was stirred and cooled to 5°. To this suspension was added dropwise 4.2 g. (0.041 mole) of (−)-2-methylbutanoic-2-*d* acid ($\alpha^{25}D$ −14.2° corresponding to 80% optical purity assuming that the deuterated and non-deuterated acids have the same rotation), in 60 ml. of anhydrous ether. The reaction mixture, kept between 8–10° during the addition, was allowed to warm to room temperature, stirred for an additional hour, recooled in an ice-bath and decomposed first by dropwise addition of water and then by addition of 6 *N* sulfuric acid. The ether layer was separated, the aqueous layer extracted with ether and the combined ether extracts washed with 10% sodium bicarbonate, with water and dried over anhydrous sodium sulfate. The ether was removed through a column and the product distilled at 127–129°; yield 3.05 g. (85%), $\alpha^{25}D$ 3.62 ± 0.02° (neat) corresponding to 76% optical purity assuming that the rotation of the deuterated and non-deuterated compounds are the same. Deuterium analysis[18] showed 0.65 atom per molecule.

(−)-1-Chloro-2-methylbutane-2-*d*.—The above alcohol was converted to the chloride with thionyl chloride and pyridine.[2] Because of the small quantity, optical rotation and deuterium analysis were not taken, but there is no reason to suspect loss of either optical purity or deuterium in this process.

The Action of the Grignard Reagent from (−)-1-Chloro-2-methylbutane-2-*d* on Trimethylacetaldehyde.—The above chloride (1.4 g., 0.013 mole) was converted to the Grignard reagent using 0.34 g. (0.014 mole) of triply sublimed magnesium[22] which was treated with 1.2 g. (0.014 mole) of tri-

(16) K. Wallenfels, *et al.*, *Biochem. Z.*, **329**, 1782 (1957); see also C. Shifrin and N. O. Kaplan, *Adv. in Enzymol.*, **22**, 354 (1960).

(17) This material was part of the same sample reported in ref. 7 and used in the fermentation experiments. Its deuterium content was therefore identical.

(18) J. Graff and D. Rittenberg, *Anal. Chem.*, **24**, 878 (1952); mass spectographic determinations by Stanford Research Institute.

(19) Ethyl methylethylmalonate was prepared in two steps according to the method of R. Adams and R. M. Kamm, "Organic Syntheses," Coll. Vol. I, Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 250, from ethyl malonate and ethyl iodide in sodium ethoxide, followed by treatment of the product in an identical manner with methyl iodide. The product, b.p. 100–104°, was isolated in 67% yield.

(20) D. J. G. Ives and M. R. Nettleton, *J. Chem. Soc.*, 1085 (1948).

(21) Although (−)-2-methyl-1-butanol (primary active amyl alcohol) is readily available from fusel oil, resolution of either the acid or of the 3-nitrophthalate of the alcohol as reported by W. Marckwald and A. McKenzie, *Ber.*, **34**, 485 (1901), is a laborious and very unsatisfactory process. The ester made from 3-nitrophthalic anhydride is a mixture of position isomers as well as optical isomers which would make this procedure wasteful in the case of the deuterated alcohol. Furthermore, Marckwald found that exhaustive crystallization of the brucine salt of the acid 3-nitrophthalate was slow and inefficient. For this reason we chose the partial resolution of the *dl*-2-methylbutanoic acid. Attempted resolutions by strychnine, cinchonine, cinchonidine, quinine and (+)-α-phenylethylamine were fruitless.

(22) We wish to acknowledge with gratitude the gift from Dow Chemical Co. of the specially purified magnesium used in these studies.

methylacetaldehyde by the same procedure used in the case of trimethylacetaldehyde-1-*d*. On removal of the ether, the crude oil containing the neopentyl alcohol-1-*d*, as well as the normal addition product, was treated with phthalic anhydride in the usual manner.[7] The crude crystals were recrystallized to give 700 mg. (25% yield based on the (−)-1-chloro-2-methylbutane-2-*d*), m.p. 68.5–70.0°. After a second and third recrystallization the m.p. was constant at 68.5–69.5°. Because of the small amount of material it was difficult to obtain accurate rotations, but within experimental error they were unchanged at $\alpha^{25}D$ −0.07 ± 0.02° (*l* 1, *c* 40; acetone). After the fourth recrystallization a precise value of $\alpha^{27}D$ −0.072 ± 0.010° (*l* 1, *c* 39.9; acetone), $[\alpha]^{27}D$ −0.180 ± 0.010° was obtained in a Rudolph recording spectropolarimeter. A deuterium analysis[18] revealed 0.56 atom per molecule. The infrared spectrum of this compound was identical with that obtained from the enzymatic reduction of trimethylacetaldehyde-1-*d*[7] with the exception of the differences due to the relative amounts of hydrogen and deuterium in the two samples.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF WISCONSIN, MADISON 6, WISC.]

The Effect of Solvent on Spectra. V. The Low Intensity (n → π*) Electronic Transition of Cyclic Ketones

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A series of cycloalkanones with ring size (*n* = 4–10, 15) has been examined in the near ultraviolet region in a series of solvents covering a broad polarity range. The transition energies (E_T) were plotted against the solvent polarity standard, Z (ref. 4). Cyclobutanone was found to have a n → π*-transition with rather low sensitivity to solvent, and brief examination of two other cyclobutanones suggested that such low sensitivity may be characteristic of these rings. The transitions for the ketones with *n* = 5 through 10 correlate rather well with Z, and the correlation for cyclohexanone is so good that it can be used as a secondary standard of solvent polarity. It was found that the slope of the correlation for cyclopentadecanone, *n* = 15, was unexpectedly low. Low solvent sensitivity for the n → π*-transition of the C_{15}-ketone was rationalized by postulating that the molecule tended toward "folded" conformations in polar solvents, but was "open" or "extended" in non-polar solvents. The C_{15}-ketone absorption band obeyed Beer's law in all solvents.

Not only are all measures of solvent polarity empirical, but the application of a particular measure to a chemical or physical problem depends upon the congruency of the physical process from which the measure was derived to that under study. The dielectric constant, which averages both the molecular and polymolecular inhomogeneities of a liquid solvent, is not very satisfactory as a measure of solvent polarity on the molecular level. The dielectric constant of the first layer of water molecules around an ion, for example, must be appreciably different from that of the measured (macroscopic) dielectric constant.[2] For most chemical processes,[3] and for spectroscopic transitions, the detailed properties of the solvent group (cybotactic region)[4] immediately around the species of concern control the course of events. For the consideration of the effect of solvent polarity on the microscopic level, it is more desirable to choose model processes which are in their turn subjected to a detailed and searching analysis. For kinetic processes, the rate of solvolysis of *t*-butyl chloride covers a reasonable range of solvent polarity[3,5]; the parameter based on these rates is called a **Y** value. A more general parameter became available with the discovery that the charge-transfer absorption band of 1-ethyl-4-carbomethoxypyridinium iodide was extremely sensitive to the solvent[4]; the transition energy corresponding to the absorption band was defined as the **Z**-value for the solvent in which it was measured.

Solvent polarity values defined on the basis of molecular processes can serve a number of useful purposes. Correlation of rates or of spectroscopic maxima can lead to the estimation of rates or maxima in solvents for which the rate or maximum has not been or can not be measured. Response to solvent change, which is an important criterion of chemical mechanism or for establishing the nature of an electronic transition, can be placed upon a semi-quantitative basis. Last, anomalous behavior with respect to an expected correlation can call attention to chemically interesting situations.

The purpose of the present paper is to examine the effect of solvent on the low intensity (n→π*) electronic transition of cycloalkanones. It will be seen that **Z**-values are useful in the analysis of the results.[6]

Results

The ketones used in this investigation were all carefully purified. Our experience indicated that a number of the cyclic ketones were sensitive to photochemically-induced oxidation. One important criterion of purity was therefore the lack of a maximum or shoulder in the ultraviolet absorption curve between 2200 and 2600 Å., where α,β-unsaturated ketones and other impurities would absorb. The other more usual criteria of purity (melting point, boiling point, refractive index, derivatives, etc.) were also utilized. In the case of cyclobutanone, it proved impractical to remove 2 or 3% of two volatile impurities (detected by vapor phase chromatography), but the identical results given by two different samples afford confidence in the supposition that the contaminants are non-light-absorbing in the region of the maximum of cyclobutanone.[7]

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(7) The observation concerning the fact that impurities *more volatile* than cyclobutanone are present even in purified ketone was also